CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205747Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	205747
Submission Date(s):	Class 2 Resubmission: November 26, 2014 Original: May 10, 2013;
Brand Name	Humalog
Generic Name	Insulin Lispro Injection (rDNA Origin)
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Eli Lilly and Company
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Insulin lispro TRIS U-200
Proposed Indication	Humalog (Insulin Lispro Injection) is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
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1 Executive Summary

Insulin Lispro Injection (rDNA Origin) is a rapid-acting human insulin analog indicated to improve glycemic control in patients with diabetes mellitus. Insulin Lispro Injection is marketed by the sponsor under the trade name, Humalog U-100 (100 units/mL), and is currently available in presentations of 10-mL (b) (4) vials, 3-mL cartridges, and 3-mL prefilled KwikPen. The sponsor developed a 200-units/mL (U-200) concentrated version of Humalog, and is seeking marketing approval. The current NDA application is supported by a single study evaluating the bioequivalence of insulin lispro TRIS U-200 formulation (test) relative to that of the marketed insulin lispro phosphate U-100 (reference) after subcutaneous (SC) administration of 20 units (U) to healthy subjects.

Throughout the document, insulin lispro TRIS U-200 formulation (test) is referred to as U-200, and insulin lispro phosphate U-100 (reference) is referred to as U-100.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCPII) has reviewed the clinical pharmacology data submitted under NDA 205747 and finds it acceptable to support the approval.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The pharmacokinetic (PK) and pharmacodynamic (PD) comparability of U-200 formulation relative to that of U-100 was adequately demonstrated by the PK/PD study (IOQM) results. The data showed that PK and PD (time-action) profile of U-200 is comparable to that of U-100 upon single subcutaneous administration at 20 U dose level.

Mean PK and PD profile by treatment is presented in Figure 1 below.

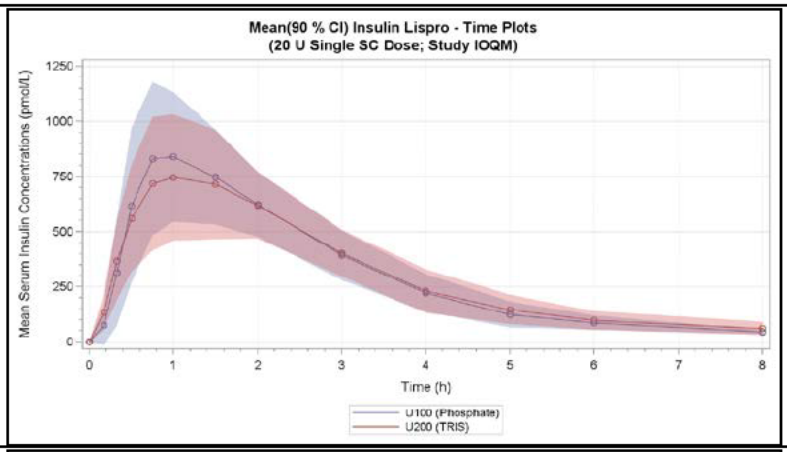
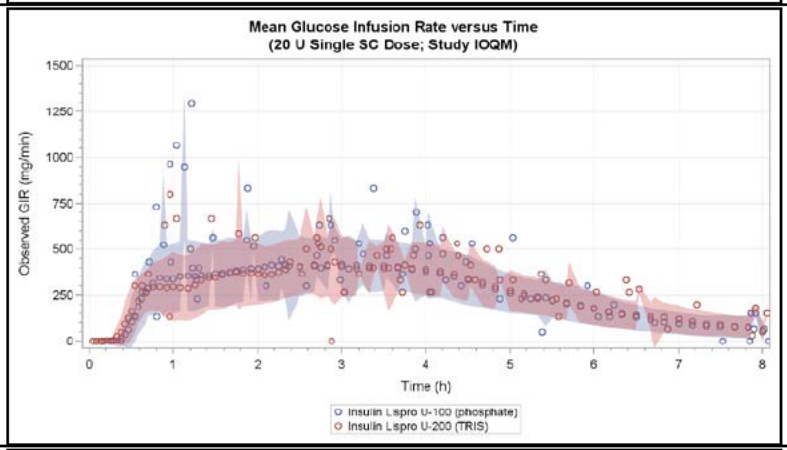
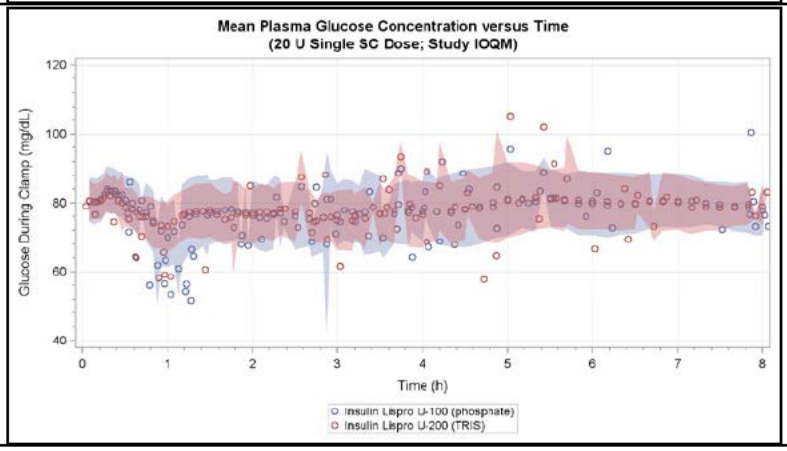
Insulin	
GIR	
Glucose	

Figure 1 **Mean serum insulin lispro, glucose infusion rate (GIR) and plasma glucose-time profiles from single SC dose of U-100 or U-200 (IOQM)**

The results from study IOQM show that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25. In addition, there was no difference in median difference in time to peak plasma insulin concentration (T_{max}) between the two treatments (median T_{max} = 1.0 hour for both treatments; 95% CI: - 0.25, 0.00) [p-value=0.06]. In addition, median difference (95% CI) [p-value] for T_{max} showed no difference between the two treatments 0.00 (-0.25, 0.00) [0.06]. The $T_{GIR,max}$ when compared using the Wilcoxon two sample revealed no statistically significant differences ($p<0.001$).

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1 What is the relevance and importance of the clinical pharmacology data in establishing the comparability of the PK and PD profile of two formulations of insulin in the context of the current submission?

The importance of information generated in the PK and PD experiments in the context of the current study rests on two concepts:

1. *Comparability of Per Unit Dose-Response:*
   In euglycemic clamp studies, glucose lowering effect is typically measured as the glucose utilization per unit insulin dose and presented as GIRAUC. The comparable overall glycemic effect (GIRAUC) between two treatments ensures the comparability of the pharmacodynamic response per unit dose of insulin.

2. *Time-action profile drives method of clinical use for insulin products:*
   The PK and PD profiles (time to onset, peak action, and duration of action – collectively regarded as *time-action profile*) forms the fundamental principal in defining the safe and effective use of an insulin product. In general, for a meal-time insulin the time of administration with respect to meal is determined such that the time to peak insulin action approximately matches with the time of post-prandial glucose excursion. Comparable time-action profile of insulin lispro delivered from U-200 and U-100 would confer same clinical use instructions for the two formulations.

In context of the current NDA submission, the test product, Humalog KwikPen™ 200 U/mL device is a mechanical, prefilled pen injector that delivers a subcutaneous injection of insulin lispro using standard 3 mL (b) (4) cartridges. The KwikPen device has been on the market since 2008. The Humalog KwikPen 200 U/mL mechanism has been modified by the sponsor (b) (4) This mechanical modification allows the patient to have the same user interface with the device as the Humalog KwikPen 100 U/mL, meaning that each click of the pen dial delivers 1 insulin unit.

2.1.2 What is the Regulatory History for the Humalog U-200 product?

The sponsor had originally submitted a supplement to NDA 020563 on 15 March 2013 proposing the addition of a new insulin lispro, 200 U/mL (U-200), formulation in a KwikPen prefilled device to the approved labeling of Humalog U-100. The user fee staff and the division at the Agency determined that an NDA (505(b)(1) application) would be required. The sponsor submitted NDA 205747 for insulin lispro U-200 on 10 May 2013. The U-200 clinical development program focused on a single PK/PD comparability study.

The study data showed comparable PK and PD profiles for U-200 and U-100, however, the sponsor had failed to retain clinical samples at the study site as per the requirement of 21 CFR Part 320.38. The Agency had identified additional issues with the device. The sponsor was issued a complete response (CR) letter for NDA 205747 on 10 March 2014.

The sponsor held a Type A meeting with the Agency on 7 May 2014, and agreed to submit a new BE study, additional biocompatibility data, and additional human factors validation testing to test the

proposed risk minimization activities by a knowledge based assessment and to test visual dialing of the dose by a knowledge based and performance assessment.

2.1.3 What are the important design features of the clinical pharmacology studies and the analyses used to support the current application?

The clinical pharmacology program performed to evaluate the comparability of the PK/PD (time-action) profile of Humalog U-200 in reference to Humalog U-100 included a single Phase 1 PK/PD trial conducted in healthy volunteers (Table 1).

The study had the following basic design factors:

- The study was conducted in a replicate cross-over fashion in healthy subjects at 20U/kg doses of test and reference treatments.
- The clamp duration was 8 hours.
- While PK sampling was discrete with samples at -30 min, 0 min (pre-dose), 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 360 and 480 min post-dose, the PD measurements (GIR) were performed every minute. Plasma glucose was assessed at -30, -20, -10, 0 min; followed by every 5 to 30 minute intervals up to 8 hours relative to dosing with an option to sample as frequently as every 2.5 minutes)
- A locally weighted scatterplot smoothing (LOESS) function was applied to all individual GIR versus time profiles in each treatment group. The fitted data for each subject were used to calculate the primary PD parameters, peak GIR effect (R_{max} or GIR_{max}) and total GIR effect (Gtot or AUCGIR0-t, t=8 h).
- Pre-defined criteria to conclude PK and PD similarity was less than ±20% difference is PK and PD parameters between test and reference products, which was to be concluded if the least-square (LS) geometric mean ratios and 90% confidence intervals (CI) for comparison of test and reference parameters fall within the pre-specified range of 0.80 to 1.25, inclusive. These ratios were evaluated for PK parameters (peak plasma concentration (C_{max}), area under the curve ($AUC_{0\text{-}8h}$) for baseline adjusted insulin concentrations) and PD parameters [GIR_{max} (or R_{max}), $AUC_{GIR,0\text{-}8h}$ (or G_{tot})].

Table 1: Overview of study with pharmacokinetic assessments relevant to the clinical pharmacology of Humalog U-200

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase I Relative Bioavailability (F3Z-EW-IOQM)					
To demonstrate the bioequivalence of PK parameters (area under the concentration versus time curve [AUC] from time zero to t_{last} where t_{last} is the last time point with a measurable concentration [AUC(0-t_{last})], AUC from time zero to infinity [AUC(0-∞)], and maximum observed serum concentration [C_{max}]) for the insulin lispro TRIS U-200 formulation relative to that of insulin lispro phosphate U-100 after SC administration of 20 U to healthy subjects.	Single-center, investigator- and subject-blind, 2-sequence, 4-period, randomized, crossover, 8-hour euglycemic clamp study	• Test : insulin lispro TRIS U-200 formulation (test [T] on 2 occasions) • Reference: insulin lispro phosphate U-100 formulation (reference [R] on 2 occasions). Subjects were admitted to the CRU on the evening prior to each dosing day and fasted for approximately 8 hours prior to each dose. Following dose administration, each subject underwent an approximately 8-hour euglycemic clamp procedure and remained in the CRU for the duration of the clamp period.	38 healthy subjects (35 male and 3 female)	Healthy M or F, age 21-50 years, with a BMI of 18.5 to 29.9 kg/m^2, inclusive	Treatments A, B, C and D: single-dose The treatments were replicated such that each formulation was administered twice on different occasions to healthy subjects over 4 study periods. Each period took approximately 10 hours. There was an interval of approximately 4 to 14 days between doses. A follow-up visit occurred 7 to 14 days after the last dose.

Overview of the euglycemic clamp method used for PK/ PD assessment of U-200 versus U-100

Insulin PK/PD studies are commonly conducted using the euglycemic (means "same glucose") clamp technique where, insulin is injected into subjects and glucose is infused to prevent the expected decrease in blood glucose concentration, thus ''clamping'' blood glucose to a predetermined basal level. The rate of glucose infusion and total amount of glucose infused approximates the rate of glucose disappearance and net PD effect (i.e., glucose-lowering effect) of the tested insulin (typically the resulting sum of the suppression of hepatic glucose production and the stimulation in glucose utilization)[1].

The study schematic including the euglycemic clamp procedure used by the sponsor for evaluating PK and PD of U-200 relative to U-100 in healthy subjects is shown in Figure 2 below:

[1] Pharmacokinetics and Pharmacodynamics of Basal Insulins. Francesca Porcellati, M.D., Ph.D., Geremia B. Bolli, M.D., and Carmine G. Fanelli,. Diabetes Technology & Therapeutics Volume 13, Supplement 1, 2011.

