

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
206538Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3 Feb 2015
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206538
Applicant	Sanofi-Aventis
Date of Submission	25 Apr 2014
PDUFA Goal Date	25 Feb 2015
Proprietary Name / Established (USAN) names	Toujeo/ Insulin glargine injection
Dosage forms / Strength	300 units of insulin glargine per mL (U-300) available as <ul style="list-style-type: none"> • 1.5 mL cartridges, for subcutaneous injection using an irreversibly integrated pen-injector
Proposed Indication	Indicated to improve glycemic control in adults (b) (4) with diabetes mellitus
Recommended Action	Approval

Cross Discipline Team Leader Review

1. Introduction

This memo serves as the cross-discipline team leader memo for NDA 206538 for insulin glargine solution for injection, a combination product of insulin glargine in a 300 unit per mL concentration, and a disposable pen injector device.

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of the development program for Toujeo.

2. Background

Product Information

Insulin glargine (HOE901-U300) was developed under IND 112400. The proprietary name of the drug is Toujeo. Toujeo is a three-times concentrated formulation of insulin glargine, i.e. U-300. The approved U-100 formulation of insulin glargine (Lantus - HOE901-U-100) was developed under IND 49078 and approved in April 2000 under NDA 21081. It is important to note that this NDA is being submitted under the 505(b)(1) pathway. The Sponsor of this NDA, Sanofi-Aventis, is also the Sponsor of Lantus.

Toujeo has the same composition as the current commercial formulation of insulin glargine 100 units/mL (Lantus), with adjustment of 3-times the amount of active pharmaceutical ingredient (300 units/mL insulin glargine) and corresponding zinc (b) (4) content. Toujeo is planned to be available as a 1.5 mL cartridge in the SoloStar pre-filled (disposable) pen and provides a maximum of 80 units in one dose.

Insulin glargine is human insulin analog which is modified by the addition of 2 Arginine residues at positions 31 and 32 of the β -chain and the substitution of Glycine for Asparagine at position 21 of the α -chain (b) (4)

insulin glargine is intended for use as a basal insulin.

Regulatory History

On 21 Apr 2006, the Sponsor requested a Type C meeting under IND 049078 (HOE901/Lantus) to discuss the development plan for a 300 units/mL formulation in a

disposable pen device and registration as prior approval supplement. Preliminary written responses were provided to the Sponsor 21 Jul 2006 which stated that their proposed bioequivalence study was acceptable from a design standpoint for eventual approval of the concentrated formula. The Sponsor then requested cancellation of the face to face meeting.

It appears that the Sponsor originally intended to submit the marketing application for the U-300 formulation as a prior approval supplement, but the Sponsor conducted the bioequivalence study and found that the two formulations were not bioequivalent. The U-300 formulation appeared to have a flatter PK/PD profile and longer duration of PD effect than the U-100 formulation. The Sponsor requested a PIND meeting 3 Jun 2011 (and then before the meeting could take place on 26 Aug 2011, the Sponsor opened a new IND for the insulin glargine 300 unit/mL formulation. Therefore, written responses were provided to the Sponsor in lieu of a meeting).

Notably, at that time the planned development of the U-300 formulation had been changed quite a bit. The Sponsor was now proposing 4 pivotal phase 3 studies to support an indication for glycemic control in both type 1 diabetes and type 2 diabetes (type 2 with three clinical scenarios: insulin naïve, basal insulin therapy, and basal/bolus insulin therapy) [REDACTED] (b) (4)

[REDACTED] FDA indicated that these [REDACTED] (u) (4) were problematic for a number of reasons and would be a review issue. Details regarding the advice given to the Sponsor by FDA in this regard can be found in Dr. Condarco's primary Clinical review.

In presubmission meetings, the general approach of non-inferiority studies vs. Lantus in the patient populations for whom Toujeo was intended was agreed upon. It was agreed that 6 months of treatment data at the time of submission of the NDA was acceptable.

3. CMC/Device

CMC

The CMC review was conducted by Dr. Xavier Ysem. Dr. Ysem is recommending approval of this NDA with no recommendations for postmarketing requirements. In addition, an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA is approvable.

Summary of CMC findings:

The manufacturing site for Toujeo is:

Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst

65926 Frankfurt am Main
Germany

Drug substance:

The applicant referenced approved Sanofi NDA 21-081 (LANTUS Insulin glargine [rDNA origin]) and corresponding 2009/2010 Annual Report (14 Sept. 2010 submission) for drug substance information.

The drug substance, Sanofi's insulin glargine (HOE901), is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism (see also section 2 – product information). The drug substance is the same as the one described by the Sponsor in their approved NDA 21-081(Lantus). All CMC information is referred by cross-reference to the drug substance section of Sanofi's NDA 21-081.

Drug product (see figure below):

The multiple-dose drug product contains (b) (4) solution of insulin glargine (300 units/mL), in a 1.5 mL cartridge irreversibly integrated with a pen-injector. HOE901-U-300 has the same composition as the current commercial formulation of insulin glargine 100 units/mL, with adjustment of 3-times the amount of active pharmaceutical ingredient (300 units/mL insulin glargine) and corresponding zinc content (b) (4)



Drug product composition – Each 1 mL of drug product solution contains (b) (4) (300 units) of insulin glargine, 2.7 mg m-cresol (b) (4) Zinc (b) (4) and 20.0 mg of 85% glycerol (b) (4), in Water for Injection.

The manufacturing process (b) (4) correspond to those approved for the marketed insulin glargine solution for injection 100 units/mL process. Drug product specifications are similar to those for approved insulin glargine solution for injection 100 units/mL (NDA 21-081) (b) (4). Tests and acceptance criteria are typical for parenteral protein solutions. The CMC

review team performed risk assessment on the factors that can impact product quality and concluded that the potential risk to overall product quality is acceptable. The suitability of the packaging materials (cartridges and closures) was substantiated by the extractables and leachables studies and the results of the stability tests.

Dr. Ysern stated that based on the provided long-term, accelerated, stress, in-use, and photostability stability data, and their statistical evaluation, the proposed 30 months shelf life for the drug product (shelf life storage directions: prior first use store between 2 °C and 8 °C protected from light, do not freeze), and the proposed in-use period (b) (4) (in-use storage directions: store at room temperature (up to 30 °C) protected from light), are both fully supported by the data and are granted. However, the Clinical Microbiology reviewer stated that (b) (4) no (b) (4) data was provided to support the (u) (4) use period for opened-in-use units stored at room temperature (see section 6). The Sponsor submitted data on 4 Feb 2014 to support the (b) (4) in-use period. Review of this new information by Dr. Sweeney was conducted; the conclusion was the data are not sufficient to support the (b) (4) in-use period.

“The applicant performed (b) (4) testing (b) (4). However, the USP/Ph.Eur. tests only include (b) (4). The applicant should perform USP/Ph.Eur. (u) (4) testing on product formulated with less than the minimum release/stability (u) (4) content (b) (4).”

Device

CDRH Device Review

The Division requested a consult from CDRH/ODE for device constituent part design review of this NDA which is for a combination product.

The recommendation from the CDRH device reviewer, Ryan McGowan, is approval, with no recommendations for postmarketing requirements. This recommendation was based on review of the intended design and design control information for the subject device constituent part.

There were no deficiencies related to the design of the device. This conclusion was based on a thorough review including clinical use history within the Toujeo clinical trials and review of postmarketing device-related complaints for the Lantus SoloStar device (the U-100 version of the Toujeo SoloStar device) which is substantially similar to the Toujeo SoloStar device.

However, the CDRH reviewer noted that the sponsor did not conduct clinical studies with the final finished combination product as described within the submission. Instead, two other device presentations were used. These devices are described as “Devices A and B” within the submission.

From a device design/engineering perspective, the CDRH reviewer concluded that the functionality of devices A and B is sufficiently similar to the to-be-marketed system to allow for clinical conclusions made with A and B to be translated to the to-be-marketed system. However the reviewer wishes to acknowledge that this position does not include an assessment of device usability or other clinical concerns (see discussion of DMEPA review).

Two recommendations for potential product labeling revisions include:

1) An explicit warning that the user should not use solvents other than water to clean the device. This is recommended [REDACTED] (b) (4)

2) A statement of the brand/type of needles the device is permitted to be used with (currently only the needle manufacturers are listed). This is recommended as the device has only been verified to function with ISO11608-2 compatible insulin needles.

DMEPA Device Review

The recommendation from the DMEPA reviewer, Dr. Sarah Vee, is approval, with no recommendations for postmarketing requirements. This recommendation was based on human factors review, and review of container and carton labeling from a medication error perspective.

Human factors assessment of Toujeo SoloStar comprised of three parts (i.e. usability, differentiation, and comprehension questions) to ensure that the product is safe for use in each step of medication use process. These were all found acceptable. Particularly, the Human Factors Study demonstrated that users are able to use the prefilled pen safely and effectively with no reported instances of calculation errors (i.e. multiplying or dividing by 3, resulting in 3-fold over or under doses). However, DMEPA raises theoretical concerns regarding the U-300 insulin concentration and that misunderstanding of the concentration may result in serious harm to the patient, especially in cases of overdose. DMEPA states that that postmarketing reports show medication errors with a marketed concentrated insulin product (i.e. Humulin R U-500) where misunderstanding of the concentrated nature of the product resulted overdoses that led to patient harm, including death. As a result, DMEPA concluded that proper education and training should be provided prior to first injection to ensure that the users are able to safely use Toujeo SoloStar.

