

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**205747Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205747

SUPPL # N/A

HFD # N/A

Trade Name Humalog U-200

Generic Name insulin lispro

Applicant Name Eli Lilly

Approval Date, If Known May 26, 2015

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The NDA is supported by a single study evaluating bioequivalence of the proposed insulin lispro U-200 formulation relative to the approved insulin lispro U-100 formulation, after subcutaneous administration of 20 units to healthy subjects.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20563	Humalog U-100
NDA# 21017	Humalog Mix 75/25
NDA# 21018	Humalog Mix 50/50

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

## **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:





Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON  
ORIGINAL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CALLIE C CAPPEL-LYNCH  
05/08/2015

WILLIAM H CHONG  
05/08/2015  
Signing on behalf of Dr. Jean-Marc Guettier (Division Director)

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 205747	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Humalog Established/Proper Name: insulin lispro (rDNA origin) Dosage Form: injection		Applicant: Eli Lilly and Company Agent for Applicant (if applicable): N/A
RPM: Callie Cappel-Lynch		Division: Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>• Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)           <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)</li> </ul> </li> </ul> <p>Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
<b>Actions</b> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>May 26, 2015</u></li> <li>• Previous actions (specify type and date for each action taken)</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  CR- March 10, 2014
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): Type 5  
 (confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters *(including approval letter with final labeling)* AP- May 26, 2015  
CR- March 10, 2014

**Labeling**

❖ Package Insert *(write submission/communication date at upper right of first page of PI)*

- Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*  Included
- Original applicant-proposed labeling  Included

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*

- Medication Guide
- Patient Package Insert
- Instructions for Use
- Device Labeling
- None

- Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*  Included
- Original applicant-proposed labeling  Included

❖ Labels **(full color carton and immediate-container labels)** *(write submission/communication date on upper right of first page of each submission)*

- Most-recent draft labeling  Included

❖ Proprietary Name

- Acceptability/non-acceptability letter(s) *(indicate date(s))*
- Review(s) *(indicate date(s))*

Letters: February 26, 2015,  
January 14, 2014, August 8, 2013  
Reviews: February 12, 2015,  
January 7, 2014, August 8, 2013

❖ Labeling reviews *(indicate dates of reviews)*

RPM: July 11, 2013  
DMEPA: March 13, 2015,  
February 15, 2014  
DMPP/PLT (DRISK): May 11,  
2015  
December 5, 2013  
OPDP: March 5, 2015, April 2,  
2014  
SEALD:  None  
CSS:  None  
Product Quality see product  
quality review dated February 10,  
2014 pg 71-72  
Other:  None

**Administrative / Regulatory Documents**



<ul style="list-style-type: none"> <li>❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (<i>indicate date of each review</i>)</li> <li>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</li> </ul>	<p>July 18, 2013</p> <p><input checked="" type="checkbox"/> Not a (b)(2)</p>
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>N/A</u></li> <li>If PeRC review not necessary, explain: This application does not trigger PREA.</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<p>May 26, 2015                  May 22, 2015                  May 19, 2015 (2)                  May 18, 2015                  May 12, 2015                  May 7, 2015                  May 5, 2015                  May 4, 2015                  March 31, 2015                  March 17, 2015                  March 16, 2015                  March 4, 2015                  December 31, 2014                  December 10, 2014                  February 19, 2014                  October 31, 2013                  September 11, 2013                  July 23, 2013                  June 26, 2013                  May 28, 2013                  May 17, 2013</p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input type="checkbox"/> N/A or no mtg May 7, 2014</p>
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> No mtg Written responses issued August 21, 2012</p>
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> No mtg</p>
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	<p>Type C Written responses issued July 25, 2014</p>

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	May 26, 2015 February 20, 2014
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review (see CDTL Review)
• Clinical review(s) ( <i>indicate date for each review</i> )	May 18, 2015 June 20, 2013
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See cross-discipline team leader review dated May 26, 2015 (pg. 10 )
Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )	N/A
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	January 28, 2014
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None



Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	May 1, 2015 February 10, 2014 June 24, 2013
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	March 26, 2015 February 2, 2015 August 20, 2014 April 18, 2014 February 8, 2014 July 24, 2013
Nonclinical <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (indicate date for each review)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	Other reviews: February 10, 2014 February 3, 2014 June 27, 2013 June 18, 2013 Microbiology: March 20, 2015, January 21, 2014 June 13, 2013,
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	Device Reviews: May 13, 2015 May 7, 2015 January 6, 2015 February 12, 2014 February 6, 2014 December 19, 2013 October 3, 2013 July 11, 2013



❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	February 10, 2014, pages 72-73
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	N/A
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the "preferred" name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

N/A

- Finalize 505(b)(2) assessment

N/A

❖ For Breakthrough Therapy (BT) Designated drugs:

- Notify the CDER BT Program Manager

N/A

❖ For products that need to be added to the flush list (generally opioids): Flush List

- Notify the Division of Online Communications, Office of Communications

N/A

❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email

 Done

❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter

N/A

❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name

 Done

❖ Ensure Pediatric Record is accurate

 Done

❖ Send approval email within one business day to CDER-APPROVALS

 Done

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate@lilly.com)  
**Subject:** NDA 205747 Labeling Comments  
**Date:** Tuesday, May 26, 2015 9:53:00 AM  
**Attachments:** [Minor Edits 5\\_26\\_2014\\_proposed.docx](#)

---

Hi Sumitra,

Please see the attached labeling with minor FDA comments/edits. Please send revised labeling formally ASAP.

Thanks,  
Callie

14 Pages of Draft Labeling have been Withheld in Full as  
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/s/  
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CALLIE C CAPPEL-LYNCH  
05/26/2015

**From:** CappellLynch, Callie  
**To:** ["Sumitra M Ghate"](mailto:Sumitra.M.Ghate)  
**Subject:** RE: NDA 205747  
**Date:** Friday, May 22, 2015 4:42:00 PM  
**Attachments:** [Clean version FDA edits to Lilly edits 5 20 15 humalog-u200-proposed.docx](#)  
[FDA edits to Lilly edits 5 20 15 humalog-u200-proposed.docx](#)

---

Hi Sumitra,

Please see the attached labeling with FDA edits. I have attached a track changes and clean version.

Extensive formatting and re-organization were made to the D&A section. Changes are consistent with the Dosage and Administration Section of the Labeling for Human Prescription Drug and Biological Products Content and Format March 2010 Guidance. The content of the instructions did not change from the previous version. These changes were made to enhance clarity of the instructions and eliminate practice of medicine instructions which were not relevant to the specific product.

Please review and comment on the clean version and return to us by OOB Tuesday.

We have no additional comments on the PPI, IFU, or carton and container at this time. If you have any questions, please contact me.

Thanks,  
Callie

---

**From:** Sumitra M Ghate [[mailto:ghate\\_sumitra\\_m@lilly.com](mailto:ghate_sumitra_m@lilly.com)]  
**Sent:** Friday, May 22, 2015 3:28 PM  
**To:** CappellLynch, Callie  
**Subject:** RE: NDA 205747

Ok...thanks. Really appreciate all your correspondence over the past few days!

Sumitra

**Sumitra M. Ghate :** Advisor, Global Regulatory Affairs

---



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M [REDACTED] (b) (6)  
:: F 317.276.1652  
:: [www.lilly.com](http://www.lilly.com)

---

**From:** CappellLynch, Callie [<mailto:Callie.CappellLynch@fda.hhs.gov>]  
**Sent:** Friday, May 22, 2015 3:24 PM  
**To:** Sumitra M Ghate  
**Subject:** RE: NDA 205747

Hi Sumitra,

I planned to leave by 6pm, however, if we don't have anything yet, but it is near completion I'll wait. I'll keep you as updated as possible with the information I have.

Thanks,  
Callie

---

**From:** Sumitra M Ghate [[mailto:ghate\\_sumitra\\_m@lilly.com](mailto:ghate_sumitra_m@lilly.com)]  
**Sent:** Friday, May 22, 2015 3:16 PM  
**To:** CappelLynch, Callie  
**Subject:** NDA 205747

Hi, Callie –

Can you tell me what time you are planning to leave for the day? I have asked our operations group to be on hold so that we can submit to the NDA today through the gateway, so trying to understand if there is a time cut-off after which we should not be expecting a response today.

Thanks!

Sumitra

**Sumitra M. Ghate :** Advisor, Global Regulatory Affairs

---



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M (b) (6)  
:: F 317.276.1652  
:: www.lilly.com

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/22/2015

**From:** CappelLynch, Callie  
**To:** ["Sumitra M Ghaté"](#)  
**Subject:** RE: NDA 205747 labeling comments  
**Date:** Tuesday, May 19, 2015 6:52:00 PM  
**Attachments:** [image002.png](#)  
[image003.png](#)  
[image004.png](#)  
[image005.png](#)

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Hi Sumitra,

Please see our proposal below. If you have additional questions, please contact me. As we are not working from the label itself, the numbering in the example below may not be completely accurate. When you send the revised label, please ensure that numbering and cross references are correct.

Change section 5.4 of Warnings and Precautions to:

#### **5.4 Medication Errors**

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between HUMALOG and other insulins, instruct patients to always check the insulin label before each injection.

Do not transfer HUMALOG U-200 from the HUMALOG KwikPen to a syringe. The markings on the syringe will not measure the dose correctly and can result in overdosage and severe hypoglycemia

(b) (4)

**With regard to the specific populations question:** The hypoglycemia warning cross-references Section 8.6 and 8.7 in the drug label and these Sections should be added to the Humalog label with the following language and cross-reference to the PK Section. Section 8 is reserved for unique efficacy or safety considerations in special populations (i.e., not a repeat of PK/PD descriptive data in Section 12).

#### **8.6 Renal Impairment**

Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring [see *Clinical Pharmacology* (12.3)].

#### **8.7 Hepatic Impairment**

Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring [see *Clinical Pharmacology* (12.3)].

**With regard to Section 17:** Change the language to command language as per the HUMULIN N label and include the following headings. Most of the W&Ps should figure in this Section.

17.1 Keep as is

17.2 **Hypoglycemia:** Replace first paragraph with language from Hypoglycemia Section of HUMULIN N label adapted to HUMALOG.

17.3 **Hypersensitivity Reactions:** Adapt Hypersensitivity Section language from HUMULIN N to HUMALOG

17.4 **Medication Errors:** Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Inform patients that HUMALOG U-200 contains 2 times as much insulin in 1 mL as HUMALOG U-100.

Inform patients that the HUMALOG U 200 KwikPen dose counter shows the number of units of HUMALOG U 200 to be injected and that no dose (b) (4) is required.

Instruct patients to NOT transfer HUMALOG U 200 from the HUMALOG KwikPen to a syringe. The markings on the syringe will not measure the dose correctly and this can result in overdosage and



severe hypoglycemia

**17.5 Administration Instruction for HUMALOG U-200**

Instruct patients to NOT mix HUMALOG U-200 with any other insulin.