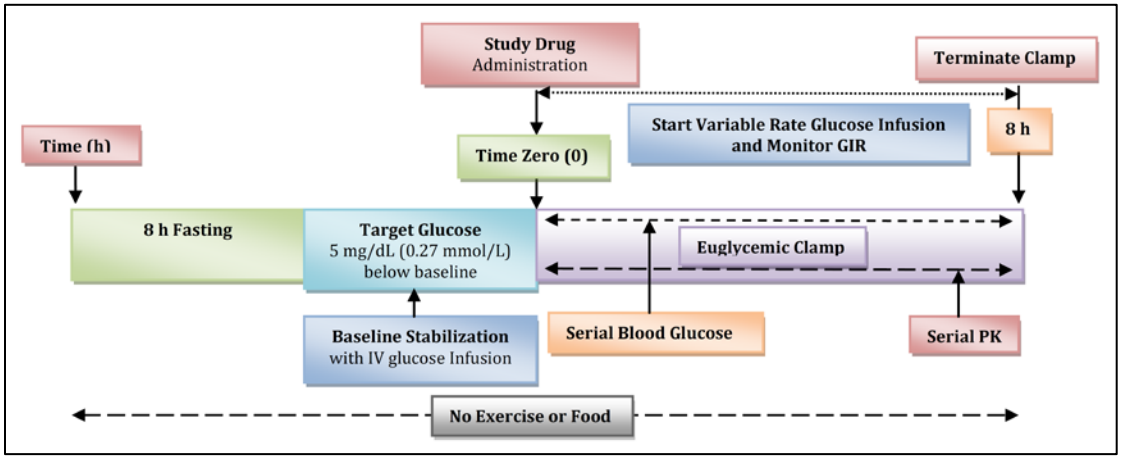


Figure 2 **Schematic of euglycemic clamp study for PK and PD evaluation to characterize insulin time-action profile in healthy subjects (Study IOQM)**

In the current PK/PD study (IOQM) in healthy volunteers, the clamp procedures were performed using a manual technique, wherein, the GIR was manually adjusted based upon blood glucose measurements taken at regular intervals. The clamp procedure was performed the morning after an overnight fast of approximately 8 hours. On the morning of the study, a small catheter was placed into a forearm vein, for infusion of glucose. Another catheter was placed at the wrist or hand, or in the case of difficult venous access, in the forearm as close to the wrist as possible, for blood sampling. The time of insulin dosing was defined as time zero, and the study insulin was administered by SC injection into the abdominal wall by trained site personnel at approximately the same time of day in each treatment period. Following dosing, glucose was infused intravenously at a variable rate to maintain or 'clamp' blood glucose concentrations within each subjects' glucose target. For individual subjects, a mean pre-dose fasting blood glucose (FBG) value was calculated from up to 3 pre-dose blood glucose measurements, and the subject's blood glucose target was defined as 5 mg/dL (0.27 mmol/L) below this mean pre-dose FBG value. Blood samples were obtained at the bedside for immediate determination of whole blood glucose concentrations using an automated glucose oxidase technique or other appropriate analytical method. Throughout the 8-hour clamp procedure, the GIR required to maintain euglycemia and blood glucose concentrations were documented, and samples were collected for pharmacokinetic (PK) analysis. The GIRs required to maintain target glucose levels and blood glucose concentrations were documented throughout the procedure. Any missed glucose samples or deviations of more than 5 minutes from scheduled glucose sampling time points were noted. At the end of the clamp, the subjects were fed and medically assessed before discharged from the clinic.

2.1.4 What is the composition of to-be-marketed formulation of Humalog U-200?

The composition for Humalog U-200 and U-100 formulations are shown in Table 2.

Table 2 Composition of Humalog U-200 and U-100 Formulations

Ingredient	Proposed Commercial 200 U/mL Quantity/mL	Commercial Humalog 100 U/mL Quantity/mL	Function
Insulin Lispro	200 Units	100 Units	Active ingredient
Tris (Hydroxymethyl aminomethane) (TRIS)	5 mg	--	(b) (4)
Dibasic Sodium Phosphate	--	1.88 mg	
Zinc Oxide	q.s. to give a Zn^{++} content of (b) (4) mg/100 Units	q.s. to give a Zn^{++} content of 0.0197 mg/100 Units	
Metacresol	3.15 mg	3.15 mg	
Glycerin	16 mg	16 mg	
Water	(b) (4		
Hydrochloric Acid	q.s.	q.s.	pH adjustment[a]
Sodium Hydroxide			

Abbreviations: q.s. = quantum sufficient (as much as is sufficient); Zn = zinc.
[a] adjustment to pH 7.0 - 7.8.

(Source Humalog U-200 NDA eCTD module 2.7.1; Summary of Biopharmaceutic Studies and Associated Analytical Methods, , Table 2.7.1.1, page 7)

2.1.5 What are the proposed dosages and routes of administration?

The sponsor has proposed the following dosing recommendation for Humalog U-200:

"Humalog U-200 is for subcutaneous injection use only.

Administer Humalog U-100 or Humalog U-200 within 15 minutes before a meal or immediately after a meal. Use in a regimen with an intermediate- or long-acting insulin. (b) (4)

2.1.6 Was an OSIS (Office of Study Integrity and Surveillance) inspection requested for the clinical study?

An inspection request was sent to the Office of Study Integrity and Surveillance (OSIS) to audit the clinical and bioanalytical sites. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance recommended accepting data without an on-site inspection. The rationale for this decision was that OSI inspected the clinical and bioanalytical sites within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI). (see communication dated 02 February 2015 (Document Reference ID 3696108 and 3696034) and 26 March 2015 (Document Reference ID 3721816) from Shila S Nkah in DARRTS.

2.2 General Clinical Pharmacology

2.2.1 What is known about the PK characteristics of the approved drug, Humalog U-100?

The pharmacokinetics and pharmacodynamics of insulin from Humalog U-100 as described in the product monograph for Humalog Kwikpen (*http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020563s124lbl.pdf*) is shown in the highlighted box below:

Pharmacodynamics

Humalog has been shown to be equipotent to human insulin on a molar basis. One unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin. Studies in normal volunteers and patients with diabetes demonstrated that Humalog has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

The time course of action of insulin and insulin analogs, such as Humalog, may vary considerably in different individuals or within the same individual. The parameters of Humalog activity (time of onset, peak time, and duration) as designated in Figure 1 should be considered only as general guidelines. The rate of insulin absorption, and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables.

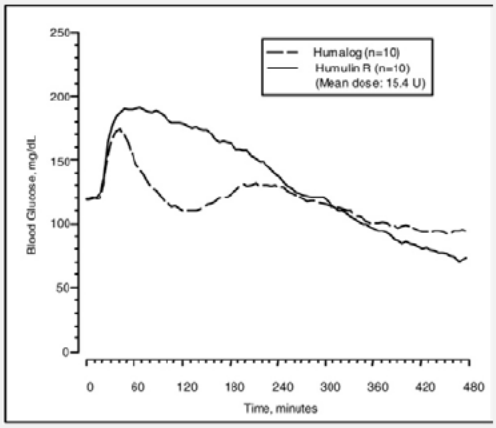


Figure 1: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a]

[a]Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Pharmacokinetics

Absorption and Bioavailability — Studies in healthy volunteers and patients with diabetes demonstrated that Humalog is absorbed more quickly than regular human insulin. In healthy volunteers given subcutaneous doses of Humalog ranging from 0.1 to 0.4 unit/kg, peak serum levels were seen 30 to 90 minutes after dosing. When healthy volunteers received equivalent doses of regular human insulin, peak insulin levels occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes (see Figure 2).

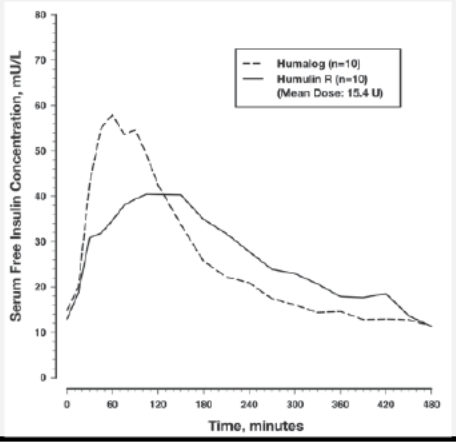


Figure 2: Serum Humalog and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or Humalog (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a]

[a]Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Humalog was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 unit/kg at abdominal, deltoid, or femoral subcutaneous sites. After Humalog was administered in the abdomen, serum drug levels were higher and the duration of action was slightly shorter than after deltoid or thigh administration. Bioavailability of Humalog is similar to that of regular human insulin. The absolute bioavailability after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

Distribution — When administered intravenously as bolus injections of 0.1 and 0.2 U/kg dose in two separate groups of healthy subjects, the mean volume of distribution of Humalog appeared to decrease with increase in dose (1.55 and 0.72 L/kg, respectively) in contrast to that of regular human insulin for which, the volume of distribution was comparable across the two dose groups (1.37 and 1.12 L/kg for 0.1 and 0.2 U/kg dose, respectively). Metabolism — Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of Humalog is identical to that of regular human insulin.

Elimination — After subcutaneous administration of Humalog, the $t_{1/2}$ is shorter than that of regular human insulin (1 versus 1.5 hours, respectively). When administered intravenously, Humalog and regular human insulin demonstrated similar dose-dependent clearance, with a mean clearance of 21.0 mL/min/kg and 21.4 mL/min/kg, respectively (0.1 unit/kg dose), and 9.6 mL/min/kg and 9.4 mL/min/kg, respectively (0.2 unit/kg dose). Accordingly, Humalog demonstrated a mean $t_{1/2}$ of 0.85 hours (51 minutes) and 0.92 hours (55 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses, and regular human insulin mean $t_{1/2}$ was 0.79 hours (47 minutes) and 1.28 hours (77 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses.

2.2.2 Does the PK and PD data from the clinical pharmacology study support the comparability claim for the to-be-marketed formulation of insulin lispro U-200 in reference to the marketed insulin lispro U-100?

Yes, the evidence presented by the PK/PD study IOQM supports that PK and PD profile of U-200 is comparable to U-100.

Mean serum insulin concentration-time plot, mean glucose infusion rate versus time plot, and mean plasma glucose versus time plot are presented in Figure 3, 4 and 5, respectively. The serum insulin concentrations, mean glucose infusion rates, and mean plasma glucose levels for the two treatments were similar.

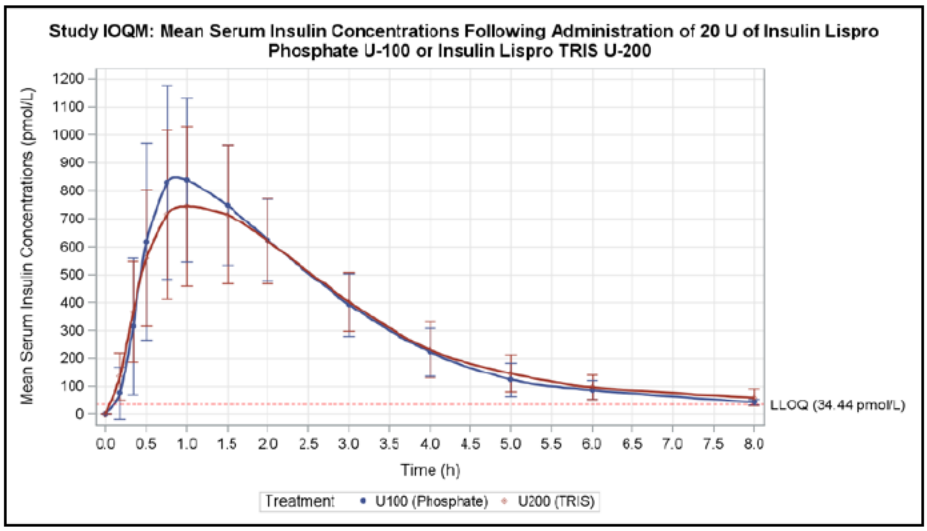


Figure 3: Mean serum insulin versus time following subcutaneous administration of U-200 and U-100 (Full Dataset)

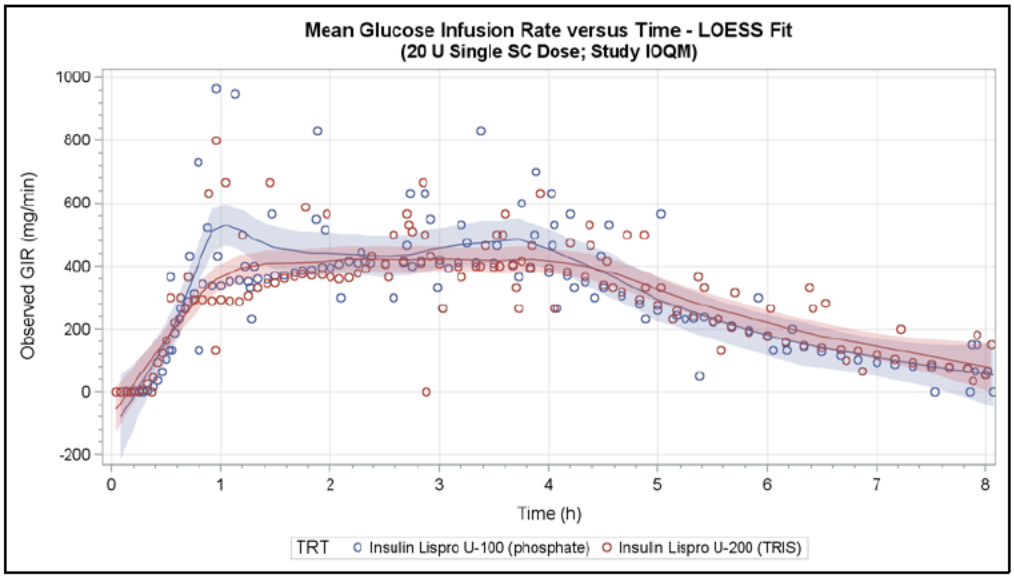


Figure 4: Mean glucose infusion rate versus time following subcutaneous administration of U-200 and U-100 (Full Dataset)