DMEPA also proposed minor revisions to the container label, carton and insert labeling to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4. Nonclinical Pharmacology/Toxicology

The recommendation from the product quality microbiology reviewer, Dr. Jeffrey Quinn, is approval with no recommendations for postmarketing requirements.

The toxicological data submitted for the approval of Lantus (insulin glargine, 100 units/mL) supports NDA 206538 given the minor formulation changes represented in the Toujeo SoloStar (insulin glargine, 300 units/mL) drug product.

A local tolerance study was conducted with Toujeo SoloStar as a bridge to the Lantus drug product. Both formulations of insulin glargine showed acceptable local tolerance profiles in rabbits following subcutaneous injection, the intended clinical route of administration.

The excipients used in Toujeo SoloStar (HOE901-U300) were based on the commercially available formulation Lantus (HOE901-U-100). The excipients are stated to be well known for parenteral drugs and are listed in Ph. Eur. and USP.

No impurities or degradation products have been specified individually as the concentrations are equal to or below the ^{(b) (4)} identification threshold when the drug product is stored as recommended. Quantities of unidentified and identified leachable and extractable impurities did not exceed ^{(b) (4)} ng/mL.

5. Clinical Pharmacology/Biopharmaceutics

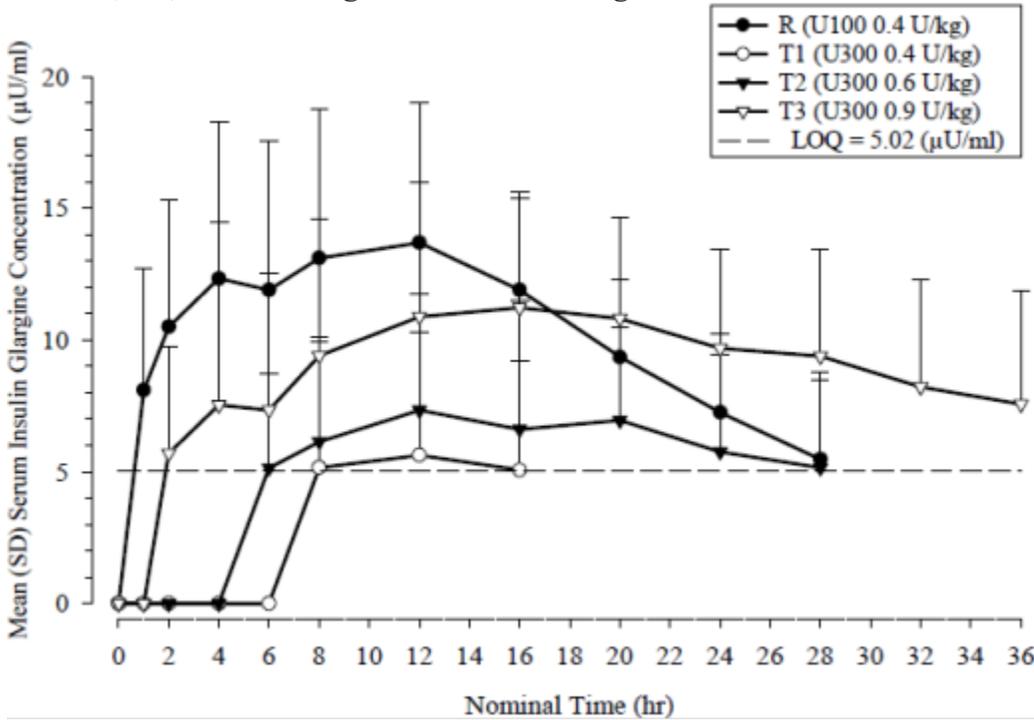
The recommendation from the clinical pharmacology reviewer, Dr. Lau, is approval with no recommended postmarketing requirements.

The sponsor submitted 6 clinical pharmacology studies of Toujeo to characterize and compare the pharmacokinetics/pharmacodynamics (PK/PD) characteristics to Lantus. These were reviewed by the Office of Clinical Pharmacology reviewer. See review for details. A high level summary of important findings is provided in this section.

As stated previously, the Sponsor noted early in development of the U-300 formulation of glargine that it had different PK/PD characteristics than the U-100 formulation.

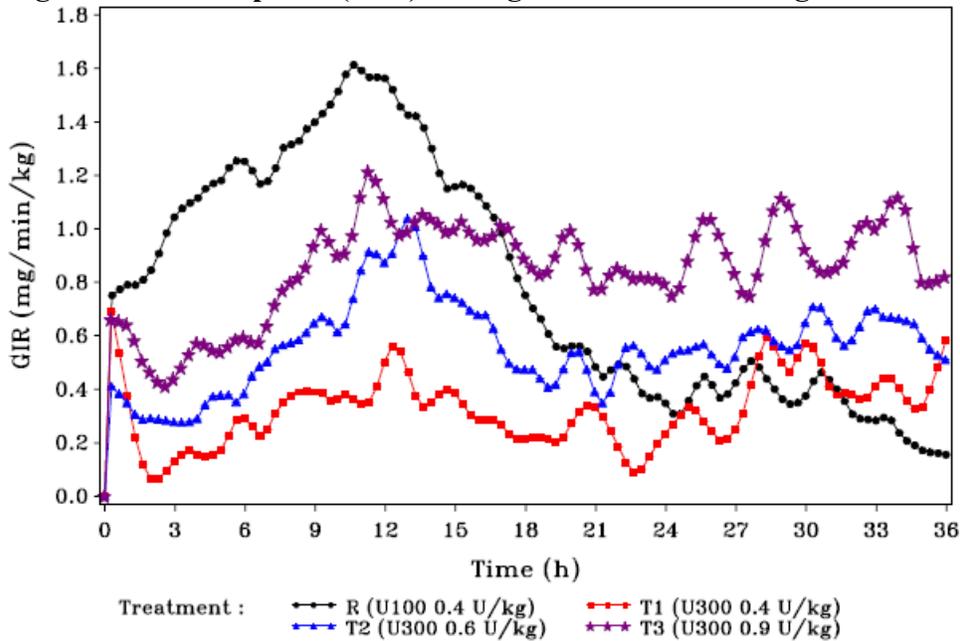
A single dose study (PKD11627) assessed the PK and PD of SC single rising doses of 0.4, 0.6, and 0.9 U/kg U-300 as well as 0.4 U/kg U-100 (Lantus) in a 4-sequence crossover design euglycemic clamp study with 5 – 18 days as washouts in 24 T1DM patients. Serum insulin glargine concentrations were measured for PK (Figure 1), and the glucose infusion rate (GIR) was the measure of the PD response (Figure 2). The horizontal dotted line in Figure 1 represents the quantitation limit. For further quantitative data, i.e. tables generated from the same data that generated these figures, please see the clinical pharmacology review.

Figure 1 – PK, Mean (SD) serum insulin glargine concentration-time profiles of single dose 0.4, 0.6, and 0.9 U/kg U-300 and 0.4 U/kg U-100.



Source: Study PKD11627 Report, Figure 8, Page 106/126

Figure 2 – PD Response (GIR) of Single Dose Insulin Glargine PK/PD Study



Source: Study PKD11627's Report, Figure 3, Page 85/126

This single dose PK/PD study shows that:
PK

- The mean serum insulin glargine concentration versus time profiles of 0.4, 0.6, and 0.9 U/kg U-300 are generally flatter than that of the 0.4 U/kg U-100.
- Compared to U-100, the exposure over the clamp period of 36 hours (AUC₀₋₃₆) was significantly lower for U-300 0.4 U/kg and 0.6 U/kg and was similar for U-300 0.9 U/kg.
- U-100 showed the highest C_{max}.
- T_{max} occurred at 12 hours for all doses except at 16 hours for U-300 0.9 U/kg.
- For the 0.4U/kg dose of U-300 serum insulin glargine concentration did not reach the quantifiable level until 8 hours post-dose whereas the same dose of U-100 reached the quantifiable level after one hour. This finding would have implications for converting a patient from an i.v. insulin infusion to subcutaneous insulin in a hospital setting because the i.v. insulin would need to be continued for a longer time period if using U-300 vs. U-100 glargine.

PD

- The GIR-AUC_{0-24h} and GIR-AUC_{0-36h} all show a trend of dose-dependent increase.
- U-300's time to onset of action after the 1st dose on average was about 6 hours (delayed 3 hours compared to U-100). Again, this finding would have implications for converting a patient from an i.v. insulin infusion to subcutaneous insulin in a hospital setting.
- U-300 0.4 U/kg and 0.6 U/kg required an overall lower amount of exogenously administered glucose (GIR-AUC₀₋₃₆) compared to U-100 0.4 U/kg (i.e. less PD effect) but U-300 0.9 U/kg GIR-AUC₀₋₃₆ was greater than that of U-100 0.4 U/kg (i.e. more PD effect). Therefore, unit-to-unit the PD effect of U-300 appears to be lower for U-300.

