

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
206538Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206538

SUPPL # NA

HFD #

Trade Name Toujeo SoloStar

Generic Name insulin glargine subcutaneous injection, 300 Units/mL

Applicant Name sanofi-aventis U.S. LLC

Approval Date, If Known February 25, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

NA

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

NA

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

No

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 021081 LANTUS (insulin glargine [rDNA origin]) injection

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

NA

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

YES NO

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

YES NO

If yes, explain:

NA

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

YES NO

If yes, explain:

NA

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

EFC12456, EFC11628, EFC11629, and EFC12347

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

Investigation #4 YES NO

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

NA

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

NA

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

EFC12456, EFC11628, EFC11629, and EFC12347

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

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

Investigation #1 EFC12456

IND # 112400 YES !
! NO
! Explain:

Investigation #2, EFC11628

IND # 112400 YES !
! NO
! Explain:

Investigation #3, EFC11629

IND # 112400 YES !
! NO
! Explain:

Investigation #4, EFC12347

IND # 112400 YES !
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Not applicable

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

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

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

NA

Name of person completing form: Richard Whitehead, M.S.
Title: Senior Regulatory Health Project Manager
Date: 2/24/2015

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Division Director

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

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

/s/

RICHARD E WHITEHEAD
02/25/2015

JEAN-MARC P GUETTIER
02/26/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 206538	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Toujeo Established/Proper Name: insulin glargine, U-300 Dosage Form: Injection		Applicant: Sanofi-Aventis U.S. LLC Agent for Applicant (if applicable): N/A
RPM: Richard Whitehead, M.S.		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: </p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 25, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): insulin (confirm chemical classification at time of approval)	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation	
NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies	
<input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required	
Comments:	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action and date: AP 2/25/15
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included See AP letter dated 2/25/15 for final labeling
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert 2/25/15 <input checked="" type="checkbox"/> Instructions for Use 2/25/15 <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included See AP letter dated 2/25/15 for final labeling
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included See AP letter dated 2/25/15 for final labeling
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	7/07/14 7/02/14
❖ Labeling reviews (indicate dates of reviews)	RPM: SRPI 2/23/15 DMEPA: 1/16/15; 11/03/14 DMPP/PLT: 2/17/15 DRISK: 1/28/15 OPDP: 2/23/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>2/11/2015</u> If PeRC review not necessary, explain: 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	2/25/15 (2); 2/24/15; 1/29/15(2); 1/13/15; 1/05/15; 12/17/14; 12/10/14; 11/21/14; 9/29/14; 7/07/14 (2); 7/03/14; 5/02/14
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	N/A
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg 10/25/13 (IND 112400) <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A Pre-IND 9/07/11 (IND112400)
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	2/25/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	2/25/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review see CDTL review 2/25/15 1/28/15; 6/13/14 <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	See page 232 of the Clinical Review dated 1/28/15
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	1/28/15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	1/29/15 (2); 1/15/15; 11/17/14 (3)
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	1/26/15; 6/06/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	1/28/15; 6/13/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	1/16/15; 6/13/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	1/22/15; 6/02/14
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	1/30/15; 6/03/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	CDRH 1/26/15; 11/12/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 60 DNDQAIH 1/22/15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	NA
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	NA
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 2/24/15 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done

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/s/

RICHARD E WHITEHEAD
03/02/2015

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: Re: NDA206538 Toujeo: agreed labeling
Date: Wednesday, February 25, 2015 5:08:24 PM
Attachments: ToujeoSoloStar-1Count-Label-Single Patient-draftB.PDF
ToujeoSoloStar-3Count-Carton-Single Patient and FPO pen-draftC.PDF
ToujeoSoloStar-5Count-Carton-Single Patient and FPO pen-draftC.PDF
TOUJEO-proposedppi-25Feb2015.doc
TOUJEO-proposed-solostar-ifu-25Feb15.doc
Toujeo-annotatedpi-24feb15-track changes-Sanofi response-25Feb15-final.doc

Antonella,

We acknowledge receipt and note your agreement to the attached labeling dated February 25, 2015 for NDA206538 Toujeo.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Loizito@sanofi.com [<mailto:Antonella.Loizito@sanofi.com>]
Sent: Wednesday, February 25, 2015 4:49 PM
To: Whitehead, Richard
Subject: FW: NDA206538 Toujeo: agreed labeling

Dear Rich,

Attached are all pieces of labeling as exchanged today for NDA 206538.

In order to obtain approval today, Sanofi agrees that the labeling submitted herein constitutes adequate directions for use.

We thank the Division and Office members for the dialogue that we have engaged in over the past few weeks. However, Sanofi maintains that the inclusion of comparative data (per our labels dated Feb 4, 10 and 23, 2015) are in keeping with the provisions outlined in the PLR and are neither false nor misleading.

Regards,
Antonella

From: Whitehead, Richard [<mailto:Richard.Whitehead@fda.hhs.gov>]
Sent: Wednesday, February 25, 2015 12:42 PM
To: Loizito, Antonella R&D/US
Subject: NDA206538 Toujeo: agreed labeling

Antonella,

I am resending all of the agreed labeling to this point for NDA206538 Toujeo. These can be submitted to you application. I will send the PI shortly.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

34 Page(s) of Draft Labeling has been Withheld in Full as B4
(CCI/TS) immediately following this page

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/s/

RICHARD E WHITEHEAD
02/25/2015

From: Whitehead, Richard
To: Antonella.Loizito@sanofi.com
Subject: NDA206538 Toujeo: Patient Labeling
Date: Monday, February 23, 2015 11:56:35 AM

Antonella:

Please see the response below to your proposed (b) (4) in-use citing the CMC information:

“The data that you provided in your amendment was reviewed and it was determined the data is not sufficient to support the (b) (4) in-use period. (b) (4)

You should perform USP/Ph.Eur. (b) (4) testing on product formulated (b) (4) and the test should be extended to (b) (4) days to support the (b) (4) product use period.”

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Loizito@sanofi.com [<mailto:Antonella.Loizito@sanofi.com>]
Sent: Monday, February 23, 2015 11:38 AM
To: Whitehead, Richard
Subject: RE: NDA206538 Toujeo: Patient Labeling

Dear Rich,

Regarding the in-use period in the labeling, the PPI and IFU you sent today still includes the “28 days” in-use period. In our responses to the labels this morning, we proposed (b) (4) in-use citing the CMC information we submitted on February 4, 2015.

Has this information been considered by FDA? And if so, what is FDA's decision on the duration of the in-use period?

This will help in how we respond to the PPI and IFU.

Regards,
Antonella

From: Whitehead, Richard [<mailto:Richard.Whitehead@fda.hhs.gov>]
Sent: Monday, February 23, 2015 9:36 AM
To: Lozito, Antonella R&D/US
Subject: NDA206538 Toujeo: Patient Labeling

Antonella,

DMPP and OPDP's review of the Toujeo (insulin glargine [rDNA origin] injection) PPI and IFU is complete. Attached is a marked-up and a clean copy of our revisions to the PPI and IFU in Word. Please return agreed labeling today Monday, February 23, 2015.

In addition to content, Patient Labeling often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please let us know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
02/24/2015

PeRC Meeting Minutes
February 11, 2015

PeRC Members Attending:

Lynne Yao

Rosemary Addy ([redacted] Non-responsive [redacted] reviews only)

George Greeley

Ruthanna Davi

Wiley Chambers

Tom Smith

Karen Davis-Bruno

Peter Starke

Daiva Shetty

Andrew Mulberg

Greg Reaman

Andrew Mosholder [redacted] Non-responsive [redacted]

Hari Cheryl Sachs

Julia Pinto

Olivia Ziolkowski

Gilbert Burckhart

Kevin Krudys

Barbara Buch

Rachel Witten

Dianne Murphy

Maura O'Leary [redacted] Non-responsive [redacted]

Kim Dettlebach [redacted] Non-responsive [redacted]

Sonal Vaid [redacted] Non-responsive [redacted]

Nisha Jain [redacted] Non-responsive [redacted]

Adrienne Hornatko-Munoz [redacted] Non-responsive [redacted]

Agenda

Non-responsive

10:50	NDA	206538	Toujeo SoloStar (Partial Waiver/Deferral/Plan) *Agreed iPSP	A long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
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Non-responsive

3 Page(s) has been Withheld in Full as Non Responsive immediately following this page

Non-responsive

Toujeo SoloStar

- Proposed Indication: A long-acting human insulin analog indicated to improve to improve glycemic control in adults with diabetes mellitus
- The Division noted that the sponsor submitted an Agreed iPSP with this application for the proposed indication.
- The Division clarified that upon review of the data provided in the application that no additional indications/dosing regimens would be granted [REDACTED] (b) (4) [REDACTED]. Therefore, the Division believes that this application is not subject to PREA.
- PeRC Recommendations:
 - The PeRC agreed that this application is not subject to PREA. However, if the sponsor is granted a different dosing regimen in the future, then PREA would be triggered.
 - The PeRC also noted that a WR can be issued that would include any studies/information that would be of public health benefit to a pediatric population. A WR could potentially include comparative studies on the development of hypoglycemia. The PeRC encouraged the Division to negotiate any such studies with the sponsor before issuing a WR.

