

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**205747Orig1s000**

**CHEMISTRY REVIEW(S)**

## **NDA 205747**

# **Humalog (b) (4) KwikPen**

[Insulin Lispro U-200 (200 units/mL) filled into 3.0 mL cartridges and assembled into a prefilled pen injector capable of providing a total of 600 units of insulin lispro.]

**Ely Lilly and Company**

**Xavier Ysern, PhD  
ONDQA/ DNQA III/ Branch VII**

**CMC Review for DMEP**

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<i>[There are no deficiencies to be communicated to the Applicant]</i>	

## Chemistry Review Data Sheet

**Chemistry Review Data Sheet****1. NDA 205-747****2. Review #:** 1**3. Review Date:** 07-Feb-2013**4. Reviewer:** Xavier Ysem, PhD**5. Previous Documents:**Previous DocumentsDocument Date

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**6. Submission(s) Being Reviewed:**Submission(s) ReviewedDocument Date

Original

10-May-2013

Amendment(s)

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**7. Name & Address of Applicant:**

Name: Eli Lilly and Company (Lilly)  
Address: Lilly Corporate Center  
Indianapolis, IN 46285  
Representative: Joerg Pfeifer, PhD  
Advisor – Global Regulatory Affairs-U.S.  
Telephone: (317) 276-2146  
Alternatively:  
Dr. Elizabeth C. Bearby  
Senior Director, Global Regulatory Affairs - U.S.  
Telephone: (317) 276-1203

**8. Drug Product Name/Code/Type:**

a) Proprietary Name: Humalog® (b) (4) KwikPen (Proposed name)  
Non-Proprietary Name (USAN): Insulin Lispro Injection (rDNA origin)  
b) Code Name/# (ONDC only): LY275585 (Lilly's insulin lispro drug substance code name)  
c) Chem. Type/Submission Priority: - Chem. Type: 5 (new formulation [and new strength])  
- Submission Priority: S

**9. Legal Basis For Submission:** 505(b)(1)**10. Pharmacological Category:** Treatment of Hyperglycemia.**11. Dosage Form:** Sterile parenteral solution**12. Strength/Potency:** 200 U/mL**13. Route of Administration:** s.c. Injection



## The Chemistry Review for NDA 21-809

## I. Recommendations

## A. Recommendation and Conclusion on Approvability

The application can be approved from the CMC perspective.

## B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

## II. Summary of Chemistry Assessments

## A. Description of the Drug Product(s) and Drug Substance(s)

· **Drug Substance** Insulin lispro LY275585

Lilly's insulin lispro code name LY275585, an analog of human insulin, is the same drug substance used in Humalog, described under Applicant's active NDA 20-563, approved on 16-Jun-1996. Lilly's insulin lispro is produced by recombinant DNA technology utilizing *Escherichia coli* as the production organism. (b) (4)

Insulin lispro, chemical name LysB28, ProB29-human insulin, empirical formula  $C_{257}H_{389}N_{66}O_{77}S_6$ , molecular weight of 5813.63 Da, is an insulin analog that has a lysine at residue B28 and proline at B29; these residues are reversed in endogenous human insulin.

The penultimate lysine and proline residues on the C-terminal end of the B-chain, which are reversed in insulin lispro at position B28 and B29 in insulin lispro (Humalog®), were engineered (b) (4)

No changes were required for the drug substance. Reference is made to the currently approved NDA 20-563 for all quality information related to the drug substance, insulin lispro.

Insulin lispro drug substance should be stored (b) (4)

The re-evaluation date is (b) (4) months.

· **Drug Product** Humalog® (b) (4) KwikPen™

The drug product, Humalog® (b) (4) KwikPen™, is a pen delivery device containing Humalog® U-200 (insulin lispro 200 Units/mL) solution for injection prefilled into a 3 mL cartridge preassembled into a new pen injector capable of providing a total of 600 Units of insulin lispro.