Multiple Dose PK/PD Study (TDR11626) compared the PK and PD of 8 daily SC doses of 0.4 U/kg U-300 (T1) with 0.4 U/kg of U-100 (R1) in a cohort of 18 T1DM patients and the PK and PD of 8 daily SC doses of 0.6 U/kg U-300 (T2) with 0.4 U/kg of U-100 (R2) in another cohort of 12 T1DM patients. After the 8th day of dosing, blood glucose concentrations of the patients were maintained within a range 100 mg/dL \pm 20% via intravenous infusion of glucose solution (euglycemic clamp) until 36 hours postdose (clamp end). Figure 3 shows the PK results, and Figure 4 shows the PD results (GIR over time). For further quantitative data, i.e. tables generated from the same data that generated these figures, please see the clinical pharmacology review.

These data suggest that:

PK

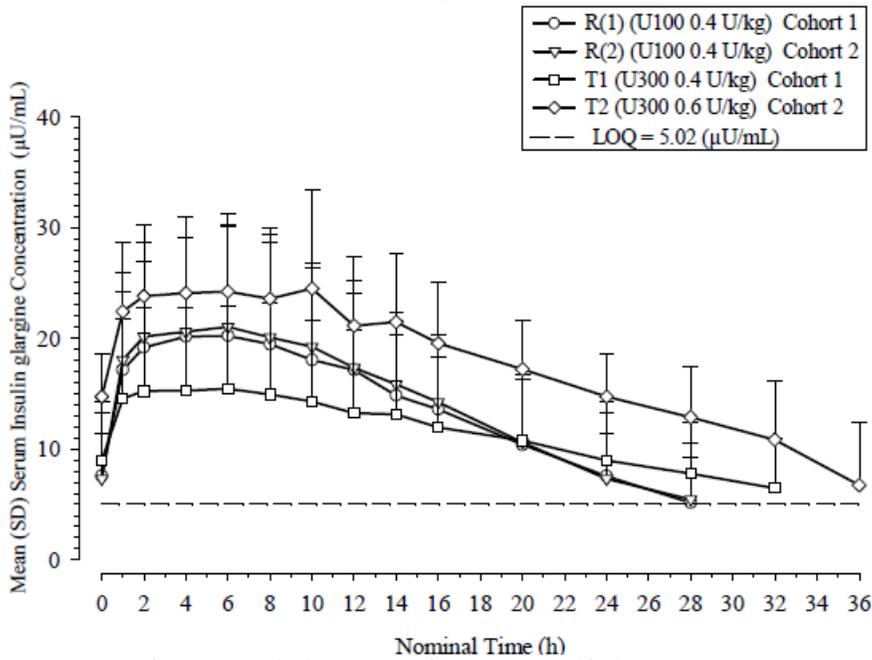
- The steady state profiles of serum insulin glargine for treatments with U-300 0.4 U/kg (T1) and 0.6 U/kg (T2) were generally flat.
- The mean insulin glargine concentrations for the reference treatments with 0.4 U/kg U-100 R1 and R2 were nearly overlapping (internal validity).
- There was detectable exposure until 32 and 36 hours postdose, for U-300 0.4 U/kg (T1) and 0.6 U/kg (T2), respectively (compared with 28 hours for U-100).
- Both doses of U-300 showed longer mean terminal half-life than U-100.
- Among the 0.4 U/kg U-300 (T1) and 0.6 U/kg U-300 (T2) doses, the mean daily total exposure was 331 μ U*h/mL and 500 μ U*h/mL, and for R1 and R2 of 0.4 U/kg U-100

- were similar (389 $\mu\text{U}\cdot\text{h}/\text{mL}$ and 380 $\mu\text{U}\cdot\text{h}/\text{mL}$), suggesting lower exposure for equivalent dose (0.4 U/kg) of U-300 vs. U-100.
- Although not directly tested, the clinical pharmacology reviewer estimated that for the comparison of 0.4 U/kg U-300 vs. 0.4 U/kg U-100 at steady state, a 10 – 20% increase in the U-300 dose would put the U-300 exposure in a similar range to the exposure for U-100. This is relevant in the context of the overall higher doses in the range of 11-17.5% required to achieve similar glycemic control with Toujeo vs. Lantus in the phase 3 trials (see section 7).

PD

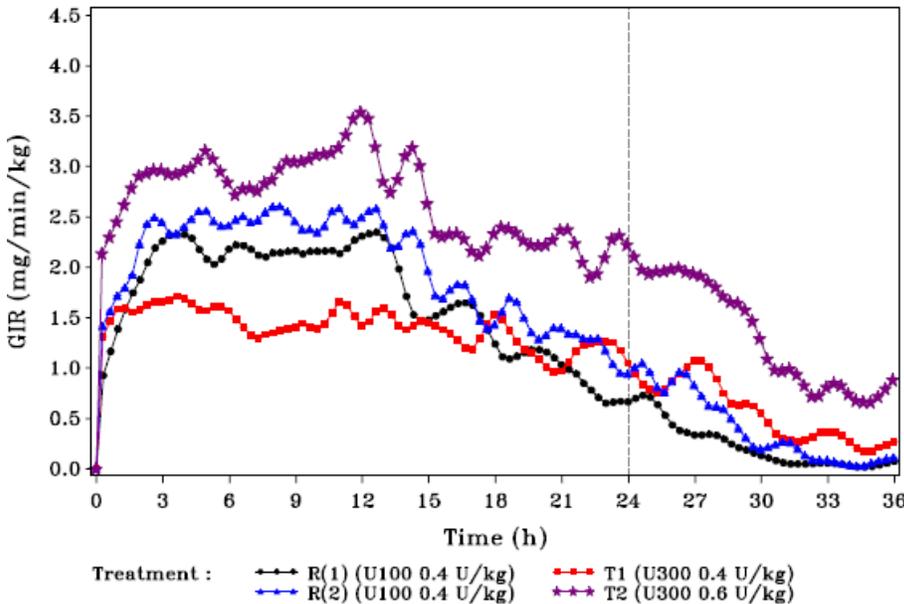
- The mean smoothed body weight-standardized GIR curve of 0.4 U/kg U-300 (T1) forms a plateau below the curves of 0.4 U/kg U-100 (R1 and R2) for about 15 hours postdose. Thereafter, the curves of R1 and R2 cross over the curve of T1 indicating an earlier end of the comparator action.

Figure 3 - Mean (SD) serum insulin glargine concentration-time profiles of 0.4 and 0.6 U/kg U-300 and 0.4 and 0.4 U/kg U-100 at steady state.



Source: Study TDR11626 Report, Figure 10, 126/162

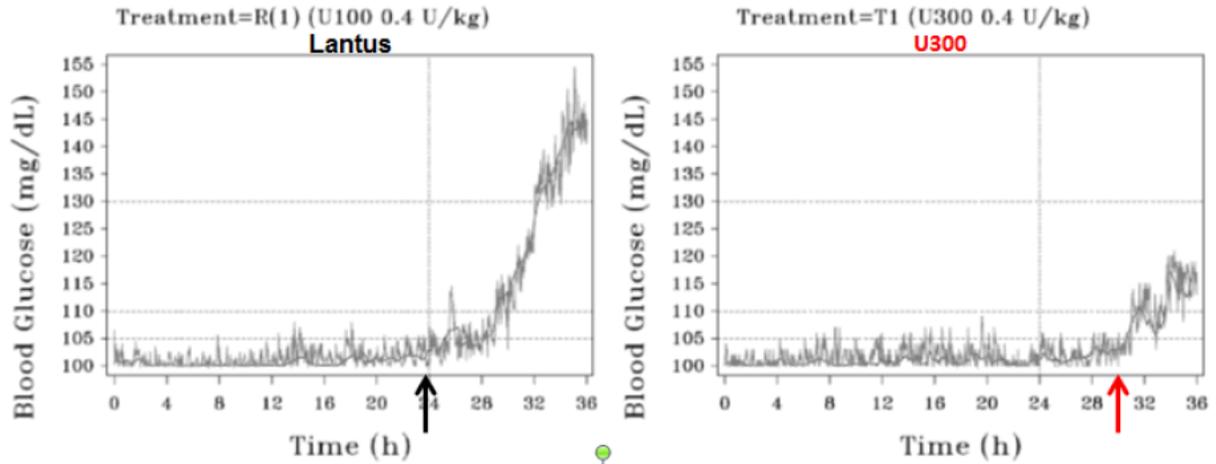
Figure 4 - Mean smoothed body weight-standardized GIR profiles over time for Study TDR11626



Source: Study TDR11626 Report, Figure 4, 92/162

Figure 5 shows that the effect of 0.4 U/kg U-300 to maintain the median blood glucose concentrations persists beyond 24 hours upon once daily dosing at steady state in euglycemic clamp.

Figure 5 - Median blood glucose concentration-time profiles for Study TDR11626



Source: Modified from Study TDR11626 Report, Figure 7 Page 100/162, borrowed from Dr. Lau’s clinical pharmacology review

Taken together these data suggest that at steady state, U-300 has an overall lesser PD effect than U-100 but that the PD effect of U-300 at steady state persists longer than the PD effect of U-100. This predicts that the GIR-AUC₀₋₂₄ should be lower for U-300 compared to U-100 but the difference in PD effect would be attenuated by looking at the GIR-AUC₀₋₃₆.

Based on calculations presented by the Sponsor and confirmed by the clinical pharmacology review, this appears to be the case. In study TDR11626, patients required less glucose (as measured by GIR-AUC) on 0.4 U/kg U-300 (T1) than on 0.4 U/kg U-100 (R1) to maintain BG control within the first 24 hours of the clamp period showing that the PD response from U-300 is lower than U-100 on a unit-to-unit basis at steady-state (Table 1). For 0.4 U/kg U-300 (T1), the ratios of geometric means of its GIR-AUC over those of 0.4 U/kg U-100 were 0.73 and 0.85 for 24 hours and 36 hours, respectively.