Non-responsive

2 Page(s) has been Withheld in Full as Non Responsive immediately following this page

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/s/

GEORGE E GREELEY
02/23/2015

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling
Date: Thursday, January 29, 2015 3:50:13 PM

Antonella,

We find the revised container label acceptable.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Loizito@sanofi.com [mailto:Antonella.Loizito@sanofi.com]
Sent: Thursday, January 29, 2015 12:26 PM
To: Whitehead, Richard
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Thanks Rich.

Please see attached for a revised version of the pen label in response to DMEPA's comment. The "Rx ONLY" statement has been unbolded, and the "Subcutaneous use only" statement has been bolded.

Does DMEPA agree with the proposed revision to the pen label?

Regards,
Antonella

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, January 29, 2015 11:59 AM
To: Loizito, Antonella R&D/US
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

We don't expect any other comments regarding those items.

From: Antonella.Loizito@sanofi.com [mailto:Antonella.Loizito@sanofi.com]
Sent: Thursday, January 29, 2015 11:43 AM
To: Whitehead, Richard
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Thanks Rich,

In response to the below request, in order to avoid sending you multiple versions of the pen label, do you expect further comments from DMEPA or any other group on the pen and/or carton labels?

Regards,
Antonella

From: Whitehead, Richard [<mailto:Richard.Whitehead@fda.hhs.gov>]
Sent: Thursday, January 29, 2015 10:56 AM
To: Lozito, Antonella R&D/US
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Antonella,

Yes, DMEPA is referring to the carton and container labels submitted to the NDA on January 8.

The comment is for the container (pen) label only that they submitted on January 8.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEI/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Lozito@sanofi.com [<mailto:Antonella.Lozito@sanofi.com>]
Sent: Thursday, January 29, 2015 10:32 AM
To: Whitehead, Richard
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Thank you Rich.

To confirm, DMEPA is referring to the carton and container labels submitted to the subject NDA on January 8, 2015, correct?

Also, does the below comment also apply to the carton as well as the container (pen) label?

Regards,
Antonella

From: Whitehead, Richard [<mailto:Richard.Whitehead@fda.hhs.gov>]
Sent: Thursday, January 29, 2015 10:21 AM
To: Lozito, Antonella R&D/US
Subject: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Antonella,

Please see the comment from the Division of Medication Error Prevention and Analysis (DMEPA)

regarding your NDA 206538 Toujeo SoloStar Carton and Container Labeling:

“The revised container label can be improved from a medication error perspective. We recommend that the “Rx ONLY” statement be revised to be less prominent than other important information such as the “Subcutaneous use only” statement.”

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov



Lot :

EXP :

NDC 0024-5869-01



Toujeo® SoloStar®
insulin glargine (rDNA origin) injection

For Single Patient Use Only

300 Units/mL (U-300)

Subcutaneous use only. Rx ONLY
Do not remove insulin with syringe
Always use a new needle

Do not mix with other insulins
sanofi-aventis U.S. LLC Origin Germany 50110720
<MAT> XXXXXX **450 units/1.5mL prefilled pen**

(b) (4)

FOR FDA SUBMISSION ONLY

Reference ID: 3694535

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/s/

RICHARD E WHITEHEAD
01/29/2015

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling
Date: Thursday, January 29, 2015 10:56:18 AM

Antonella,

Yes, DMEPA is referring to the carton and container labels submitted to the NDA on January 8.

The comment is for the container (pen) label only that they submitted on January 8.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Loizito@sanofi.com [mailto:Antonella.Loizito@sanofi.com]
Sent: Thursday, January 29, 2015 10:32 AM
To: Whitehead, Richard
Subject: RE: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Thank you Rich.

To confirm, DMEPA is referring to the carton and container labels submitted to the subject NDA on January 8, 2015, correct?

Also, does the below comment also apply to the carton as well as the container (pen) label?

Regards,
Antonella

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, January 29, 2015 10:21 AM
To: Loizito, Antonella R&D/US
Subject: NDA 206538 Toujeo SoloStar: Carton and Container Labeling

Antonella,

Please see the comment from the Division of Medication Error Prevention and Analysis (DMEPA) regarding your NDA 206538 Toujeo SoloStar Carton and Container Labeling:

“The revised container label can be improved from a medication error perspective. We recommend that the “Rx ONLY” statement be revised to be less prominent than other important information such as the “Subcutaneous use only” statement.”

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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RICHARD E WHITEHEAD
01/29/2015

From: Antonella.Lozito@sanofi.com
To: Whitehead.Richard
Subject: RE: NDA206538 Toujeo: Information Request
Date: Tuesday, January 13, 2015 12:32:50 PM

Hi Rich,
I confirm receipt.

Regards,
Antonella

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Tuesday, January 13, 2015 11:40 AM
To: Lozito, Antonella R&D/US
Subject: NDA206538 Toujeo: Information Request

Antonella,

In reference to NDA206538 Toujeo, please see the request for information below:

1. Within submission section 3.2.P.2 you have provided a “use risk analysis” as related to the insulin glargine - solution for injection - 300 U/mL human factors study. The Agency is unable to locate any additional risk management documentation for the combination product and/or device constituent part of the combination product. Please provide, or provide the existing location within the file of, risk analysis documentation for physical/functional aspects of the combination product (i.e. risk analysis information which covers risks that do not originate from the usability of the combination product).
2. Within the submission, you have provided summary documentation of a number of performance tests conducted on the combination product. However, the Agency is unable to locate the specific test reports which support the conclusions made within the summary documents. Additionally, within the summary reports, results are often stated as “acceptable per standard”. For each of the below referenced test report summary documents, please provide all low-level test documents which support the summaries and conclusions drawn and include actual test values meeting acceptance criteria:
 - a. Pen injector: performance test (ISO 11608-1)
 - b. Pen injector: performance test (ISO 11608-3 and 13926-2) – cartridge
 - c. Container closure system: pen injector - needle reuse study
 - d. Pen injector: biocompatibility (ISO 10993-1)
 - e. STABILITY DATA - Dose accuracy pen injector during storage

For item e, above, please provide the most updated test records available

3. Within the submission 3.2.P.8.3, you provided two documents related to in-use performance of the combination product, *STABILITY DATA - Primary stability: In-use* ((b) (4) and green pen) and *STABILITY DATA Primary stability: In-use* ((b) (4) pen).
 - a. Please state if these in-use assessments were sensitive to functionality of the device constituent part (injector). Examples of device constituent part functionality

may include but may not be limited to: dose delivered, presence of visual and tactile feedback, ability to assemble needle on injector, etc.

- b. If your firm does consider these tests as having challenged device constituent part functionality, please provide
 - i. The most updated copies of the test summaries provided as *STABILITY DATA - Primary stability: In-use* (b) (4) and green pen) and *STABILITY DATA Primary stability: In-use* (b) (4) pen).
 - ii. All test documents which support these summary reports
4. Within the submission 3.2.P.8.3, you have provided a description of the stability test plan for the combination product.
 - a. The Agency is unable to locate test information which challenged the presentation of “*Drug product in 1.5 mL cartridges assembled in the pen injector*” to assessments of device functionality (i.e. tests which demonstrate the injector is able to perform as expected after artificial or real time aging). Please provide information which supports that the device constituent part will behave as expected after aging.
 - b. The Agency is unable to locate information which challenged device constituent part functionality after shipping pre-conditioning. Please provide information which supports that the device constituent part will behave as expected after shipping.
5. For questions 3-4, above. If your firm does not have sufficient information to demonstrate functionality of the device within the tests referenced, it may be possible to provide evidence of functionality of currently marketed products which are substantially similar in device design. Such a response, if provided, should include sufficient rationale for why differences between the subject product and marketed product is not be expected to impact assessments of stability or in-use evaluations.

Provide response to these questions by **January 15**. Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/13/2015

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: NDA206538 Toujeo: Information Request
Date: Monday, January 05, 2015 1:33:08 PM

Antonella,

We want to further evaluate the data from which the percent dose change (Question 2 and Question 3 copied below), in your response dated 16-Dec-2014, was obtained. Please provide BOTH the data you used to derive the percent change as well as the code you used. Furthermore, for Study PDY12777, please provide similar data from which percent dose change can also be derived.

AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 2:

Regarding the 120-Day Safety Update Report:

Based on Table 2 – “Mean average daily basal, mealtime and total insulin doses (U) at the 12-month on-treatment baseline and during the 4-week follow-up period - 4-week follow-up population (for EFC11628)”, it is unclear how the percent dose changes (for basal, prandial and total insulin) were calculated (page 402- 403 of the report). Please explain.

AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 3:

Regarding the 120-Day Safety Update Report:

Based on Table 2 – “Mean average daily basal, mealtime and total insulin doses (U) at the 12-month on-treatment baseline and during the 4-week follow-up period - 4-week follow-up population (for EFC11629)”, it is unclear how the percent dose changes (for basal, prandial and total insulin) were calculated (page 415- 416 of the report). Please explain.

