# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>209196</th>
<th>NDA Supplement #</th>
<th>N/A</th>
<th>If NDA, Efficacy Supplement Type: N/A (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name:</td>
<td>Admelog</td>
<td>Applicant: Sanofi-Aventis U.S. LLC</td>
<td>Agent for Applicant (if applicable): N/A</td>
<td></td>
</tr>
<tr>
<td>Established/Proper Name:</td>
<td>insulin lispro</td>
<td>RPM: Callie Cappel-Lynch</td>
<td>Division: Metabolism and Endocrinology Products</td>
<td></td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>injection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For ALL 505(b)(2) applications, two months prior to EVERY action:
- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - [X] No changes
  - [ ] New patent/exclusivity (notify CDER OND IO)
  - Date of check: September 1, 2017

**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.

### Actions

- Proposed action
- User Fee Goal Date is December 11, 2017
- Previous actions (specify type and date for each action taken)
  - TA September 1, 2017

### Application Characteristics

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.

Reference ID: 4200281

Version: 05/09/17
NDA 209196
Page 2

Review priority:  □ Standard  □ Priority
Chemical classification (new NDAs only):  Type 5 – New Formulation or New Manufacturer
(confirm chemical classification at time of approval)

☐ Fast Track  ☐ Rx-to-OTC full switch
☐ Rolling Review  ☐ Rx-to-OTC partial switch
☐ Orphan drug designation  ☐ Direct-to-OTC
☐ Breakthrough Therapy designation

( NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

<table>
<thead>
<tr>
<th>NDAs: Subpart H</th>
<th>BLAs: Subpart E</th>
<th>REMS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Approval based on animal studies</td>
<td>□ Approval based on animal studies</td>
<td>ETASU</td>
</tr>
</tbody>
</table>

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

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only) N/A

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action □ Yes □ No
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? □ No □ Yes
  - If so, specify the type

- Patent Information (NDAs only)
  - Patent Information:
    Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. □ Verified
  - Not applicable because drug is an old antibiotic.

## CONTENTS OF ACTION PACKAGE

<table>
<thead>
<tr>
<th>Officer/Employee List</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)</td>
</tr>
</tbody>
</table>

Documentation of consent/non-consent by officers/employees

Reference ID: 4200281
### Action Letters

- Copies of all action letters (including approval letter with final labeling)
  - AP December 11, 2017
  - TA September 1, 2017

### Labeling

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Original applicant-proposed labeling
  - Included - attached to approval letter
  - Included

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Original applicant-proposed labeling
  - Medication Guide
  - Patient Package Insert
  - Instructions for Use
  - Device Labeling
  - Included - attached to approval letter
  - Included

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

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - February 1, 2017
  - January 11, 2017

- **Labeling reviews** *(indicate dates of reviews)*

### Administrative / Regulatory Documents

- **RPM Filing Review**/*Memo of Filing Meeting** *(indicate date of each review)*
  - May 3, 2017

- **All NDA 505(b)(2) Actions**
  - Date each action cleared by 505(b)(2) Clearance Committee
  - October 24, 2017
  - August 30, 2017

- **NDAs/NDA supplements only**:
  - Exclusivity Summary *(signed by Division Director)*
  - Completed (Do not include)

- **Application Integrity Policy (AIP) Status and Related Documents**
  - http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- Applicant is on the AIP | ☒ Yes ☐ No
- This application is on the AIP
  - If yes, Center Director's Exception for Review memo (indicate date)
  - If yes, OC clearance for approval (indicate date of clearance communication)
- Pediatrics (approvals only)
  - Date reviewed by PeRC N/A
  - If PeRC review not necessary, explain: Application does not trigger PREA
- Breakthrough Therapy Designation | ☒ N/A
  - Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)
  - CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)
  - CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)
    *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*
- 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, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)* | included
- 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
- Minutes of Meetings | ☒ N/A or no mtg
  - If not the first review cycle, any end-of-review meeting (indicate date of mtg)
  - Pre-NDA/BLA meeting (indicate date of mtg) | April 16, 2016
  - EOP2 meeting (indicate date of mtg) | November 7, 2014
  - Mid-cycle Communication (indicate date of mtg)
  - Late-cycle Meeting (indicate date of mtg)
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)
- Advisory Committee Meeting(s) | ☒ No AC meeting
  - Date(s) of Meeting(s)

### Decisional and Summary Memos
- Office Director Decisional Memo (indicate date for each review) | ☒ None
- Division Director Summary Review (indicate date for each review) | See concurrence to CDTL review
- Cross-Discipline Team Leader Review (indicate date for each review) | December 7, 2017
  - August 31, 2017
- PMR/PMC Development Templates (indicate total number) | ☒ None
### Clinical