Table 1 – GIR Point Estimates of Ratios between U-300 and U-100 in Multiple-Dose PK/PD Study TDR11626

Treatment Ratio	Parameter	Estimate	90% CI	95% CI
0.4 U/kg U-300 / 0.4 U/kg U-100	GIR _{max}	0.81	0.68 – 0.97	0.65 – 1.01
	GIR-AUC ₀₋₂₄	0.73	0.56 – 0.94	0.53 – 0.99
	GIR-AUC ₀₋₃₆	0.85	0.70 – 1.03	0.67 – 1.08

Source: modified from Dr. Lau’s Table 7

[Redacted text] (b) (4)

[Redacted text] (b) (4)

However, Dr. Tran (CMC) notes that Lantus and Toujeo have the same active ingredient, the same potency of 6 nmol/Unit, the same glargine to zinc ratio, and comparable stability trends. The Sponsor used the same reference standard from the European Pharmacopeia to test both products; according to Dr. Tran, this is how the potency of 6 nmol/U is demonstrated. The observed PK/PD difference may result from the slower *in vivo* drug release from the precipitate that insulin glargine forms after injection because proteins ‘prefer’ to be in the precipitate form at higher concentrations. I agree with Dr. Tran’s view that the unit dose definition should be based on CMC potency characteristics, and I believe that the *in vivo* PD differences can be addressed through labeling. Labeling would need to address the lower overall PD effect at steady state of U-300 vs. U-100, and the longer time of onset of action of U-300 vs. U-100.

Dr. Lau ultimately recommended approval of this NDA despite his concerns about potency differences because he notes that the 4 pivotal “clinical efficacy and safety trials for T1DM and T2DM patients show that U-300 is noninferior to U-100 in terms of lowering hemoglobin A1C (efficacy measurement) with comparable adverse events between U-300 and U-100 especially for hypoglycemia.” I agree with Dr. Lau’s conclusion. While I agree with Dr. Lau

(b) (4)

I believe there is no regulatory basis to not approve an insulin product based on lack of unit-to-unit equivalence based on PK. See section 11 for further discussion of this issue.

This difference in the glucose lowering effect on a unit-to-unit dose basis was consistent with the higher average basal insulin daily dose utilization (range 11% to 17.5%) observed in the Phase 3 efficacy/safety trials in both type 1 diabetes and type 2 diabetes patients (discussed in section 7 of this review). The clinical pharmacology review presents figures that show that a higher daily dose of basal insulin was used over the course of the study for the T1DM pivotal trial 12456 when the basal insulin was administered in the morning vs. in the evening (see Figure 8 from Dr. Lau’s review). The clinical pharmacology review recommends labeling Toujeo for dosing in the evening with the assumption that this would translate into patients using less basal insulin on a daily basis. I disagree with the recommendation, in part, because the daily prandial insulin dose was higher in the group of patients who received basal insulin in the evening suggesting that the higher basal dose used by patients who dosed their basal insulin in the morning was offset by slightly less prandial insulin use. This pattern of a lower daily dose of basal insulin if given in the evening is consistent with the pattern for Lantus and may be related to daily fluctuations in glucose based on meal and activity patterns rather than to Toujeo, *per se*. Further, as noted by Dr. Kettermann the statistical reviewer, comparing morning and evening injection groups within the U-300 group, the morning injection resulted in a larger decrease of HbA1c than the evening injection (although the LS mean difference between U-300 morning and evening injection group was not clinically relevant). Lantus is

labeled for use once daily at any time, but at the same time each day. I believe Toujeo should be labeled similarly. I do agree that the labeling should communicate the finding that a higher daily dose of U-300 may be needed to achieve similar glucose control compared with U-100.

Time to Reach Steady State

Data from Study TDR11626 also were used to establish the time to reach steady state for U-300 vs. U-100. The clinical pharmacology reviewer stated that because of methodological issues it was difficult to determine the time to reach steady state. Therefore, Dr. Lau examined the M1 metabolite (insulin glargine’s major circulating metabolite) to estimate that U-300 appears to reach steady state on Day 7 in the 0.4 U/kg daily dose group and on Day 5 in the 0.6 U/kg daily dose group. The Sponsor is proposing (b) (4). However, Dr. Lau disagrees with the Sponsor’s conclusions because these numbers were generated using modeling that in Dr. Lau’s view is not justified. Please see his review for details.

Intra-subject variability

The sponsor used Study PKD13560 to assess the intra-subject variability of U-300 exposure. Study PKD13560 compared 2 different U-300 formulations. Thus, Dr. Lau concluded that Study PKD13560 may be inappropriate for intra-subject variability assessment. Using data from Study PKD10086 (the PK and PD of 2 replicate single SC doses of 0.4 U/kg U-300 and 2 replicate single SC doses of 0.4 U/kg U-100 via euglycemic clamp in healthy volunteers) he concluded that the intra-subject variability of U-300 is higher than those of U-100 for insulin glargine PK and PD parameters. See table below borrowed from Dr. Lau’s review.

Parameter	U300’s Intra-subject Variability, CV%	U100’s Intra-subject Variability, CV%
INS-AUC ₀₋₂₄	21.0	16.2
INS-C _{max}	25.6	20.0
GIR-AUC ₀₋₂₄	40.3	19.6
GIR _{max}	41.3	24.5

Source: Reviewer’s analysis.

Agency labeling recommendation state to include mechanisms for known sources of variability in response (e.g., disease severity, hormonal status, concomitant drugs, age, genetic or racial/ethnic factors, diurnal variation, environmental factors) however it is unknown why the intra-subject variability for U-300 appears higher than for U-100 and there were no apparent clinically significant implications of this finding. Therefore, I do not believe the data for intra-subject variability is important for section 12 of the Toujeo label.

(b) (4) U-300
 The Sponsor proposed (b) (4)

The clinical pharmacology reviewer does not agree with the sponsor’s proposal. (b) (4)

(b) (4)

Clin pharm recommended Labeling Action: Dosage and Administration and Clinical Pharmacology:

a. The pharmacokinetics/pharmacodynamics (PK/PD) comparison of U-300 to Lantus demonstrates that the glucose lowering effect of U-300 is lower than Lantus on a unit-to-unit basis.

b. The PK/PD differences were consistent with the observed higher average basal insulin dose utilization in the efficacy/safety trials in both type 1 diabetes and type 2 diabetes patients. This information needs to be adequately conveyed to the prescribers of TOUJEO.

6. Clinical Microbiology

The recommendation from the product quality microbiology reviewer, Dr. Sweeney, is approval with no recommended postmarketing requirements.

The microbiology reviewer has one recommendation for product labeling as follows: The package insert states that unopened disposable prefilled pens should be stored in a refrigerator (2°C - 8°C), and opened-in-use units should be stored at room temperature for a maximum of (b) (4) days.

(b) (4) testing of product (b) (4) was performed (b) (4) no (b) (4) data was provided to support the (b) (4) use period for opened-in-use units stored at room temperature. The Microbiology Reviewer recommends that the (b) (4) storage period specified in the package insert be changed to 28 days, and will participate in labeling discussions regarding the (b) (4) in-use time. The applicant's justification for the (b) (4) use period is based on (b) (4)

7. Clinical/Statistical- Efficacy

The reader is referred to separate discipline reviews by Clinical (Dr. Tania Condarco) and Biostatistics (Dr. Anna Kettermann). In this section I summarize the major efficacy findings for this NDA.

To support efficacy of the U-300 formulation for the indication 'to improve glycemic control in adults with diabetes mellitus' the sponsor submitted 4 pivotal phase 3 studies of 26 weeks duration, three in T2DM adult patients and one in T1DM adult patients. All four were open-label, parallel group, randomized controlled trials of Toujeo vs. the active comparator Lantus.

The primary endpoint in all four studies was change from baseline to Month 6 in HbA1c. All four trials met the primary objective to show that Toujeo was non-inferior to Lantus (NI margin 0.4%). Dr. Kettermann notes that the sponsor did not provide justification for the chosen NI margin, but that based on precedent 0.4% is acceptable. A stepwise closed testing approach was used for the primary efficacy variable to test NI and superiority sequentially. The superiority of HOE901-U-300 to Lantus was not identified in any of the studies. The prespecified analysis method for EFC11628 and EFC11629 as Last Observation Carried Forward (LOCF) and for EFC12456 and EFC12347 was Mixed Model for Repeated Measures (MMRM). Trials EFC11628 and EFC11629 had been planned prior to the Agency recommending MMRM over LOCF for handling of missing data.

A 16-week exploratory study in T1DM patients was also conducted by the Sponsor which supports the T1DM indication, but is not discussed in detail here -see Dr. Condarco's review.