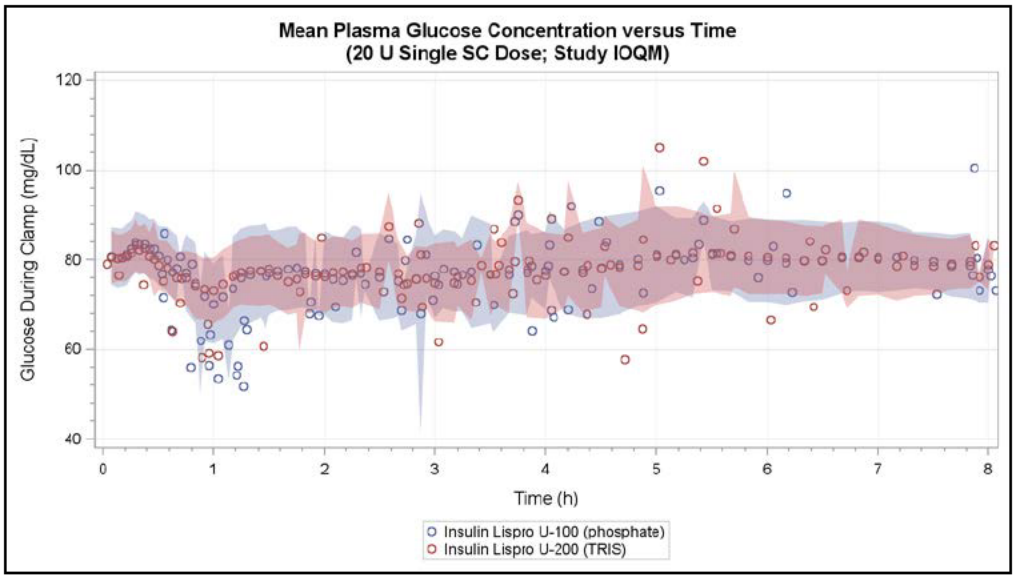


Figure 5: Mean plasma glucose concentration versus time following subcutaneous administration of U-200 and U-100 (Full Dataset)

Summary statistics of insulin PK and PD parameters is presented in Table 3 below.

Table 3 Summary statistics for primary PK and PD parameters (Full Data)

Type	Parameter	U-200 (Test)	U-100 (Reference)
PK	C_{max} (pmol/L)	794.5 ± 290.5	908.8 ± 340.9
	AUC_{0-t} (pmol·h/L)	2263 ± 395	2303 ± 408
	T_{max}* (h)	1.0 (0.5 – 3.0)	1.0 (0.5 – 2.0)
PD	GIR_{max} (mg/min)#	516.6 ± 1.41	558.8 ± 1.40
	$GIRAUC_{0-t}$ (mg)#	119426 ± 1.35	122671 ± 1.36
	$T_{GIR,max}$* (min)	154 (29 – 372)	121 (29 – 282)

*Median (Range); #Reported as R_{max} and G_{tot}, respectively in the sponsor's reports

The results of the statistical analysis for the pre-specified PK and PD metrics are presented in Table 4 below.

Table 4Statistical analysis results for primary PK and PD parameters (Full Data)

Type	Parameter	GMR (90% CI)*
PK	C_{max} (pmol/L)	0.87 (0.83 – 0.92)
	AUC_{0-t} (pmol·h/L)	0.99 (0.96 – 1.01)
PD	GIR_{max} (mg/min)	0.95 (0.90 – 1.00)
	$GIRAUC_{0-t}$ (mg)	0.98 (0.94 – 1.02)

The results show that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25. In addition, median difference (95% CI) [p-value] for T_{max} showed no difference between the two treatments 0.00 (-0.25, 0.00) [0.06] using Hodges-Lehmann method. The $T_{GIR,max}$ when compared using the Wilcoxon two sample (Proc NPAR1WAY in SAS platform) revealed no statistically significant differences ($p<0.001$). Note that since GIR was continuously assessed (every minute), $T_{GIR,max}$ assessment is not prone to the ascertainment bias introduced by the usual method of discrete sampling times.
However, a close examination of the GIR profiles at the individual subject level revealed that in several subjects glucose had escaped the clamp (see Figure 6).

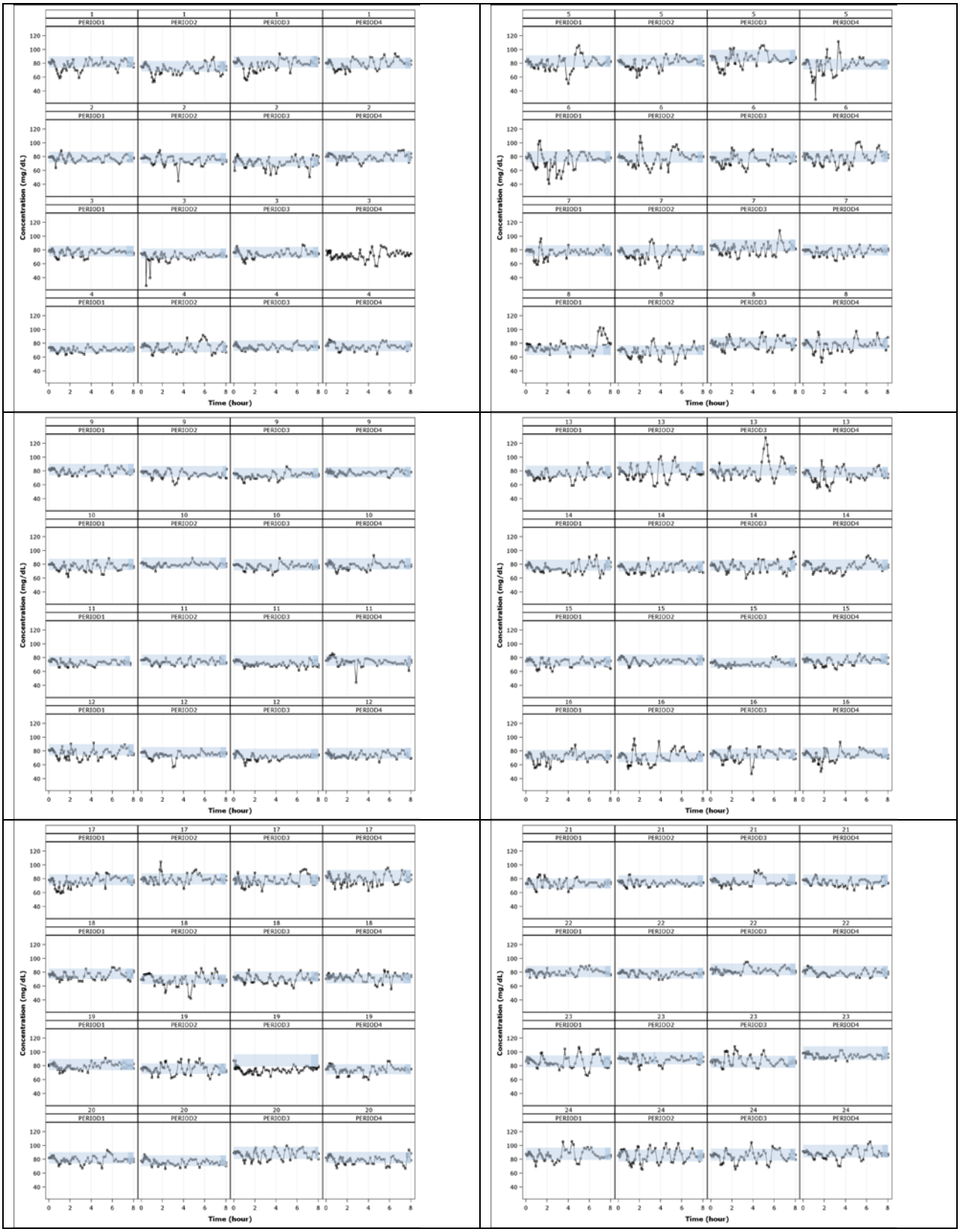


Figure 6 Glucose Concentration versus Time in each period for each subject – Study IOQM

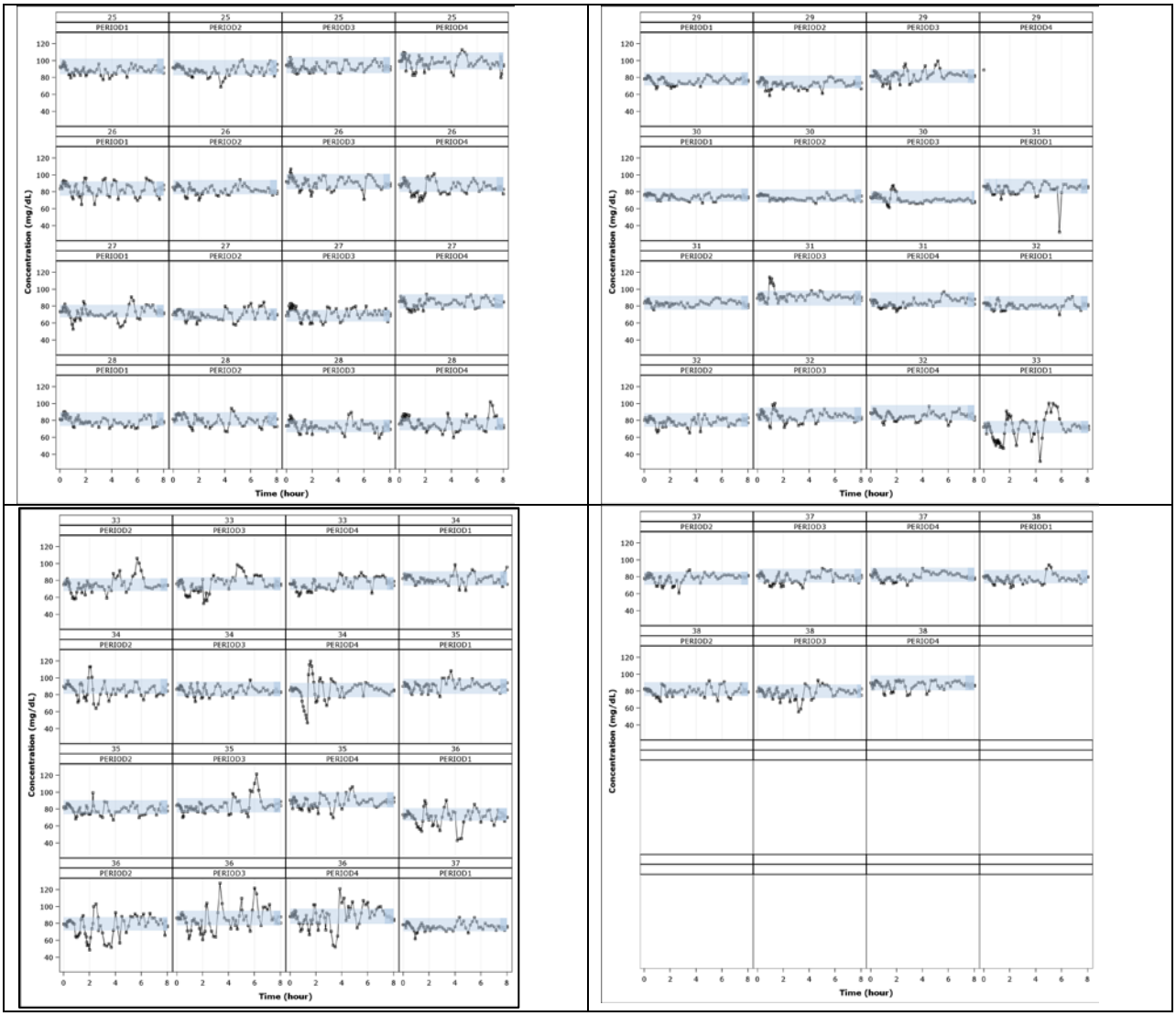


Figure 6 (cont.) **Glucose Concentration *versus* Time in each period for each subject – Study IOQM**

The sponsor was contacted for clarification on the study procedures with the following questions (Agency's questions in **bold** and sponsor's response in *italics*):

(a) 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 ±5% or ±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?

The sponsor's response was as follows:

There were no pre-specified tolerance limits for Study IOQM as this type of a limit would be highly unusual for a euglycemic glucose clamp procedure. The European Medicines Agency (EMA) guidance suggests that calculating mean values, root mean square deviation, and coefficient of variation of the blood glucose concentrations would provide an estimate of overall quality of clamp performance (EMA 2015). There is no absolute limit stated for an acceptable variability, but rather, the EMA guidance suggests that the

results should be discussed and compared to reported literature values when available. The Sponsor is not aware of published data on euglycemic clamps for rapid acting insulin.

The Lilly clamp technique used in Study IOQM is standardized as much as possible, and Study IOQM was double blinded, to minimize any operator-related variability or bias. In Study IOQM, the operators were trained to maintain the blood glucose level as close to the target level as possible. Generally, they adjusted the glucose infusion rate (GIR) using ranges defined in an algorithm as a guideline. The algorithm states that a subject with a blood glucose measurement below the glucose target should have an intravenous glucose infusion commenced. Thereafter, if the blood glucose is within ± 2 mg/dL from the target, the algorithm suggests no adjustment to the GIR. For absolute deviations of blood glucose between 2 to 5 mg/dL from target, the algorithm suggests an adjustment of the GIR of between 10 to 20 mL/hour, and deviations greater than 5 mg/dL from target, result in larger adjustments. All clamp operators are trained to reference the algorithm, but ultimately have discretion over individual GIR changes for protection of the subject's safety and adherence to the target blood glucose concentration.