Humalog® U-200 (insulin lispro 200 Units/mL) is a concentrated version of approved Humalog® U-100 (insulin lispro 100 Units/mL) solution for injection with a few changes. The initial formulation, used in the clinical trial, differed from Humalog U-100 in (1) the concentration of lispro which was incremented from U-100 to U-200, (2) a slight change to the zinc/insulin ratio from 0.0197 mg Zn<sup>+2</sup>/100 Unit (Humalog) to (b) (4) Zn<sup>+2</sup>/100 Unit (U-200) (b) (4)

(b) (4)

(b) (4)

(b) (4)

The manufacturing procedure for Insulin Lispro U-200, (b) (4) is (b) (4)

The stability of Humalog 200-U is supported by primary (including leachables and extractables), supportive, and stress data (chemical stress, photostability and freeze/thaw cycles). Supporting stability studies were conducted (b) (4)

The available primary stability data (3 lots; available data: 12 months storage condition (2 - 8 °C) and 3 months accelerated condition (30 °C)), and supportive data from batches manufactured at the Applicant's Fegersheim site (3 lots; available data: 24 months at the storage condition and 3 months accelerated) and from pilot scale batches (3 lots; available data: 18 months storage condition and 3 months accelerated condition (30 °C)) is all within specifications.

Analysis of the data from primary (registration) lots and supportive lots allowed to correlate the stability of the drug product under the two stability conditions (b) (4)

(b) (4)

(b) (4)

The proposed shelf-life of 36 month when stored at refrigerated conditions 2 °C to 8 °C, and may remain for patient use through 28 days at a maximum temperature of 30 °C, which is fully supported by the provided stability data and their analysis, is granted.

Insulin Lispro 200-U is delivered using the 600 Unit KwikPen™ pen-injector device, which is a prefill pen-injector device containing a filled 3 mL (b) (4) cartridge capable of delivery of doses from 1 to 60 Unit is (b) (4) as a single injection.



## I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

### Introduction

In this submission Lilly seeks approval for a new insulin lispro U-200 formulation and its associated delivery device under the proposed name “Humalog <sup>(b) (4)</sup> KwikPen”. The new insulin lispro U-200 formulation is a concentrated version of the existing insulin lispro U-100 formulation.

This submission was originally sent to the Agency as a supplemental NDA submission to Humalog NDA 20-563 on 15 March 2013. In a teleconference with the Applicant on 24 April 2013, the Agency stated that an original NDA would be required for this formulation and device.

### S Drug Substance *Satisfactory*

The drug substance LY275585 is Lilly’s Insulin Lispro. Information on the quality of the drug substance is referred to the approved drug substance information in Lilly’s NDA 20-563. No changes have been made to the approved drug substance Insulin Lispro described under approved and active NDA 20-563. For clarity, some information on the drug substance is summarized as follows.

#### S.1 General Information

##### S.1.1 Nomenclature

International Non-proprietary Name (INN): Insulin Lispro

Chemical Name (USAN):

1. 8<sup>A</sup>-L-threonine-10<sup>A</sup>-L-isoleucine-28<sup>B</sup>-L-lysine-29<sup>B</sup>-L-proline-30<sup>B</sup>-L-threonine insulin (ox)
2. 28<sup>B</sup>-L-lysine-29<sup>B</sup>-L-proline insulin (human)

U. S. Adopted Name (USAN):

Insulin Lispro

British Approved Name:

Insulin Lispro

Lilly Laboratory Code:

LY275585

Chemical Abstracts Number:

133107-64-9

Identification number of the production strain:

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

##### S.1.2 Structure

Empirical Formula: C<sub>257</sub>H<sub>383</sub>N<sub>65</sub>O<sub>77</sub>S<sub>6</sub>

Molecular Weight: 5808 amu

Structural Formula: Lispro is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. Lispro is identical in structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B chain. Human insulin is Pro(B28), Lys(B29), whereas Lispro is Lys(B28), Pro(B29). As in human insulin, Lispro contains two interchain disulfide bonds and one intrachain disulfide bond. A representation of the primary structure of Lispro is shown in Figure S.1.2-2.