**17.5 Women of Reproductive Potential:** Adapt language from HUMULIN N

**17.6 CSCI pumps** keep as is.

Thanks,

Callie

---

**From:** Sumitra M Ghate [mailto:ghate\_sumitra\_m@lilly.com]

**Sent:** Tuesday, May 19, 2015 4:39 PM

**To:** CappelLynch, Callie

**Subject:** RE: NDA 205747 labeling comments

Hi, Callie –

I just left you a voicemail a few minutes ago. We are going to need a bit more detail on specifically what FDA is requesting per the last sentence in your email below, “Please also update the special populations section and drug interactions section per the Humulin N label. Section 17 will need to be updated per changes to section 5.”

Questions:

- Is the first sentence referring to the “specific populations” under 12.3 and NOT Section 8. – Please confirm
- Is the second sentence is asking us to add and revise ONLY the language as per section 5 (e.g. Hypoglycemia and Hypersensitivity)? Assuming that doesn’t include adding the other subsections (Females w/ repro potential and expiration date) or changing the other proposed Humalog info? The Humulin N label is quite a bit different from the Humalog label so trying to understand exactly what FDA is asking. See below so you have a better idea of what I’m asking.

**Humulin N section 17:**

**17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (*Patient Information and Instructions for Use*).

**Never Share a HUMULIN N Pen, HUMULIN N KwikPen, or Syringe Between Patients**

Advise patients that they must never share a HUMULIN N pen or HUMULIN N KwikPen with another person, even if the needle is changed. Advise patients using HUMULIN N vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

**Hypoglycemia**

Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia especially at initiation of HUMULIN N therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Instruct patients on the management of hypoglycemia.

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery [see *Warnings and Precautions* (5.3)].

Inform patients that accidental mix-ups between HUMULIN N and other insulins have been reported. Instruct patients to always carefully check that they are administering the correct insulin (e.g., by checking the insulin label before each injection) to avoid medication errors between HUMULIN N and other insulins.

**Hypersensitivity Reactions**

Advise patients that hypersensitivity reactions have occurred with HUMULIN N. Inform patients on the symptoms of hypersensitivity reactions [see *Warnings and Precautions* (5.4)].

**Females with Reproductive Potential**

Advise females of reproductive potential with diabetes to inform their doctor if they are pregnant or are contemplating pregnancy [see *Use in Specific Populations* (8.1)].

**Visual Inspection Prior to Use**

Instruct patients to visually inspect HUMULIN N before use and to use HUMULIN N only if it contains no particulate matter and appears uniformly cloudy after mixing [see *Dosage and Administration* (2.1)].

**Expiration Date**

Instruct patients not to use HUMULIN N after the printed expiration date.

Proposed Humalog Section 17 (this doesn't include recent revisions made in label negotiations...shown as example only):

**17 PATIENT COUNSELING INFORMATION**

(b) (4)

**Sumitra M. Ghate:** Advisor, Global Regulatory Affairs



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M (b) (6)  
:: F 317.276.1652  
:: www.lilly.com

---

**From:** Cappellynch, Callie [<mailto:Callie.Cappellynch@fda.hhs.gov>]  
**Sent:** Tuesday, May 19, 2015 3:09 PM  
**To:** Sumitra M Ghate  
**Subject:** NDA 205747 labeling comments  
**Importance:** High

Hi Sumitra,

Please see the labeling comments below for NDA 205747. We ask that you incorporate these comments and provide a revised label by COB tomorrow instead of today. If you have any questions, please call me.

We note that the Highlight Section and Section 5 is outdated. Please use the same language that is in use for Humulin N for both of these sections with the exception of the *Never Share* Bullet and and the (b) (4)

[Redacted] *bullet.*

The updated language is preferred and is more consistent with labeling guidances (identifies risks first, uses direct language, describes mitigation strategies, uses cross-reference to special population to identify heightened risks in specific subgroups). The following risks common across the drug class should be included.

- *Changes in Insulin Regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)

- *Hypoglycemia*: May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. ([5.3](#), [7](#), [8.6](#), [8.7](#))
- *Hypersensitivity Reactions*: May be life-threatening. Discontinue HUMULIN N, monitor and treat if indicated. (b) (4)
- *Hypokalemia*: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (b) (4)
- Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage
- reduction or discontinuation if heart failure occurs. (b) (4)

## 5.2 Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions ([5.3](#))] or hyperglycemia. These changes should be made cautiously and under close medical supervision and the frequency of blood glucose monitoring should be increased.

## 5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including HUMULIN N. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions ([7](#))], or in patients who experience recurrent hypoglycemia.

### Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of HUMULIN N may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see Clinical Pharmacology ([12.2](#))]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see Drug Interactions ([7](#))]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations ([8.6](#), [8.7](#))].

### Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

(b) (4)

## Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMULIN N. If hypersensitivity reactions occur, discontinue HUMULIN N; treat per standard of care and monitor until symptoms and signs resolve [see Adverse Reactions ([6](#))]. HUMULIN N is contraindicated in patients who have had hypersensitivity reactions to HUMULIN N or any of its excipients [see Contraindications ([4](#))].

(b) (4)

## **Hypokalemia**

All insulin products, including HUMULIN N, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

(b) (4)

## **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists**

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including HUMULIN N, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

Please also update the special populations section and drug interactions section per the Humulin N label. Section 17 will need to be updated per changes to section 5.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/19/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 labeling comments  
**Date:** Tuesday, May 19, 2015 3:09:00 PM  
**Importance:** High

---

Hi Sumitra,

Please see the labeling comments below for NDA 205747. We ask that you incorporate these comments and provide a revised label by COB tomorrow instead of today. If you have any questions, please call me.

We note that the Highlight Section and Section 5 is outdated. Please use the same language that is in use for Humulin N for both of these sections with the exception of the *Never Share* Bullet and the (b) (4) (b) (4) *bullet*.

The updated language is preferred and is more consistent with labeling guidances (identifies risks first, uses direct language, describes mitigation strategies, uses cross-reference to special population to identify heightened risks in specific subgroups). The following risks common across the drug class should be included.

- *Changes in Insulin Regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.2)
- *Hypoglycemia:* May be life-threatening. Monitor blood glucose and increase monitoring frequency with changes to insulin dosage, use of glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment; and in patients with hypoglycemia unawareness. (5.3, 7, 8.6, 8.7)
- *Hypersensitivity Reactions:* May be life-threatening. Discontinue HUMULIN N, monitor and treat if indicated. (b) (4)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (b) (4)
- Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage
- reduction or discontinuation if heart failure occurs. (b) (4)

## 5.2 Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.3)] or hyperglycemia. These changes should be made cautiously and under close medical supervision and the frequency of blood glucose monitoring should be increased.

## 5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including HUMULIN N. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual

and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions ([7](#))], or in patients who experience recurrent hypoglycemia.

#### Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of HUMULIN N may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see Clinical Pharmacology ([12.2](#))]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see Drug Interactions ([7](#))]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations ([8.6](#), [8.7](#))].

#### Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

(b) (4)

## **Hypersensitivity Reactions**

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMULIN N. If hypersensitivity reactions occur, discontinue HUMULIN N; treat per standard of care and monitor until symptoms and signs resolve [see Adverse Reactions ([6](#))]. HUMULIN N is contraindicated in patients who have had hypersensitivity reactions to HUMULIN N or any of its excipients [see Contraindications ([4](#))].

(b) (4)

## **Hypokalemia**

All insulin products, including HUMULIN N, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

(b) (4)

## **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists**

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including HUMULIN N, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards



of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered. Please also update the special populations section and drug interactions section per the Humulin N label. Section 17 will need to be updated per changes to section 5.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/19/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 Labeling comments  
**Date:** Monday, May 18, 2015 9:07:00 AM  
**Attachments:** [insulin\\_lispro HUMALOG 200U KwikPen 205747 FDA comments5.18.15 marked .docx](#)  
[insulin\\_lispro HUMALOG 200U KwikPen PPI FDA comments 5.18.15 marked.docx](#)  
[nda205747-humalog-u200-proposed fda comments 5.18.15.docx](#)

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Hi Sumitra,

Please see the attached labeling with FDA edits. We request that you send revised labeling by COB tomorrow, May 19, 2015.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

If you have any questions, please contact me.

Thanks,  
Callie

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CALLIE C CAPPEL-LYNCH  
05/18/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 Information Request  
**Date:** Tuesday, May 12, 2015 9:08:00 AM  
**Importance:** High

---

Hi Sumitra,

Please see the information request below for NDA 205747. We are requesting response by noon tomorrow, May 13, 2015.

We note that the rationale for the proposed patient population is not based on any potential benefit to patients. Provide a rationale for when use of this concentrated insulin product is appropriate. As your U-200 product may introduce confusion and the potential for dosing errors, we are interested in your position on what population might benefit from U-200 given this potential risk.

If you have any questions, please contact me.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/12/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra_M_Ghate_(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 Information Request  
**Date:** Thursday, May 07, 2015 2:16:00 PM  
**Importance:** High

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Hi Sumitra,

Please see the information request below for NDA 205747. It is imperative that we receive a response to this IR as quickly as possible and no later than COB May 12, 2015. If you have any questions, please contact me.

Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (i.e., Management Responsibility, Design Controls, Purchasing Controls, and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/07/2015



**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 Carton and Contain Comments  
**Date:** Tuesday, May 05, 2015 2:16:00 PM

---

Hi Sumitra,

We received your submission dated May 5, 2015, containing revised carton and container labels for NDA 205747. We have the following comment:

In addition to 200 units per mL, we recommend that you place the statement "U-200" on the container label and carton labeling to be consistent with your existing insulin products. For example 200 units per mL (U-200).

Please send revised labeling by COB Friday, May 8, 2015. If you have any questions, please contact me.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/05/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate@lilly.com)  
**Subject:** NDA 205747 Labeling comments  
**Date:** Monday, May 04, 2015 1:34:00 PM  
**Attachments:** [FDA edits 5.4.15 Humalog U-200 PI.docx](#)

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Hi Sumitra,

Please see the attached PI with FDA comments for NDA 205747. We request that you send revised labeling by COB Monday, May 11, 2015.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change" or "COMPANY comment."

If you have any questions, please contact me.

Thank you,  
Callie

15 Pages of Draft Labeling have been Withheld in Full as B4  
(CCI/TS) immediately following this page

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/s/  
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CALLIE C CAPPEL-LYNCH  
05/04/2015

**From:** CappellLynch, Callie  
**To:** ["Sumitra M Ghate"](#)  
**Subject:** RE: NDA 205747: Request for Clarification on Carton and Container Labeling comments  
**Date:** Tuesday, March 31, 2015 3:40:00 PM

---

Hi Sumitra,

Please see our response below. If you have additional questions, please feel free to contact me.