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/05/2015

From: Whitehead, Richard
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: RE: NDA206538 Toujeo: labeling
Date: Wednesday, December 17, 2014 3:48:00 PM

Antonella,

Please see the response from DEMPA:

Your proposal appears acceptable; however, please submit the revised C & C and we will review and let you know if we have any further comments.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Antonella.Loizito@sanofi.com [<mailto:Antonella.Loizito@sanofi.com>]
Sent: Wednesday, December 17, 2014 3:38 PM
To: Whitehead, Richard
Subject: RE: NDA206538 Toujeo: labeling

Thank you Rich.

Regarding the statement "For Single Patient Use Only", we intend to add the statement to the Toujeo carton and container as we had proposed for the Lantus and Apidra carton and container labels, i.e., in red bold text on contrasting white background of the carton and container (pen) labels.

Does DMEPA agree that this **red bold text on contrasting white background** is acceptable?

Should we be expecting further comments from DMEPA on labeling?

Regards,
Antonella

From: Whitehead, Richard [<mailto:Richard.Whitehead@fda.hhs.gov>]
Sent: Wednesday, December 17, 2014 12:09 PM
To: Loizito, Antonella R&D/US
Subject: NDA206538 Toujeo: labeling

Antonella,

DMEPA recommends the following changes to be implemented prior to approval of NDA206538 Toujeo:

A. Physician Insert: Section 2.2 Initiation of TRADENAME therapy

1. Add the statement: “Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. [REDACTED] (b) (4)

[REDACTED].”

B. Pen Label and Carton Labeling

1. Add the statement “For Single Patient Use Only”. The safety warning, “For Single Patient Use Only”, should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked. We also recommend using a red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
12/17/2014

From: Antonella.Loizito@sanofi.com
To: Whitehead.Richard
Subject: RE: NDA206538 Toujeo: Information Request
Date: Tuesday, December 09, 2014 3:00:12 PM

Thanks Rich, I confirm receipt.

Regards,
Antonella

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Tuesday, December 09, 2014 2:11 PM
To: Loizito, Antonella R&D/US
Subject: NDA206538 Toujeo: Information Request

Antonella,

Please see the following request for information:

1. For your investigations of immunogenicity response and clinical outcomes, you have provide analyses of central tendency, e.g. correlations between antibody titer and HbA1c, risk of hypoglycemia, etc. These types of analyses can dilute out the effect of immunogenicity in individual patients with high titer responses. Provide immunogenicity analyses and patient level data for patients with 'high' titer antibody response only, as defined in the NDA ($\geq 1/64$). Your submission should also include a listing and analysis of adverse event reports potentially related to immunogenicity for these patients.

1. Based on Table 2 – “Mean average daily basal, mealtime and total insulin doses (U) at the 12-month on-treatment baseline and during the 4-week follow-up period - 4-week follow-up population (for EFC11628)”, it is unclear how the percent dose changes (for basal, prandial and total insulin) were calculated (page 402- 403 of the report). Please explain.

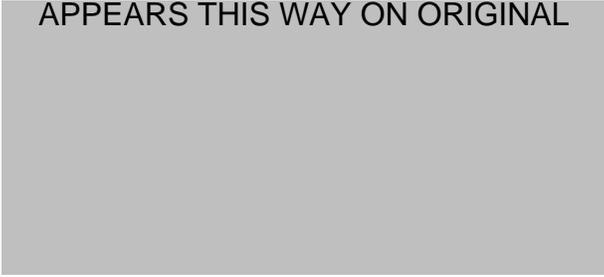
2. Based on Table 2 – “ Mean average daily basal, mealtime and total insulin doses (U) at the 12-month on-treatment baseline and during the 4-week follow-up period - 4-week follow-up population (for EFC11629)”, it is unclear how the percent dose changes (for basal, prandial and total insulin) were calculated (page 415- 416 of the report). Please explain.

Please provide answers to these questions as soon as possible, preferably by Friday December 12, 2014 and confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



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/s/

RICHARD E WHITEHEAD
12/10/2014

From: Antonella.Lozito@sanofi.com
To: [Whitehead, Richard](#)
Subject: RE: NDA206538 Toujeo: Information Request
Date: Friday, November 21, 2014 11:32:44 AM

Hi Rich,

I have a question for clarification on item #5 below.

In the "response-dated-10sep2014.pdf", we responded to FDA's request for tables showing the change in basal insulin dose (in Units and Units/kg) per week by arm (not the total dose administered).

Can you please confirm that the reviewer is now requesting graphs for the change in basal and prandial insulin (in Units and Units/kg) by study visit by arm?

Regards,
Antonella

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, November 20, 2014 10:06 AM
To: Lozito, Antonella R&D/US
Subject: NDA206538 Toujeo: Information Request

Antonella,

Please provide the following information for NDA206538 Toujeo within one week of receipt of this request.

Financial disclosure form:

1. Clarify why in Section 4 of the financial disclosure form: "CLINICAL INVESTIGATORS WHOSE FINANCIAL DISCLOSURE IS MISSING OR INCOMPLETE", states that there were 3 investigators who did not provide financial disclosure information, but only 2 investigators are listed in Table 4.
2. Explain why only two 3454 forms (with box #3 checked – expressing due diligence) are attached if there were 3 investigators who did not provide financial disclosure information.

120- safety report question:

3. 120 day safety report states that 1 death occurred since the NDA submission in study EFC12449. The narrative associated with this death states the patient was taking glargine. It is unclear if the patient was taking U300 or U100. Please clarify ISS question
4. Clarify why in Table 38 of the ISS, "Daytime hypoglycemia" added to "Nocturnal hypoglycemia" does not equal "All hypoglycemia"

Question regarding "response-dated-10sep2014.pdf" submitted on 9/23/2014:

5. For each of the pivotal studies (EFC12456, EFC11628, EFC11629 and EFC12347) please graph:
 - the units of basal insulin +/- standard error and units of prandial insulin +/- standard error titrated over the study visits.
 - the units/kg of basal insulin +/- standard error and units/kg of prandial insulin +/-

standard error titrated over the study visits.

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
11/21/2014

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: NDA206538 Toujeo: Information Request
Date: Monday, September 29, 2014 12:08:22 PM

Antonella,

In reference to NDA206538 Toujeo, please provide response to the following two requests for information:

1. Update the drug substance and drug product specifications for impurities (related/degradation) to provide acceptance criteria for each known impurity, largest single unknown impurity, and total (known and unknown) impurities.
2. Provide methodology (i.e. what variables) you used to create "**Table 100 - All TEAEs by primary SOC and PT during the main on-treatment period: T1DM and T2DM study pools - Safety population**" located in the ISS. We are unable to reproduce the findings listed for the T1DM population.

Provide an estimated date of completion for this Information Request. Let me know if you have any questions and please confirm receipt of the email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/29/2014



NDA 206538

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

sanofi-aventis U.S. LLC
Attention: Antonella Lozito, Pharm.D.
Associate Director
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your New Drug Application (NDA) dated and received April 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, Toujeo SoloStar (insulin glargine [rDNA origin]) injection, 300 Units/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **February 25, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **January 28, 2015**.

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

We request that you submit the following information:

1. Provide full documentation (or identify location in your submission) of performance testing that was conducted on the pen injector.
2. The applicant provided SAS codes for calculations involving only primary endpoint (HbA1C). There were no SAS codes submitted supporting other endpoints. Additionally, SAS program codes were not provided for any of the sub studies. Please provide SAS programs for all efficacy endpoints that will appear in the product label.
3. Provide the location of the raw and smoothed datasets (if applicable) for both glucose infusion rate and blood glucose concentration as well as the codes used to generate the smoothed profiles for Studies PKD10086, PKD13560, PKD11627, PKD12270, and TDR11626 or submit these data.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the partial waiver granted on March 19, 2014, for the pediatric study requirement for this application for pediatric patients less than 1 year of age for the type I diabetes mellitus and a partial waiver less than 10 years for type II diabetes mellitus.

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

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

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/s/

RICHARD E WHITEHEAD

07/07/2014

R. Whitehead signing for J.M. Guettier



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206538

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: Antonella Lozito, PharmD
Associate Director, Global Regulatory Affairs

Dear Dr. Lozito:

Please refer to your New Drug Application (NDA) dated and received April 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Glargine [rDNA origin] Injection, 300 Units/mL.

We also refer to your correspondence, dated and received April 30, 2014, requesting review of your proposed proprietary name, Toujeo SoloStar.