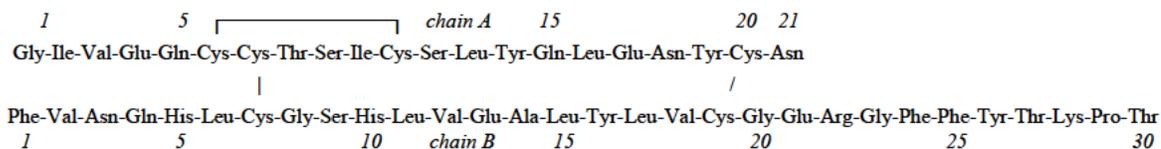


Figure S.1.2-1. Primary Structure of Insulin Lispro.

**S.1.3 General Properties**

<b>Table S.1.3-1. Insulin Lispro General Properties (From NDA 20-563)</b>	
<i>Property</i>	<i>Value</i>
Physical Form	White to off-white powder.
Isoelectric Point (pI)	~ 5.6
Hygroscopicity	(b) (4)
Solubility <sup>a</sup>	(b) (4)

**S.2 Manufacture**

**S.2.1 Manufacturer(s)**

<b>Table S.2.1-1. Insulin Lispro General Properties (From NDA 20-563)</b>	
<i>Responsibility(ies)</i>	<i>Facility Site</i>
Administrative	Eli Lilly and Company Indianapolis, Indiana 46285 Central File Number: 1819470
(b) (4)	Eli Lilly and Company Indianapolis, Indiana 46285 Central File Number: 1819470
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	Eli Lilly and Company Indianapolis, Indiana 46285 Central File Number: 1819470
(b) (4)	(b) (4)
(b) (4)	Eli Lilly and Company (b) (4)

61 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

## II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

### A. Labeling, Package Insert and Patient Package Insert *Pending*

#### 1. Physician Package Insert (PI)

Although the Physician Package Insert (PI) is still under negotiation (several disciplines involved), the two sections of the PI that rely in Chemistry input, “Description” and “How Supplied” sections, appear adequately described.

#### 2. Patient Package Insert (PPI or Patient Information)

Similarly to the Package Insert, the review of the Patient Package Insert is also multidisciplinary and still ongoing. However, the response to the CMC related questions such as What is HUMALOG?, What is HUMALOG (b) (4) KwikPen?, What are the ingredients in HUMALOG U-200?, and How should I store HUMALOG in the HUMALOG (b) (4) KwikPen?, appear adequately addressed in the PPI.

Instructions for the use of the Humalog® (b) (4) KwikPen™ (Instruction for Use) are also provided, again, its evaluation is multidisciplinary and still ongoing.

#### 3. Container and Carton Labeling

Copies of the proposed cartridge holder, pen body label and carton labels have been provided and reproduced in Figures A-1, A-2 and A-3, respectively. Again, its review is multidisciplinary and still ongoing.



Figure A-1. Humalog® (b) (4) Cartridge holder Label.  
(See also Figure R.2-1)



Figure A-2. Humalog® (b) (4) KwikPen™ Pen Label.  
(See also Figure R.2-1)



Figure A-3. Humalog® (b) (4) KwikPen™ Carton Label. [Carton contains two 3 mL Prefilled Pens.]  
(See Figure R.2-3)

*Comment: Review ongoing. Recommendation on the adequacy of the proposed proprietary names, carton and container labels, package insert and patient package insert, involve the Office of Drug Safety (ODS), the Division of Medical Errors and Technical Support (DMETS), and Clinical, PharmTox and Chemistry disciplines. Final decision on these recommendations resides with the Division Director of the Division of Metabolic and Endocrine Products (DMEP).*

**B. Environmental Assessment or Claim of Categorical Exclusion** *Satisfactory*

According to the Applicant, approval of this application will not increase the use of Humalog to a level that will reach 1 ppb in the aquatic environment. Total use of Humalog in the United States will be far below (b) (4) Kg/year, the approximate use level necessary to result in an expected introduction concentration into the aquatic environment of 1 ppb.