We do not agree with your proposal.

1. The placement of the "For Single Patient Use Only" and the concentration statements are in line with all other insulin products.
2. The yellow boxed warning was tested as part of the human factors study to ensure that users do not use a syringe to withdraw the product. There were errors in the previous human factors study thus this statement should be remain on the pen label. You may consider reducing the prominence of the statement by using smaller font if you wish to increase the white space.

Thanks,  
Callie

---

**From:** Sumitra M Ghate [mailto:ghate\_sumitra\_m@lilly.com]  
**Sent:** Monday, March 30, 2015 9:29 PM  
**To:** CappellLynch, Callie  
**Subject:** RE: NDA 205747: Request for Clarification on Carton and Container Labeling comments

Hi, Callie.

I wanted to let you know that we submitted the label amendment today with the changes for the Humalog U200 carton and container (pen) label per your email request below. In the cover letter for the submission, Lilly is requesting that FDA review and reconsider two points related to the carton/container request. I don't know how this will get reviewed so wanted to make you aware that it was there. The relevant text from the cover letter is given below in blue:

Lilly has made the revisions to the carton and container label as requested by FDA, which are included in this submission. However, Lilly has two requests for FDA to please consider related to the requested changes:

1. FDA requested that the boxed 200 units per mL concentration statement be relocated under the "For Single Patient Use Only" statement. Lilly respectfully requests FDA to reconsider this placement. Lilly prefers that this important concentration statement be placed closer to the tradename, either directly above or directly under generic name for better identification, especially considering the fact that both Humalog 100 units/mL and Humalog 200 units/mL have the same tradename and generic name: "Humalog KwikPen" and "Insulin Lispro," respectively. (Note: "Humalog KwikPen" is conditionally approved for Humalog 200 units/mL)

2.

(b) (4)

(b) (4)

Should FDA agree to the above request(s), Lilly will submit another label amendment to the NDA to revise accordingly.

Best regards –

Sumitra

**Sumitra M. Ghate** : Advisor, Global Regulatory Affairs



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M (b) (6)  
:: F 317.276.1652  
:: www.lilly.com

---

**From:** CappellLynch, Callie [<mailto:Callie.CappellLynch@fda.hhs.gov>]  
**Sent:** Tuesday, March 17, 2015 12:30 PM  
**To:** Sumitra M Ghate  
**Subject:** RE: NDA 205747: Request for Clarification on Carton and Container Labeling comments

Hi Sumitra

For both the carton labeling and pen label:

1. Keep the white box but move its location so that it is under "For Single Patient Use Only".
2. (b) (4)

Regarding your third question, we have no comments at this time, however, please keep in mind that review is ongoing and therefore we may have additional comments in the future.

Thanks,  
Callie

---

**From:** Sumitra M Ghate [[mailto:ghate\\_sumitra\\_m@lilly.com](mailto:ghate_sumitra_m@lilly.com)]  
**Sent:** Monday, March 16, 2015 10:07 PM  
**To:** CappellLynch, Callie  
**Subject:** NDA 205747: Request for Clarification on Carton and Container Labeling comments

Hi, Callie –

I would like to ask for clarification on what FDA is requesting related to your email on carton/container labeling below. I provided screen prints of the carton and pen labels below to make it easier to see what I'm describing (I realize they are a little hard to read!).

I have three questions as follows:

- On the proposed carton label, [redacted] (b) (4)  
[redacted]  
[redacted]  
[redacted]

**Question 1:** Which of these is FDA requesting that we do for carton label:

[redacted] (b) (4)

- On the proposed pen label, [redacted] (b) (4)  
[redacted]

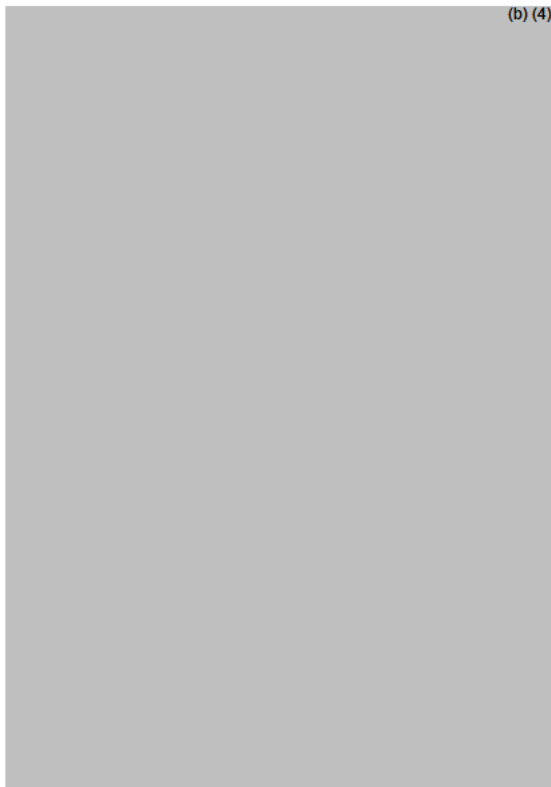
**Question 2:** Which of these if FDA requesting that we do for pen label:

[redacted] (b) (4)

**Question 3:** There was no mention in your email of the language on the yellow sticker on the pen cartridge holder, which is the same text as the other yellow warnings on the carton and pen labels. Did FDA review this as part of the container (pen) label...and hence I should assume there were no comments?

**Proposed Carton Label:**

(b) (4)



**Proposed Pen Label:**

(b) (4)



Thank you!

Sumitra

**Sumitra M. Ghate : Advisor, Global Regulatory Affairs**



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M (b) (6)  
:: F 317.276.1652  
:: www.lilly.com



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**From:** CappelLynch, Callie [<mailto:Callie.CappelLynch@fda.hhs.gov>]  
**Sent:** Monday, March 16, 2015 8:55 AM  
**To:** Sumitra M Ghatge  
**Subject:** NDA 205747 Labeling comments

Hi Sumitra,

Please see the below labeling comment regarding the carton and container labels for NDA 205747.

1. Revise the proprietary name, established name and strength presentation to read:

Humalog Kwikpen  
Insulin lispro injection, USP  
For Single Patient Use Only  
200 units/mL

We request that you resubmit the revised labels by March 30, 2015. If you have any questions, please contact me.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
03/31/2015

**From:** CappelLynch, Callie  
**To:** ["Sumitra M Ghate"](mailto:Sumitra.M.Ghate)  
**Subject:** RE: NDA 205747: Request for Clarification on Carton and Container Labeling comments  
**Date:** Tuesday, March 17, 2015 12:29:00 PM

---

Hi Sumitra

For both the carton labeling and pen label:

1. Keep the white box but move its location so that it is under "For Single Patient Use Only".
2. [REDACTED] (b) (4)

Regarding your third question, we have no comments at this time, however, please keep in mind that review is ongoing and therefore we may have additional comments in the future.

Thanks,  
Callie

---

**From:** Sumitra M Ghate [mailto:ghate\_sumitra\_m@lilly.com]  
**Sent:** Monday, March 16, 2015 10:07 PM  
**To:** CappelLynch, Callie  
**Subject:** NDA 205747: Request for Clarification on Carton and Container Labeling comments

Hi, Callie –

I would like to ask for clarification on what FDA is requesting related to your email on carton/container labeling below. I provided screen prints of the carton and pen labels below to make it easier to see what I'm describing (I realize they are a little hard to read!).

I have three questions as follows:

- On the proposed carton label, [REDACTED] (b) (4)

**Question 1: Which of these is FDA requesting that we do for carton label:**

[REDACTED] (b) (4)

(b) (4)

- On the proposed pen label, (b) (4)

**Question 2:** Which of these if FDA requesting that we do for pen label:

(b) (4)

**Question 3:** There was no mention in your email of the language on the yellow sticker on the pen cartridge holder, which is the same text as the other yellow warnings on the carton and pen labels. Did FDA review this as part of the container (pen) label...and hence I should assume there were no comments?

**Proposed Carton Label:**

(b) (4)

**Proposed Pen Label:**

(b) (4)

Thank you!

Sumitra

**Sumitra M. Ghate** : Advisor, Global Regulatory Affairs



:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M (b) (6)  
:: F 317.276.1652  
:: www.lilly.com

---

**From:** CappellLynch, Callie [<mailto:Callie.CappellLynch@fda.hhs.gov>]  
**Sent:** Monday, March 16, 2015 8:55 AM  
**To:** Sumitra M Ghate  
**Subject:** NDA 205747 Labeling comments

Hi Sumitra,

Please see the below labeling comment regarding the carton and container labels for NDA 205747.

1. Revise the proprietary name, established name and strength presentation to read:

Humalog Kwikpen  
Insulin lispro injection, USP  
For Single Patient Use Only  
200 units/mL

We request that you resubmit the revised labels by March 30, 2015. If you have any questions, please contact me.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
03/17/2015

**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate@lilly.com)  
**Subject:** NDA 205747 Labeling comments  
**Date:** Monday, March 16, 2015 8:55:00 AM

---

Hi Sumitra,

Please see the below labeling comment regarding the carton and container labels for NDA 205747.

1. Revise the proprietary name, established name and strength presentation to read:

Humalog Kwikpen  
Insulin lispro injection, USP  
For Single Patient Use Only  
200 units/mL

We request that you resubmit the revised labels by March 30, 2015. If you have any questions, please contact me.

Thanks,  
Callie

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CALLIE C CAPPEL-LYNCH  
03/16/2015



**From:** CappellLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** NDA 205747 Information Request  
**Date:** Wednesday, March 04, 2015 3:51:00 PM

---

Hi Sumitra,

Please see the information request below for NDA 205747. If you have any questions, please contact me.

To complete our assessment of the Study F3Z-EW-IOQM we need the following information:

1. We note that for the euglycemic clamp procedure, the target glucose was specified as 5 mg/dL below the average of 3 pre-dose fasting blood glucose values. However, we could not locate the information on the tolerance limits for the euglycemic clamp (for example, if this was within  $\pm 5\%$  or  $\pm 10\%$  of clamp target glucose, etc.) in the study report and protocol. Please clarify if and what was the pre-specified acceptable tolerance limit for the glucose clamp?
2. Based on our review of the plasma glucose versus time data over the clamp duration (using the xg.xpt file in the tabulation data sets), it seems there are subjects in whom, the glucose values did not stay on the clamp target. Please provide your rational and justification for the GIR data from such subjects being truly representative of the pharmacodynamic effect of the exogenous insulin.