We have completed our review of the proposed proprietary name, Toujeo SoloStar and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your April 30, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lyle Canida, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1637. For any other information regarding this application, contact Richard Whitehead, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
07/07/2014

From: [Whitehead, Richard](#)
To: ["Antonella.Loizito@sanofi.com"](mailto:Antonella.Loizito@sanofi.com)
Subject: NDA 206538: Toujeo SoloStar (insulin glargine [rDNA origin]): proprietary name review
Date: Thursday, July 03, 2014 10:16:50 AM

Antonella,

We have completed our review of the proposed proprietary name, Toujeo SoloStar, and have concluded that this name is acceptable. If any of the proposed product characteristics as stated in your April 30, 2014 submission are altered, the name must be resubmitted for review.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
07/03/2014



NDA 206538

NDA ACKNOWLEDGMENT

sanofi-aventis U.S. LLC
Attention: Antonella Lozito, Pharm.D.
Associate Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Dr. Lozito:

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

Name of Drug Product: insulin glargine [rDNA origin] injection, 300 Units/mL; HOE901-U300

Date of Application: April 25, 2014

Date of Receipt: April 25, 2014

Our Reference Number: NDA 206538

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **Tuesday, June 24, 2014** in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RICHARD E WHITEHEAD
05/02/2014



IND 112400

MEETING PRELIMINARY COMMENTS

Sanofi US Services Inc.
Attention: Antonella Lozito, PharmD
Associate Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop: 55D-215A
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for HOE901-U300 (insulin glargine [rDNA origin]) injection.

We also refer to your correspondence, dated and received August 19, 2013, requesting a meeting to discuss clinical, statistical, device, and regulatory aspects of the planned NDA to support registration and approval of HOE901-U300 in adults with diabetes mellitus.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comment



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 25, 2013; 10:30 AM-12 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 112400
Product Name: HOE901-U300 (insulin glargine [rDNA origin]) injection
Indication: long-acting human insulin analog product indicated to improve glycemic control in adults with diabetes mellitus

Sponsor/Applicant Name: Sanofi US Services Inc.

FDA ATTENDEES (tentative)

Office of Drug Evaluation II

Curtis Rosebraugh, MD, Director
Mary Parks, MD, Deputy Director
Sara Stradley, Associate Director for Regulatory Affairs (Acting)

Office of New Drugs, Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD, Director (Acting) and
Ali Mohamadi, MD, Clinical Team Leader
Amy Egan, MD, Deputy Director of Safety
Lisa Yanoff, MD, Clinical Reviewer
Karen Davis Bruno, PhD, Nonclinical Reviewer and Team Leader
Richard Whitehead, MS, Regulatory Project Manager
Julie Van der Waag, MPH, Chief, Project Management Staff
Mehreen Hai, PhD, Safety Regulatory Project Manager

Office of Biostatistics

Mark Rothmann, PhD, Biostatistics Team Leader
Lee Ping Pian, PhD, Biostatistics Reviewer

Office of Biotechnology Products, Division of Therapeutic Proteins

Daniela Verthelyi, Biologist
Laura Salazar-Fontana, Senior Staff Fellow

Office of Clinical Pharmacology

Lokesh Jain, PhD, Clinical Pharmacology Team Leader
S.W. Johnny Lau, PhD, Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment (ONDQA)

Su Tran, PhD, Product Quality Team Leader
Xavier Ysern, PhD, Product Quality Reviewer

Office of Manufacturing and Product Quality

Tara Gooen, Division of Good Manufacturing Practice Assessment
Mahesh Ramanadham, Division of Good Manufacturing Practice Assessment

Office of Pharmaceutical Science, New Drug Microbiology Staff

Bryan Riley, PhD, Microbiologist
Vera Viehmann, Microbiologist
John Metcalfe, Microbiologist
Don Henry, Project Manager

Office of Surveillance and Epidemiology (OSE)

Yelena Maslov, Team Leader (Division of Medication Error Prevention and Analysis)
Sarah Vee, PharmD, DMEPA Reviewer
Bindi Nikhar, Medical Officer (Division of Pharmacovigilance)
Christine Chamberlain, Medical Officer (Division of Pharmacovigilance)
Cynthia LaCivita, PharmD, (Division of Risk Management)
Margarita Tossa, MS, Regulatory Project Manager

Office of Scientific Investigations, Division of Good Clinical Practice, Good Clinical Practice Assessment Branch

Cynthia Kleppinger, MD, Medical Officer
Janice Pohlman, MD, Medical Officer
Kassa Ayalew, Compliance Medical Officer

Office of Combination Products

Patricia Love, MD, MBA, Deputy Director
Bindi Nikhar, MD, Senior Clinical Advisor

Center for Devices and Radiological Health

Patricia Beaston, MD, PhD, Medical Officer
Keith Marin, Combination Products Team Leader
Richard Chapman, Supervisory General Engineer
Quynh Nguyen, Combination Products Human Factors Specialist
Ron Kaye, Products Human Factors Team Leader

Office of Bioinformatics, Electronic Submissions Group

Virginia Hussong, Supervisory Program Analyst

SPONSOR ATTENDEES

Sanofi

Reinhard Becker, MD, PhD, MSc, Clinical Pharmacology
Emmanuelle Boelle, PhD, Biostatistics
Svetoslav Dimitrov, MD, Global Pharmacovigilance & Epidemiology
Frank Erbstein, PhD, Medical Devices, Project Management Diabetes
Stanislav Glezer, MD, MBA, Global Project Leader
Eckhard Leifke, MD, Clinical Development, Diabetes Division
Antonella Lozito, PharmD, Global Regulatory Affairs
Rima Nassar, PhD, Global Regulatory Affairs
Agnes Riva-Pezzali, Global Regulatory Affairs
John A. Schalago MS, RAC, Global Head Combination and Medical Devices
Florian Shauderna, Dipl.-Ing., Team Leader Usability, Medical Devices

Monika Ziemen, Dr. med., MD, Clinical Development, Diabetes Division

(b) (4)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **Friday, October 25, 2013, 10:30AM-12PM, 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1309, Silver Spring, Maryland 20903**, between Sponsor and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to discuss the clinical, statistical, device, and regulatory development of the planned NDA to support registration and approval of HOE901-U300 (International Nonproprietary Name: insulin glargine [rDNA origin] injection) in adults with diabetes mellitus.

Insulin glargine is a recombinant human insulin analog that is a long-acting, parenteral blood glucose-lowering agent. Insulin glargine is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines remain at the C-terminus of the B-chain.

IND112400 was submitted to FDA on August 26, 2011, and no clinical hold issues were identified. The sponsor submitted a Type C meeting request which was denied on March 5, 2013. The sponsor was informed that we were denying the meeting because the topics of this meeting were consistent with a type B pre-NDA meeting. The sponsor was asked re-submit this meeting request no more than six months before your planned NDA submission date. The sponsor planned to submit a New Drug Application (NDA) in the first quarter of 2014 and

submitted a Type B meeting request. DMEP granted this as a Type B meeting on August 30, 2013. The briefing package was received on September 20, 2013. The sponsor has provided a list of 23 questions with topics from several disciplines including clinical pharmacology, clinical statistics, safety, device, human factors testing, regulatory, eCTD structure, narratives and case report forms, labeling, pediatrics, financial disclosure and clinical investigators. DMEP has convened subject matter experts within FDA across several disciplines to provide guidance at this meeting.

2. DISCUSSION

2.1. CLINICAL PHARMACOLOGY

Question 1: Clinical pharmacology studies (PKD10086, PKD11627 and TDR11626) were conducted comparing the PK/PD profile of HOE901-U300 to that of Lantus in healthy subjects and in patients with T1DM. These 3 studies will form the basis for labeling relating to human PK and PD of HOE901-U300 to be provided in the USPI.

Does the Division agree that the clinical pharmacology package is adequate to support registration and labeling of HOE901-U300?

FDA Response to Question 1: In general, your proposed clinical pharmacology package appears adequate to support the NDA for HOE901-U300. However, we remind you to propose and justify (b) (4) in the NDA for HOE901-U300.

Question 2: Registration (b) (4) will be supported by demonstrating bioequivalence between the 1.5 mL cartridge (standard formulation) and the (b) (4) formulations in study PKD13560.

Provided bioequivalence is demonstrated, does the Division agree (b) (4) ?

FDA Response to Question 2: Your proposal is acceptable.

2.2 CLINICAL

Question 3: Results of the immunogenicity (anti-insulin antibodies [AIA]) assessment in patients with T2DM on basal insulin (EFC11628 and EFC11629) who have completed the 6-months main study periods will be presented in the NDA. The AIA results after completion of the 12-month study duration for these patients and AIA results after completion of the 6-month main study periods and 12-month study duration for insulin-naïve patients with T2DM (EFC12347) and patients with T1DM (EFC12456) will be provided post approval.

Does the Division agree with this proposal for the immunogenicity assessment to be provided in the NDA?

FDA Response to Question 3: Yes, we agree with your proposal for the immunogenicity assessments to be provided in the NDA as outlined in your briefing document.

We also refer to previous advice given on February 7, 2013.

Question 4: Clinical studies conducted with HOE901-U300 are intended to support administration of HOE901-U300 (b) (4)

[Redacted]

Does the Division agree (b) (4)

[Redacted] ?

FDA Response to Question 4: No, we do not agree at this time (b) (4)

[Redacted] We will consider your proposal during the review of your application.