Important factors to be considered by the clamp operator include the time delay inherent in measuring a glucose sample (approximately 2 minutes for the method at Lilly_NUS Centre for Clinical Pharmacology), the rate of change of the glucose from the last reading, the absorption phase of the insulin (early, peak/plateau, or late) and a subject's response to previous GIR adjustments which may indicate that subject's insulin sensitivity.

(b) 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.

The sponsor asked the Agency for clarification:

Would FDA please provide clarification on specifically which subjects, whose glucose values did not stay on the clamp target, that FDA is asking rationale and justification for? We are asking because for the clamp technique, blood glucose values usually do not correspond to the exact target value but vary around the target. An inherent variation in the GIR is expected due to measurement delay between sampling and resetting the glucose infusion and the subsequent delay of change in blood glucose levels in response to GIR changes. As there is some variation from target glucose values at any given timepoint for all subjects, we are unclear if there are specific subject data that FDA is referring to.

The Agency had the following response:

Section 10.2.3 Glucodynamic Evaluations (Glucose Clamp Procedure) 4th paragraph of protocol F3Z-EWIOQM(a) states "The target value for blood glucose concentrations is defined as 5 mg/dL (0.27 mmol/L) below the mean of at least 3 predose FBG concentrations measured on the day of the glucose clamp. The GIRs required to maintain target glucose levels and blood glucose concentrations will be documented throughout the procedure. Any missed glucose samples or deviations of more than 5 minutes from scheduled glucose sampling time points will be noted."

We evaluated the data assuming a conservative range of ±10% variation around the mean baseline FBG concentrations. Typical mean FBG baseline was approximately 80 mg/dL for the population, therefore our allowance was around 8 mg/dL above and below the mean baseline FBG concentrations, greater than the limit specified in the protocol. Based on this criterion, it appears that for a number of subjects, plasma glucose did not seem to stay within ±10% of clamp target. A listing of subjects in whom, plasma glucose did not seem to stay within ±10% of clamp target shown below in Table 1. Representative plot of glucose versus time for select subjects from this list are shown below in Figure 1. In the figure the blue band represents ±10% of clamp target.

Table 1: Subject and Period numbers where plasma glucose did not seem to stay within ±10% of clamp target

Subject	Period
2	2
3	2
5	1
5	4
6	1
6	2
8	1
12	1
13	2
13	3
13	4
16	1
16	2
23	1
31	1
31	3
33	1
34	4
35	3
36	1
36	2
36	3
36	4

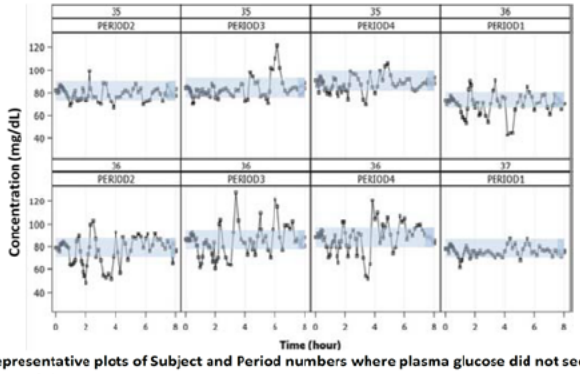


Figure 1: Representative plots of Subject and Period numbers where plasma glucose did not seem to stay within ±10% of clamp target

The sponsor response to the clarification was as follows:

Multiple factors may contribute to variability of the clamp and the clamp data. Variation of a subject's blood glucose above and below the target is expected during a euglycaemic clamp procedure due to a subject's physiological responses and the inherent variability related to the clamp methodology; glucose measurements are not continuous but performed at time intervals, there is a delay between sampling and resetting the GIR, and there is a delay between the GIR adjustment and the subsequent blood glucose change. This can be more apparent in a euglycaemic clamp with a rapid acting insulin, where fluctuations in blood glucose may be greater and thus GIR changes may need to occur more frequently than with a long acting insulin.

The coefficient of variation CV(%) is a universally accepted measure of variability, and hence the CV of the blood glucose by treatment can be used as a measure of the quality of the performance of the clamp study (EMA 2015). This analysis of clamp quality was performed for Study IOQM using the estimation of the mean intra-individual CV (%) of the glucose values by treatment. The average mean and average CV (%) for both treatments indicate acceptable variability (Table 4.1).

Additionally, the glucose concentration means and 90% confidence intervals (CI) for insulin lispro 100 U/mL and 200 U/mL overlap (Figure 4.1), which illustrates that inherent variability present in the clamp procedure affecting the glucose profiles is comparable between the 2 formulations.

Table 4.1. Overall Glucose Variability by Treatment for Study F3Z-EW-IOQM

Treatment	Average Mean (mg/dL)	Average CV (%)
Insulin Lispro Phosphate U-100	78.40	8.10
Insulin Lispro TRIS U-200	78.27	7.41

Abbreviation: CV= coefficient of variation
Program Loc.: /lillyce/prd/ly275585/f3z_ew_ioqm/programs_stat/lglu_cv.sas
Dataset Loc.: /lillyce/prd/ly275585/f3z_ew_ioqm/final/data/shared/sdtm
Output Loc.: /lillyce/prd/ly275585/f3z_ew_ioqm/programs_stat//tfl_output
Last Run: 17MAR15 17:40

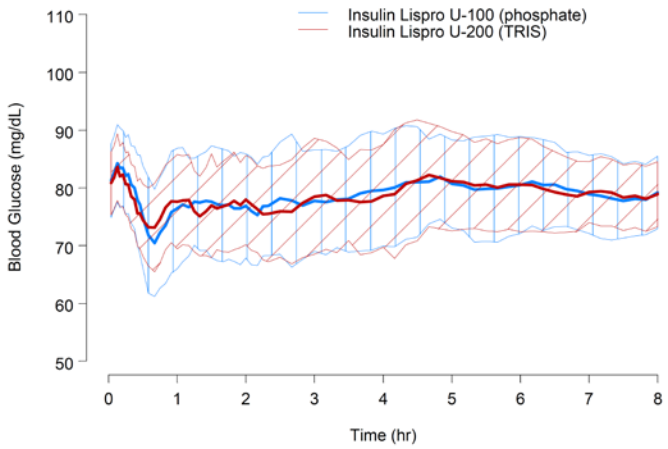


Figure 4.1. Mean (+/- standard deviation) glucose concentrations following a single subcutaneous administration of 20U of insulin lispro phosphate U-100 (blue) and insulin lispro TRIS U-200 (red).

It is also relevant to evaluate the quality of the individual GIR profiles including the corresponding blood glucose profiles. Variability data for each subject was examined and there was generally no bias between treatments (Appendix 1). Day- to-day variability is expected with individual data, and variability may increase due to physiological responses to the procedure. Test conditions are standardized as much as possible to reduce variability through the protocol instructions, for example, physical activity, fasting, food, alcohol, medication and smoking. Although the clamp technique can be standardized, there are other factors, such as study- or procedure-related stress, which may influence a subject's insulin sensitivity and can contribute to the variability.

Additionally, administration of insulin lispro 200 U/mL versus insulin lispro 100 U/mL resulted in comparable GIR versus time profiles, which was consistent with the pharmacokinetic (PK) observations. The comparability was further confirmed by the ratios of geometric means which were close to unity and their 90% CIs were contained within 0.8 -1.25 for both total amount of glucose infused (Gtot) and maximum glucose infusion rate (Rmax). Estimates of between and within-subject variability for key glucodynamic parameters were comparable between formulations as well.

The fluctuations noted by FDA were transitory in nature and unlikely to affect the overall pharmacodynamic (PD) conclusions. As described above, the variability of the glucose values from the target (CV%) are to be expected for a euglycemic clamp study with a rapid acting insulin and the GIR data are representative of the PD effect of the exogenous insulin. The overall average variabilities of the insulin lispro 100 U/mL and insulin lispro 200 U/mL treatments are comparable. Therefore, the PD similarity results are considered valid.

Review Team's Comments:

The euglycemic clamp based insulin PK/PD studies generally specify the target glucose (±10% or ±5%) for at least 30 min prior to dose and that post-treatment, glucose will be "kept constant" or "maintained at target level". While there does not seems to be a universally acceptable objective criteria to evaluate the quality of clamp, it does not preclude the need to judge the quality of clamp data for a given PK/PD study. The very fundamental objective of euglycemic clamp is to achieve and maintain constant glucose. To obtain precise estimation of the pharmacodynamic effect using the glucose infusion rate, the evidence of glucose being constant upon adjustment of GIR is highly desirable. Therefore, a sensitivity analysis of the PK/PD data was conducted (see section 2.2.3 below) after excluding subjects in whom the glucose over time data did not appropriately demonstrate the "constancy of glucose" – glucose values being outside ±10% from target for majority of clamp duration. It is also important to note that while mean (95% CI) glucose over time data, as presented by the sponsor, may be useful in comparison across two treatments in general; the evaluation of clamp integrity should ideally be performed at individual level in a prospective manner. While this assessment of clamp integrity was somewhat subjective and post-hoc in nature, regardless of the final outcome, this issue needs further research and discussion to design objective methods to test the clamp integrity and ensure the overall quality of PK/PD data from such studies.

2.2.3 How do the PK and PD profiles (duration of action) of U-200 and U-100 compare after performing a sensitivity analysis:

A sensitivity analysis was conducted by excluding subjects who showed clamp excursions from the overall dataset. PK and PD analysis of the reduced dataset did not change the outcome of the analysis of the full dataset, and showed that U-200 and U-100 are bioequivalent. The geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25. In addition, median difference (95% CI) [p-value] for T_{max} showed no difference between the two treatments 0.00 (-0.25, 0.00) [0.06] using Hodges-Lehmann method. The $T_{GIR,max}$ when compared using the Wilcoxon two sample (Proc NPAR1WAY in SAS platform) revealed no statistically significant differences ($p<0.001$) between U-200 and U-100.

Mean serum insulin concentration-time plot, mean glucose infusion rate versus time plot, and mean plasma glucose versus time plot following sensitivity analysis are presented in Figure 7, 8 and 9, respectively.

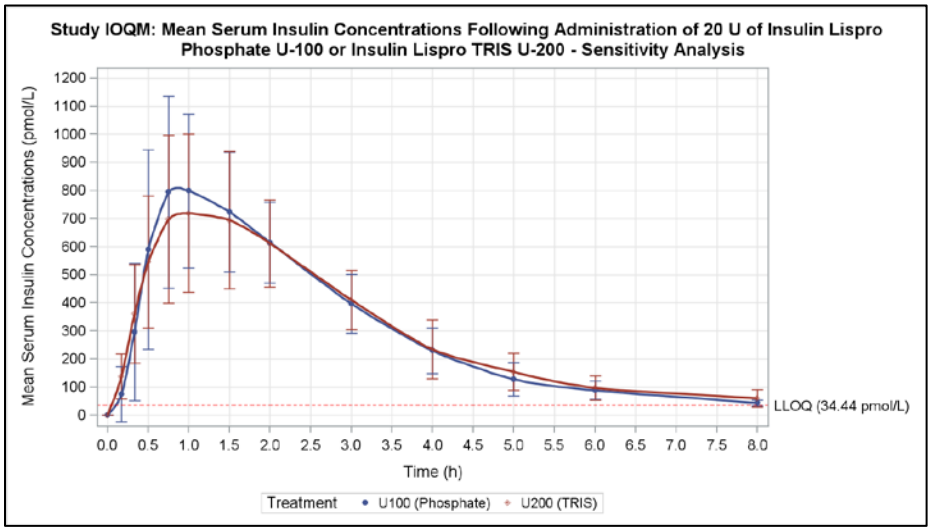


Figure 7: Mean serum insulin versus time following subcutaneous administration of U-200 and U-100 (Sensitivity Analysis)

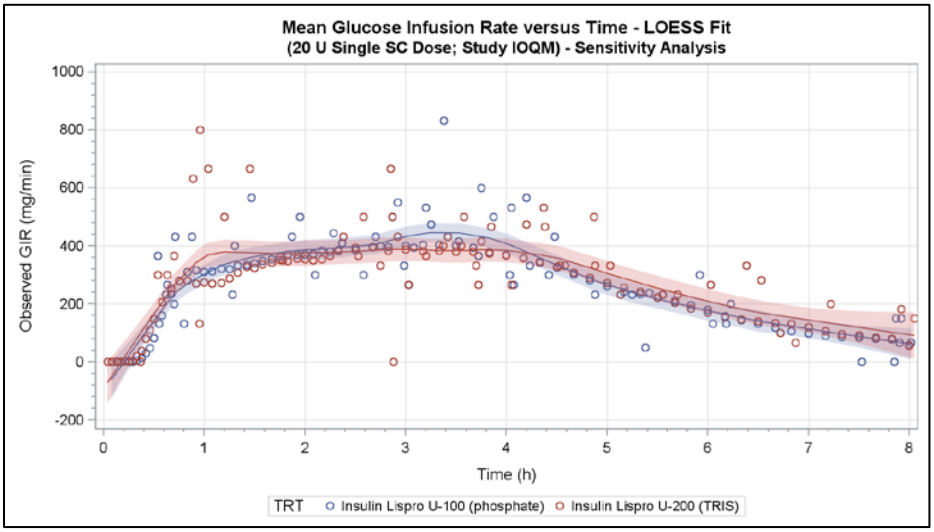


Figure 8: **Mean glucose infusion rate versus time following subcutaneous administration of U-200 and U-100 (Sensitivity Analysis)**