Thanks,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
03/04/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 205747

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Lilly Corporate Center  
c/o Eli Lilly and Company  
Drop Code 2543  
Indianapolis, IN 46285

ATTENTION: Sumitra M. Ghate, B.A., B.S.  
Advisor – Global Regulatory Affairs-US Diabetes

Dear Ms. Ghate:

Please refer to your New Drug Application (NDA) dated and received November 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Lispro Injection, 200 units/mL.

We also refer to your correspondence, dated and received December 11, 2014, requesting review of your proposed proprietary name, Humalog KwikPen.

We have completed our review of the proposed proprietary name, Humalog KwikPen and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 11, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie CappelLynch, Regulatory Project Manager, in the Office of New Drugs at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
02/26/2015

**From:** CappelLynch, Callie  
**To:** [Sumitra M.Ghate \(ghate\\_sumitra\\_m@lilly.com\)](mailto:Sumitra.M.Ghate(ghate_sumitra_m@lilly.com))  
**Subject:** Information Request NDA 205747  
**Date:** Wednesday, December 31, 2014 9:20:00 AM

---

Hi Sumitra,

Please see the below information request for NDA 205747. If you have any questions, please contact me.

We could not locate the plasma glucose data and the derived PK parameters (typically pp.xpt) for insulin in your submission dated November 26, 2014, (Study F3Z-EW-IOQM). If you have already provided the data, please point to the location or path from where the data files may be retrieved. If you have not provided the data, please provide the requested data in SAS transport format.

Thanks,

Callie Cappel-Lynch  
Regulatory Project Manager  
Food and Drug Administration  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
301-796-8436

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CALLIE C CAPPEL-LYNCH  
12/31/2014



NDA 205747

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Eli Lilly and Company  
Attention: Sumitra Ghatе  
Consultant, Global Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Ms. Ghatе:

We acknowledge receipt on November 26, 2014, of your November 26, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog (insulin lispro [rDNA origin] injection) 200 units/mL.

We consider this a complete, class 2 response to our March 10, 2014, action letter. Therefore, the user fee goal date is May 26, 2015.

If you have any questions, call me at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Callie Cappel-Lynch, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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CALLIE C CAPPEL-LYNCH  
12/10/2014





NDA 205747

**MEETING REQUEST-  
WRITTEN RESPONSES**

Eli Lilly and Company  
Attention: Sumitra Ghate  
Consultant, Global Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Ms. Ghate:

Please refer to your New Drug Application (NDA) dated and received May 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog (insulin lispro [rDNA origin] injection) 200 units/mL.

We also refer to your submission dated May 13, 2014, containing a Type C meeting request. The purpose of the requested meeting was to discuss your supplemental Summative Human Factors (SHF) protocol for Humalog KwikPen, 200 units/mL.

Further reference is made to our Meeting Granted letter dated May 19, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 25, 2014, background package.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## WRITTEN RESPONSES

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Application Number:** 205747  
**Product Name:** Humalog (insulin lispro [rDNA origin] injection) 200 units/mL  
**Indication:** Improve glycemic control in adults and children with diabetes mellitus  
**Sponsor/Applicant Name:** Eli Lilly and Company  
**Regulatory Pathway:** 505(b)(1)

### 1.0 BACKGROUND

Humalog (insulin lispro) is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. Humalog (insulin lispro) injection 100units/mL was approved under NDA 020563 on June 14, 1996.

On March 15, 2013, Eli Lilly submitted a new supplement to NDA 020563 proposing the addition of a new insulin lispro U-200 formulation and its associated device to various labeling documents of the currently approved Humalog U-100 formulation. It was determined by the user fee staff and the division, that a new drug application with clinical data would be required in order to market this product. On May 10, 2013, Eli Lilly submitted NDA 205747 for insulin lispro U-200.

On March 10, 2014, FDA issued a complete response (CR) letter for NDA 205747. On April 15, 2014, Eli Lilly requested an End of Review Meeting to discuss and gain alignment on the information required to address the FDA complete response letter.

On May 7, 2014, The End of Review Meeting was held. During this meeting FDA agreed to review the human factors protocols for studies required to address the deficiencies in the CR letter. On May 13, 2014, Lilly submitted a Type C meeting request to discuss their supplemental Summative Human Factors (SHF) protocol for Humalog KwikPen, 200 units/mL.

### 2.0 QUESTIONS AND RESPONSES

Question 1: Does FDA agree with the study design as defined in the attached protocol, including the tasks and planned user groups to be evaluated?

**FDA Response to Question 1: The supplemental Summative Human Factors (SHF) study protocol includes general methodology that is adequate for collecting HF data. We have the following concerns regarding:**

**I. The questions intended to be used for knowledge-based assessments of the intended users. Your protocol outlined the following questions:**

#	Moderator Question
1	What do the instructions say about removing insulin from the pen with a syringe? Answer: Do not transfer insulin from your pen to a syringe
2	What should you do if your pen does not work? Answer: Any of the following: Try a new needle, use a backup pen, call pharmacist, call HCP, call Lilly
3	What do the Instructions for Use tell you in Step 3 about selecting your dose by counting clicks? Answer: Do not dial your dose by counting clicks.

**Figure 1: Instructional Materials Assessment - Patient and Caregiver Questions and Sample Answers**

#	Moderator Question
1	If you had a patient taking 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what dose would you have them dial on the 200 U/ml Humalog KwikPen? Answer: 10 units
2	What does the document say about transferring insulin from the pen to a syringe? Answer: Do not transfer from the pen to a syringe.

**Figure 2: Instructional Materials Assessment – Prescriber Questions and Sample Answers**

While these questions are designed to assess the user’s general knowledge about the use of your device, we do not believe that they provide adequate focus on the use-scenarios we are concerned about.

For patients and caregivers, we recommend that you use the following questions, in order, for your subjective data collections:

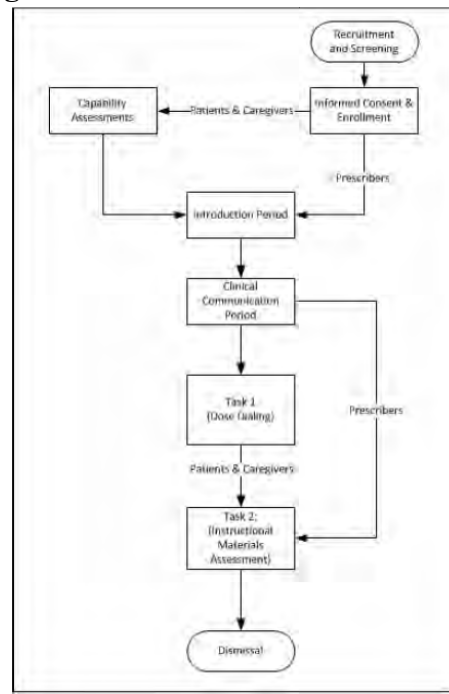
1. If this injector becomes jammed, how would you inject your insulin dose? (Note to moderator: collect all of the responses from study participants)
2. Would you use a syringe with this product? [Yes or No]
  - a. If “yes”: How would you use it? (Note to moderator: collect all of the responses from study participants)
  - b. If “no”: Why not? (Note to moderator: collect all of the responses from study participants)
3. Is there a printed warning on this peninjector? [Yes, No, or I don’t know]
  - a. If “yes”: What does it say?
  - b. If “no”: Show the pen to the participant and ask if they see the warning now and ask why do you think you did not see it? (Note to moderator: collect all of the responses from study participants).
  - c. If “I don’t know”: Show the pen to the participant and ask if they see the warning now. (Note to moderator: collect all of the responses from study participants).

For healthcare providers, i.e. prescribers, we recommend that you use the following questions, in order, for your subjective data collections:

1. If your patient typically uses 10 units with the 100U/ ml Humalog KwikPen and you are switching them to the 200U/ml Humalog KwikPen, what would you tell them to dial on the new peninjector?

2. If this injector becomes jammed, how would you inject your insulin dose? (Note to moderator: collect all of the responses from study participants)
3. Would you use a syringe with this product? [Yes or No]
  - a. If “yes”: How would you use it? (Note to moderator: collect all of the responses from study participants)
  - b. If “no”: Why not? (Note to moderator: collect all of the responses from study participants)
4. Is there a printed warning on this peninjector? [Yes, No, or I don’t know]
  - a. If “yes”: What does it say?
  - b. If “no”: Show the pen to the participant and ask if they see the warning now and ask why do you think you did not see it? (Note to moderator: collect all of the responses from study participants).
  - c. If “I don’t know”: Show the pen to the participant and ask if they see the warning now. (Note to moderator: collect all of the responses from study participants).

II. The study design with respect to the healthcare providers/prescriber. You provided the following flow diagram:



We are unclear why the prescribers are not expected to perform the dose dialing task.

Question 2: Does FDA agree that the supplemental HF study, if successful, will be adequate to address the FDA comments related to human factors provided in the 10 March 2014 CR letter?

**FDA Response to Question 2:** Provided that you satisfactorily address the issues raised in Question 1, and our review of the resulting data from your supplemental study demonstrates that mitigations are effective; we should not have any further questions regarding the human factors component of the submission.

**Additional FDA Comments:**

**We acknowledge your request to have the Office of Prescription Drug Promotion (OPDP) review the Instruction for Use. Review of this cannot be performed until substantially complete labeling is available. We also acknowledge your request to have OPDP review the health care provider and patient communication documents provided in the meeting briefing document. However, OPDP considers these promotional materials. Therefore, you may submit a request directly to OPDP for advisory comments on these materials. We remind you that comments will only be provided on claims or presentations that have not been published or disseminated and are not currently in use. We also remind you that all promotional materials must be submitted to FDA via Form-FDA 2253 at the time of initial dissemination or publication in accordance with 21 CFR 314.81(b)(3)(i).**

**3.0 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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/s/  
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JEAN-MARC P GUETTIER  
07/25/2014



NDA 205747

**REVISED MEETING MINUTES**

Eli Lilly and Company  
Attention: Sumitra Ghate  
Consultant, Global Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Ms. Ghate:

Please refer to your New Drug Application (NDA) dated and received May 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog (insulin lispro [rDNA origin] injection) 200 units/mL.

We also refer to the teleconference between representatives of your firm and the FDA on May 7, 2014. The purpose of the meeting was to discuss and gain alignment on the information required to address the FDA complete response letter issued March 10, 2014.

We further refer to our previous communication on May, 30, 2014, in which we acknowledge an error in the organization of the meeting discussion section.