However, we have the following concerns regarding your proposal:

a. [Redacted] (b) (4)

b. [Redacted] (b) (4)

Question 5: The Sponsor seeks confirmation from the Division on the sponsor's approach to assessing the CV safety of HOE901-U300 which was outlined in the Pre-IND briefing package.

Can the Division please confirm their agreement?

FDA Response to Question 5: Your approach to assessing CV safety is acceptable. However, if a cardiovascular safety signal emerges during our review of your application, we may request additional information and/or analyses.

Question 6: [REDACTED] (b) (4)

Does the Division agree [REDACTED] (b) (4)

FDA Response to Question 6: No, we do not agree at this time [REDACTED] (b) (4)

This will be a review issue. However, as we noted in our pre-IND advice letter, we have concerns about this [REDACTED] (b) (4)

In addition, we have the following concerns:

You propose to evaluate [REDACTED] (b) (4)

We do not entirely agree [REDACTED] (b) (4)

2.3 STATISTICAL

2.3.1 Analysis and Presentation of Efficacy Data in NDA

Question 7: Does the Division agree with the analyses and presentation of results from clinical studies (as outlined in Section 2 of the SCE/ISE SAP) intended to support the efficacy of HOE901-U300 in the treatment of patients with T1DM and T2DM?

FDA Response to Question 7: Yes, we agree.

2.3.2. Analysis and Presentation of Safety Data in NDA

Question 8: Does the Division agree with the proposed pooling strategies and presentation of results of Phase 1 data intended to support the safety of HOE901-U300?

FDA Response to Question 8: Yes, we agree.

Question 9: Does the Division agree with the analyses and presentation of Phase 2/3 study results intended to support the safety of HOE901-U300 in the treatment of patients with T1DM and T2DM?

FDA Response to Question 9: Yes, we agree.

2.4 Device Differentiation/ Pen Injector

Question 10: As requested by the Division, Sanofi herein provides the pen differentiation study protocol and requests concurrence on the design and objectives of the proposed study (provided in Appendix Section 13.6), in particular with regard to the following:

- a) Study participants
- b) Comparator pen-device selection
- c) Task scenarios for each user group

FDA Response to Question 10:

- a) Study participants

Your proposal is acceptable. However, please ensure that study participants who are patients include some individuals with disease-related visual/tactile impairment (retinopathy, neuropathy).

b) Comparator pen-device selection

We recommend that you include the Humulin N Pen in your differentiation study.

c) Task scenarios for each user group

We recommend the following revisions to the tasks for each user group:

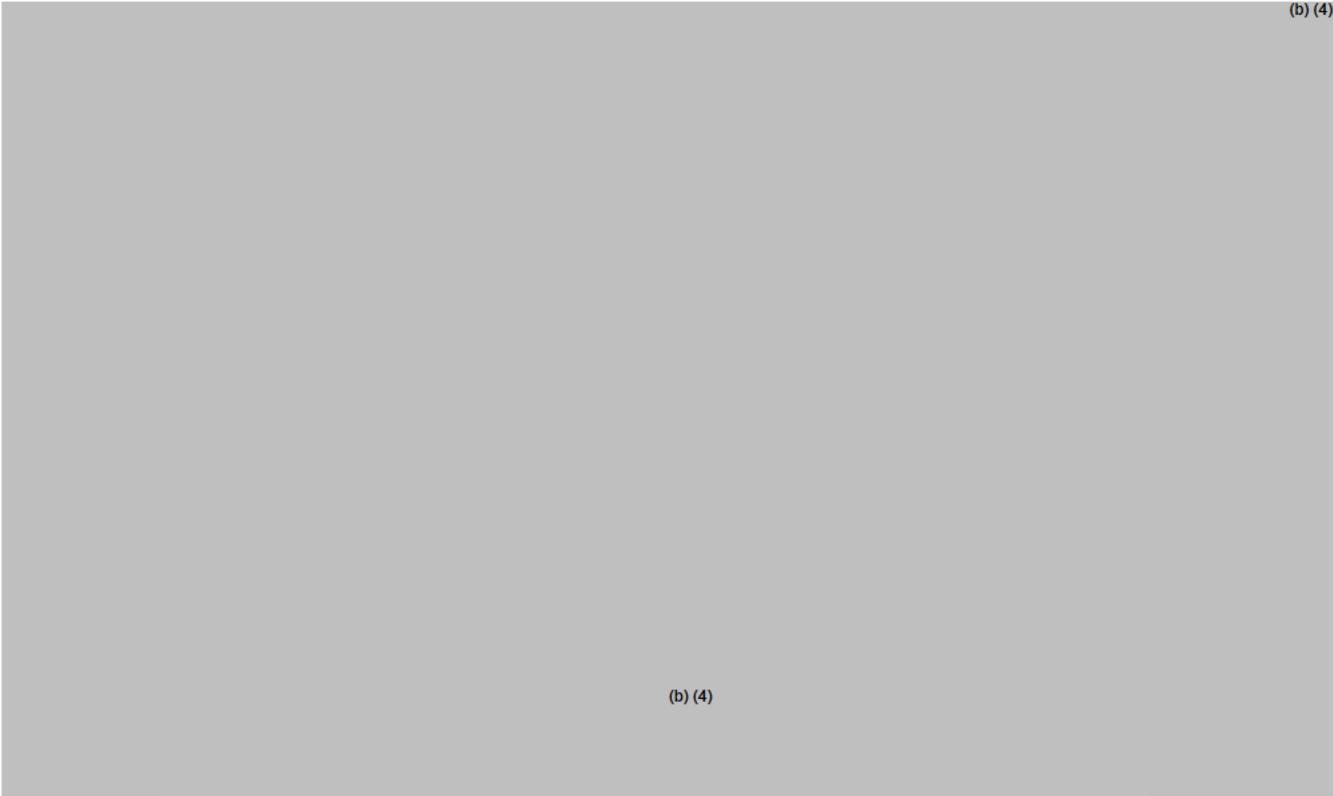
- **Nurses: Eliminate tasks 1 and 2 and focus on task 3 since the nurses would not be storing devices but selecting them from a cabinet/bin stocked by pharmacy.**
- **Pharmacists: We agree with task 1. However, we recommend that task 3 be specific as described below:**
 - **Task should be to select and dispense the correct pen injector after given a prescription for U300 insulin glargine, determining the correct number of pens to dispense for a 30-day supply (e.g. Prescription for 18 units of U300 insulin glargine once daily, how many pens should be dispensed for a 30-day supply).**

2.5

(b) (4)

(b) (4)

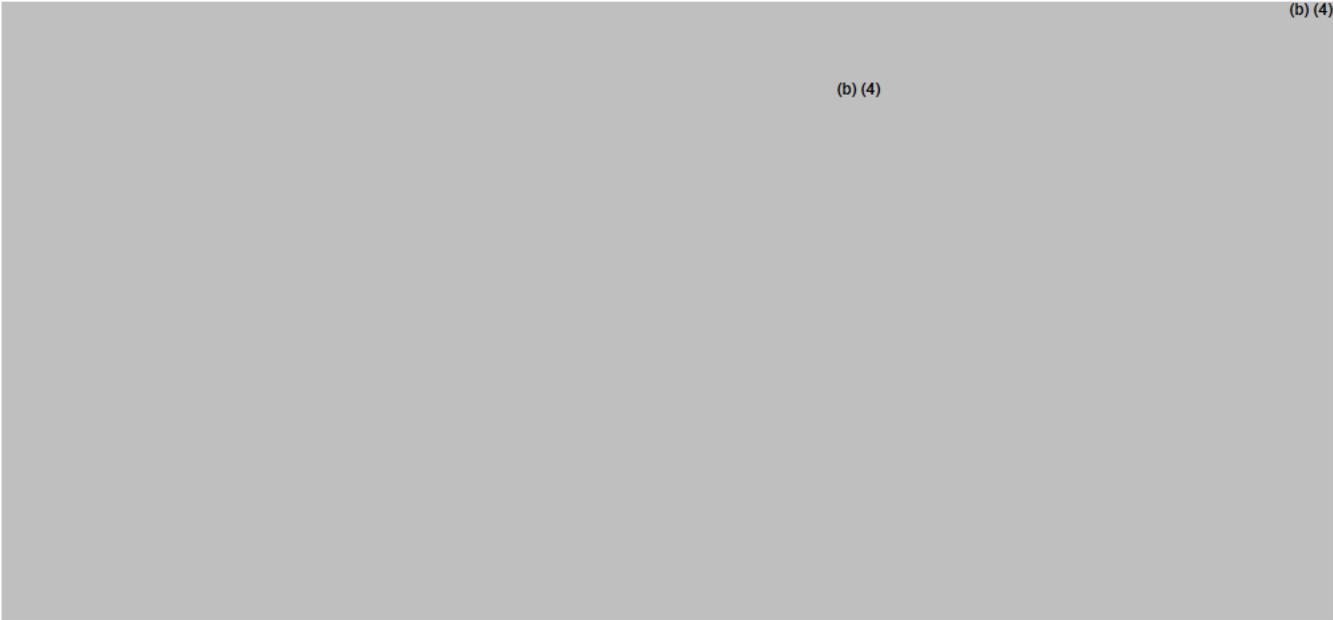
(b) (4)



(b) (4)

2.6

(b) (4)



(b) (4)

(b) (4)

(b) (4)



Additional Comments:

(b) (4)

1.