The proposed action would not be expected to have adverse effects on human health or the environment. While approval of the application could increase the production and use of Humalog, the quantity of the active ingredient, insulin lispro, entering the environment will not increase. Humalog is not expected to reach the aquatic environment and, even if it did, the use of Humalog will be far below the level needed to reach 1 ppb in the aquatic environment. increase. Actions associated with this submission will not present serious harm to the environment, nor

will actions adversely affect a species, or critical habitat of a species, protected by the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna.<sup>1</sup>

As no impact on the environment is expected, Eli Lilly and Company claims a categorical exclusion for this application pursuant to 21 CFR 25.15 (d) based on the exclusion allowed by 21 CFR 25.31 (b). Eli Lilly and Company knows of no extraordinary circumstances that exist that could require an environmental assessment.

*Evaluation: The applicant requests categorical exclusion for the submission of the Environmental Impact Assessment based on that the calculated Expected Introduction Concentration (EIC) of insulin at the point of entry into aquatic environment is lower than 1 part per billion (ppb). The request meets categorical exclusion criterion under 21 CFR §25.31(b) and it is **granted**.*

**C. Establishment Inspections**      *Satisfactory*

The sites involved in the manufacture, testing and packaging of the drug substance (Table S.2.1-1) and drug product (Table P.3.1-1) were requested for inspection. An acceptable recommendation for those sites was issued by the Office of Compliance (OC) on 19-Dec-2013 (EER summary report attached).

**III. List of Deficiencies to be Communicated**

None

ATTACHED:

	<u>Page</u>
EER Summary Report dated 20-Dec-2013 (3 Pages) .....	74

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<sup>1</sup> The in vivo degradation of insulin has been studied following subcutaneous and intravenous injections (Duckworth 1988; Duckworth et al. 1998). The uptake and degradation of insulin occurs predominantly in liver, kidney, muscle, and adipocytes, with the liver being the major organ involved in the clearance of insulin. In liver, muscle, and adipocytes, insulin binds to the cell surface either via insulin receptors or other, less specific sites. Binding is followed by degradation on the cell surface or cellular uptake and subsequent degradation. It has also been shown that some insulin can be internalized, then cycle back to the cell surface where it is released, apparently intact. Metabolism by the kidney is predominated by glomerular filtration, followed by proximal tubular reabsorption and intracellular degradation. Less than 1 % of filtered insulin is excreted intact in urine. Even if intact insulin were eliminated from humans it would be discharged to either a sewage treatment facility or a septic tank where microbial degradation of the protein would occur.  
Duckworth WC. 1988. Insulin degradation: mechanisms, products, and significance. *Endocr Reviews* 9(3):319-345.  
Duckworth WC, Bennett RG, Hamel FG. 1998. Insulin Degradation: Progress and Potential. *Endocr Reviews* 19(5):608-624.



# CHEMISTRY REVIEW



## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

<b>Application:</b>	NDA 205747/000	<b>Sponsor:</b>	ELI LILLY AND CO
<b>Org. Code:</b>	510		LILLY CORPORATE CENTER
<b>Priority:</b>	5		INDIANAPOLIS, IN 46285
<b>Stamp Date:</b>	10-MAY-2013	<b>Brand Name:</b>	HUMALOG (LISPRO INSULIN) INJECTION 600 U
<b>PDUFA Date:</b>	10-MAR-2014	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	INSULIN LISPRO
<b>District Goal:</b>	09-JAN-2014	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; INJECTION; INSULIN LISPRO; 200UNT/1ML

<b>FDA Contacts:</b>	X. YSERN	Prod Qual Reviewer		3017961779
	D. MILLER	Micro Reviewer	(HFD-003)	3017963854
	R. MCKNIGHT	Product Quality PM		3017961765
	S. TRAN	Team Leader		3017961764

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 19-DEC-2013	by C. CAPACCI-DANIEL ()	3017963532
	PENDING	on 18-JUN-2013	by EES_PROD	
	PENDING	on 18-JUN-2013	by EES_PROD	
	PENDING	on 18-JUN-2013	by EES_PROD	
	PENDING	on 18-JUN-2013	by EES_PROD	