A corrected copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:

Revised FDA Meeting Minutes from End-of-Review meeting held on May 7, 2014



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A  
**Meeting Category:** End Of Review

**Meeting Date and Time:** May 7, 2014 3:00pm-4:00pm  
**Meeting Location:** Teleconference

**Application Number:** 205747  
**Product Name:** Humalog Kwikpen 200units/mL  
**Indication:** Improve glycemic control in adults and children with diabetes mellitus  
**Sponsor/Applicant Name:** Eli Lilly

**FDA ATTENDEES**  
**CDER Participants:**

Division of Metabolism and Endocrinology (DMEP), Office of New Drugs

Jean-Marc Guettier, M.D.	Director,
William Chong, M.D.	Team Leader, Acting
Julie Van der Waag, M.P.H.	Chief, Project Management Staff
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager

Office of Surveillance and Epidemiology

Yelena Maslov, Pharm.D.	Team Leader, Division of Medication Error and Prevention Analysis (DMEPA)
-------------------------	---

**CDRH Participants:**

General Hospital Devices Branch, Division of Anesthesiology, General Hospital, and Infection

Lana Shiu, M.D.	Medical Officer
Patricia Beaston, M.D.	Medical Officer
Bifeng Qian, Ph.D.	Biocompatibility Reviewer
Elizabeth Claverie	Branch Chief, ODE/DAGRID/INCB
QuynhNhu Nguyen, M.S.	Human Factors Reviewer
Richard Chapman	Branch Chief



## SPONSOR ATTENDEES

Elizabeth Bearby, Pharm.D.,  
Diabetes

(b) (4)

LeeAnn Chambers, M.B.A.

Debra Conner, B.S.

Sumitra Ghatge, B.S., B.A.

Jim Malone, M.D.

(b) (4)

Tina Rees, Ph.D.

Anthony Schaff, B.S.

John Towns, Ph.D.

John Ayres, M.D.

Senior Director, Global Regulatory Affairs, US-

Consultant, Technical and Manufacturing Services -  
Devices

Senior Research Scientist, Global Regulatory  
Affairs, US-Devices

Research Scientist, Global Regulatory Affairs, US-  
Devices

Advisor, Global Regulatory Affairs, US-Diabetes

Senior Director, Medical, Diabetes and  
Endocrinology, Insulin and Devices

Consultant Engineer, Delivery Device Research and  
Development, Human Factors

Senior Clinical Research Scientist, Devices

Advisor, Delivery Device Research and  
Development

Senior Director, Global Regulatory Affairs, US-  
Devices)

Senior Director, Global Patient Safety-Product  
Health Safety Assessment

## 1.0 BACKGROUND

Humalog (insulin lispro) is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. Humalog (insulin lispro) injection 100units/mL was approved under NDA 020563 on June 14, 1996.

On March 15, 2013, Eli Lilly submitted a new supplement to NDA 020563 proposing the addition of a new insulin lispro U-200 formulation and its associated device to various labeling documents of the currently approved Humalog U-100 formulation. It was determined by the user fee staff and the division, that a new drug application with clinical data would be required in order to market this product. On May 10, 2013, Eli Lilly submitted NDA 205747 for insulin lispro U-200.

On March 10, 2014, FDA issued a complete response (CR) letter for NDA 205747. On April 15, 2014, Eli Lilly requested an End of Review Meeting to discuss and gain alignment on the information required to address the FDA complete response letter.

## 2.0 DISCUSSION

### 2.1. Device- Biocompatibility

**Question 1:** Does the FDA agree that 3 mL cartridge rubber disc qualification testing conducted by (b) (4) and Lilly and results of those tests described above, which will be provided in the NDA resubmission, are acceptable for addressing FDA's request in Comment 2 of the complete response letter?

**FDA Response to Question 1:** Yes, we agree.

**Meeting Discussion Question 1:** No discussion occurred.

**Question 2:** Does FDA agree that the information provided in Table 4.1 above to clarify the subject device in NDA 205747 versus other Lilly KwikPen devices satisfies FDA's request in Comment 3 of the complete response letter?

**FDA Response to Question 2:** The response is adequate to address the deficiency.

**Meeting Discussion Question 2:** No discussion occurred.

**Question 3:** Lilly intends to provide the information above and all aforementioned MSDS reports in the NDA resubmission. Does FDA agree that this satisfies the request in Comment 4 of the complete response letter?

**FDA Response to Question 3:** It is noted (b) (4) in the subject device. However, the MSDS provided does not clearly identify (b) (4). We recommend that you clearly identify all (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data.

**Lilly Preliminary Response Question 3:** Lilly acknowledges FDA's requests to identify all (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition and toxicological data. Lilly is working to collect the information package from our vendors (b) (4) that were not provided in the MSDSs in the background materials and will provide a table with this information in the NDA resubmission.

Does FDA agree that providing the chemical name, CAS reg. No., composition and toxicological data (b) (4) in the NDA resubmission will address FDA's comments cited in the complete response letter? As these conversations with our vendors are on-going, if we run into a supplier that does not want to provide the info to Lilly because of the proprietary nature of that information, is there a way that the supplier can provide this information directly to FDA?

**Meeting Discussion Question 3:** There will be two options:

1. For proprietary or trade secret information, you may submit a Master File which is used as a repository by the FDA. The Master File is accessed by the FDA only upon receipt of a letter of access by the Master File holder.

- Alternatively, you may provide the chemical name and identity, the percentage of the chemical used in your final device, health problems associated with the chemical, and available toxicological data (reference doses, LD<sub>50</sub>, NOAEL, and LOAEL) to justify that the safety concerns related to the use of the chemical in your device are negligible.*

Question 4: Lilly will provide the background information given above along with the MSDS reports for all of the materials used in the subject device in the NDA resubmission. Does FDA agree that this satisfies FDA's request from Comment 5 of the complete response letter?

**FDA Response to Question 4: The MSDS provided does not identify [REDACTED] (b) (4). We recommend that you clearly identify all [REDACTED] (b) (4) used in the subject device, including the chemical name, CAS reg. No., composition, and toxicological data.**

*Lilly Preliminary Response Question 4: Same as the Lilly preliminary response for Question 3*

**Meeting Discussion Question 4: Same as the meeting discussion for Question 3**

Question 5: Does FDA agree that a separate chemical analysis of the leachables of the device [REDACTED] (b) (4) is not required if biocompatibility testing is conducted per the ISO 10993 standard on the final finished device components that have user contact?

**FDA Response to Question 5: The justification provided for not performing the chemical leachable analysis may be acceptable, if the biocompatibility testing provided in firm's future submission is adequate and appropriate to support the subject device.**

**Meeting Discussion Question 5: No discussion occurred**

Question 6: Does FDA agree that submission of the results from the biocompatibility testing per the ISO 10993 standard using the final finished subject device components listed in Table 4.2 will meet FDA's request?

**FDA Response to Question 6: We recommend that you provide a complete biocompatibility testing report that includes a detailed description of the test device and sample preparation, description of the test procedures, appropriate controls, summary of test results, test criteria, and conclusion. Our determination will be based on review of the final test report and data submitted.**

*Lilly Preliminary Response Question 6: Lilly agrees to perform biocompatibility testing on the device as requested by FDA to address the complete response letter and will provide the information requested from the preliminary meeting comments in the NDA resubmission.*

*Does FDA have any comments on the testing plan Lilly provided by email to Ms. Callie-Cappel Lynch on May 5, 2014?*

***Meeting Discussion Question 6: Based on the limited information provided, the study proposal appears to be reasonable and acceptable. However, our final determination will be based on review of the official, complete test reports submitted.***

## **2.2. Device- Human Factors**

**Question 7:** Lilly asserts that an additional HF study is not warranted as: 1) the basic cartridge/advancing drive mechanism design is inherent in all insulin pen injectors and design modifications attempting to bar cartridge accessibility (to dissuade syringe extraction) is impractical and/or would cause a new set of failures, 2) IFU revisions would not likely mitigate FDA's cited use errors but could likely cause a new set of use errors, and 3) the key messages in the communication plan as described in the Risk Management program have in essence been validated in the summative human factors report and found to be effective. Further, the proposed communication plan would have its own post marketing assessments.

Does FDA agree that further mitigation and HF testing is not required and the information provided above addresses FDA's request in the complete response letter?

**FDA Response to Question 7: Your meeting package describes your proposal to utilize a post marketing risk minimization plan to address the use-related issues observed in your recent human factors validation study report (reference 32R2-KwikPen-VL7662-v001).**

**This plan includes**

(b) (4)

**We acknowledge your proposal; however, we remain concerned about the use-related issues that were observed in your HF study report. In the CR letter, we identified four areas of concerns, where we believe that performance observations and subjective feedback indicated the need for mitigations. Our list of issues, in order of priority, is as follows:**

- a. Two use-related observations were noted that could result in overdose (CR letter comment # 8d). One user, an adult patient, did not see the warning and withdrew and transferred U-200 insulin into a U-100 syringe. The other user, a Registered Nurse, stated that she understood the warning but when she had access to a U-100 syringe, she used the syringe to withdraw U-200 insulin from the pen injector. The RN did not correct for the difference in concentration, and if administered to a patient this would lead to a 2x overdose scenario which may lead to patient harm. Because healthcare provider (HCPs) and patients who use insulin have access to U-100 syringes, this use error represents a known risk that should be mitigated. While you developed the warning message that is placed directly on the pen injector and in the key messages to HCPs and patients, these observations indicate that the warning is not effective in preventing users from using U-100 syringe to withdraw the U-200 insulin in cases involving a jammed pen injector or other situations where users may need an alternative method to administer the U-200 insulin. The warning messages should be dramatically emphasized to successfully communicate this hazard and the danger**

**associated with the use of a U-100 syringe in these situations. There is also a need to provide a clear description of the proper course of action a user should take. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.**

*Lilly Preliminary Response Question 7a: FDA provided a response related to the 2 use errors observed in the validation study where a nurse and an adult patient extracted with a U100 syringe. We share FDA's concern for the potential risk of overdose. We would like to note that we specifically recruited patients who had a self-reported history of syringe extraction and hence the Human Factors validation study was enriched with these subjects and was not representative of a typical diabetic patient population. Additionally, both of the extraction related use errors occurred with untrained subjects (those who had not been given the either the patient or HCP key messages). None of the 38 subjects in the study who were given the key messages leaflet had a use error of withdrawing with a syringe. Additionally, the nurse was erroneously given a syringe by the moderator, and hence, as noted on pg 37 of the HFE/UE report, the nurse use error was an artifact of the study.*

*It is important to note that the warning of syringe extraction is a predominate and significant warning and is placed in multiple prominent locations in our proposed labeling. The document attached to this email provides a comprehensive list of the warnings provided in our proposed labeling and the specific text of those warnings. The patient and DHCP communications also provide key messages on the hazards of syringe extraction.*

*We acknowledge FDA's request that Lilly "enhance the warning messages regarding extraction dramatically" and to "provide a clear description of the proper course of action a user should take." After receiving FDA's feedback, we did a thorough review of our user interface, accessories, labeling and training. We do not believe that any further changes to the warnings will change the user interface and Lilly asserts that we have reduced the risk down to a level that will be resistant to elimination or mitigation through any potential modifications to the user interface, accessories, labeling, or training.*