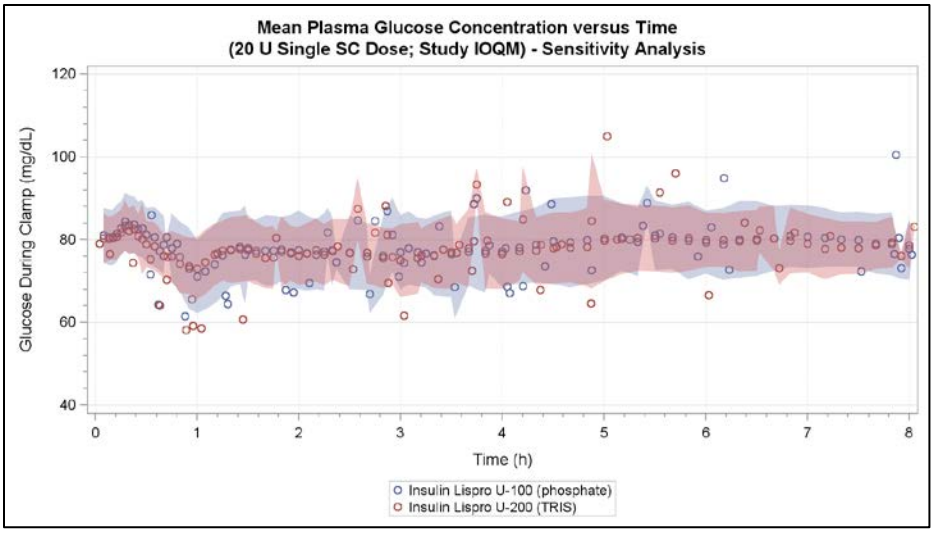


Figure 9: **Mean plasma glucose concentration versus time following subcutaneous administration of U-200 and U-100 (Sensitivity Analysis)**

Summary statistics of insulin PK and PD parameters following sensitivity analysis is presented in Table 5 below.

Table 5Summary statistics for primary PK and PD parameters following sensitivity analysis

Type	Parameter	U-200 (Test)	U-100 (Reference)
PK	C_{max} (pmol/L)	770.8 ± 287.2	873.8 ± 334.9
	AUC_{0-t} (pmol·h/L)	2260 ± 396	2273 ± 397
	T_{max}* (h)	1.0 (0.5 – 3.0)	1.0 (0.5 – 2.0)
PD	GIR_{max} (mg/min)#	498.3 ± 1.39	519.3 ± 1.3
	$GIRAUC_{0-t}$ (mg)#	115862 ± 1.35	118020 ± 1.35
	$T_{GIR,max}$* (min)	152 (29 – 372)	127 (29 – 282)

*Median (Range); #Reported as R_{max} and G_{tot}, respectively in the sponsor's reports

The results of the statistical analysis of the reduced dataset for the pre-specified PK and PD metrics are presented in Table 6 below.

Table 6Statistical analysis results for primary PK and PD parameters following sensitivity analysis

Type	Parameter	GMR (90% CI)*
PK	C_{max} (pmol/L)	0.87 (0.82 – 0.93)
	AUC_{0-t} (pmol·h/L)	0.99 (0.96 – 1.01)
PD	GIR_{max} (mg/min)	0.97 (0.92 – 1.03)
	$GIRAUC_{0-t}$ (mg)	0.99 (0.94 – 1.06)

Overall Conclusions:

- The sensitivity analysis confirms that the pre-defined criteria of geometric mean ratios and 90% CI to fall within 0.8 to 1.25 were met for both C_{max} and AUC_{0-8h}.
- The PK profile of U-200 is comparable to that of U-100.
- In addition, time of peak insulin concentration (T_{max}) was also comparable between U-200 and U-100.
- The PD profile of U-200 is comparable to U-100 with regards to GIR_{max} and $GIRAUC_{0-8h}$ (computed from loess smoothed data). The pre-defined criteria of geometric mean ratios and 90% CI to fall within 0.8 to 1.25 were met for both PD parameters.
- Time of peak insulin action $T_{GIR,max}$ was also comparable between U-200 and U-100.

2.2.4 Were the active moieties in the plasma/serum appropriately identified and measured to assess the pharmacokinetics?

Yes. Serum insulin and plasma glucose were appropriately identified and measured to assess the PK/PD parameters. Glucose infusion rate was recorded as specified in the manual euglycemic clamp procedure.

2.2.5 Were the single dose tolerability profiles between U-200 and U-100 comparable?

Both U-200 and U-100 were well tolerated following single SC doses in healthy subjects, with no apparent differences between formulations. A total of 97 treatment emergent adverse events (TEAEs) (all causalities) were reported following treatment with U-200 and U-100 (Table 7). The most common TEAEs were procedural reactions at catheter-, infusion-, injection-, and vessel puncture-sites, and none of these events were considered related to study treatment.

Of the 97 TEAEs, 59 events occurred in 25 subjects administered U-200 and 38 events occurred in 21 subjects administered U-100. Five subjects who received one or more doses of study drug reported 7

events that were mild in severity and related to study drug as judged by the investigator. The majority of TEAEs reported during the study were mild in intensity. There were no clinically significant alterations in laboratory, urinalysis, or vital sign values.

Table 7Frequency of Subjects with Treatment-Emergent Adverse Events (All Causalities) for Study F3Z-EW-IOQM

System Organ Class MedDRA Preferred Term	Number of Adverse Events* [Number of Subjects with Adverse Event] (Percentage of Subjects with Adverse Event) 20 U Insulin lispro TRIS U-200 (N=38)	20 U Insulin lispro phosphate U-100 (N=38)	All (N=38)
General disorders and administration site conditions			
Catheter site related reaction	9 [7] (18.4%)	5 [5] (13.2%)	14 [9] (23.7%)
Infusion site swelling	5 [5] (13.2%)	5 [4] (10.5%)	10 [8] (21.1%)
Infusion site pain	5 [5] (13.2%)	4 [4] (10.5%)	9 [8] (21.1%)
Application site erythema	3 [2] (5.3%)	2 [1] (2.6%)	5 [3] (7.9%)
Infusion site bruising	3 [3] (7.9%)	1 [1] (2.6%)	4 [4] (10.5%)
Injection site bruising	3 [3] (7.9%)	1 [1] (2.6%)	4 [4] (10.5%)
Pyrexia	2 [2] (5.3%)	1 [1] (2.6%)	3 [3] (7.9%)
Vessel puncture site bruise	1 [1] (2.6%)	2 [2] (5.3%)	3 [3] (7.9%)
Vessel puncture site pain	2 [2] (5.3%)	1 [1] (2.6%)	3 [3] (7.9%)
Infusion site rash	1 [1] (2.6%)	1 [1] (2.6%)	2 [2] (5.3%)
Vessel puncture site reaction	1 [1] (2.6%)	1 [1] (2.6%)	2 [2] (5.3%)
General disorders and administration site conditions			
Thirst	2 [1] (2.6%)		2 [1] (2.6%)
Catheter site pain		1 [1] (2.6%)	1 [1] (2.6%)
Infusion site discomfort		1 [1] (2.6%)	1 [1] (2.6%)
Infusion site erythema		1 [1] (2.6%)	1 [1] (2.6%)
Injection site erythema		1 [1] (2.6%)	1 [1] (2.6%)
Vessel puncture site anaesthesia	1 [1] (2.6%)		1 [1] (2.6%)
Vessel puncture site swelling	1 [1] (2.6%)		1 [1] (2.6%)
Total	39 [21] (55.3%)	28 [17] (44.7%)	67 [26] (68.4%)
Nervous system disorders			
Headache	2 [2] (5.3%)	1 [1] (2.6%)	3 [3] (7.9%)
Dysgeusia	2 [1] (2.6%)	1 [1] (2.6%)	3 [1] (2.6%)
Dizziness		1 [1] (2.6%)	1 [1] (2.6%)
Nervous system disorders			
Dizziness postural	1 [1] (2.6%)		1 [1] (2.6%)
Hypoaesthesia	1 [1] (2.6%)		1 [1] (2.6%)
Lethargy	1 [1] (2.6%)		1 [1] (2.6%)
Total	7 [4] (10.5%)	3 [3] (7.9%)	10 [6] (15.8%)
Injury, poisoning and procedural complications			
Scratch	2 [2] (5.3%)		2 [2] (5.3%)
Arthropod bite		1 [1] (2.6%)	1 [1] (2.6%)
Contusion		1 [1] (2.6%)	1 [1] (2.6%)
Wound	1 [1] (2.6%)		1 [1] (2.6%)
Total	3 [3] (7.9%)	2 [2] (5.3%)	5 [5] (13.2%)
Respiratory, thoracic and mediastinal disorders			
Cough	2 [2] (5.3%)		2 [2] (5.3%)
Oropharyngeal pain	1 [1] (2.6%)	1 [1] (2.6%)	2 [2] (5.3%)
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	1 [1] (2.6%)		1 [1] (2.6%)
Total	4 [3] (7.9%)	1 [1] (2.6%)	5 [4] (10.5%)
Gastrointestinal disorders			
Abdominal distension		1 [1] (2.6%)	1 [1] (2.6%)
Nausea		1 [1] (2.6%)	1 [1] (2.6%)
Total		2 [2] (5.3%)	2 [2] (5.3%)
Infections and infestations			
Upper respiratory tract infection	1 [1] (2.6%)	1 [1] (2.6%)	2 [2] (5.3%)
Total	1 [1] (2.6%)	1 [1] (2.6%)	2 [2] (5.3%)
Skin and subcutaneous tissue disorders			
Cold sweat	1 [1] (2.6%)		1 [1] (2.6%)
Erythema	1 [1] (2.6%)		1 [1] (2.6%)
Total	2 [2] (5.3%)		2 [2] (5.3%)
Investigations			
Heart rate increased		1 [1] (2.6%)	1 [1] (2.6%)
Total		1 [1] (2.6%)	1 [1] (2.6%)
Metabolism and nutrition disorders			
Food craving	1 [1] (2.6%)		1 [1] (2.6%)
Total	1 [1] (2.6%)		1 [1] (2.6%)
Musculoskeletal and connective tissue disorders			
Neck pain	1 [1] (2.6%)		1 [1] (2.6%)
Total	1 [1] (2.6%)		1 [1] (2.6%)
Psychiatric disorders			
Anxiety	1 [1] (2.6%)		1 [1] (2.6%)
Total	1 [1] (2.6%)		1 [1] (2.6%)
Overall Total	59 [25] (65.8%)	38 [21] (55.3%)	97 [32] (84.2%)

*Adverse events with a change in severity are only counted one time at the highest severity
MedDRA version 16.1
N = Number of subjects studied

2.3 Analytical

2.3.1 Is the analytical method for Serum Insulin appropriately validated?

Serum Insulin:

Free lispro insulin in human serum was measured using a RIA assay. The method was validated for a range of 0.100 to 30.000 ng/mL, based on the analysis of 0.150 mL of plasma. This radioimmunoassay (RIA) measures "free" lispro insulin (not bound to endogenous anti-insulin antibodies) in human serum. This RIA method is specific for lispro insulin, and does not cross-react with endogenous human insulin.

(b) (4)

Lispro insulin in study samples is then determined by interpolation from the standard curve. The sponsor stated that due to the small assay response at the 30 ng/mL quality control (QC), the upper limit of quantification (ULOQ) was truncated to the 15.0 ng/mL high validation QC. During validation, intra- and inter-assay precision and accuracy were within the pre-specified validation limits of 25% at the lower limit of quantification (LLOQ) and 20% at all other levels.

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in Table 8. Additional parameters captured during the validation of the assay are presented in Table 9

Table 8 Summary of key descriptive parameters for Insulin bioanalytical assay in serum used in clinical study

Study Number/Report Number	Study Title	Analytical Laboratory	Assay Range	LLOQ	Accuracy	Precision
Protocol F3Z-EWIOQM (Contract Lab Project # 8300-397)	Determination of Insulin Lispro (LY275585) in Human Serum by RIA in Support of Protocol F3Z-EW-IOQM	(b) (4)	Lispro Insulin0.200 to 15.000 ng/mL	Lispro Insulin0.200 ng/mL	Lispro Insulin96.6% - 102 2% at 0.200 – 30.000 ng/mL	Lispro Insulin2.6% - 7.0% at 0.100 – 15.000 ng/mL

Table 9 Bioanalytical method Validation for Serum Insulin

Analytical Validation Report 8215145 Location(s)	F3Z-EW-IOQM Clinical Study Report, Section 11.3.	
This analytical method was used in the following studies:	F3Z-EW-IOQM	
Short description of the method	Ligand Binding (RIA)	
Biological matrix	Human Serum	
Analyte Location of product certificate	Lispro Insulin (LY275585) 8215145	
Internal standard (IS) Location of product certificate	NA (not applicable to ligand binding) NA	
Calibration concentrations (ng/mL)	0.100[a], 0.200, 0.300, 1.000, 2.500, 5.000, 10.000, 20.000[a], 30.000[a]	
Quantitation Range (ng/mL)	0.200 – 15.000	
Average recovery of the drug (%)	NA	
Average recovery of the IS (%)	NA	
Lower limit of quantification (ng/mL)	0.200	
QC concentrations (units)	0.200, 0.300, 2.000, 4.000, 15.000 ng/mL	
Between-run accuracy range (%AR)	88.4 to 102.7	
Between-run precision range (%RSD)	4.2 to 11.8	
Within-run accuracy range (%AR)	79.0 to 108.8	
Within-run precision range (%RSD)	0.5 to 17.7	
Matrix Factor (MF) (all QC) IS normalized MF (all QC) CV (%) of IS normalized MF (all QC) % of QCs with >85% and <115% n.v. % matrix lots with mean <80% or>120% n.v.	NA	NA
Bench-top stability (Room Temperature) (hr)	24	
Refrigerated Temperature (2 - 8°C) Stability (hr)	72	
Stock stability	34 months (-60 to -80ºC)	
Processed stability (hr)	NA	
Freeze and thaw stability (cycles)	6 cycles	
Long term storage stability	12 months (-15 to -30°C, -60 to -80°C)	
Dilution linearity	up to 128000 fold	
Selectivity	The method is selective for lispro insulin, does not cross-react with endogenous insulin, and met the selectivity spike recovery accuracy acceptance criteria of 100 +/- 20% recovery in at least 80% of the samples tested.	
Partial validation Location(s)	NA	
Cross validation(s) Location(s)	NA	

Abbreviations: AR = analytical recovery, C = Celsius; CV = coefficient of variation; IS = internal standard; NA = not applicable, n.v. = nominal value; QC = quality control; RIA = radioimmunoassay; RSD = relative standard deviation.