Dr. Kettermann confirmed the statistical analyses of the four pivotal studies which were as follows:

- EFC12456: T1DM basal/bolus insulin therapy (switch study)
- EFC11628: T2DM basal/bolus insulin therapy (switch study)
- EFC11629: T2DM basal insulin in combination with oral antidiabetic therapies (switch study)
- EFC12347: T2DM basal insulin in combination with oral antidiabetic therapies (insulin naïve)

The four studies submitted are representative of a broad range of diabetes patients and adequately represent the majority of intended users of Toujeo. The study population consisted of adult patients at least 18 years of age with a screening HbA1c in the range of ≥ 7.0 to $\leq 10.0\%$ for insulin-pretreated patients (EFC11628, EFC11629, and EFC12456) and ≥ 7.0 to $\leq 11.0\%$ in insulin-naïve patients (EFC12347). In general, the inclusion and exclusion criteria were appropriate. In trial EFC12456 (T1DM) there were four randomized groups: Toujeo administered in the evening, Toujeo administered in the morning, Lantus administered in the evening, and Lantus administered in the morning to explore the effect of time of administration on safety and efficacy, but the trial was powered for the overall comparison between Toujeo and Lantus.

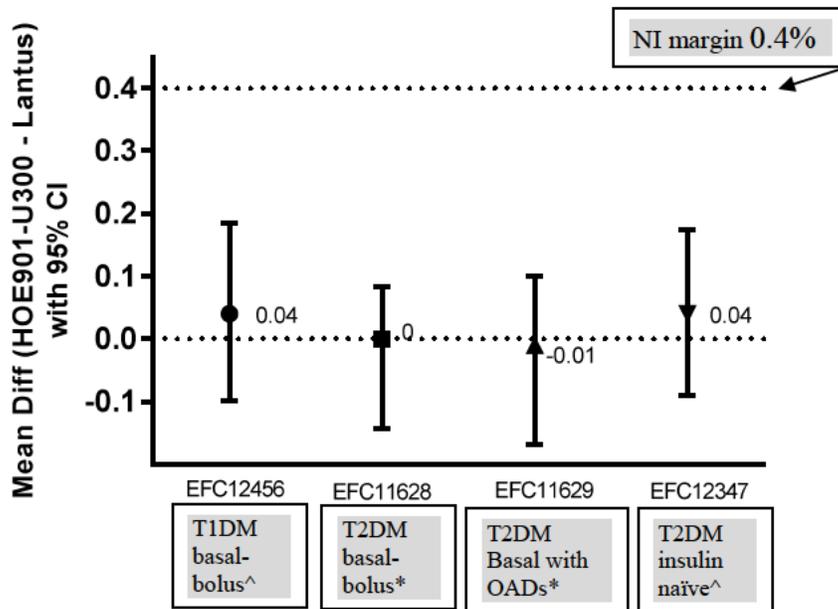
In all trials in which basal insulin was already being used by patients, dosing with study basal insulin, i.e. Toujeo or Lantus was intended to be initiated with a 1:1 conversion ratio and administered once daily. However, in the trials it appears that investigators lowered starting doses of basal insulins slightly despite the 1:1 recommendation. In trial EFC12347 basal insulins were started at a dose of 0.2 U/kg once daily. Investigators were instructed to titrate basal insulin every 3 to 4 days. A titration algorithm was provided to investigators with a pre-breakfast fasting plasma glucose goal of 80-130 mg/dL for the T1DM trial, and 80-100 mg/dL for the T2DM trials.

Per Dr. Kettermann's review the studies included 549 randomized patients with T1DM and 2496 randomized patients with T2DM; 717 (23.5%) patients were aged 65 years or older and

488 (16%) patients had some degree of renal impairment (GFR [MDRD] ≤ 60 mL/min). The majority of the patients were Caucasian/white (n=2667; 87.6%), other ethnicities were represented by n=210 (6.9%) Black, n=144 (4.7%) Asian/Oriental, and n=463 (15.2%) were Hispanic. Geographical areas included North America, South America, Europe, South Africa, and Japan. Both Dr. Kettermann and Dr. Condarco point out that the percentage of Black patients is under-representative of the proportion of Black diabetics in the U.S. and recommend that the demographic details of the study population(s) be included in labeling with a disclaimer that although the trends in noninferiority were similar among different races, sample sizes were too small to produce robust conclusions for non-whites. This recommendation seems reasonable. Subgroup analyses do not suggest the need for additional postmarketing studies to be performed in Black patients.

Figure 6 and Table 2, adapted from Dr. Condarco’s and Dr. Kettermann’s reviews summarize the efficacy findings for the four pivotal trials. Figure 6 displays the pre-specified analysis results, i.e. LOCF or MMRM, whereas Table 2 shows both. In Figure 6, if the upper bound of the 95% confidence interval is below 0.4% then Toujeo is considered ‘non-inferior’ to Lantus (goal met in all four studies). Point estimates of the treatment difference above the 0.0 line favor the comparator Lantus. For all analyses the 95% CI includes 0, suggesting no difference in efficacy between Toujeo and Lantus based on change in HbA1c after six months of treatment.

Figure 6 – Efficacy Results of the Pivotal Trials – Treatment Difference in LS Mean Change from Baseline to Month 6



Source: Adapted from Dr. Condarco’s review

^MMRM method

*LOCF method

Table 2 – Efficacy Results of the Pivotal Trials

Study	Treatment	N	Baseline	Endpoint	Change from baseline
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	group		Mean	Mean	LS Mean	LS Mean difference (95% CI)
Type 1 Diabetes						
EFC12456 T1DM basal-bolus	Toujeo	273	8.13	7.70	-0.40	0.05 (-0.08, 0.18)*
	Lantus	273	8.12	7.68	-0.44	0.04 (-0.10, 0.18)^
Type 2 Diabetes						
EFC11628 T2DM basal-bolus	Toujeo	404	8.14	7.25	-0.83	-0.002 (-0.11, 0.11)*
	Lantus	400	8.14	7.28	-0.83	-0.02 (-0.13, 0.09)^
EFC11629 T2DM basal + OADs	Toujeo	403	8.28	7.57	-0.57	-0.01 (-0.14, 0.12)*
	Lantus	405	8.22	7.56	-0.56	-0.02 (-0.15, 0.11)^
EFC12347 T2DM insulin naive	Toujeo	432	8.49	7.08	-1.42	0.019 (-0.12, 0.16)*
	Lantus	430	8.58	7.05	-1.46	0.04 (-0.09, 0.17)^
Source: adapted from primary reviews						
^MMRM method						
*LOCF method						

Dr. Kettermann notes that missing data is not a significant concern with regard to these analyses. She states that MMRM is not the appropriate tool for assessing the impact of missing, but the concern is mitigated by the fact that LOCF and MMRM gave similar results to each other in all four studies, and the amount of missing data was not overwhelmingly large. Please see her review for a thorough discussion of missing data issues.

Insulin Dosing and Titration

Because insulin drugs are individually titrated to glycemic goals, an assessment of insulin doses administered including a comparison between groups, as well as an examination of basal bolus insulin ratios are important for efficacy assessments of insulin drugs.

Data from the Toujeo application show consistently across the four pivotal trials that more basal insulin (units per day) was required on average for Toujeo-randomized groups than Lantus-randomized groups to achieve similar glycemic control. The relative basal insulin difference varied by trial (Table 3) but ranged from 11% to 17.5%. The difference in prandial insulin use between Toujeo-randomized groups and Lantus-randomized groups (in trials 11628 and 11629) was small, i.e. not clinically relevant, and therefore, is not shown here; see Dr. Condarco’s review. The higher insulin doses required for Toujeo to reach similar glycemic control is not surprising given the lesser PD effect noted in clinical pharmacology studies. While there is no basis to not approve Toujeo based on this finding, I agree with the clinical pharmacology reviewer that this lack of unit-to-unit dose equivalence should be noted in labeling.

Table 3 - Difference in Insulin Doses between Toujeo and Lantus Randomized Groups

Study	Treatment group	Starting mean basal insulin dose (units/kg/day)	Ending mean basal insulin dose (units/kg/day)	Mean difference in basal insulin dose (units/kg/day)	Percent difference
Type 1 Diabetes					
EFC12456 T1DM basal-bolus	Toujeo	27	40.5	6	17.5%
	Lantus	27.5	34		
Type 2 Diabetes					
EFC11628 T2DM basal-bolus	Toujeo	70	103	10	11%
	Lantus	71	94		
EFC11629 T2DM basal + OADs	Toujeo	62	91	9	12%
	Lantus	64	82		
EFC12347 T2DM insulin naïve	Toujeo	18	59	7	15%
	Lantus	19	52		
Source: adapted from Dr. Condarco's primary review					



In the pivotal trials, all three that involved a switch scenario, i.e. converting from a commercial basal insulin product to Toujeo at randomization (EFC12456, EFC11628, and EFC11629) the mean pre-breakfast Self Monitored Plasma Glucose, i.e. fingerstick glucose value, at week 1 was notably increased from baseline. The only trial that did not demonstrate this manifestation was trial EFC12347 in which patients were insulin naïve at enrollment.