*However, as FDA has requested in the complete response letter that we add further mitigations, Lilly acknowledges that the Patient and DHCP communications, [REDACTED] (b) (4) [REDACTED] could be revised to significantly highlight the severe consequence of syringe extraction, along with providing the proper course of action if the pen malfunctions in the patient communication. We are working with our health literacy group to revise these communications.*

*Lilly's proposal to the FDA request in the preliminary comments is as follows: Lilly proposes to test these communications in a Human Factors study that will be a knowledge based assessment (not a performance assessment). Furthermore, Lilly proposes to add additional language to the USPI in section 2. Dosage and Administration directing healthcare professionals to instruct their patients on proper use and dosing of the U200 pen and the severe consequences of extracting with a syringe. The USPI will not be part of the knowledge assessment, but label language will be discussed with FDA during labeling negotiations.*

*Does FDA agree that Lilly's proposal to test the enhanced patient and healthcare professional communications in a knowledge assessment based Human Factors study and submission of the results in the NDA resubmission will address the FDA's comment cited in the Humalog U200 complete response letter? Does FDA have any further concerns or comments related to this topic?*

**Meeting Discussion Question 7a: We agree that a knowledge based assessment is adequate to evaluate the revised patient and Health Care Provider (HCP) communication. Lilly will provide the protocol for review via a Type C meeting request. Lilly will include in the protocol a rationale for not including the PI as part of the assessment. FDA agreed to ask the Office of Prescription Drug Promotion (OPDP) for a consult in reviewing the revised patient and HCP communications and stated that the OPDP review would be completed within the Type C meeting PDUFA timeframe.**

- b. Three of 16 prescribers performed dose/units conversion in their heads which resulted in writing prescriptions that use ½ of the units specified in the tasks (CR letter comment # 8a). These observations indicate that the key messages included in your HF study did not make users aware of critical information associated with the pen design and its drug concentration. The critical information regarding the dialed dose, the prescribed dose, and drug concentration contained in the messages to HCPs should be better emphasized to successfully communicate this hazard. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.**

*Lilly Preliminary Response Question 7b: FDA provided feedback on the 3 use errors where prescribers did a unit conversion in their head and wrote a prescription for ½ the dose. Lilly would like to reiterate that one of those errors was study artifact as the prescriber had written correctly in the first scenario but thought that since she was being asked again, she should do something different. Regardless, we acknowledge FDA's request to better emphasize the critical information regarding the dialed dose, the prescribed dose, and drug concentration contained in the messages to HCPs. All three of these critical messages are already captured in our proposed Dear Healthcare Professional letter (draft letter provided on pg 75-75 of the background materials).*

*Lilly's proposal to FDA's request in the preliminary comments is as follows: Lilly proposes to revise the Dear HCP letter to reformat and highlight the critical risk information and test the new communication in a human factors knowledge assessment study.*

*Does FDA agree that the proposal to test the revised DHCP by a knowledge assessment based Human Factors study and submission of the results in the NDA resubmission will address the FDA's comment cited in the complete response letter? Does FDA have any further concerns or comments related to this topic?*

**Meeting Discussion Question 7b: We agree that a knowledge based assessment is adequate to evaluate the Dear HCP letter.**



- c. One caregiver and four patients dialed the incorrect dose (CR letter comment # 8b). One participant described confusion about the position of the zero in the dose window, another indicated that the error was based on counting the clicks, and the third said that she counted the clicks and performed visual confirmation. While you may not intend to have users use the clicks to determine the dialed dose, the clicks are auditory feedback to the users and many users might be accustomed to using an injector with audible clicks and use click counts when dialing a dose. Therefore, if you intend for users to focus on the visual feedback i.e. view/verify dialed dose via dose window, you need to emphasize the proper action in the instructions for use and clarify to the user that the auditory feedback should not be used for dialing dose. Please make the necessary modifications and provide data demonstrating that the additional mitigations are effective.**

*Lilly Preliminary Response Question 7c: Regarding the use errors where 1 caregiver and 4 patients dialed the incorrect dose, FDA stated that if Lilly intended to users to focus on visual feedback, then Lilly needs to emphasize the proper action in the instructions for use and clarify to the user that auditory feedback should not be used for dialing dose.*

*Lilly's proposal to FDA's request in the preliminary comments is as follows: As requested, Lilly agrees to add a statement in the IFU to discourage users from using audible feedback to dial their dose and rather to visually check their dose. The revised IFU will be tested in for knowledge assessment (not a performance assessment) human factors study.*

*Does FDA agree that Lilly's proposal to revise the IFU to add a statement to discourage auditory feedback (i.e. counting clicks) and test the revised IFU in a knowledge assessment based human factors study and submission of the results in the NDA resubmission will address the FDA's comment cited in the complete response letter?*

*Meeting Discussion Question 7c: FDA would like a full performance human factors study to address this issue. Both a performance test and knowledge assessment are needed. Lilly agreed to perform.*

*In addition, FDA provided general guidance regarding the additional human factors validation testing to be performed to address issues identified in 7a-7c:*

- *Include 15 lay users (patients and caregivers combined), and 15 HCPs*
- *Have the user interact with the device and labeling in a realistic manner.*
- *Use open ending but specific questions to explore performance and to obtain user feedback on the modified user interface (i.e. patient and HCP communication, and dear HCP letter)*

*Post-Meeting Comments:*

1. **Protocol should be designed to evaluate and demonstrate improved user performance and understanding regarding visual check of dose. Protocol should also be designed to evaluate understanding of the information about syringe warning, information about the dialed dose, the prescribed dose, and drug concentration.**
  2. **Provide revised patient and HCP communication, and Dear HCP letter (with tracked-changes) for review.**
- d. For use-related issues associated with pulling the pen injector out prematurely when the dialing window has not reset to zero (CR letter comment # 8c), we agree with your assessment and that no further action is needed given that the results were largely due to study artifacts.

**Meeting Discussion Question 7d: No discussion occurred.**

**Additional Discussion:**

1. Lilly confirmed that the key messages that were previously validated in the Human Factors study will be included in the Dear Health Care Provider letter.

Additionally, Lilly asked how IFU labeling be evaluated by different review Divisions within the FDA once they validate their IFU and whether any major edits will take place. The Agency replied that all the Divisions that are responsible for evaluation of the IFU are working together as a team and the recommendations related to the IFU will pertain to information that was not affected by validation through Human Factors study.

**Additional Advice:**

1. We recommend that you consider characterizing endogenous insulin profile (if necessary for baseline correction) by collecting c-peptide data in your planned repeat bioequivalence (BE) study.

**3.0 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**



There were no issues requiring further discussion.

## **5.0 ATTACHMENTS AND HANDOUTS**

Attached are two handouts provided by the sponsor. The first document contains proposed warnings the applicant plans to add to labeling. The second document contains a biocompatibility testing plan.

3 Pages of Draft Labeling have been Withheld in Full as B4  
(CCI/TS) immediately following this page

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/s/  
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JEAN-MARC P GUETTIER  
07/14/2014

**From:** [Sumitra M.Ghate](#)  
**To:** [CappellLynch, Callie](#)  
**Cc:** [Sumitra M.Ghate](#)  
**Subject:** RE: NDA 205747 Information Request  
**Date:** Wednesday, November 13, 2013 4:53:45 PM

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Hi, Callie –

Humalog U-100 Lot number **A677287** was purchased by LNUS in Singapore for use as study drug in the BE study IOPY that was submitted in NDA 205747.

Semi-finished drug product lot number A618757 was produced in the Lilly Indianapolis Parenteral manufacturing facility and released in May 2009 accordance with the approved batch formula and product specifications contained in NDA 20563. Lot A618757 was packaged into three packaging batches: A618757A, A618757C, A618757D.

Lot A618757A was packaged for shipment to the Lilly facility in Geissen, Germany, for final package/labeling into **A677287** and distribution to Singapore. Lots A618757C, A618757D was final package/labeled for distribution to Argentina and the US, respectively. Lot A618757D was released for distribution for sale in the US market.

Let me know if you have any further questions.

Sumitra

**Sumitra M. Ghate :** Advisor, Global Regulatory Affairs

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:: Lilly Corporate Center  
Indianapolis, IN 46285  
:: P 317.433.3486  
:: M [REDACTED] (b) (6)  
:: F 317.276.1652  
:: www.lilly.com

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**From:** CappellLynch, Callie [mailto:Callie.CappellLynch@fda.hhs.gov]  
**Sent:** Wednesday, November 13, 2013 10:39 AM  
**To:** Sumitra M Ghate  
**Subject:** NDA 205747 Information Request

Hi Sumitra,

Could you please let us know where Humalog U-100 Package lot #A677287 was manufactured, and if this lot was approved for sale in the U.S. ? Sorry for the short notice, but if you could let us know by COB today, that would be greatly appreciated. If you need more information please contact me.

Thank you,  
Callie

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/s/  
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CALLIE C CAPPEL-LYNCH  
02/19/2014



DEPARTMENT OF HEALTH AND HUMAN  
SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 205747

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company  
Lilly Corporate Center  
Drop Code 2543  
Indianapolis, IN 46285

Attention: Sumitra M. Ghate, PhD.  
Advisor – Global Regulatory Affairs – U.S.

Dear Dr. Ghate:

Please refer to your New Drug Application (NDA) dated May 10, 2013, received May 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Insulin Lispro Injection, 200 Units/mL.

We also refer to your October 28, 2013, correspondence, received October 28, 2013, requesting review of your proposed proprietary name, Humalog KwikPen. We have completed our review of the proposed proprietary name, Humalog KwikPen and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 28, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Callie Cappel Lynch at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
01/14/2014



NDA 205747

**INFORMATION REQUEST**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin lispro (rDNA origin) injection.

We are reviewing your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Device:**

1. Although the accuracy testing meets the standard (ISO 11608-1) of  $\pm 0.005$  mL for doses smaller than 0.1 mL and  $\pm 5\%$  for doses of 0.1 mL or greater. The results reported for 1U raise clinical concerns. (b) (4)

[REDACTED]

Therefore, it is not unreasonable to expect that patients will use the pen to, at times, deliver smaller doses of insulin lispro. As such, it is important that patients and the healthcare providers prescribing and instructing the patient on the use of this product understand the performance at the lower end of the dose range. Provide additional accuracy testing in the lower claimed range. The results of accuracy testing should be reported in both volume and percentage error and presented in tabular form for inclusion into the product labeling.

2. You have not provided any biocompatibility data for the insulin lispro 200 units/mL KwikPen. (b) (4)  
[REDACTED] you have indicated that the color of the 200 unit/mL pen is different. Please provide a list of all materials of construction of the 100 unit/mL and 200 unit/mL KwikPens, biocompatibility testing for the 100 unit/mL pen and Materials Safety Data

Sheets (MSDS) for (b) (4) the 200 unit/mL pen. We require this information by December 10, 2013.