[a] Anchor points

3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204961. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

APPEARS THIS WAY ON ORIGINAL

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regulation of glucose metabolism is the primary activity of insulins and insulin analogs, including insulin lispro. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

HUMALOG has been shown to be equipotent to human insulin on a molar basis. One unit of HUMALOG has the same glucose-lowering effect as one unit of regular human insulin. Studies in normal volunteers and patients with diabetes demonstrated that HUMALOG has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

The time course of action of insulin and insulin analogs, such as HUMALOG, may vary considerably in different individuals or within the same individual. The parameters of HUMALOG activity (time of onset, peak time, and duration) as designated in Figure 1 should be considered only as general guidelines. The rate of insulin absorption, and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables [see Warnings and Precautions (5.2)].

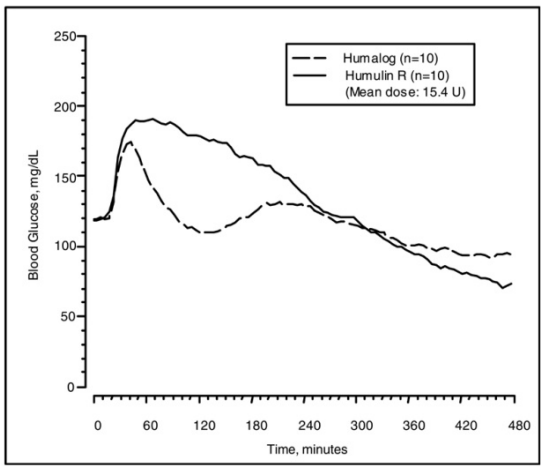


Figure 1: Blood Glucose Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].

[a]Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

Intravenous Administration of HUMALOG U 100 — The glucose lowering effect of intravenously administered HUMALOG was tested in 21 patients with type 1 diabetes. For the study, the patients' usual doses of insulin were held and blood glucose concentrations were allowed to reach a stable range of 200 to 260 mg/dL during a one to three hours run-in phase. The run-in phase was followed by a 6-hour assessment phase. During the assessment phase, patients received intravenous HUMALOG at an initial infusion rate of 0.5 units/hour. The infusion rate of HUMALOG could be adjusted at regular timed intervals to achieve and maintain blood glucose concentrations between 100 to 160 mg/dL.

The mean blood glucose levels during the assessment phase for patients on HUMALOG therapy are summarized below in Table 4. All patients achieved the targeted glucose range at some point during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 17 of 20 patients treated with HUMALOG. The average time (±SE) required to attain near normoglycemia was 129 ± 14 minutes for HUMALOG.

Table 4: Mean Blood Glucose Concentrations (mg/dL) During Intravenous Infusions of HUMALOG U-100

Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous[a]
0	224 ± 16
30	205 ± 21
60	195 ± 20
120	165 ± 26
180	140 ± 26
240	123 ± 20
300	120 ± 27
360	122 ± 25

[a] Results shown as mean ± SD

(b) (4)

12.3 Pharmacokinetics

Absorption and Bioavailability — Studies in healthy volunteers and patients with diabetes demonstrated that HUMALOG is absorbed more quickly than regular human insulin. In healthy volunteers given subcutaneous doses of HUMALOG ranging from 0.1 to 0.4 unit/kg, peak serum levels were seen 30 to 90 minutes after dosing. When healthy volunteers received equivalent doses of regular human insulin, peak insulin levels occurred between 50 to 120 minutes after dosing. Similar results were seen in patients with type 1 diabetes (see Figure 3).

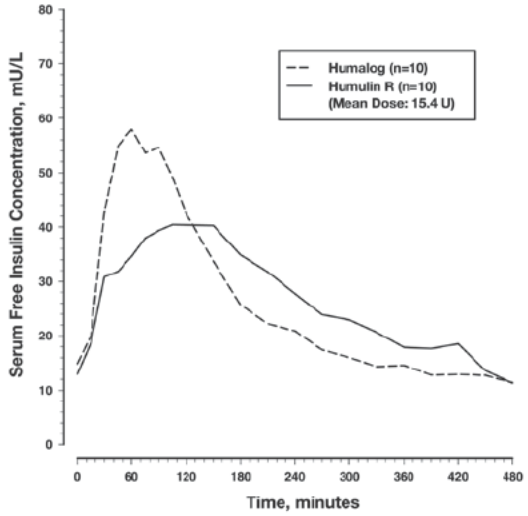


Figure 3: Serum HUMALOG and Insulin Levels After Subcutaneous Injection of Regular Human Insulin or HUMALOG (0.2 unit/kg) Immediately Before a High Carbohydrate Meal in 10 Patients with Type 1 Diabetes[a].
[a]Baseline insulin concentration was maintained by infusion of 0.2 mU/min/kg human insulin.

HUMALOG U 100 was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 unit/kg at abdominal, deltoid, or femoral subcutaneous sites. After HUMALOG was administered in the abdomen, serum drug levels were higher and the duration of action was slightly shorter than after deltoid or thigh administration. Bioavailability of HUMALOG is similar to that of regular human insulin. The absolute bioavailability after subcutaneous injection ranges from 55% to 77% with doses between 0.1 to 0.2 unit/kg, inclusive.

(b) (4)

Distribution — When administered intravenously as bolus injections of 0.1 and 0.2 U/kg dose in two separate groups of healthy subjects, the mean volume of distribution of HUMALOG appeared to decrease with increase in dose (1.55 and 0.72 L/kg, respectively) in contrast to that of regular human insulin for which, the volume of distribution was comparable across the two dose groups (1.37 and 1.12 L/kg for 0.1 and 0.2 U/kg dose, respectively).
Metabolism — Human metabolism studies have not been conducted. However, animal studies indicate that the metabolism of HUMALOG is identical to that of regular human insulin.
Elimination — After subcutaneous administration of HUMALOG, the $t_{1/2}$ is shorter than that of regular human insulin (1 versus 1.5 hours, respectively). When administered intravenously, HUMALOG and regular human insulin demonstrated similar dose-dependent clearance, with a mean clearance of 21.0 mL/min/kg and 21.4 mL/min/kg, respectively (0.1 unit/kg dose), and 9.6 mL/min/kg and 9.4 mL/min/kg, respectively (0.2 unit/kg dose). Accordingly, HUMALOG demonstrated a mean $t_{1/2}$ of 0.85 hours (51 minutes) and 0.92 hours (55 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses, and regular human insulin mean $t_{1/2}$ was 0.79 hours (47 minutes) and 1.28 hours (77 minutes), respectively for 0.1 unit/kg and 0.2 unit/kg doses.
Specific Populations

(b) (4)

(b) (4)

Renal Impairment — Type 2 diabetic patients with varying degree of renal impairment showed no difference in pharmacokinetics of regular insulin and HUMALOG. However, the sensitivity of the patients to insulin did change, with an increased response to insulin as the renal function declined. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including HUMALOG, may be necessary in patients with renal dysfunction [see Warnings and Precautions (5.7)].

Hepatic Impairment — Type 2 diabetic patients with impaired hepatic function showed no effect on the pharmacokinetics of HUMALOG as compared to patients with no hepatic dysfunction. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including HUMALOG, may be necessary in patients with hepatic dysfunction.

(b) (4)

4 APPENDIX

APPEARS THIS WAY ON ORIGINAL

4.1 OCP Filing Memo

The filing memo was issued for the original NDA submission which received a CR letter. The sponsor responded to the CR letter with the current submission, additional filing memo was not issued

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/s/

SURYANARAYANA M SISTA
05/01/2015

MANOJ KHURANA
05/01/2015

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	NDA 20-5747
Submission Date(s):	May 10, 2013
Brand Name	Humalog
Generic Name	Insulin Lispro Injection (rDNA Origin)
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Eli Lilly and Company
Submission Type; Code	505 (b)(2)
Formulation; Strength(s)	• Insulin lispro TRIS U-200
Proposed Indication	• Humalog (Insulin Lispro Injection) is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
Dosage & Administration	• Humalog U-100 (100 units/mL) or U-200 (200 units/mL) Subcutaneous Injection: Administer Humalog U-100 or U-200 within 15 minutes before a meal or immediately after a meal. Use in a regimen with an intermediate- or long-acting insulin. (b) (4) [redacted]
Clinical Pharmacology Review Team	Suryanarayana Sista,

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1 Executive Summary

Insulin Lispro Injection (rDNA Origin) is a rapid-acting human insulin analog indicated to improve glycemic control in patients with diabetes mellitus. Insulin Lispro Injection is marketed by the sponsor under the trade name, Humalog U-100 (100 units/mL), and is currently available in presentations of 10-mL (b) (4) vials, 3-mL cartridges, and 3-mL prefilled KwikPen. The sponsor is developing a 200-units/mL (U-200) concentrated version of Humalog. The current NDA is supported by a single study evaluating the bioequivalence of insulin lispro TRIS U-200 formulation relative to that of insulin lispro phosphate U-100 after subcutaneous (SC) administration of 20 units (U) to healthy subjects.

1.1 Action and Recommendation

The Office of Clinical Pharmacology (OCP) initiated a request on 10 July 2013 to OSI through DMEP to inspect the records of the pivotal bioequivalence study entitled "*Evaluation of Bioequivalence of Two formulations of Insulin Lispro in Healthy Subjects*" (Study F3Z-EW-IOPY).

- The inspection of the clinical site, Lilly-NUS Centre for Clinical Pharmacology, Singapore, conducted by ORA investigator Kellia Hicks and OSI/DBGLPC scientist Seongeun Cho from 11/7/2013 to 11/15/2013 found that the sponsor did not retain samples of the reference standard used in the bioequivalence study and did not release them to FDA upon request as required by 21 CFR Part 320.138. For details, see Dr. Cho's inspection report dated 08 Feb 2014, in DARRTS.
- A meeting was held on December 5, 2013 between DMEP (Drs. Guettier, Mahoney, Balakrishnan and Ms. CappelLynch), OSI (Dr. Cho) and OCP (Drs. Sahajwalla, Jain, Khurana and Sista) to discuss the findings from inspection of the bioequivalence study at Lilly-NUS site.
- The team agreed that based on the failure to adhere to 21 CFR Part 320.138, the sponsor would receive a **Complete Response** letter, and that given the failure to retain reserve samples of the reference product at the clinical site, inspection of bioanalytical site (b) (4) is not needed at this time.
- This NDA contained only one study (Study F3Z-EW-IOPY), which is considered inadequate for the above mentioned study conduct failures. Therefore, this reviewer didn't perform a review of findings from this study and only sponsor reported results are briefly described in later sections.

1.2 Summary of Important Clinical Pharmacology Findings

Humalog (Insulin Lispro) U-200 (200 units/mL) is a sterile drug product that is indicated for the treatment of patients with diabetes mellitus. Proposed presentation of this product is 3.0 mL cartridges and pre-assembled, prefilled pen injector capable of providing a total of 600 units of insulin lispro.

The proposed dosing regimen for Humalog U-200 is as follows:

HUMALOG U-100 (100 units/mL) or U-200 (200 units/mL)	
Subcutaneous Injection	Administer Humalog U-200 within 15 minutes before a meal or immediately after a meal. Use in a regimen with an intermediate- or long-acting insulin. (b) (4)

Pharmacokinetic Analysis:

Sponsor's pharmacokinetic analysis showed that the test formulation insulin lispro TRIS U-200 formulation was bioequivalent to the reference formulation insulin lispro phosphate U-100. The geometric least squares mean ratios for $AUC_{0\text{-}8}$, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, and C_{max} values were 0.994, 0.990, 0.993 and 0.933, respectively. All of the 90% CIs for the ratios were contained within the prespecified interval (0.80,1.25).

The time to peak concentration (T_{max}) values from the insulin lispro TRIS U-200 formulation and insulin lispro phosphate U-100 formulation were also similar, with a median difference of 15 minutes and a 95% CI of the difference that includes zero (Figure 1).

Statistical analysis of the key pharmacokinetic properties of Humalog U-200 and U-100 as reported by the sponsor are summarized in Table 1.