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 1819470 FEI: 1819470  
ELI LILLY AND COMPANY

**DMF No:** INDIANAPOLIS, , UNITED STATES 462850001 **AADA:**

**Responsibilities:** (b) (4)  
DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE LABELER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 19-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Profile:** DEVICE KIT ASSEMBLER **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 19-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 19-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 18-JUN-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 9610945 FEI: 3002807475  
LILLY FRANCE SAS  
RUE DE COLONEL LILLY B.P. 10  
FEGERSHEIM, FRANCE

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER

**Profile:** (b) (4) OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 29-JUN-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** (b) (4) AADA:

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER

**Profile:** CONTROL TESTING LABORATORY OAI Status: NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 10-DEC-2013

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE  
DISTRICT RECOMMENDATION

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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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XAVIER J YSERN  
02/10/2014

DANAE D CHRISTODOULOU  
02/10/2014

I concur with the reviewer's conclusions and recommendations

# ONDQA Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

1. NEW DRUG APPLICATION NUMBER: 205747

2. DATES AND GOALS:

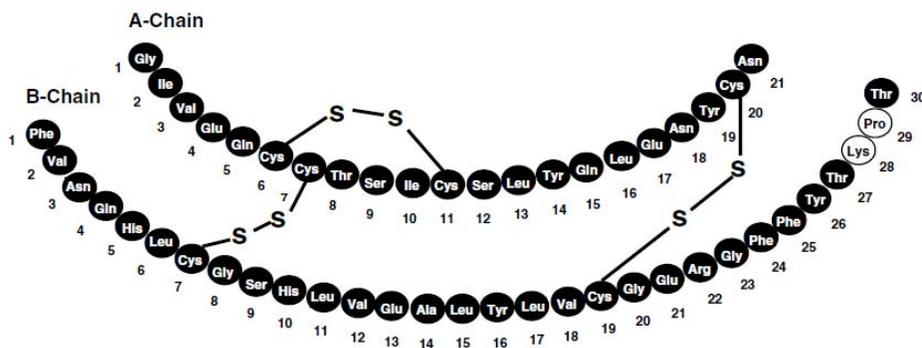
Letter Date: 5/10/2013	Submission Received Date : 5/10/2013
PDUFA Goal Date: 3/10/2014 (NDA is not part of "The Program")	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Humalog (b) (4) KwikPen
Established or Non-Proprietary Name (USAN):	Insulin lispro injection (rDNA)
Dosage Form:	Solution
Route of Administration	Subcutaneous injection
Strength/Potency	200 units/mL, 600 units/cartridge (pre-assembled in pen injectors)
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of hyperglycemia

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

Chemical Name (USAN): 1. 8<sup>A</sup>-L-threonine-10<sup>A</sup>-L-isoleucine-28<sup>B</sup>-L-lysine-29<sup>B</sup>-L-proline-30<sup>B</sup>-L-threonine insulin (ox)

2. 28<sup>B</sup>-L-lysine-29<sup>B</sup>-L-proline insulin (human)

U. S. Adopted Name (USAN): Insulin Lispro

6. NAME OF APPLICANT (as indicated on Form 356h): Lilly

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code):	5
(Application Type):	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DMEP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Establishment Evaluation Request (EER)	x		To be sent by the ONDQA PM
Pharmacology/Toxicology		x	
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment			To be determined by Primary Reviewer
CDRH	x		To be sent by the OND PM
Other			

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**CMC Summary:  
Critical Issues and Complexities**