(b) (4)

2. [Redacted] (b) (4)

3. [Redacted] (b) (4)

[Redacted] (b) (4)

Pen:

1. **Remove** [Redacted] (b) (4)

2. **Relocate the “Solostar” statement to the bottom of the label.**

3. **We recommend that the concentration statement (i.e., 300 mg/mL) be the most prominent information on the labeling in addition to the proprietary name. We request this revision to help prevent selection errors with the additional concentrations of insulin glargine on the market.**

4. **We recommend that a different color be used for the pen and the label** [Redacted] (b) (4)

[Redacted] (b) (4)

2.7 Regulatory Pathway

Question 13: [Redacted] (b) (4)

2.8 E-CTD Structure

Question 14: Does the Division agree with the proposed Table of Contents for the e-CTD?

FDA Response to Question 14: See response to question 15.

Question 15: Does the Division agree with providing pen-injector-specific information and data, including the human factors information for the delivery device, in Module 3.2.R, Regional Information, of the eCTD?

FDA Response to Question 15: No we do not agree with the proposal to submit the information in Module 3.2R. Instead the pen-injector details should be submitted to Module 3.2.P.7 as follows.

1. For eCTD format and use of the system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”

2. **Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.**
3. **We recommend the following when including and referencing device information:**
 - a. **You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.**
 - b. **In 3.2.P.7 you could include a leaf titled something similar to the following, "Table of Contents for Drug-Device Autoinjector. This leaf/document, could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.**
 - c. **The leaf titles should be clear, concise and indicative of the document's content.**
4. **Module 1.4.4 cross reference to other applications is a location where you can provide references to other applications and you can include copies of an application's table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of authorization, 1.4.2 Statement of right of reference, 1.4.3 List of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.**
5. **Although it's not required, providing a "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters can be helpful. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information is located.**
6. **Please ensure that performance/accuracy testing for the U300 pen is included.**
7. **Please include any clinically-relevant information regarding pen usage (e.g. pen failures) in the clinical study report, or provide a hyperlink within the clinical study report to the corresponding information elsewhere in your submission.**

Question 16: Given the active substance (insulin glargine) is the same in Lantus and HOE901-U300, Sanofi plan to cross-reference the nonclinical summaries and study reports submitted to the Lantus NDA under Module 1.4.4 of the NDA for HOE901-U300. The only nonclinical study report to be provided in Module 4 of the NDA is for the local

tolerability study in rabbits that compared HOE901-U300 with the marketed Lantus formulation.

Does the Division agree to the sponsor's proposal for cross-referencing nonclinical information previously submitted to the Lantus NDA in the HOE901-U300 NDA?

FDA Response to Question 16: Yes, this is acceptable.

Question 17: Given the drug substance (insulin glargine) is the same in Lantus and HOE901-U300, Sanofi plans to cross-reference the drug substance section of the original paper Lantus NDA 021081 and all subsequent supplements and annual reports under Module 1.4.4 of the NDA for HOE901-U300. The Lantus NDA 021081 will be the central repository for all drug substance information. Data required under 21 CFR 314.50(d)(1)(ii) (Drug Product) will be provided under Module 3.2.P in the NDA for HOE901-U300.

Does the Agency agree with this approach?

FDA Response to Question 17: Yes, we agree.

2.9 Narratives and Case Report Forms (CRFs)

Question 18: Does the Division agree with the Sponsor's proposal for the provision of patient narratives and case report forms (CRFs)?

FDA Response to Question 18: Yes we agree. We have the following comments:

Narratives for deaths, serious adverse events, adverse events leading to discontinuation, severe hypoglycemia events, and hypersensitivity events should be well-written, manually-generated narratives.

Narratives should be hyperlinked to the corresponding data tables/figures in the individual CSRs for ease of review.

2.10 Labeling

Question 19: Proposed draft labeling for HOE901-U300 will be provided in accordance with content and format requirements of the January 2006 Physicians Labeling Rule. Specific sections of the proposed USPI will be the same as those in the currently approved Lantus USPI. For such sections, Sanofi plans to electronically annotate to the corresponding sections of the approved Lantus USPI.

Does the Division agree with this approach?

FDA Response to Question 19: For your proposed HOE901-U300 labeling in your NDA, your plan to electronically annotate to the listed corresponding sections of the Lantus label is acceptable.

The specific sections of the HOE901-U300 in any approved labeling that may refer to the Lantus labeling will be determined during our review of your application.

Question 20: Sanofi plans to request FDA's review of a new proprietary name for HOE901-U300. Does the Division agree that it would be possible to grant a new tradename for this new product?

FDA Response to Question 20:

Yes, we agree that it is possible to grant a new tradename for this product. However, you should be aware that traditionally insulins with different concentrations have been managed under a single proprietary name (e.g., Humulin R U-100 and Humulin R U-500). If you propose a new tradename, we will consider the risks that may be associated with using a new proprietary name, in particular the increased risk of duplicate therapy. We encourage you to consider the risks associated with the use of a new proprietary name versus the same name as insulin glargine U-100, and to provide your rationale supporting the safety of using a novel proprietary name for your product. We may also take your HF testing into consideration when reviewing your proposed proprietary name.

2.11 120-day Safety Update

Question 21: Does the Division agree with the proposed content and format of the 120-Day Safety Update Report?

FDA Response to Question 21: Please clarify the total exposure numbers you anticipate for the additional unblinded and blinded safety data.

2.12 Pediatrics

Question 22: Does the Division agree with the sponsor's position that the NDA for HOE901-U300 is exempt from PREA requirements?

FDA Response to Question 22

No, we do not agree that an NDA for HOE901-U300 would be exempt from PREA requirements. Dosing regimens for insulin products are dependent on the PK/PD profiles of these products. The formulation and PK/PD profiles for HOE90-U300 are different than those of Lantus. You have not provided adequate justification for your position that HOE901-U300 does not represent a new dosing regimen and should be exempted from PREA requirements. In addition, your supportive rationale lacks information on how you actually plan to develop dosing recommendations for pediatric use for the U300 formulation.

FDASIA was enacted on July 9, 2012, and sets forth the requirement for sponsors to submit an initial PSP (iPSP) to FDA no later than 60 days after an end-of-phase 2 meeting, or at another time agreed upon with the Agency. FDASIA also sets forth the 90 day period given to FDA to review an iPSP, the 90 day period for sponsors to submit an agreed iPSP, and the 30 day period for FDA to confirm its agreement with a sponsor's agreed iPSP. FDASIA indicates that the effective date of these provisions is January 5, 2013.

The Draft Guidance for Industry entitled "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans" published by FDA in July 2013 does not change the requirements set forth in FDASIA, but is intended to facilitate sponsors' ability to comply with FDASIA.

2.12 Financial Disclosure of Clinical Investigators

Question 23: Sanofi plans to submit financial certification and disclosure from clinical investigators who conducted the Phase 2 study (PDY12777) as well as the four global pivotal Phase 3 clinical studies (EFC11628, EFC11629, EFC12347 and EFC12456).

Does the Division agree with the sponsor's plan for submission of financial certifications and disclosures?

FDA Response to Question 22: Yes, we agree.

ADDITIONAL FDA COMMENTS:

Manufacturing Process - Device Constituent Part

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

The following recommendations apply to the location of device manufacturing information in the marketing application.

- 1. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.**
- 2. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.**

3. **Suggestions on the types of documents to submit for review related to 21 CFR Part 820 can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>**
4. **To facilitate the review process, we recommend an "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information is located. Also, it would identify documents addressing 21 CFR part 820 regulations, and the manufacturing of the finished combination product.**

Clinical

5. **In your presentation of reasons for discontinuation in your individual CSRs and in the integrated summaries, the category of “other” without further explanation is not acceptable. You should provide verbatim terms for these discontinuations due to “other” so that FDA reviewer(s) can determine if there are any additional adverse events or discontinuations due to lack of efficacy.**

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/contract research organization (CRO) inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, the Applicant can identify the location(s) and/or provide link(s) to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format).

- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).**

1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal Investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued at each site

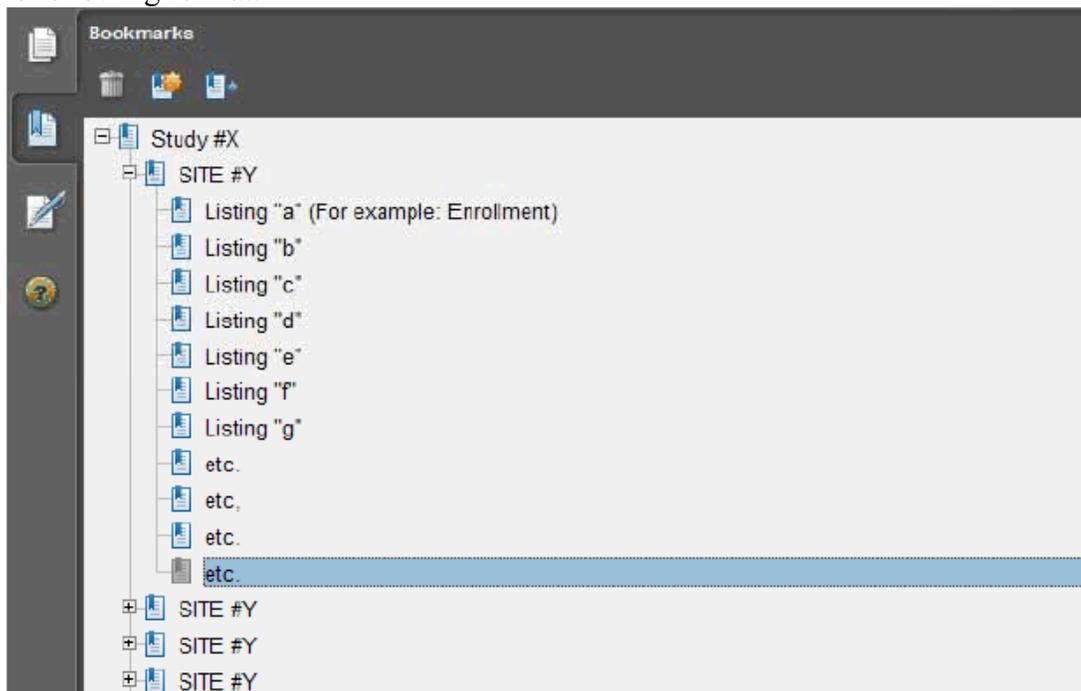
3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per-protocol subjects/ non per-protocol subjects and reason not per-protocol
 - e. By subject, listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject, listing of AEs, SAEs, deaths and dates
 - g. By subject, listing of protocol violations and/or deviations reported in the NDA/BLA, including a description of the deviation/violation
 - h. By subject, listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject, listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject, listing of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

RICHARD E WHITEHEAD
10/23/2013



PIND 112400

MEETING PRELIMINARY COMMENTS

sanofi aventis
Attention: Antonella Lozito, Pharm.D.
Associate Director, Global Regulatory Affairs
200 Crossing Boulevard
Mailstop: BX2-700B
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your Pre-Investigational New Drug Application (PIND) file for HOE901 (insulin glargine [rDNA origin]), U-300, injection, and to your correspondence dated and received June 3, 2011, requesting a Pre-IND meeting.

We also refer to your Investigational New Drug Application (IND) submitted on August 29, 2011, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for HOE901 (insulin glargine [rDNA origin]), U-300, injection.

Based on the nature of your questions, the information included in your Pre-IND meeting briefing package, and your recently submitted IND, we have determined that a 'face-to-face' Pre-IND meeting is no longer necessary and are granting written responses instead. We note that your briefing document contained protocol synopses for your proposed phase 3 trials and that full protocols were recently submitted with your IND. Therefore, we are deferring our comments on your phase 3 protocols until after we have completed our review of the full protocols. We are aiming to provide written responses regarding the full protocol designs within approximately 60 days following your IND submission. We strongly recommend that you await our comments before you implement these studies.

The questions included in your Pre-IND meeting briefing document are repeated below in regular text followed by our responses in **bold**.

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DEVELOPMENT

Question 1

Sanofi-aventis plans to use two investigational devices (A and B) in Phase III clinical trials, and develop Device C for commercial use. To establish comparability between each of Devices A and B and commercial Device C, a comprehensive bench study according to ISO11608 will be performed. Additionally, sanofi-aventis will conduct design validation/verification and human factor/usability studies on Device C to demonstrate the safety and effectiveness of the commercial device.

Does the Agency agree with our proposed strategy to support registration of Device C (intended for commercial use) by:

1. using bench performance testing according to ISO11608 to demonstrate that Device C (intended for commercial use) is functionally similar to Device A and B (for use in Phase III clinical trials), and

FDA Response: Although you state that Devices A, B and C will be in compliance with ISO 11608, you will need to submit complete test reports of their performance testing for FDA review. The complete test reports for Devices A and B will need to be reviewed prior to initiation of your phase 3 trials, whereas the test report for Device C will need to be included in your marketing application. Additionally, you will need to clarify which parts of ISO 11608 the devices conform to.

a. You have indicated that Device A, Device B, and Device C pen injectors will be in compliance with ISO 11608. However, you have not provided any results from your bench performance testing to evaluate the function of your devices. FDA is concerned that without this information, safety and effectiveness of your devices cannot be established. Please provide a complete test report (including the test name, test protocol, raw data, analysis of data including mean and standard deviation, acceptance criteria, and conclusion) for all the tests you have conducted.

b. You have indicated that you will be in compliance with ISO 11608 in relation to testing your devices. However, ISO 11608 has four parts and you have not specified which parts of ISO 11608 you will be in compliance with. This information is needed to ensure that testing on your device is done appropriately. Please specify which parts of ISO 11608 you will be in compliance with.

c. You have not provided biocompatibility testing for your devices. In order to fully evaluate the performance of your devices, FDA requires results of your biocompatibility testing. Because your devices are surface devices with skin contact for a period less than 24 hours, biocompatibility testing in accordance with ISO 10993-1 should be followed. Please refer to the guidance documents titled Blue Book Memo, G95-1, Use of International Standard ISO-10993, and Biological Evaluation of Medical Devices Part 1: Evaluation and Testing at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm>. In accordance with ISO 10993-1, Cytotoxicity, Sensitization, Intracutaneous Reactivity should be completed. Please provide a complete report for each of these biocompatibility tests (including entire protocol, acceptance criteria, raw data of test results, and conclusion).

(b) (4)

d. You have indicated (b) (4) However, you have not provided any (b) (4) information for the fluid pathway of your devices. FDA needs this information (b) (4) Therefore, please address the following:

1. **Provide a description** [redacted] (b) (4)
2. **Please be advised** [redacted] (b) (4)
3. **Provide a description of your validation method** [redacted] (b) (4)
4. [redacted] (b) (4)
5. **Address pyrogenicity testing for your device by providing a description of the method use (e.g. Limulus Amebocyte Lysate test) with results.**
6. **Provide a brief description of the packaging for your device.**

2. conducting human factor and design validation studies for Device C?

FDA Response: The briefing material did not include a discussion on how you plan to evaluate use-related risks and did not contain a protocol for a Human Factors (design validation study) for Device C. At this time, we recommend that you provide the risk analysis and protocol for a comprehensive review.

The briefing package only references that you will be conducting human factors and design validation studies for device C. However, it does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to the proposed commercial device (Device C). The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated. We recommend that you submit a draft of the test protocol for FDA review before you implement the study and await our feedback to ensure that your methods will be acceptable.

Your validation study protocol should include a clear description of the items listed below.

A. Devices and Labeling Used and Training

Incorporate design elements to provide appropriate pen differentiation such as label size and format, dose knob, pen body color, tactile features, etc. and systematically evaluate each conceptual design element used for Device C to demonstrate that these design elements provide adequate differentiation between Device C and currently marketed pen devices within your product line, and, if feasible between products across product lines. Include a warning on the pen or label that warns against withdrawal of insulin from the pen into a syringe.

For design validation, the devices used in your testing should represent the final design, which includes the commercial device version, final Instructions for Use, and any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. You should provide at least some lag time between training and the testing. When you design your Human Factors/usability validation protocol, include this analysis and ensure that representative (i.e., realistic) training is given to all test participants. Describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Assess the adequacy of the user instructions for your device as either part of your Human Factors/Usability effort or in a separate study in which representative users review the Instructions for Use and assess it for clarity and its ability to support their safe and effective use of your device. The adequacy of the labeling on the device itself should be evaluated as part of the Human Factors/Usability validation study to the extent that if it is inadequate, this will be evidenced by subjective user feedback and possible failures.

If you decide to include the assessment of clarity of Instructions for Use and training as part of the validation study, FDA expects that the results demonstrating effectiveness of your training and Instructions for Use will be analyzed separately from the results of use performance.

B. Device User Interface

To establish the scope and facilitate understanding of the testing you perform, provide a graphical depiction of the user interface for your device. Also explain the overall interaction between users and the user interface and refer to it as necessary when discussing task priority, specific test results or residual risk.

C. Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing. In order to adequately assess user performance and safety, the

tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. Also include specific tasks within the protocol for dose-setting, dose confirmation, and strength identification. Follow a case-based protocol approach for these tasks that reflects real-life scenarios (e.g. use of more than one pen in a therapeutic regimen) and are consistent with the actual use of the product to manage diabetes. Also include case-based scenarios that include pen malfunction or similar scenarios, which would invite opportunity for withdrawal of insulin from the device to evaluate if label warnings adequately deter misuse of the product. This will assess the risk of insulin withdrawal from the device into a U100 syringe, which would result in a potential overdose of U300 insulin.