Figure 7 - Mean (\pm SE) pre-breakfast SMPG by visit for each of the 4 pivotal trials
T1DM Trial EFC12456 T2DM Trial EFC11628

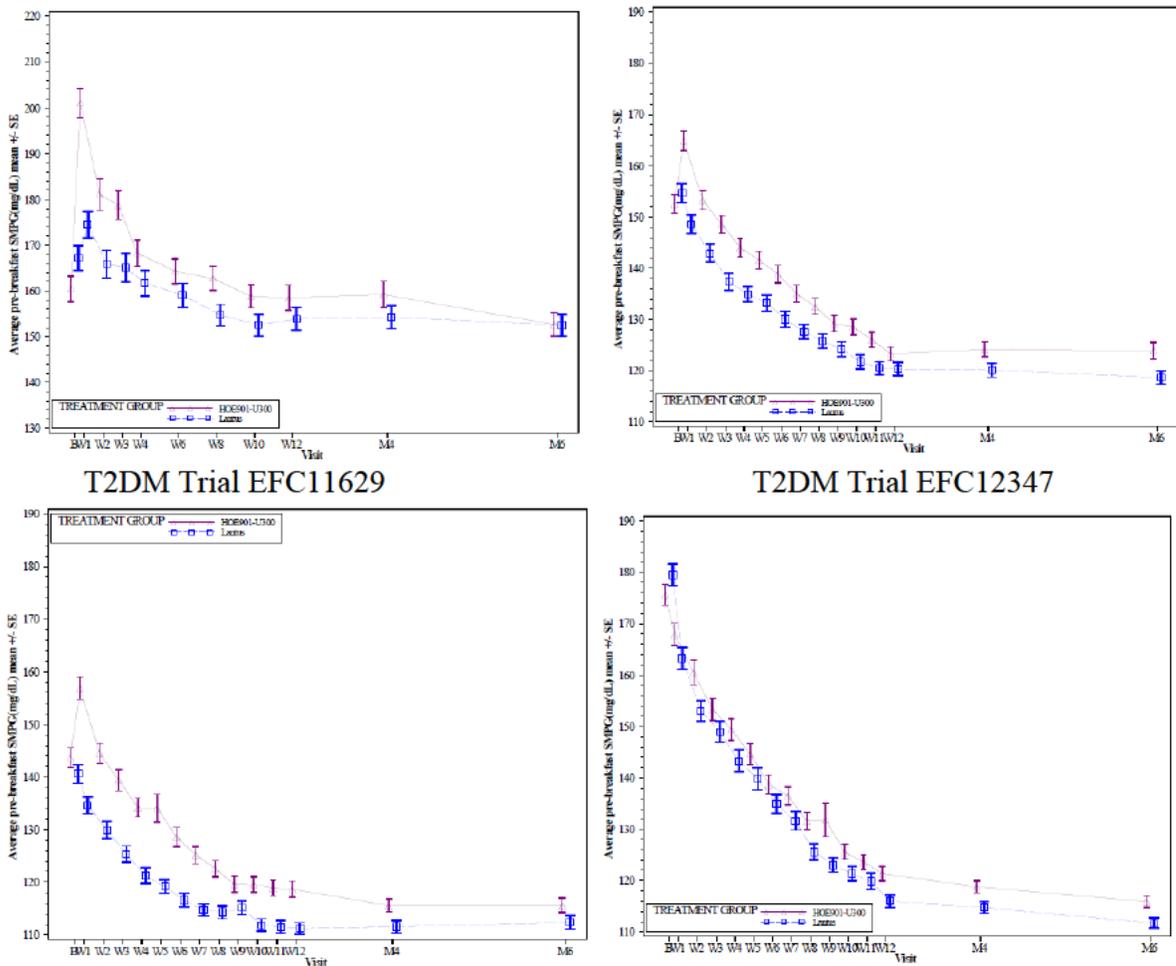


Figure source: Sponsor's figures submitted to FDA upon request

There is also concern that this lack of dose equivalence could lead to hypoglycemia when changing from Toujeo to Lantus. (b) (4)

[Redacted]

(b) (4)

The Sponsor has proposed [Redacted] (b) (4)

[Redacted] Both Dr. Condarco and Dr. Kettermann recommend against including this [Redacted] (b) (4)

(b) (4)

[Redacted]

[REDACTED] (b) (4)

Based on the submitted data, it appears that there are no efficacy or safety concerns [REDACTED] (b) (4)

[REDACTED]

From a statistical perspective Dr. Kettermann concluded that there was difficulty in interpretation of analysis [REDACTED] (b) (4)

[REDACTED]

In general, I believe that it's probably likely that [REDACTED] (b) (4) would not result in a compromise of efficacy or safety of the use of Toujeo. However, I agree with the primary reviewers that the submitted data are not sufficiently robust [REDACTED] (b) (4). In presubmission regulatory interactions between the sponsor and the Agency, the Division did not state exactly what type of data would be needed [REDACTED] (b) (4)

[REDACTED]

(b) (4) Therefore, I do not agree (b) (4) as the sponsor has proposed as follows (b) (4) and there are insufficient data (b) (4)

Secondary Endpoints

Fasting Plasma Glucose

In the Toujeo program fasting plasma glucose was a secondary endpoint, although not a main secondary endpoint. Nevertheless, FPG results are usually included in diabetes product labels. For all trials the results of fasting plasma glucose analyses supported the primary efficacy analysis, except that numerically the change in fasting plasma glucose from baseline to month 6 consistently favored the Lantus arm. The statistical analysis performed by the Sponsor should be interpreted with caution as the analyses were not controlled for type 1 error.

Table 4 – Centrally Measured Fasting Plasma Glucose Results

Study	Treatment group	Baseline N	Baseline Mean (mg/dL)	Endpoint Mean (mg/dL)	Change from baseline	
					LS Mean	LS Mean difference (95% CI)
Type 1 Diabetes						
EFC12456 T1DM basal-bolus	Toujeo	234	186	175	-17	3 (-10, 17)^
	Lantus	236	199	173	-20	
Type 2 Diabetes						
EFC11628 T2DM basal-bolus	Toujeo	376	157	130	-23	2 (-4.3, 7.7)*
	Lantus	385	160	130	-25	
EFC11629 T2DM basal + OADs	Toujeo	375	148	128	-18	3 (-2.7, 9.4)*
	Lantus	379	142	123	-22	
EFC12347 T2DM insulin naive	Toujeo	398	179	120	-59	7 (1.8, 12.2)^
	Lantus	387	184	114	-70	
Source: Sponsor's data ^MMRM method *LOCF method						

Hypoglycemia

Hypoglycemia is the most common and most clinically important adverse reaction related to insulin use. In this review hypoglycemia is discussed in this section, in part, because Dr. Kettermann conducted statistical analyses related to hypoglycemia (b) (4)

Hypoglycemia is inextricably linked to glycemic control. The tighter glycemic control one aims for and/or achieves, the higher the risk of hypoglycemia. Therefore, all analyses of hypoglycemia in the Toujeo application are complicated by the fact that glycemic control was not equivalent throughout the trial. Although by the 6-month endpoint, glycemic control as measured by HbA1c was almost equivalent between Toujeo and Lantus arms of the 4 pivotal trials, achievement of glycemic control in Toujeo groups lagged behind glycemic control in Lantus groups as evidenced by pre-breakfast SMPG measurements (refer to Figure 7). Dr. Kettermann showed that the lead time (number of days) to first event was slightly higher (longer time to event) in U-300 arms, which is consistent with the pattern of glucose values observed in the trials. Further, for a reliable assessment of hypoglycemia risk, incidence or event rate of hypoglycemia should be measured at a time when insulin doses are relatively stable, e.g. for at least 3 months. In the Toujeo trials insulin was being titrated up through the month 6 endpoint. Extension data for all four trials were not submitted with the NDA as noted in this review.

(b) (4)
 What can be concluded from the data is that hypoglycemia incidence for Toujeo treated patients appears to be in line with previously reported incidence for diabetes trials, and that there were no clinically important differences between Toujeo and Lantus with regard to hypoglycemia. The
 (b) (4)
 Agency's point of view is that reducing the risk of hypoglycemia can be achieved by lowering the dose of insulin
 (b) (4)

For completeness sake, the rates of severe hypoglycemia (defined as requiring assistance from another person) and documented symptomatic hypoglycemia are shown in Table 5. However, the Agency does not believe these comparisons should be used to make comparative safety conclusions with regard to hypoglycemia between Toujeo and Lantus. The data appear to generally favor Toujeo, although there are some comparisons that favor Lantus. For example, for *severe hypoglycemia -Week 9 through 26-Entire 24 hour Period* only two of the four comparisons favor Toujeo. Of all the definitions of hypoglycemia shown in this table, that particular definition would be the most reliable because it includes severe hypoglycemia incidence during a timeframe after initial dosing and titration (although a measure of severe hypoglycemia after dose titration was completed would be better; as noted above, this is not available for these trials because insulin continued to be titrated through week 26).

Table 5 - Incidence* of Hypoglycemia in Toujeo Pivotal Trials

		Severe			Documented Symptomatic(<54 mg/dL)		
Study	Treatment group	Entire Study Period Entire 24 hour Period	Week 1-8 Entire 24 hour Period	Week 9-26 Entire 24 hour Period	Entire Study Period Entire 24 hour	Entire Study Period Nocturnal (midnight	Entire Study Period Daytime (6 AM to

					Period	to 6 AM)	midnight)
Type 1 Diabetes							
EFC12456 T1DM basal-bolus	Toujeo	6.6%	3.3%	4.0%	69.0%	40.9%	65.3%
	Lantus	9.5%	5.1%	5.1%	69.8%	38.9%	62.9%
Type 2 Diabetes							
EFC11628 T2DM basal-bolus	Toujeo	5.0%	1.5%	4.5%	37.4%	12.1%	32.4%
	Lantus	5.7%	2.7%	3.5%	41.5%	16.9%	35.1%
EFC11629 T2DM basal + OADs	Toujeo	1.0%	0.2%	0.7%	20.6%	8.2%	16.4%
	Lantus	1.5%	0.5%	1.2%	26.8%	11.6%	21.4%
EFC12347 T2DM insulin naive	Toujeo	0.9%	0.2%	0.7%	7.6%	3.2%	5.3%
	Lantus	0.9%	0.5%	0.5%	13.9%	6.4%	9.8%
Source: Sponsor's data							
* Percent (%) of patients with at least one hypoglycemia event during the main on-treatment period							

The Sponsor also presented hypoglycemia data by exposure-adjusted event rate; these are not presented here because the analyses are generally consistent with the incidence rate data and do not add any important information. Refer to Dr. Condarco's primary review for a discussion of exposure-adjusted event rate data. Dr. Condarco noted that in the T1DM trial the exposure-adjusted event rate of severe hypoglycemia was lower in the Toujeo vs. Lantus group (for EFC12456: 30 per patient-year vs. 43 per patient-year). However, the lower event rate of severe hypoglycemia observed in the U-300 arm is likely attributable to a higher rates of severe hypoglycemia in a few individual patients in the Lantus group (for example, 14 events in one patient).