<b>Summary of Critical CMC Issues Previously Discussed with the Applicant (if any):</b>			
From FDA's letter dated 21-AUG-2012 in reference to the meeting package received on 02-APR-2012:			
<u>Question 5</u> Does FDA agree with Lilly's proposal for establishment of in-use dating?			
<b>FDA Response: Yes, your proposal for the establishment of in-use dating is acceptable.</b>			
<u>Question 6</u> Does the FDA agree with the proposed stability strategy and the proposal for establishing expiry dating?			
<b>FDA Response: Your proposed stability testing strategy appears to be acceptable.</b>			
<u>Question 7</u> 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?			
<b>FDA Response: Your proposed CMC data package appears to be acceptable.</b>			
<b>Critical CMC Issues or Complexities (note issues or if there are none)</b>			
None			
<b>Does the submission contain any of the following elements?</b>			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No
<b>Is a team review recommended?</b>			
Yes	No	Suggested expertise for team	
x		Microbiology (sterile product) – review by Denise Miller Biopharmaceutics (biowaiver request) – review by Minerva Hughes	
<b>Summary or Highlights of the Application (not already mentioned in other sections)</b>			
<ul style="list-style-type: none"> <li>The referenced NDA 20563 (same applicant) is approved for Humalog U-100 (100 Units/mL), which has the identical drug substance as the new product. The new product ("U-200") is a more concentrated formulation at 200 Units/mL (b) (4). The submission was previously submitted to FDA as NDA 20563 Supplement 140 on Mar. 15, 2013. The applicant was informed by FDA that the submission must be resubmitted as a new NDA, due to new policy regarding user fees: NDA 20563 (Humalog U-100) is for subcutaneous and intravenous injection, while the new product (Humalog U-200) is only for subcutaneous injection, thus requiring a new NDA.</li> <li>The established name of the product is "insulin lispro" based on the dosage strength, which is acceptable per current CDER's policy on nomenclature.</li> <li>Compared to the clinical formulation, the commercial product has (b) (4).</li> </ul>			

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

(b) (4) No bioequivalence study was conducted to bridge the two formulations (a biowaiver request should be submitted – see the Biopharmaceutics filing review). The CMC reviewer will evaluate (b) (4). The Biopharmaceutics reviewer will evaluate (b) (4). Both reviewers will evaluate the formulation design of experiments studies. The studies were conducted (b) (4) via stability-indicating parameters.

- Compared to the clinical product manufacture, the process of the commercial product has a (b) (4) pH target (b) (4). The clinical product was packaged (b) (4) while the commercial product is packaged in a (b) (4) cartridge for use with a pen injector. No bioequivalence study was conducted to bridge these differences. The CMC reviewer will determine whether these differences would warrant a biowaiver evaluation from the Biopharm reviewer.
- All aspects of the pen injector (design, functionality, specification, etc.) will be reviewed by CDRH (consult request to be sent by DMEP).

**Drug Substance**

The drug substance, insulin lispro, is a human insulin analog that is a rapid-acting, blood glucose-lowering agent. The drug substance has Lys28 and Pro29 in the B chain, which are the reverse of the positions in the native insulin. It is manufactured from host E. coli (b) (4).

Reference is made by the applicant to the approved NDA 20563 (same applicant) for all approved information on the drug substance, a re-review of the approved information may not be necessary in support of this new NDA. A copy of the approved drug substance specification is included in Attachment 3 of this review.

**Drug Product**

Composition. A copy of the product composition is included in Attachment 1 of this review.

(b) (4) the excipients are the same as those in the approved U-100 product of the referenced NDA 20563 (b) (4). The mass quantity of the drug substance is (b) (4) units/mg (b) (4).

- **Overage.** An overage of up to (b) (4) % of the drug substance may be used in the manufacturing batch formula (b) (4).
- **Overfill.** The drug product is packaged in a (b) (4) cartridge (see Container closure comments below). Each cartridge has a target fill of (b) (4) mL (b) (4) for a deliverable total volume of 3.0 mL/cartridge. The overfill is within USP limits for mobile liquids.
- **Metacresol.** Each product cartridge will be for multiple doses. (b) (4)

Manufacture. The manufacturing process of the drug product is (b) (4)

All sterility assurance information will be evaluated by the Microbiology reviewer.