The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user. Please provide use-related risks analysis.

D. User Tasks and Tasks Priority

FDA needs to understand that you have conducted a comprehensive analysis of user tasks and as part of this analysis have established relative priority of the tasks you selected for testing in terms of the potential clinical impact of inadequate performance (e.g., “task failure”) for each. You have not provided any discussion of user task analysis, task priority, nor have you provided a testing protocol developed from these analyses. If you have performed this work, please submit it for FDA review or initiate the development of a Human Factors/Usability evaluation, development, and validation testing protocol. Note that Human Factors/usability is most effectively applied to the design of the device user interface when it is initiated early in the design process. Also provide a rationale for the tasks you include in your testing and their relative priority and describe all activities in which your test participants will engage during the test.

E. Comprehensiveness of Task Set

For Human Factors/usability validation testing, FDA needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related failures that could have an undesirable clinical impact. Provide a rationale for the completeness of the user tasks you include in your Human Factors/Usability validation testing.

F. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Describe the testing environment and realism of the simulated use in sufficient detail and justify how they were appropriate for validation testing.

G. Study Participants

You should include as many representative users in your Human Factors/Usability validation as your analysis indicates are necessary to achieve a reasonable validation.

Note that FDA expects a minimum of 15 study participants per user group in the Human Factors/Usability Validation study. Therefore, plan to submit results of a study that includes a minimum of 15 participants per group of distinct users consistent with your indicated population of users, and also describe sufficient demographic information to indicate how these participants are representative of the intended population of users. If users fall into distinct groups that are expected to interact differently with the device or carry different risk profiles (e.g. different specialties that are more or less knowledgeable of diabetes treatment, physicians vs. nurses, and health care providers who dispense, train patients and administer the drug product, as well as caregivers who may administer the drug product etc.) then the testing should include representative samples from each of these groups, divided roughly evenly but where the total is no less than 25. We also recommend that you consider including U500 insulin users, who are aware of differences in insulin concentration, as a test group to help inform and validate any proposed concentration differentiation during your Human Factors testing.

Historically color differentiation has been a feature in differentiating pens in your product line as well as other manufacturers' insulin products. Therefore, include color-blind participants in your Human Factors testing, specifying the type of color-blindness each participant has.

Regardless of the number of groups you test, provide a rationale that these groups are representative of the overall population of users for your device.

For devices sold in the United States, FDA has consistently requested that participants in a validation test be representative of the U.S. population and to reside in the U.S. Note that study participants should not be your own employees, or those who have been exposed to the products prior to the testing.

H. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-

critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants’ adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – FDA expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and Instructions for Use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Describe and provide a rationale for including each type of data you collect.

Note that results of your validation studies should include capture of user performance failures, where failure of a task is defined as an action or lack of action on the part of the user that could lead to clinical harm to the patient. Test results (see “Report” below) should include success and failures for all critical tasks. In addition, and even if performance of all tasks is acceptable, the output that establishes critical treatment parameters resulting from the interaction for each use scenario should be evaluated for adequacy. Each instance of task or overall scenario failure should be evaluated to determine its cause. This evaluation should include subjective feedback concerning the cause of the failure from the perspective of the test participant involved and obtained immediately following the test scenario. Finally, your protocol should enable identification and capture of unanticipated task failures and not be limited to pre-established failure modes.

I. Report

FDA expects to review a report of the human factors/usability evaluation and validation testing. The report should begin with a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions. A summary of relevant portions of preliminary analyses, evaluations, and the validation testing should be used as support of this conclusion. The test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are required. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the user interface should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design

flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

We strongly recommend that you submit your draft protocol in advance for FDA review in order to ensure that your methods and the resulting data will be acceptable. Guidance on Human Factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Note that FDA recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to Human Factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Question 2

Sanofi-aventis plans to use two investigational devices, A and B, in the proposed Phase III clinical trials. These devices will be in compliance with ISO11608 and FDA standards and regulations. The IND submitted to support initiation of the clinical trials, and subsequent IND amendments, will include detailed documentation concerning device description and test results of ISO11608.

Does the Agency agree with our proposed strategy of using two investigational devices (A and B) in the Phase III program supported by satisfactory ISO11608 testing to demonstrate safe administration and dose accuracy, and submitting all relevant device description and testing in the IND?

FDA Response: Your briefing document references two injection pens that you state were cleared in 2007 (Device A) and 2009 (Device B), however, you did not provide 510(k) numbers for these previously cleared devices. You have indicated that several changes have been made to device A and B and that these changes do not affect the functionality or the dose accuracy of the device. Even though you state that both devices will be in compliance with ISO 11608, you will need to provide complete test reports of the performance testing for these devices for FDA review. Additionally, you will need to clarify which parts of ISO 11608 these devices conform to. You did not provide biocompatibility testing. Because these devices will be in contact with the skin, cytotoxicity, irritation, and sensitization testing would need to be completed. With regard to Drug/Device interactions, standard industry practices and documentation per published Center for Drug Evaluation and Research (CDER) and International Conference on Harmonisation (ICH) guidances will apply, including long term and accelerated stability requirements, in-use stability requirements, and sterility assurance requirements for the cartridge-packaged drug product. You will need to provide detailed information ^{(b) (4)} for all three pen injectors and ^{(b) (4)} information on the fluid pathway for the pen injectors.

Question 3

Sanofi-aventis plans

(b) (4)

Does the Agency agree with our proposed strategy (b) (4) for HOE901-U300 to support registration and approval of Device C?

FDA Response: No. We do not agree with your plan

(b) (4)

In accordance with Good Review Management Principles and Practices (GRMPs) timelines, a complete NDA should be submitted for filing, and we cannot guarantee that we will review unsolicited amendments.

(b) (4)

CLINICAL DEVELOPMENT

Question 4

The sponsor is planning to perform clinical studies in the following patient populations:

- Patients with T2DM on high dose basal insulin (*Studies EFC11628 and EFC11629*)
Two randomized, controlled, 6-month clinical studies with 6-month comparative extension periods, each study enrolling approximately 800 patients with T2DM treated with high dose basal insulin to demonstrate the efficacy, safety and the potential clinical benefit of the improved, peak-less time-action profile and the lower injection volume of HOE901-300 in comparison with Lantus®. These studies will be submitted in an initial new NDA.
- Patients with T1DM and insulin-naïve patients with T2DM (*Studies EFC12346 and EFC12347*)

(b) (4)

a) Based on the results of studies (EFC11628 and EFC11629), the sponsor plans to submit an initial NDA (b) (4)

A supplemental NDA will follow using studies EFC12346 and EFC12347 (b) (4)

Does the Agency agree that the proposed Phase III studies, if positive, could support approval of the respective indications in sequence?

FDA Response: Your overall approach described above appears reasonable. Note that with this approach Study EFC12346 and Study EFC12347 will each need to be submitted as separate supplemental New Drug Applications and a separate user fee would be needed for each study.

Clarify why you are limiting the maximum dose to only 80 units for Device C (the same maximum dose available with your U-100 pen), particularly given that you are seeking an indication for patients who require high doses of insulin.

We note that you are also planning to seek an indication for patients with type 1 diabetes and insulin-naïve type 2 diabetes. These patients may not have high insulin requirements. Therefore, it is possible that some of these patients may use HOE901-U300 but at a later date change to Lantus. We are concerned that a change from HOE901-U300 to Lantus could lead to overdosing of Lantus and hypoglycemia based on the lower pharmacokinetic exposure (AUC and Cmax) with HOE901-U300 compared to Lantus. Clarify how you intend to address this concern.

We acknowledge receipt of your IND containing full protocols for your proposed phase 3 studies. We are aiming to provide written comments on these full protocols within approximately 60 days following your IND submission. We strongly recommend that you await our comments before you implement these studies.

b) In the initial and supplemental NDAs, the sponsor plans to submit results from the first 6 months treatment phases in order to support the aforementioned indications. Does the Agency agree that the proposed HOE901-U300 development plan based on 6 months data at time of submission supports its use in the proposed patient populations?

FDA Response: Yes, we agree that 6 months of treatment data at the time of NDA submission is acceptable.

Question 5

The primary efficacy analysis will plan to demonstrate non-inferiority of HOE901-U300 to Lantus® with regards to change from baseline to endpoint of HbA1c. (b) (4)

(b) (4) The analysis will be prespecified in the study protocol.

(b) (4)

FDA Response: We agree that type 1 error should be controlled (b) (4)

(b) (4) **However, we would like you to be aware of our preliminary concerns** (b) (4) **Any additional concerns will be**

communicated to you when we send our comments on your full protocols included in the IND.

(b) (4)

ADDITIONAL COMMENT:

Clarify which devices were used for subcutaneous insulin administration in the Phase 1 studies (PKD10086, PKD11627 and TDR11626).

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

The web page may be found at the following link:

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/
ElectronicSubmissions/ucm248635.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm)

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

RACHEL E HARTFORD
09/07/2011