8. Safety

The pooled Phase 2/3 safety database consisted of 304 subjects with T1DM exposed to U-300 and 1242 subjects with T2DM exposed to U-300. The total exposure to Toujeo at the time of NDA submission was 133 subject-years in the T1DM population and 586 subject-years in the T2DM population. The median duration of exposure was 183 days for both T1DM and T2DM populations. 76% of patients with T1DM were exposed for at least 25 weeks and 89% of patients with T2DM were exposed for at least 25 weeks. The total exposure at 6 months is consistent with the FDA draft guidance for products for diabetes mellitus, but there is relatively sparse 1-year data (at the time of NDA submission). However, at pre-submission meetings, the safety program was agreed upon with the Sponsor in light of the fact that Toujeo has the same active ingredient as Lantus for which there is considerable experience and safety data. As noted above, FDA agreed that the 6 month safety extensions for the pivotal phase 3 studies were not required at the time of NDA submission.

The pooled safety database to compare incidence of adverse events between Toujeo and comparator (Lantus) was composed of patients from the two T1DM studies (EFC12456 - 6

months/26 weeks; PDY12777 - 16 weeks), and the three T2DM studies with data included up to the 6 month timepoint, i.e. at the time of the primary efficacy assessment. The safety database is adequately representative of the majority of intended users of Toujeo, for example among type 2 diabetes patients, there were patients early in their diabetes course (insulin naïve) and sicker patients (already on basal/bolus therapy). Safety data from the 6 month extensions were submitted unblinded due to the open label nature of the trials, in the 120-day safety update. Dr. Condarco reviewed the safety data in the 120-day safety update and concluded that these data did not change the overall safety findings for Toujeo found in the original NDA submission. The data discussed below reflect the safety findings in the original NDA pooled Phase 2/3 safety database.

Overall, there were no important safety findings in the Toujeo development program that were unexpected. Hypoglycemia, an expected safety finding, is discussed separately in section 7. The general safety assessment revealed a safety profile very similar to Lantus. This included the following findings:

Deaths:

There were a similar number of deaths (eight) in the U-300 group compared with the Lantus group (five). The deaths spanned multiple SOC and PTs and no deaths appeared to be causally related to Toujeo (or Lantus for that matter). No unusual deaths were reported, i.e. all were reasonably expected in a population of patients with diabetes, e.g. myocardial infarction, renal failure, and sudden cardiac death.

Nonfatal Serious Adverse Events (SAEs):

Nonfatal SAEs occurred in 5.9% of U-300-treated patients and 7.2% of Lantus-treated patients in the T1DM population. Nonfatal SAEs occurred in 5.2% of U-300-treated patients and 5.0% of Lantus-treated patients in the T2DM population.

Among T1DM patients the most commonly reported nonfatal SAE was hypoglycemia which was balanced between treatment groups (3.0% and 3.9% for U-300 and Lantus, respectively). Other than hypoglycemia nonfatal SAEs were not reported in >1% for any Preferred Term or SOC. Nonfatal SAEs were not unexpected for the patient demographic. For example, there was one malignancy – a case of malignant melanoma which is not uncommon in younger patients. Overall, there was no pattern to the nonfatal SAEs among T1DM patients that suggested a safety concern.

Among T2DM patients, the most commonly reported nonfatal SAEs were those one would expect in a T2DM population, e.g. infections (1.1% in each treatment group) and cardiac disorders (1.3% in the U-300 treatment group and 1.2% in the Lantus treatment group), with no other SOC showing frequency >1%. Additionally, within each SOC the events spanned multiple Preferred Terms. Overall, there was no pattern to the nonfatal SAEs among T2DM patients that suggested a safety concern.

Dropouts due to Adverse Events:

Dropouts due to AEs were balanced between treatment groups and not unreasonably high. Among both the T1DM and T2DM populations the dropout rate due to AEs was less than 2%.

AEs leading to dropout spanned multiple SOCs; there was no pattern to these events. Dr. Condarco concluded that there was no safety concern regarding dropouts, and I agree with this assessment.

Submission Specific Safety Concerns:

Hypoglycemia is discussed in section 7 of this review. Other AEs of interest presented by the Sponsor included injection site reactions, hypersensitivity reactions, and cardiovascular events (CV events). Injection site reactions are a particular concern for this application because of the higher concentration of insulin delivered to the subcutaneous space. Hypersensitivity reactions are a concern for all insulin drugs, and CV events are a concern for all diabetes drugs because CV death is the most common cause of death among patients with diabetes mellitus.

Injection site reactions were identified using the following MedDRA searches:

- Under SOC General disorders and administration site conditions: HLTs Administration site reactions NEC (Not elsewhere classified), Injection site reactions, Infusion site reactions and Application and instillation site reactions under HLT Administration site reactions

Hypersensitivity reactions were identified using the following MedDRA searches:

- Standardized MedDRA query (SMQ) Angioedema (Narrow), SMQ Severe cutaneous adverse reactions (Broad and Narrow), HLT Anaphylactic responses, and SMQ Hypersensitivity (Broad and Narrow).

Note that the studies were not designed to prospectively assess CV risk as per the 2008 Draft Guidance: *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. However, insulin products are currently exempt from this requirement. Therefore the Sponsor’s reported “CV risk assessment” was based on the usual method of safety evaluation, i.e. MedDRA coded AE reporting and standardized MedDRA queries.

Dr. Condarco also examined evidence of overdose with U-300 in light of the higher concentration and safety concerns related to switching from Lantus to U-300 and vice versa (via examination of AEs related to worsening glycemic control during the first week after randomization) in light of the lesser PD effect of U-300. Body weight gain is also a known adverse effect of insulin therapy.

Notable findings from these safety assessments include:

- Injection site reactions and Hypersensitivity reactions were relatively balanced between treatment groups and generally consistent with the current Lantus labeling. The incidence of injection site reactions is shown below. The most common preferred terms were ‘injection site bruising’ and ‘injection site pain’. There were no serious reactions.

	T1DM		T2DM	
	Toujeo	Lantus	Toujeo	Lantus
Any injection site reaction	2.6%	1.6%	2.4%	3.1%

- There was no apparent imbalance in CV risk although the incidence of any MACE event was only about 1% or less in both treatment groups.
- There were no reported accidental ‘overdose’ of U-300 due to misunderstanding of the concentration of the formulation
- There were two reports of ‘hyperglycemia’ during the first week of randomized therapy – one in each treatment group suggesting no clinically important implications of the lesser PD effect of U-300 within this early time frame. There were no reports of diabetic ketoacidosis (DKA) or severe hyperglycemia.
- There were no important differences in body weight between Toujeo and Lantus treated patients.

Common Adverse Events:

Common adverse events were comparable between Toujeo and Lantus. The only adverse events (other than hypoglycemia) reported with a frequency $\geq 5\%$ and more commonly with Toujeo were nasopharyngitis and upper respiratory tract infection. These are unlikely to be related to insulin use.

	T1DM		T2DM	
	Toujeo	Lantus	Toujeo	Lantus
Nasopharyngitis	12.8%	10.9%	7.1%	5.8%
Upper respiratory tract infection	9.5%	7.6%	5.7%	5.4%

Other Safety Analyses:

All other routine safety analyses such as laboratory findings, vital signs, electrocardiograms were reviewed by Dr. Condarco and found to be unremarkable.

9. Advisory Committee Meeting

An advisory committee meeting was *not* convened for this NDA.

10. Pediatrics

[Redacted text block with (b) (4) notation]

It was later determined by the Division and with discussion with the Pediatric Review Committee [Redacted] (b) (4) that this product will not trigger PREA, i.e. this product does not trigger PREA because it does not involve a new active ingredient, new indication, route of administration, dosage form, or dosing regimen. [Redacted] (b) (4)

[Redacted text block]

11. Other Relevant Regulatory Issues

Proprietary name of product

On 7 Jul 2014, DMEPA issued an approval letter for this NDA approving the name “Toujeo SoloStar”. However, in the majority of labeling, i.e. where only the drug is referenced, the name “Toujeo” is used without SoloStar. DMEPA clarified in an email dated 24 Feb 2014 that it is acceptable to use only Toujeo when referring to the drug. If the Sponsor developed a new device and wanted to change the ‘SoloStar’, i.e. device part of the proprietary name that could be accomplished with a new review.