**Medication Error Prevention and Analysis:**

3. During our evaluation of the Human Factors (HF) Validation Study Results for the insulin lispro, 200 units/mL, we noted that three of the 15 prescribers wrote for the incorrect number of units (cut the number of units in half) when prescribing insulin lispro, 200 units/mL insulin (p.38). This error occurred despite the fact that prescriber participants were first given the Prescriber Information Leaflet to review with key information regarding this product. This is a concerning issue because this type of error would result in underdosing, with the patient receiving half the intended dose, and could produce chronic hyperglycemia if the error is not corrected. In your report, you state that “this error resulted from respondents doing incorrect calculation of the number of units to be injected, which were calculated to be half of the needed prescriptions for all prescription types (Use-Mistake-Application of bad rule)”. Although you acknowledged that this error would produce harm, you determined the acceptability of this error is “green” per AFMEA.

Given the fact that this error would result in clinically significant underdose, please provide a detailed plan regarding how you propose to prevent this type of error once the product is marketed.

Additionally, please provide a detailed report regarding what happened in each of these three cases and why you determined this error to be acceptable per AFMEA.

4. In your HF study results, you included a distinct group of participants: “syringe extractors”. Please describe how you identified this participant population and what criteria you used to identify them.

**Clinical:**

5. Provide an estimate of the patient population size for whom you anticipate that insulin lispro 200 unit/mL KwikPen provides an additional treatment option, i.e. patients taking more than 20 units/day.



If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, MD  
Director, Acting  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JEAN-MARC P GUETTIER  
10/31/2013

**From:** Tossa, Margarita  
**To:** "Joerg Pfeifer"  
**Cc:** CappellLynch, Callie  
**Subject:** RE: TN letter for NDA 205747  
**Date:** Wednesday, September 11, 2013 1:39:00 PM  
**Importance:** High

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Hello Joerg,

Please see below in red FDA Responses to your questions.

Tank you and regards,

*Margarita*

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**From:** Joerg Pfeifer [mailto:pfeifer\_joerg@lilly.com]  
**Sent:** Wednesday, September 11, 2013 9:32 AM  
**To:** Tossa, Margarita  
**Cc:** CappellLynch, Callie; Joerg Pfeifer  
**Subject:** RE: TN letter for NDA 205747

Hello Margarita,

Thank you for your willingness to provide us additional information on the name review for this product under NDA 205747. At this point I have three areas for questions or clarification.

1. Transfer or withdrawal from syringe

FDA commented in the TN letter on six patients that would consider withdrawing drug from this pen as well as one patient who withdrew the whole contents (2<sup>nd</sup> bullet in letter). I have looked at the information that Lilly provided FDA and could not find the sections referring to those patients. Could the FDA reviewer please point me to the specific location in the NDA discussing those six and one patient scenarios respectively? I understand that FDA expects the Sponsor to know the content submitted under its NDA but have not found the specific reference and thus seek FDA's assistance.

**FDA Response:**

The information can be found on pages 65 and 66 (15.1 Patient's Respondent Response in Attachment 1-Humalog (b) (4) KwikPen Summative Human Factors Study Technical Report).

- Five would transfer to a syringe at some point during the Jammed Pen scenario
- One patient said they would need U-200 syringe and when told there is no U200 syringe, said they would use U100 syringe and do the dose conversion. (i.e., Total of 6 patients from bullet points 1 and 2)
- One patient did not do the calculation correctly and withdrew a 100% overdose (10 units on a U100 syringe).

## 2. Labeling and prescribing thoughts based on using Humalog KwikPen name

Along with FDA's request to submit "Humalog KwikPen" as the proprietary name for this product, could the review team provide some additional comments for labeling and prescribing that it would expect with use of that name? Lilly has thought much about that scenario as well. For example, with the same name for the pen, we would envision the insulin lispro U-100 and U-200 cartons to be similar in many ways with respect to text but differ in using "U-200" and "200 units per mL" instead of the U-100 text. We would also expect some differences in colors based on what was tested in the Human Factor studies and thus to differentiate the pens and packaging. Another item to consider is the prescribing of the pens. With using the same name, the physician would then have to specify U-100 or U-200 in the script. Lilly is interested in any thoughts from FDA on these or other topics that FDA considered during its review of the initially proposed name. Also, can FDA clarify the comment around revising the entire nomenclature for the Humalog KwikPen product line if a numeric modifier is desired? Would this apply to the Humalog mixtures as well or just to the Humalog (insulin lispro) U-100?

### **FDA Response:**

We may provide additional comments regarding labeling at a later date once we evaluate your Human Factors Study Results in detail. However, regarding the last part of the question evolving around the revision of the nomenclature, please refer to your external study provided by (b) (4)

The nomenclature would have to be changed for Humalog U-100.

## 3. Unique NDC

Lilly would like to confirm its understanding that a unique NDC would be required for the insulin lispro U-200 product even if the same name, Humalog KwikPen, is used as for the insulin lispro U-100 product (same name for pen but different NDC for each product).

### **FDA Response:**

Yes, that is correct.

Please let me know if you or the review team have questions about this email and I will answer quickly. I look forward to your response.

Best regards,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs  
**Eli Lilly and Company**  
Office: 317-276-2146  
Mobile: (b) (6)  
Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>



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MARGARITA V TOSSA  
09/11/2013



DEPARTMENT OF HEALTH AND HUMAN  
SERVICES

Food and Drug  
Administration Silver  
Spring MD 20993

NDA 205747

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Attention: Joerg Pfeifer, Ph.D.  
Advisor - U.S. Regulatory Affairs

Dear Dr. Pfeifer:

Please refer to your New Drug Application (NDA) dated May 10, 2013, received May 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for insulin lispro (rDNA origin) injection, 200 Units/mL.

We also refer to your request, dated and received May 10, 2013, for review of your proposed proprietary name, Humalog <sup>(b) (4)</sup> KwikPen. We have completed our review of the proposed proprietary name and have concluded the <sup>(b) (4)</sup> is unacceptable for the following reasons:

<sup>(b) (4)</sup>

We note that you have not proposed an alternate proprietary name for review. However, we concur with the recommendation from [REDACTED] (b) (4)

[REDACTED] unless you revise your entire nomenclature for the Humalog Kwikpen product line. Thus, we request you submit Humalog Kwikpen as the proprietary name for this product. We recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Callie Cappel-Lynch at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research



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/s/  
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CAROL A HOLQUIST  
08/08/2013



NDA 205747

**FILING COMMUNICATION**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

Please refer to your New Drug Application (NDA) dated and received May 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for insulin lispro (rDNA origin) injection, 200 units/ml.

We also refer to your amendments dated May 30 and 31, June 3, 5, 6, 20 and 27, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 10, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 10, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Product Quality - Microbiology

1. The method suitability study for the endotoxin testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.
2. The method suitability for the sterility testing could not be located in application section 3.2.P.5.2. Provide either the location in the submission, the report, or a justification of why the study was not performed.
3. It is acknowledged that NDAs 021017 and 021018 include (b) (4) lispro solution at 200 units/ml but the (b) (4) validation studies could not be located in the electronic information of these NDAs. Submit the (b) (4) validation report to NDA 205747.

Biopharmaceutics

4. Provide a written request for a waiver of bioequivalence studies using the proposed commercial formulation, as per 21 CFR 320.22.

Devices

5. You note that the color of the KwikPen has been changed to differentiate the rapid acting insulin portfolio from the long acting insulin portfolio. Please provide materials safety data sheets for all new (b) (4) and other materials of construction that are different in the new pen.
6. Please provide information for review regarding compliance with 21 CFR 820.30 design controls, 820.50 purchasing controls, and 820.100 corrective and preventive actions.
7. The description of the manufacturing activities of the finished combination product is inadequate. Please provide information on how the finished combination product would be assembled. Please also provide information on acceptance activities.

The following guidance provides useful information regarding the types of documents to provide to address information requests 6 and 7 above: "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff" (2003). This document may be found at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The length of the highlights (HL) section 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 previously granted.

We request that you resubmit labeling that addresses these issues by August 13, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient package insert (PPI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient package insert (PPI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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MARY H PARKS  
07/23/2013

**From:** [CappellLynch, Callie](#)  
**To:** [Joerg Pfeifer](#)  
**Cc:** [fairfield\\_amy\\_marie@lilly.com](mailto:fairfield_amy_marie@lilly.com); [CappellLynch, Callie](#)  
**Subject:** Informatin Request 205747 RE: questions about Lilly products  
**Date:** Wednesday, June 26, 2013 10:30:07 AM  
**Attachments:** [image001.png](#)

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Hi Joerg,

Since we spoke this morning I did receive one information request for NDA 205747:

You indicated that the detailed information on serum LY275585 serum sample analysis can be found in (b) (4) study 8230497. However, we were unable to locate the report for (b) (4) study 8230497. If you have already submitted the report with the NDA, kindly point us to the location where we can find it. If you have not submitted the report, please submit it within 7 days

Please contact me if you have any questions.

Best Regards,  
Callie

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**From:** Joerg Pfeifer [mailto:[pfefifer\\_joerg@lilly.com](mailto:pfefifer_joerg@lilly.com)]  
**Sent:** Wednesday, June 26, 2013 8:11 AM  
**To:** CappellLynch, Callie  
**Cc:** Joerg Pfeifer  
**Subject:** questions about Lilly products

Good morning Callie,

I hope you are doing well. As I mentioned in my voice mail message, I have returned to the office although only part time for this week.

I would like to speak with you about a few topics as I indicated. On the top of my list is to learn anything about the following submissions:

(b) (4)  
(b) (4)  
(b) (4)

NDA 205,747 (Humalog (b) (4) KwikPen): Do you have any update on the filing? You had indicated that the filing process was ongoing and I would be notified of any issues. Has the review started?


(b) (4)

(b) (4)

Thank you for your assistance,  
Joerg

Joerg Pfeifer PhD  
Regulatory Advisor, Diabetes Regulatory Affairs

**Eli Lilly and Company**

Office: 317-276-2146 

Mobile:  (b) (6) 

Email: [j\\_pfeifer@lilly.com](mailto:j_pfeifer@lilly.com) | Web: <http://www.lilly.com>

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CALLIE C CAPPEL-LYNCH  
06/26/2013

**From:** [CappellLynch, Callie](#)  
**To:** [Joerg Pfeifer \(pfeifer\\_joerg@lilly.com\)](#)  
**Cc:** [fairfield\\_amy\\_marie@lilly.com](#); [CappellLynch, Callie](#)  
**Subject:** Information Request NDA 205747  
**Date:** Tuesday, May 28, 2013 8:43:51 AM  
**Attachments:** [MANUFACTURING FACILITIES.DOC](#)

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Hi Joerg,

We are asking that you provide complete information on the commercial manufacturing/testing sites. The information currently in the NDA and referenced NDA (NDA 20563) is incomplete. The attached file can be used as a guide. Please contact me with any questions.