**Drug product specification.** A copy of the drug product specification is included in Attachment 2 of this review. It includes standard attributes for an injectable solution product. (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

(b) (4)	The proposed limits on Zinc	(b) (4)
<p>will be evaluated by the CMC reviewer, with input from the Biopharmaceutics reviewer (see earlier discussion of the biowaiver issue). The NDA includes developmental information (b) (4)</p> <p>The CMC reviewer will evaluate the information and determine whether a quality control should be added to the drug product specification.</p> <p>Microbiological attributes (b) (4) will be reviewed by the Microbiology reviewer.</p> <p><u>Container closure system.</u> The list of Type III DMFs is included in the Filing Checklist of this review. (b) (4) The drug product is packaged in a (b) (4) cartridge, sealed with a rubber disc and a rubber plunger. The rubber disc components are (b) (4)</p> <p>The plunger component is (b) (4)</p> <p>A report on the extractables and leachables are provided in the NDA to be reviewed in consultation with the toxicology reviewer. The container closure integrity information and the sterility assurance of the components will be evaluated by the Microbiology reviewer.</p> <p><u>Stability.</u> The primary stability batches (A915537, A915538, and A915540) were manufactured at the commercial site, commercial (b) (4)-L scale, and packaged with the commercial container closure system. The NDA includes 12-month long term data (2-8 C°) as well as 3-month accelerated data (30 C°). Other data are: in-use, leachables, oxidative stress and pH, photostability, and freeze/thaw. The reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.</p>		
<b>Description of Any Facility Related Risks or Complexities with this Application.</b>		
<i>See EES for complete list of facilities related to this application.</i>		

**FILING REVIEW CHECKLIST**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		

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4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
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<b>B. FACILITIES*</b>				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential filing issue</i> or a <i>potential review issue</i>.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	x		

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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

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	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

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<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?			Referencing quality information in the approved NDA 20563.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS			Referencing quality information in the approved NDA 20563.
14.	Does the section contain information regarding the characterization of the DS?			Referencing quality information in the approved NDA 20563.
15.	Does the section contain controls for the DS?			Referencing quality information in the approved NDA 20563.
16.	Has stability data and analysis been provided for the drug substance?			Referencing quality information in the approved NDA 20563.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			See the Biopharmaceutics filing review.
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

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<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	x		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
(b) (4)	III		(b) (4)	7/3/2012
	III			7/5/2012
	III			7/13/2012
	III			7/16/2012

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

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<b>J. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

*See appended electronic signature page*

CMC-Lead or CMC Senior Reviewer

Division

Office of New Drug Quality Assessment

*See appended electronic signature page*

Branch Chief or Designee

Division

Office of New Drug Quality Assessment

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**Appendix 1. Composition of Drug Product (Optional)**

**2.3.P.1 Description and Composition of the Drug Product**

Insulin Lispro U-200 (200 units/mL) is a sterile drug product that is indicated for the treatment of patients with diabetes mellitus. This product will be filled into 3.0 mL cartridges and assembled into a prefilled pen injector capable of providing a total of 600 units of insulin lispro.

The following unit formula will be used in manufacturing Insulin Lispro U-200, 3.0 mL Cartridges.

**Table 2.3.P.1-1 Unit Formula for Insulin Lispro U-200, 3.0 mL Cartridges**

Ingredient	Quantity (mg/mL)	Reasonable Variations (mg/mL)	Function	Reference to Standards
<b>Active Ingredient</b>				
Insulin Lispro	(b) (4) (200 Units)	(b) (4)	Active Ingredient	USP
<b>Other Ingredients</b>				
Glycerin	16 mg	(b) (4)	(b) (4)	USP
Metacresol	3.15 mg	(b) (4)	(b) (4)	USP
Zinc Oxide <sup>4</sup>	q.s. to give a Zn <sup>2+</sup> content of 0.046 mg	(b) (4)	(b) (4)	USP
Tromethamine	5 mg	(b) (4)	(b) (4)	USP
Hydrochloric Acid Solution 10%	q.s.	(b) (4)	pH adjustment	See Footnote 2
Sodium Hydroxide Solution 10%	q.s.	(b) (4)	pH adjustment	See Footnote 3
Water for Injection	(b) (4)	(b) (4)	(b) (4)	USP

(b) (4)

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**Appendix 2. Drug Product Specification (Optional)**