Use of proprietary name ‘Lantus’ in Toujeo labeling

The Division sought input from the Office of Regulatory Policy regarding use of the proprietary name Lantus in the Toujeo label. The Sponsor is requesting to use the trade name of the comparator product (Lantus) in the Toujeo label. The Sponsor cites Humalog, Novolog, and Bydureon as precedent (which was confirmed by the Office of Regulatory Policy) for use of the comparator trade name in approved labeling by the same sponsor. In support of its request, the Sponsor raises certain scientific considerations regarding potential differences with other 100 U insulin glargine products, with which the Division agrees. Based on Division experience, U-100 insulin glargine products approved under the 505(b)(2) pathway should not be considered the ‘same’ as the listed drug. Therefore, the Office of Regulatory Policy has stated there is no reason to recommend against the use of “Lantus” in the Toujeo labeling in these specific circumstances (i.e., describe the comparator as “Lantus (insulin glargine), 100 U/mL” the 1st time it’s referenced in labeling, and subsequently describe as “Lantus”).

Unit definition of insulins and unit-to-unit conversion

Extensive discussion occurred within the Division and between the Division, the Office of Clinical Pharmacology, and the Office of Drug Evaluation II regarding the lower PD effect of U-300 compared with U-100 on a unit to unit basis.

Dr. Parks, Deputy Director of ODE II, consulted the Biosimilars Committee by email with regard to concerns raised by the Office of Clinical Pharmacology regarding the PK/PD differences between the two formulations of glargine and how that would affect the unit definition of insulins. OCP also raised concern about implication to 505(b)(2) products and biosimilars.

Dr. Parks’ email noted that based on a WHO expert committee on biological standardization, 1 Unit of insulin = 6 nmol of recombinant human insulin (RHI) and the majority of insulin preparations are marketed at a strength of 100 U/mL (600 nmoles/mL). While no approved insulin preparations are considered interchangeable, switching does occur and often the dosage conversion is on a unit-to-unit basis. Recognizing that clinical practice involves switching from insulin to insulin, FDA labels recommend close monitoring for glycemic control when this is done and when differences in PK/PD effects have been observed, labels may also advise that higher or lower amounts of insulin may be required upon switching.

Therefore, the basis for the approval recommendation is that:

1. DMEP believes the differences in PK/PD can be labeled
2. The PK/PD differences are not clinically relevant based on clinical efficacy trial data (also to be labeled)
3. We are not aware of a regulatory or legal basis for requiring company to reformulate if there are data to support labeling for safe and effective use of this product.
4. Toujeo is not being labeled as interchangeable or pharmaceutically/therapeutically equivalent to insulin glargine and will contain similar language to other insulin products about glycemic monitoring upon 'switching' between insulin products
5. This is not a 505(b)(2) application. Putting aside the protein aspect of this product, even if this was a 505(b)(2) application the company conducted a full clinical program to support labeling where differences exist between Toujeo and insulin glargine.
6. This is not a biosimilar application

Dr. Christl, Associate Director for Therapeutic Biologics, OND Therapeutic Biologics and Biosimilars Team (TBBT) agreed with this approach noting that the application contains sufficient data to support the safety and efficacy of the product for the requested indications and conditions of use. Toujeo is not being labeled to specifically be used as an alternative medication to Lantus. Therefore, there would be no information in the labeling for Toujeo that would suggest a unit-to-unit equivalence between the products. In addition, even the approved products labeled as 100 U/mL may not have unit-to-unit equivalence, thus necessitating dose titration to effect. For example, in pre-approval phase 3 studies it appeared that at higher doses Levemir may have had lower *in vivo* potency than NPH. Therefore, there is precedent for approving insulins that do not demonstrate clear unit-to-unit-equivalence.

In the context of biosimilars, the products must be the same strength and there can be no clinically meaningful differences. If this were being evaluated as a biosimilar, there would be a question of whether the product were truly the same strength, regardless of the ability to support that the observed differences in PK do not translate into clinically meaningful differences. However, these are not requirements for a 501(b)(1) NDA. Since we do not expect other U-100 products to support that they, in fact, have 100 U/mL by demonstrating similar PK to other U-100 products, we do not see a rationale for requiring a unit-to-unit equivalence through PK for Toujeo.

12. Labeling

A line-by-line labeling review is being completed separately.

High Level Labeling issues:

Lantus data in Toujeo labeling

Discussion occurred between the Division, ODE II leadership, and the OND Director regarding the appropriateness of including safety data regarding Lantus in the Toujeo label. As Toujeo has the same active ingredient as Lantus, including safety studies/data from the

Lantus label may be appropriate in certain circumstances if the safety variable is not dependent on the PK/PD differences between the products. Further, given that only 6 months of safety follow up data were submitted with the NDA, the question arises whether data from long-term trials, i.e. five years or more can be relied upon to establish the long-term safety of Toujeo.

The Sponsor proposes to include information from the ORIGIN trial [A Multicenter, International, Randomized, 2x2 Factorial Design Study to Evaluate the Effects of Lantus® (Insulin Glargine) Versus Standard Care, and of Omega-3 Fatty Acids Versus Placebo, in Reducing Cardiovascular Morbidity and Mortality in High Risk People with Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), or Early Type 2 Diabetes Mellitus: The ORIGIN Trial (Outcome Reduction with Initial Glargine Intervention)] a CV outcomes trial that was approved as an efficacy supplement on 18 Oct 2013. The ORIGIN trial was an international, multicenter, randomized trial conducted in 12,537 participants with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or early type 2 diabetes mellitus and evidence of CV disease. Participants were randomized to receive Lantus, titrated to a FPG of 95 mg/dL or less, or standard care. The trial was event driven, and median duration of follow-up was approximately 6.2 years. ORIGIN demonstrated no excess cardiovascular risk with Lantus therapy compared with standard care. In the approval decision, labeling clearly delineated important details of the ORIGIN subject population because the demography, cardiovascular risk status, and glycemic control status were not considered representative of Lantus users as a whole, particularly in relation to HbA1c values.

In addition, cancer risk has been an ongoing safety issue with Lantus since 2009 when tracked safety issue (TSI 747) was opened based on four observational studies published in *Diabetologia* (the journal of the European Association for the Study of Diabetes [EASD]), reporting some level of association between the use of insulin glargine, and other insulin analogues, and various types of cancer. In approving the ORIGIN supplement, the Division included cancer risk information for Lantus in the label because ORIGIN provided the most reliable and comprehensive analyses to date on the Lantus/cancer safety issue. Providing these data in the Lantus label emphasized FDA's finding that the epidemiologic studies reviewed were inconclusive, and that there was no clear evidence of an association between Lantus and cancer risk.

(b) (4)



It is unknown whether the PK/PD characteristics of an insulin product contribute to the CV safety profile. It is possible that part of the CV effects of insulins have to do with their potential to cause hypoglycemia. Given that the PK/PD profile of an insulin product could affect hypoglycemia risk it follows that Toujeo, despite having the same active ingredient as Lantus, could theoretically have a different CV risk profile than Lantus. The consensus of the Agency was that since Lantus has the same active ingredient as Toujeo it would be useful information for prescribers to know that the *active ingredient* has been studied in a CV outcomes trial and found to have no excess CV risk vs. standard of care. Therefore, it would be

appropriate to include data from ORIGIN in the Toujeo label with a caveat that the relevance of this information to Toujeo is unknown. The issue of cancer risk is likely more related to systemic exposure of the active ingredient than the PK/PD profile and is more reasonably extrapolated from Lantus to Toujeo.

(b) (4)

Adverse reactions

Studies with Toujeo were conducted entirely with active comparator; there are no placebo-controlled data to inform safety. While this is acceptable to support approval (insulins are difficult to blind because of injection volumes, delivery devices, etc. and it is unethical to conduct placebo controlled insulin trials in type 1 diabetes patients because these patients need insulin to survive) the Office of Prescription Drug Promotion has advised the Division to show single arm data only for common adverse events including hypoglycemia in section 6 of the Toujeo label (b) (4)

(see also discussion in section 7).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

Approval is recommended because there is substantial evidence of effectiveness from four adequate and well-controlled pivotal phase 3 trials for the claimed indication (improvement in glycemic control in patients with diabetes mellitus). In this NDA the determination of effectiveness is based on the surrogate endpoint of HbA1c which is consistent with the current approach to diabetes drug evaluation. The FDA draft guidance entitled Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention states, “For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control.” My recommendation is aligned with all of the primary reviewers. No reviewer identified deficiencies with the efficacy studies including choice of endpoint, choice of control, conduct of the studies, and appropriateness of statistical analyses including handling of missing data. Overall, the efficacy assessment of this NDA was fairly straightforward, with the exception of the observed lower *in vivo* potency (pharmacodynamic effect) of Toujeo vs. Lantus. As discussed in this review there was some concern of the clinical implication of this difference. Ultimately, all disciplines agreed that labeling could satisfactorily address this issue. Further, there is precedent for this approach as discussed above.

With regard to safety, the known and labeled risks of insulin drugs, including hypoglycemia, were assessed adequately in the Toujeo development program and found to be consistent with the known safety profile of Lantus and insulins in general. There were no unexpected safety findings, and no safety issues that need further assessment in postmarketing studies.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

No comments are recommended to the applicant at this time.

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/s/

LISA B YANOFF
02/25/2015

JEAN-MARC P GUETTIER
02/25/2015
I concur.