Figure 1 Arithmetic mean (+ Standard Deviation) serum immunoreactive insulin lispro concentration following the administration of 20 Units of insulin lispro U-100 (Phosphate) or insulin lispro U-200 (TRIS)

[Source: Sponsor's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure IOPY.2.7.1.1., Page 12]

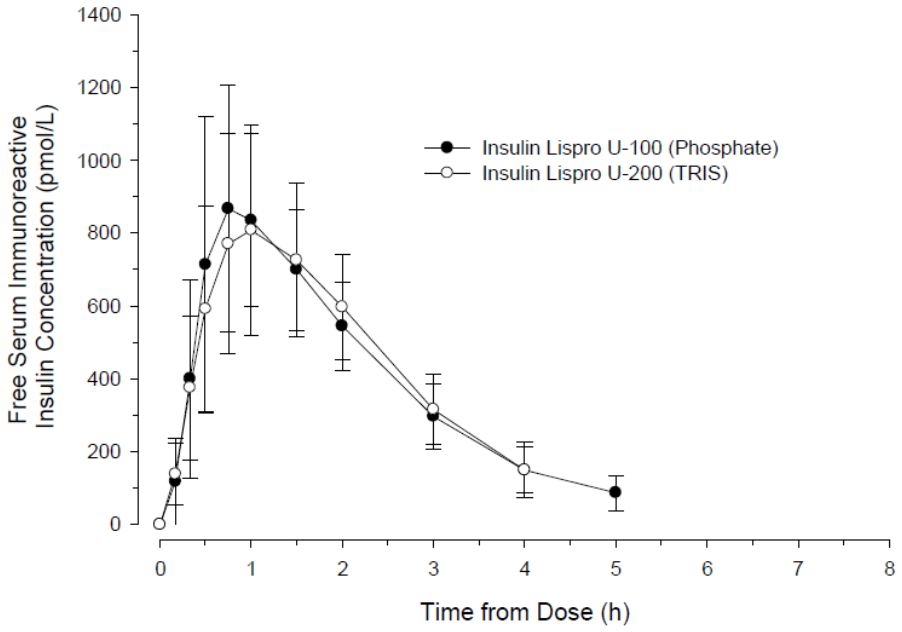

Table 1 Highlights of Humalog U-200 and U-100 Pharmacokinetics

[Source: Sponsor's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.4, Page 13]

Parameter	Geometric Least Squares Means		Ratio of geometric Least Square Means (U200:U100)	90% CI for the ratio (Lower, Upper)
	Humalog U-200	Humalog U-100		
$AUC_{0-\infty}$ (pmoL·h/L)	2020.06	2034.76	0.993	(0.952, 1.036)
$AUC_{0-tlast}$ (pmoL·h/L)	1925.27	1943.94	0.990	(0.948, 1.034)
AUC_{0-8} (pmoL·h/L)	2007.74	2020.29	0.994	(0.954, 1.036)
C_{max} (pmoL/L)	827.77	886.91	0.933	(0.897, 0.972)
T_{max} (h)[a]	1.00	0.75		

[a]Median values reported

Glucodynamic Analysis:

The glucodynamic (GD) profiles showed that the geometric mean ratios for Gtot and Rmax were 1.014 and 1.005, respectively, and the 90% CIs also within (0.80,1.25). The profiles were consistent with the pharmacokinetic observations (Figure 2).

Statistical analysis of the primary glucodynamic parameters are summarized in Table 2. The statistical analysis of the GD time variables showed median differences were small (less than 6 minutes) and the 95% CI encompassed zero.

Figure 2 Mean glucose infusion rate versus time profiles following the administration of 20 Units of insulin lispro U-100 (Phosphate) or insulin lispro U-200 (TRIS).

[Source: Sponsor's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure IOPY.2.7.1.1., Page 12]

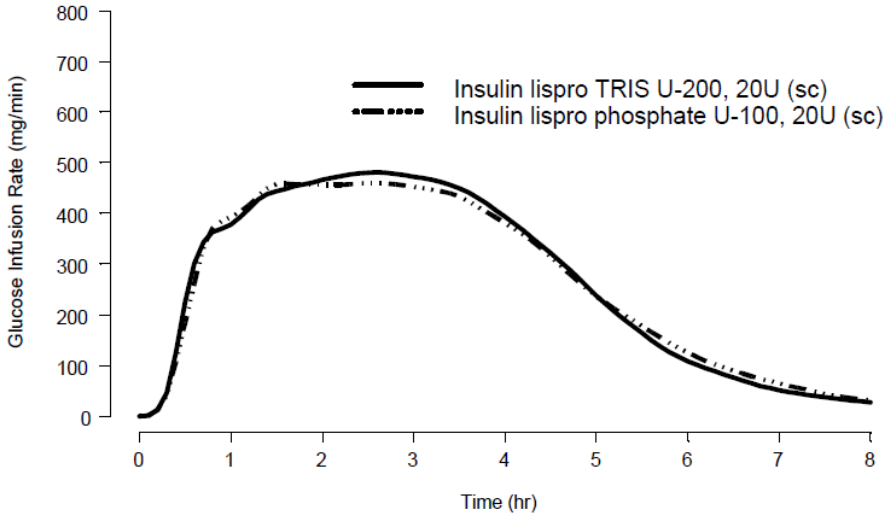

Table 2 Statistical Analysis of the Primary Glucodynamic Parameters of Humalog U-200 and U-100

[Source: Sponsor's Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.7.1.4, Page 14]

Parameter	Geometric Least Squares Means		Ratio of geometric Least Square Means (U200:U100)	90% CI for the ratio (Lower, Upper)
	Humalog U-200	Humalog U-100		
G_{TOT} (g)	124.939	123.218	1.014	(0.961, 1.070)
R_{MAX} (mg/min)	541.515	538.815	1.005	(0.958, 1.054)
	Median		Median Difference (U200-U100)	95% CI for the difference (Lower, Upper)
Early 50% T_{RMAX} (h)	0.546	0.593	-0.030	(-0.091, 0.007)
Late 50% T_{RMAX} (h)	4.839	4.763	-0.036	(-0.156, 0.098)
T_{Last} (h)	7.333	7.500	0.000	(0.000, 0.000)
T_{Onset} (h)	0.333	0.375	-0.042	(-0.042, 0.042)
T_{RMAX} (h)	2.300	2.000	0.100	(-0.400, 0.500)

1.3 Analytical

1.3.1 Is the analytical method for Insulin Lispro appropriately validated?

An OSI inspection of the bioanalytical site (b) (4) was not conducted based on non-compliance issues identified at the clinical site. Validity of the insulin lispro assay in terms of recovery, linearity, accuracy, precision and sensitivity was not verified.

2 Reviewer Comments

A thorough review of the bioequivalence study findings was not conducted since the sponsor will receive a **Complete Response** letter for failure to adhere to 21 CFR Part 320.138. Summary findings from the study have been reported above.

3 OCP Filing Memo

6 Pages have been withheld in full as duplicate copy of ClinPharm Review dated 06.24.13 immediately following this page

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/s/

SURYANARAYANA M SISTA
02/10/2014

LOKESH JAIN
02/10/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205747	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	10 May 2013		
Division:	Division of Metabolism and Endocrinology	**Team Leader:** Angelica Dorantes, Ph.D.	
		Acting Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	Eli Lilly	**Secondary Reviewer:** Team Leader	
Trade Name:	Humalog (b) (4) KwikPen (Insulin Lispro Injection (rDNA Origin))	**Date Assigned:**	24 May 2013
		GRMP Date: **PDUFA Date:**	3 Feb 2014 10 Mar 2014
Generic Name:	Insulin Lispro Injection	**Date of Review:**	3 Feb 2014
Indication:	Glycemic control in adults and children with diabetes mellitus	**Type of Submission: 505(b)2 NDA** -New formulation -New strength	
Formulation/strengths	Pre-filled syringe; 200 U/mL		
Route of Administration	Injection (subcutaneous)		
Biopharmaceutics Review Focus: Biowaiver Request			

EXECUTIVE SUMMARY

Submission: NDA 205747 seeks approval for a new insulin lispro U-200 formulation in combination with the Humalog (b) (4) KwikPen delivery device to improve glycemic control in adults and children with diabetes mellitus. The marketed Humalog® 100 units per mL (U-100) formulation is available as 10 mL vials, 3 mL prefilled pens, 3 mL cartridges and the 3 mL Humalog KwikPen™ (prefilled). Insulin lispro U-200 is a concentrated form of insulin lispro U-100 and will be supplied in one configuration, a 3 mL Humalog KwikPen. The Humalog (b) (4) KwikPen mechanism has been modified (b) (4) [redacted]

Review: To support approval, a euglycemic clamp study (Study IOPY) was conducted to evaluate the bioequivalence (BE) of a U-200 formulation relative to the Humalog U-100 formulation after subcutaneous (SC) administration of a 20 U dose to healthy subjects. Subsequent to completing the pivotal BE study, however, the formulation was changed. The changes, (b) (4) [redacted] were made (b) (4) [redacted]

This Biopharmaceutics review is focused on evaluating the Applicant's request for a waiver of an additional bioequivalence study to bridge the formulation of the product used in the pivotal BE study and the final formulation of the to-be-marketed product.

Reference is made to the Clinical Pharmacology review for additional information regarding the acceptability of BE Study IOPY to support approval.

CONCLUSION/RECOMMENDATION:

The formulation differences between the commercial and clinical product were adequately justified from a product long-term stability perspective and are not expected to have any significant impact on clinical performance. Therefore, the Applicant's request for a waiver of the requirement to complete a bioequivalence study is granted.

The proposed New Drug Application 205747 for Humalog (b) (4) KwikPen (Insulin Lispro Injection) is recommended for approval from the Biopharmaceutics perspective.

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. Richard Lostritto

BIOPHARMACEUTICS REVIEW

1.0 GENERAL INFORMATION

1.1 General

NDA 205747 was submitted in accordance with section 505(b)(2) of the FDC Act on 10 May 2013 for the use of the combination drug/device product Humalog (b) (4) KwikPen (U-200) to improve glycemic control in adults and children with diabetic mellitus. Before submitting this NDA, the Applicant filed a supplemental NDA to the Humalog (U-100) NDA 20,563 on 15 March 2013. However, in a teleconference with Lilly on 24 April 2013, FDA stated that an original NDA would be required for this new formulation and device.

To support approval, a euglycemic clamp study (Study IOPY) was conducted to evaluate the bioequivalence (BE) of a U-200 formulation relative to the Humalog U-100 formulation after subcutaneous (SC) administration of a 20 U dose to healthy subjects. Reference is made to the Clinical Pharmacology review for additional information regarding the adequacy and acceptability of Study IOPY to support approval.

1.2 Drug Substance Summary

The drug substance, insulin lispro, is a human insulin analog used to lower blood glucose. No changes were made to the drug substance that was previously approved under NDA 20563. Reference was made to NDA 20563 (approved 14 June 1996) for all quality informatin related to the drug substance.

1.3 Drug Product Summary

Humalog is a sterile, acqueous, clear, and colorless solution. The subject NDA provides for a more concentration formulation 200 units/mL compared with the currently approved 100 units/mL formulation. Each milliliter of Humalog U-200 contains insulin lispro 200 units, 16 mg glycerin, 5 mg tromethamine, 3.15 mg Metacresol, zinc oxide content adjusted to provide 0.046 mg zinc ion, trace amounts of phenol, and Water for Injection. Insulin lispro has a pH of 7.0 to 7.8. The pH is adjusted by addition of aqueous solutions of hydrochloric acid 10% and/or sodium hydroxide 10%. The solution is presented in a prefilled pen injectero, the KwikPen device.

1.4 Biopharmaceutics Review Focus

The insulin lispro drug product formulation was changed subsequent to completing the pivotal BE study. The changes, (b) (4) (b) (4) were made . This Biopharamaceutics review is focused on evaluating the Applicant's request for a waiver of an additional bioequivalence

study bridging the formulation of the product used in the pivotal BE study and the final formulation of the to-be-marketed product.

2.0 BIOPHARMACEUTICS ASSESSMENT/BIOWAIVER EVALUATION

The aims of the biopharmaceutical development strategy for the U-200 formulation were to support drug product development, to establish bioequivalence between the U-200 formulation and Humalog U-100, and to characterize the glucodynamic (GD) responses of the U-200 formulation. (b) (4)

Study IOPY compared the PK and GD of the U-200 clinical formulation to the Humalog U-100 formulation. This study concluded that (b) (4) there was no effect on AUC (0-∞), tmax or any of the GD parameter. (b) (4)

The composition of all three formulations, Humalog U-100, the U-200 clinical formulation and the commercial formulation, are tabulated below.

Table 2.7.1.1. Composition of the Commercial U-200 Formulation and Study F3Z-EW-IOPY U-200 Formulation

Ingredient	Proposed Commercial 200 U/mL Quantity/mL	F3Z-EW-IOPY200 U/mL Quantity/mL	Commercial Humalog 100 U/mL Quantity/mL	Function
Insulin Lispro	200 Units	200 Units	100 Units	Active ingredient
Tris (Hydroxymethyl aminomethane) (TRIS)	5 mg	(b) (4) mg	--	(b) (4)
Dibasic Sodium Phosphate	--	--	1.88 mg	
Zinc Oxide	q.s. to give a Zn^{++} content of (b) (4) mg/100 Units	q.s. to give a Zn^{++} content of (b) (4) mg/100 Units	q.s. to give a Zn^{++} content of 0.0197 mg/100 Units	
Metacresol	3.15 mg	3.15 mg	3.15 mg	
Glycerin	16 mg	16 mg	16 mg	
Water	(b) (4)			
Hydrochloric Acid	q.s.	q.s.	q.s.	pH adjustment[a]
Sodium Hydroxide				

Abbreviations: q.s. = quantum sufficient (as much as is sufficient); Zn = zinc.
[a] adjustment to pH 7.0 - 7.8.