**Table 2.3.P.5.1-1 Specifications for Insulin Lispro U-200, 3.0 mL Cartridges in KwikPen**

Test	Analytical Procedure	Acceptance Criteria
<b>Identification Test</b>		
HPLC Retention Time	USP	The retention time of the sample matches that of the reference standard.
<b>Potency Tests</b>		
HPLC Assay	USP	(b) (4)% of label claim <sup>1</sup> (b) (4) Units/mL
Metacresol	B03996	(b) (4)% of label claim <sup>2</sup>
<b>Purity Tests</b>		
High Molecular Weight Proteins	USP	NMT (b) %
(b) (4)	USP	NMT (b) %
Other Related Substances (Including High Molecular Weight Proteins)	USP	NMT (b) %
<b>Other Tests</b>		
Zinc	USP	NLT (b) mcg/100 Units and NMT (b) mcg/100 Units (equivalent to (b) (4) mcg/mL)
pH	USP <791>	7.0-7.8
Physical Appearance <sup>3</sup>	Visual	Clear and colorless solution
Bacterial Endotoxins	USP <85>	Not more than (b) EU/100 USP Insulin Units
Particulate Matter	USP <788>	Meets USP requirements for small volume parenterals (USP <788>).
Sterility	USP <71>	Meets USP requirements for sterility tests (USP <71>).
Color	Ph.Eur. 2.2.2	Colorless
Clarity	Ph.Eur. 2.2.1	NMT (b) (4)

NMT = Not more than    NLT = Not less than

<sup>1</sup> (b) (4)

<sup>2</sup> (b) (4)

<sup>3</sup> "Physical Appearance" is equivalent to the ICH term "Description."

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### Appendix 3. Drug Substance Specification (Optional)

#### 3.2.S.4.1 Specification

Specifications and Analytical Methods for the Drug Substance

Description: White to off-white powder

Test	Analytical Procedure	Acceptance Criteria
<b>Identification Tests</b>		
HPLC Retention Time	USP	The retention time of the main peak conforms to that of the Reference Standard.
Fingerprint	USP	Conforms to Reference Standard
Bioidentity	USP	The sample exhibits a hypoglycemic response (NLT $\frac{(b)(4)}{(4)}$ U/mg) when tested by the USP (b)(4);
<b>Potency Test</b>		
HPLC Assay	USP	NLT $\frac{(b)(4)}{(4)}$ U/mg (b)(4)
		NLT $\frac{(b)(4)}{(4)}$ % and NMT $\frac{(b)(4)}{(4)}$ % or (b)(4);
<b>Purity Tests</b>		
Purity	USP	NLT $\frac{(b)(4)}{(4)}$ %
(b)(4)	USP	NMT $\frac{(b)(4)}{(4)}$ %
Other Related Substances (including high molecular weight proteins)	USP	NMT $\frac{(b)(4)}{(4)}$ % (b)(4);
		NMT $\frac{(b)(4)}{(4)}$ % (b)(4);
High Molecular Weight Proteins (HMWP)	USP	NMT $\frac{(b)(4)}{(4)}$ %

\*NLT = not less than; NMT = not more than

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Test	Analytical Procedure	Acceptance Criteria
Loss on Drying	USP	NMT (b) (%)
Immunoreactive <i>E. coli</i> (b) (4)	G1152 (ELISA)	NMT (b) (4) ppm
Bacterial Endotoxins	USP	LT (b) (4) EU/mg
Total Aerobic Microbial Count	USP	NMT (b) (4) cfu/gram
(b) (4)	B09912 (ELISA)	NMT (b) (4) ppm
(b) (4)	B10042 (GC)	NMT (b) (%)
Phenol	B09143 (HPLC)	NMT (b) (%)
<b>Other Tests</b>		
(b) (4)	B09997 (Atomic Absorption)	NMT (b) (4) ppm
Zinc	B09980 (Atomic Absorption)	NLT (b) (4) % and NMT (b) (4) % (b) (4)

\*NLT = not less than; NMT = not more than; LT = Less than

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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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SUONG T TRAN  
06/18/2013

DANAE D CHRISTODOULOU  
06/18/2013