Thank you,  
Callie

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number  (if applicable)	Manufacturing Step(s)  or Type of Testing [Establishment Function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email Address
1.				
2.				

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CALLIE C CAPPEL-LYNCH  
05/28/2013



NDA 205747

**NDA ACKNOWLEDGMENT**

Eli Lilly and Company  
Attention: Joerg Pfeifer, Ph.D.  
Advisor, Global Regulatory Affairs- U.S.  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Dear Dr. Pfeifer:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Insulin lispro (rDNA origin) injection, 200 Units/ml

Date of Application: May 10, 2013

Date of Receipt: May 10, 2013

Our Reference Number: NDA 205747

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 9, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 205747 submitted on May 10, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-8436.

Sincerely,

*{See appended electronic signature page}*

Callie Cappel-Lynch, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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CALLIE C CAPPEL-LYNCH  
05/17/2013





NDA 020563

**MEETING REQUEST -  
Written Responses**

Eli Lilly and Company  
Attention: Jeffery R. Ferguson  
Director, GRA-CMC  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Ferguson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humalog (insulin lispro [rDNA origin]), 100 U/mL, injection.

We also refer to our November 29, 2011, communication notifying you that we would provide a written response to the questions in your November 22, 2011, meeting request within 90 days after receiving your background materials. The desk copies of the background materials were received on April 2, 2012.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Rachel Hartford  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure – Preliminary Comments

## PRELIMINARY COMMENTS

Your questions are repeated below followed by our responses in **bold** text.

### Question 1

Bioequivalence was demonstrated comparing a 20-unit dose of Humalog U-100 versus a 20-unit dose of Humalog U-200. Does FDA agree that, from a clinical perspective, this bioequivalence study as part of the overall submission package provides sufficient clinical evidence to support approval of the U-200 formulation?

**FDA Response: The PK/PD characterization of the intended Humalog U-200 commercial formulation is inadequate. While we agree that the PK/PD study (IOPY) as part of the overall submission package is sufficient to support filing of your supplemental NDA for the U-200 formulation, accepting the claim of bioequivalence is a review issue. You must also provide adequate justification and data to support your claim (b) (4) does not influence the PK and PD profiles of insulin Lispro from the intended commercial formulation.**

Does FDA agree that the changes made to the formulation do not require an additional clinical study?

**FDA Response: See response to Question 1 above.**

### Question 2

Can FDA provide comments on the proposed product name, Humalog (b) (4) KwikPen?

**FDA Response: The name you propose is a review issue that will be evaluated subsequent to your submission of an official Proprietary Name Request. (b) (4)**

(b) (4)

(b) (4)

**Note that these comments are preliminary and serve as a guide during your Human Factors Study process. Also note that any assessments on the safety or suitability of your proprietary name would be helpful to include in the proprietary name submission. They do not replace the formal Proprietary Name Review process should you elect to proceed with a modifier of any type for this product.**

Does FDA foresee any concerns regarding this name and total unit dose availability description during the trade name review process?

**FDA Response: See the response to Question 2.**

Question 3

Since the previous FDA meeting on 22 July 2011 regarding the KwikPen platform, Lilly has updated the proposed labeling based on FDA feedback and feedback from initial formative studies. The proposed labeling and packaging that will be tested in the next formative Human Factor Study (#3) and the Summative Human Factor Study are provided in Section 5.2.2 of this document. Is the differentiation provided herein (product trade name; pen label size, text, and graphics; pen body color and cap; pen dose knob color; cartridge holder; user manual and pen carton) acceptable, assuming the Summative Human Factor results confirm the safety of the product for the patient?

**FDA Response: See our response to Question 2 regarding your proposed proprietary name.**

Pen Label, Size, and Text

- 1. National Drug Code Number: We acknowledge that this product contains the same molecule as the currently marketed U-100 Humalog. However, from a medication error perspective, we encourage the use of a different middle segment for your National Drug Code (NDC) number for this product, as it will provide another mode of differentiation between the two products.**
- 2. Label Size: This pen body differs from that of your currently marketed KwikPen; therefore the pen label size is one of multiple differentiation factors, and the size of this label should not be relied upon exclusively for initial differentiation between these two products. Also, add the statement “For Single Patient Use Only” to the pen label, as there have been recent medication errors which substantiate the use of this statement on all marketed integrated pen and pen cartridge devices. A warning statement discouraging withdrawal from the cartridge with a syringe, similar to that on the cartridge should also be added to the pen label. The label size, however, is acceptable assuming the Summative Human Factor results confirm the safety of the product for the user.**

- Text: The text on the pen label itself is difficult to read. Consider a different color combination or different font/typeface to improve readability of the information, as the (b) (4) text (b) (4) is difficult to read on the pen label and also on the carton labeling.**

### Pen Device

- Pen Body Color and Cap Design: The proposed pen is well-differentiated from your current KwikPen platform; however, in previous communications and meetings you presented a pen (b) (4) The July 3, 2012 response to our May 8, 2012 Information Request reiterates your expectation that within the next three years all of your marketed pens will be implemented into this pen body design. We remind you to complete a Human Factors Study (including differentiation tasks) prior to implementation of the new pen body design for your remaining products.**

We also have concerns (b) (4)

- Pen Dose Knob Color: Consider the addition of color not only to the top surface of the dose knob, but also to the lateral surface of the dose knob (b) (4)**
- Cartridge Holder Gauge Scale and Labeling: We note that the warning not to transfer to a syringe used in Formative Human Factors Study #2 did not deter users from continuing to make this error. While we are unsure if the current warning is the one used in the formative studies, we recommend revising this statement to read (b) (4)**

### User Manual

**In section 4-e of the FAQ's add a bullet point stating the 'do not remove with a syringe' warning in the event of device failure (e.g., a jammed pen).**

### Question 4

The data from the Summative Human Factors Study, along with a history of the development, will be provided in the NDA supplement in a human factors summary section. Does FDA agree that the Summative Human Factors Study protocol as proposed is adequate to demonstrate that the device is acceptable for its intended use?

**FDA Response:** We appreciate your efforts in conducting several formative studies prior to the final HF/usability validation study. However, based on our review of the formative study # 2 results, we are concerned that numerous use errors, and operational difficulties that could lead to incorrect dosing, were experienced across the nurse and patient user groups. These results indicate that the device design, including IFU/labeling and training, are not optimized, and therefore additional mitigation strategies are necessary. Evaluate these results, implement the necessary mitigations, and provide data to demonstrate safe and effective use in your final validation study.

In addition, we understand that you are planning to conduct the third formative testing in 2012. In your submission, describe how these formative studies were/will be used to inform the design of the validation study in terms of how you have optimized the user interface to reduce use-related hazards and how you identified the critical user tasks for the validation study.

Regarding your proposed HF/usability validation study protocol, provide a use-related risk analysis and justify why the tasks/scenarios selected for each user group represent the essential/critical tasks necessary to deliver a successful injection. Also address the following:

- a. You plan to use the (b) (4) approach (page 48). Note that while this approach can be used effectively for exploratory studies, it does not represent realistic use and should not be used in a HF/usability validation study.
  
- b. Note that if users do not have access to assistance/support in actual use, then whenever the moderator provides assistance (page 48) to study participants, we would consider that as a task failure.

## **Human Factors Study Protocol Additional Comments**

### **General**

1. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.
  
2. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

3. Clarify why you only elected to use your own Humalog-based products and not any competitor's products as well for pen and carton differentiation testing. We suggest using, at the very least, insulin glargine (Lantus Solostar) pens along with your U-100 Humalog KwikPens in your differentiation testing.

## User Groups

### Patient and Caregiver Usability Testing

4. Task 2
  - a. In your satisfaction survey, once a task is added for differentiation of pens from other manufacturer's product lines, include a question for those who use more than one insulin product about ease of pen differentiation.
  - b. Provide an opportunity for open-ended feedback from all users on your satisfaction survey, as this may garner useful information and/or insight into needed product modifications or reasons for task failures.

### 5. Task 3

- a. We do not agree [REDACTED] (b) (4)  
[REDACTED] While we agree that there is a higher likelihood that withdrawal with a syringe is more likely to occur with insulin-experienced users, it may occur with an insulin-naïve patient and, therefore, should be tested during validation of the warnings on the pen labels, labeling, and User Manual.
- b. If a user uses the provided syringe to simulate extraction of the correct amount of insulin from the pen cartridge, will you count this as task success or task failure?

### Nurse Usability and Differentiation Testing

Task 2: If a user uses the provided syringe to simulate extraction of the correct amount of insulin from the pen cartridge, will this be considered task success or task failure?

### Pharmacist Usability and Differentiation Testing

Add a task for pharmacists to interpret and/or enter a prescription for U-200 Humalog to ensure that this user group will not self-convert the prescribed units written on a prescription to half of the prescribed dose, as concentration manipulation is a frequently encountered scenario by pharmacists.

## **Health Care Providers Usability Testing**

### **Tasks 1 and 2**

- a. Clarify what you will determine to be a successfully written prescription in these tasks, (i.e., which elements will you expect to be present to determine successful completion of the task).**
  
- b. To mitigate the risk of the incorrect concentration of insulin being dispensed, inclusion of the total net quantity of units to be dispensed (as opposed to writing “QS” as the net quantity to dispense), as well as the concentration of the Humalog on the written prescription should be considered when determining success criteria for this task. Emphasis on the inclusion of these two items should also be considered in your Health Care Provider education program for this product.**

### **Question 5**

Does FDA agree with Lilly’s proposal for establishment of in-use dating?

**FDA Response: Yes, your proposal for the establishment of in-use dating is acceptable.**

### **Question 6**

Does the FDA agree with the proposed stability strategy and the proposal for establishing expiry dating?

**FDA Response: Your proposed stability testing strategy appears to be acceptable.**

### **Question 7**

Does FDA agree that the proposed Chemical Manufacturing and Control (CMC) data package is acceptable to support supplemental NDA filing for the U-200 formulation, assuming data demonstrates product stability?

**FDA Response: Your proposed CMC data package appears to be acceptable.**

### **Question 8**

Does FDA agree that the proposed development plan including 1) pharmacokinetic/ pharmacodynamic (PK/PD) results demonstrating bioequivalence to Lilly’s existing 100 units/mL formulation, 2) Human Factors testing and pen differentiation and 3) CMC package to be provided, is sufficient to support the supplemental NDA filing for Humalog 200 units/mL?

**FDA Response: Yes, your proposed development plan is sufficient to support the supplemental NDA filing for Humalog 200 units/mL. Refer to the response to Question 1 above for additional information.**

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/s/  
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RACHEL E HARTFORD  
08/21/2012