The Applicant concludes that the proposed formulation changes are minor and are unlikely to affect PK for the following reasons:

(1) (b) (4)

Rationale: (b) (4)

(2) (b) (4)

Rationale: (b) (4)

(b) (4)

Reviewer's Evaluation: *Satisfactory.* (b) (4)

Thus, the provided information adequately supports the approval of the biowaiver request for the bioequivalence study needed to support approval of the final formulation.

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/s/

MINERVA HUGHES
02/03/2014

ANGELICA DORANTES
02/03/2014

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205747
Submission Date	10 May 2013
Product name, generic name of the active	Humalog (b) (4) KwikPen (Insulin Lispro Injection (rDNA Origin))
Dosage form and strength	Injection (200 Units/mL)
Applicant	Eli Lilly
Clinical Division	Division of Metabolism and Endocrinology
Type of Submission	505(b)2
Primary Biopharmaceutics Reviewer	Minerva Hughes
Secondary Biopharmaceutics Reviewer	John Duan (Acting Team Leader)
Biopharmaceutics Team Leader	Angelica Dorantes
Assignment Date	24 May 2013
Filing Date	9 July 2013
Filing Review Date	27 June 2013

I. SUBMISSION OVERVIEW

NDA 205747 seeks approval for a new insulin lispro U-200 formulation in combination with the Humalog (b) (4) KwikPen delivery device. Humalog (Insulin lispro) is a rapid acting insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. The marketed Humalog® 100 units per mL (U-100) formulation is available as 10 mL vials, 3 mL prefilled pens, 3 mL cartridges and the 3 mL Humalog KwikPen™ (prefilled). Insulin lispro U-200 is a concentrated form of insulin lispro U-100 and will be supplied in one configuration, a 3 mL Humalog KwikPen. The Humalog (b) (4) KwikPen mechanism has been modified (b) (4)

The Applicant has provided the following information to support approval of the U-200 formulation.

- A bioequivalence (BE) study comparing insulin lispro U-100 and U-200, Study F3Z-EW-IOPY
- An evaluation of (b) (4) the pharmacokinetic and glucodynamic profile of insulin lispro U-100 in Study F3Z-LC-IMAB.
- A comprehensive Human Factors Engineering program, evaluating user performance.

II. BIOPHARMACEUTICS SUMMARY INFORMATION

Subsequent to the BE study, (b) (4) Design of Experiment (DOE) studies were completed to verify that the insulin lispro U-200 formulation was suitable for commercial manufacture. (b) (4)

A comparison of the formulation differences between the marketed U-100 formulation, the U-200 formulation used in the BE study, and the proposed commercial formulation is tabulated below.

Ingredient	Proposed Commercial 200 U/mL Quantity/mL	F3Z-EW-IOPY200 U/mL Quantity/mL	Commercial Humalog 100 U/mL Quantity/mL	Function
Insulin Lispro	200 Units	200 Units	100 Units	Active ingredient
Tris (Hydroxymethyl aminomethane) (TRIS)	5 mg	(b) (4) mg	--	(b) (4)
Dibasic Sodium Phosphate	--	--	1.88 mg	
Zinc Oxide	q.s. to give a Zn^{++} content of (b) (4) mg/100 Units	q.s. to give a Zn^{++} content of (b) (4) mg/100 Units	q.s. to give a Zn^{++} content of 0.0197 mg/100 Units	
Metacresol	3.15 mg	3.15 mg	3.15 mg	
Glycerin	16 mg	16 mg	16 mg	
Water	(b) (4)			
Hydrochloric Acid	q.s.	q.s.	q.s.	pH adjustment[a]
Sodium Hydroxide				

Abbreviations: q.s. = quantum sufficient (as much as is sufficient); Zn = zinc.
[a] adjustment to pH 7.0 - 7.8.

Since the to-be-marketed formulation was not used in the bioequivalence study, a request for a biowaiver is implied. However, as per 21 CFR 320.22, the Applicant should provide a written request for the biowaiver and a deficiency is noted for the Applicant to address.

The CDER-Biopharmaceutics review will evaluate the adequacy of the Applicant's justification for not conducting BE studies on the to-be-marketed formulation (i.e., the biowaiver request).

FILING REVIEW CHECKLIST

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?		x	
2.	Is the dissolution test part of the DP specifications?		x	
3.	Does the application contain the dissolution method development report?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
4.	Is there a validation package for the analytical method and dissolution methodology?		x	
5.	Does the application include a biowaiver request?	x		The formulation used in the BE study is not the to-be-marketed formulation. Thus, a biowaiver is implied, but a written request was not included.
6.	Does the application include a IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?	x		BE study between a U-200 formulation and the marketed U-100 formulation (F3Z-EW-IOPY). The to-be-marketed formulation was not used in the BE study, and the Applicant provided some justification for a waiver.
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping? c.) Is there a site comparability protocol?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		

12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		Provide a written request for a waiver of bioequivalence studies using the proposed commercial formulation, as per 21 CFR 320.22.

COMMENTS FOR DAY 74 LETTER

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

{See appended electronic signature page}
Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
John Duan, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

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/s/

MINERVA HUGHES
06/27/2013

JOHN Z DUAN
06/27/2013

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205747 **Applicant: Eli Lilly and Company** **Stamp Date: May 10, 2013**

Drug Name: Humalog (b) (4) KwikPen (Insulin Lispro Injection (rDNA Origin)) **NDA/BLA Type: standard**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	See slides below
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
	in the clinical pharmacology section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor:

Suryanarayana M. Sista	21 June, 2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	21 June, 2013
Team Leader/Supervisor	Date

NDA 20-5747 [505 (b)(1)]
Humalog (b) (4) KwikPen (Insulin Lispro Injection (rDNA Origin))

Eli Lilly and Company

Clinical Pharmacology Review Team:

Sury Sista

Lokesh Jain (TL)

Overview: Clinical Pharmacology Program

- **Clinical Pharmacology program:** One (1) single Phase 1 study to demonstrate (a) BE, and (b) compare the glucodynamics (GD) of insulin lispro U-200 formulation relative to insulin lispro U-100 formulation after subcutaneous administration of a dose of 20 units to healthy subjects.
- **Supportive information:** (b) (4) PK and GD of an insulin lispro formulation (information originally submitted in NDA 20-563 [13 March 1995]).
- **No Additional (Bridging) study:** Proposed commercial formulation has a (b) (4) however, the sponsor contends that the change is not clinically relevant based on the supportive information submitted in NDA 20-563 [13 March 1995] .

Overview: PK & PD

- **Pharmacokinetics**
  - Geometric ratio means for AUC_{0-8}, AUC_{0-last}, $AUC_{0-\infty}$, and C_{max} values ranged between 0.933 to 0 994, and all of the 90% CIs for the ratios were contained within the pre-specified interval (0 80,1.25)
  - Median T_{max} values for the 2 treatments were within 15 minutes of each other, and were similar
- **Glucodynamics**
  - Ratios of geometric means for G_{tot} and R_{max} were 1.014 and 1.005, and the 90% CIs were within (0.80,1 25)
  - GD time variables showed median differences were small (less than 6 minutes) and the 95% CI encompassed zero

Background Regulatory Information

- August 21, 2012 communications from the Agency to the Sponsor:
  - *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) (b) (4) does not influence the PK and PD profiles of insulin lispro from the intended commercial formulation.**
- Previous agreement from FDA (16 May 2008) regarding a change proposed for the insulin lispro U-100 formulation (b) (4) (b) (4)
  - FDA Response **We agree that neither a clinical nor an *in vivo* biopharmaceutics assessment is needed to support the proposed formulation change.**

Pediatric Plan

- *Under PREA, 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.*
- The sponsor believes that none of these criteria relate to this application and therefore the requirements under PREA do not apply to this NDA.

Key Questions: Mid Cycle Deliverables

– Is the new U-200 formulation bioequivalent relative to the insulin lispro U-100 formulation in terms of pharmacokinetics and glucodynamics?

Conclusions

- This NDA is filable from OCP perspective
- OSI inspection will be requested for the pivotal BE study

Backup Slides

Composition of the Commercial U-200 Formulation and Study F3Z-EW-IOPY U-200 Formulation

Ingredient	Proposed Commercial 200 U/mL Quantity/mL	F3Z-EW-IOPY200 U/mL Quantity/mL	Commercial Humalog 100 U/mL Quantity/mL	Function
Insulin Lispro	200 Units	200 Units	100 Units	Active ingredient
Tris (Hydroxymethyl aminomethane) (TRIS)	5 mg	(b) (4) mg	--	(b) (4)
Dibasic Sodium Phosphate	--	--	1.88 mg	
Zinc Oxide	q.s. to give a Zn++ content of (b) (4) mg/100 Units	q.s. to give a Zn++ content of (b) (4) mg/100 Units	q.s. to give a Zn++ content of 0.0197 mg/100 Units	
Metacresol	3.15 mg	3.15 mg	3.15 mg	
Glycerin	16 mg	16 mg	16 mg	
Water				(b) (4
Hydrochloric Acid	q.s.	q.s.	q.s.	pH adjustment[a]
Sodium Hydroxide				

Abbreviations: q.s. = quantum sufficient (as much as is sufficient); Zn = zinc.
[a] adjustment to pH 7.0 - 7.8.

Glucodynamic Parameters of Insulin Lispro with and without Zinc in the Formulation (from NDA 20-563, March 1995)

Treatment	LYSPRO, SC No Zinc Mean ±SD	Zinc LYSPRO, SC 0.0275 mg/100U Mean ±SD
Pharmacokinetics		
C_{max} (ng/mL)[a]	4.06 ± 1.32	3.20 ± 1.33
t_{max} (min)	42 ± 20	53 ± 30
AUC(0-∞) (ng·min/mL)	415.1 ± 84.9	379.7 ± 52.2
$t_{1/2}$ (min)[b]	30.6 to 179 (46.0)	31.8 to 88.7 (55.4)
Glucodynamics		
R_{max} (mg/min)	553 ± 212	550 ± 203
t_{Rmax} (min)	99 ± 39	116 ± 43
G_{tot} (g)	80.5 ± 28.9	85.1 ± 28.2

Sources: CSR IMAB, Attachment IMAB.2.,Table C and Table D (scanned pages 373-375); Insulin Lispro: Item 8 Clinical Data Section Vol1.70 A, Table 2 and Table 3 (scanned pages 9 and 10).
Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; G_{tot} = total glucose infused throughout the clamp; R_{max} = maximum glucose infusion rate; SC = subcutaneous; SD = standard deviation; $t_{½}$ = half-life associated with the terminal rate constant; t_{max} = time of maximum drug concentration; t_{Rmax} = time of maximum glucose infusion rate.
[a] statistically significant difference
[b] range (harmonic mean)

Summary of Key PK Parameters Following Insulin Lispro U-100 (Phosphate) or Insulin Lispro U-200 (TRIS)

	Geometric Mean (CV%)	
	Humalog U-100 (Phosphate) (N = 75)	Humalog U-200 (TRIS) (N = 73)
C_{max} (pmol/L)	887 (34)	819 (32)
t_{max} (h)[a]	0.75 (0.50 – 3.00)	1.00 (0.50 – 3.00)
AUC0-t_{last} (pmol•h/L)	1940 (20)	1920 (20)
AUC_{0-8} (pmol•h/L)	2020 (19)	2000 (19)
$AUC_{0-\infty}$ (pmol•h/L)	2030 (19)	2020 (19)
$t_{1/2}$ (h)[b]	0.887 (0.442 – 1.79)	0.794 (0.423 – 2.52)
CL/F (L/h)	58.7 (19)	59.3 (19)
V_Z/F (L)	75.2 (35)	67.9 (39)

[a] Median (Range).
[b] Geometric Mean (Range).

Statistical Analysis of the Pharmacokinetic Parameters of Serum Free IRI (Study F3Z-EW-IOPY)

Statistical Analysis of the Pharmacokinetic Parameters of Serum Free IRI for Study F3Z-EW-IOPY

Parameter	Geometric least squares means A	N	n	B	N	n	Ratio of geometric least square means A:B	90% CI for the ratio (Lower, Upper)
AUC (0-8) (pmol*h/L)	2007.738	37	73	2029.292	38	75	0.994	(0.954,1.036)
AUC (0-inf) (obs.) (pmol*h/L)	2026.058	37	73	2034.763	38	75	0.993	(0.952,1.036)
AUC (0-tlast) (pmol*h/L)	1925.269	37	73	1943.936	38	75	0.990	(0.948,1.034)
CMAX (pmol/L)	827.774	37	73	886.906	38	75	0.933	(0.897,0.972)

Model: Log(pk) = sequence + treatment + period + (subject) + (error)
N is the number of subjects
n is the number of observations

Clinical Pharmacology Review Focus:

- Is the new U-200 formulation bioequivalent relative to the insulin lispro U-100 formulation in terms of pharmacokinetics and glucodynamics?

OSI Inspection will be requested for the pivotal BE study.

Bioanalytical Facility: (b) (4)

Phase 1 Clinical Facility: Eli Lilly and Company Singapore
(Principal Investigator: Danny Soon, MD)

APPEARS THIS WAY ON ORIGINAL

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

/s/

SURYANARAYANA M SISTA
06/24/2013

IMMO ZADEZENSKY
06/24/2013