<table>
<thead>
<tr>
<th>Clinical Reviews</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Clinical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>see CDTL review</td>
</tr>
<tr>
<td>- Clinical review(s) <em>(indicate date for each review)</em></td>
<td>August 14, 2017</td>
</tr>
<tr>
<td>- Social scientist review(s) *(if OTC drug) <em>(indicate date for each review)</em></td>
<td>December 23, 2016</td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review</td>
<td>See clinical reviewed dated August 14, 2017 page 15</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here □ and include a</td>
<td></td>
</tr>
<tr>
<td>review/memo explaining why not <em>(indicate date of review/memo)</em></td>
<td></td>
</tr>
<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers</td>
<td>July 26, 2017</td>
</tr>
<tr>
<td><em>(indicate date of each review)</em></td>
<td></td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate</td>
<td>N/A</td>
</tr>
<tr>
<td>date of each review)*</td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
</tr>
<tr>
<td>- REMS Documents and RFMS Supporting Document <em>(indicate date(s) of submission(s))</em></td>
<td>None</td>
</tr>
<tr>
<td>- REMS Memo(s) and letter(s) <em>(indicate date(s))</em></td>
<td></td>
</tr>
<tr>
<td>- Risk management review(s) and recommendations <em>(including those by OSE and CSS)</em></td>
<td></td>
</tr>
<tr>
<td>*(indicate date of each review and indicate location/date if incorporated into</td>
<td>None</td>
</tr>
<tr>
<td>another review)*</td>
<td></td>
</tr>
<tr>
<td>OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to</td>
<td>July 25, 2017</td>
</tr>
<tr>
<td>investigators)*</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Microbiology

- None

### Biostatistics

- No separate review

### Clinical Pharmacology

- None

---

3 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Reference ID: 4200281
### Nonclinical

- **Pharmacology/Toxicology Discipline Reviews**
  - ADP/T Review(s) *(indicate date for each review)*: No separate review
  - Supervisory Review(s) *(indicate date for each review)*: No separate review
  - Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*: July 20, 2017

- **Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)***: January 3, 2017

- **Statistical review(s) of carcinogenicity studies *(indicate date for each review)***: None

- **ECAC/CAC report/memo of meeting**: None

- **OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)***: None requested

### Product Quality

- **Product Quality Discipline Reviews**
  - Tertiary review *(indicate date for each review)*: None
  - Secondary review (e.g., Branch Chief) *(indicate date for each review)*: None
  - Integrated Quality Assessment *(contains the Executive Summary and the primary reviews from each product quality review discipline)* *(indicate date for each review)*: July 26, 2017

- **Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)***: July 18, 2017 CDRH
  - July 17, 2017 CDRH
  - July 5, 2017 CDRH

- **Environmental Assessment (check one) (original and supplemental applications)**
  - Categorical Exclusion *(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)*: July 26, 2017 integrated quality assessment page 109

- **Review & FONSI *(indicate date of review)***: None

- **Review & Environmental Impact Statement *(indicate date of each review)***: None

- **Facilities Review/Inspection**
  - Facilities inspections *(indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)*: Acceptable- December 6, 2017
  - Withhold recommendation
  - Not applicable

---

* Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Reference ID: 4200281
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>✤ For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>◦ Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>◦ Finalize 505(b)(2) assessment</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✤ For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>◦ Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>◦ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td></td>
</tr>
<tr>
<td>◦ Notify the Division of Online Communications, Office of Communications</td>
<td>N/A</td>
</tr>
<tr>
<td>✤ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✤ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✤ Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✤ Ensure Pediatric Record is accurate</td>
<td>✔ Done</td>
</tr>
<tr>
<td>✤ Send approval email within one business day to CDER-APPROVALS</td>
<td>✔ Done</td>
</tr>
<tr>
<td>◦ Take Action Package (if in paper) down to Document Room for scanning within two business days</td>
<td>✔ Done</td>
</tr>
</tbody>
</table>
Hi Nilda,

Please see the attached edits to the PI. We request that you return revised labeling by COB Tuesday.

Thanks,
Callie

---

From: Nilda.Ramos@sanofi.com [mailto:Nilda.Ramos@sanofi.com]
Sent: Tuesday, November 28, 2017 1:15 PM
To: CappelLynch, Callie <Callie.CappelLynch@fda.hhs.gov>
Subject: NDA 209196 Revised Proposed Labeling for Admelog

Callie,

Please find attached the revised labeling for Admelog. The ESG submission can’t be managed by our Publishing group until tomorrow so I am including the cover letter that will be used to officially submit this labeling tomorrow to NDA 209196.

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

/s/

CALLIE C CAPPEL-LYNCH
12/01/2017
Hi Nilda,

Please see the attached PI with FDA comments. We ask that you return revised labeling by COB Tuesday, November 28th. When you send back revised labeling, please also populate the revision and approval date fields on the label.

Thanks,
Callie

Reference ID: 4185755
23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
11/24/2017
Hi Nilda,

When you resubmit the labeling can you please incorporate the following change that was missed in the initial review of the PI:

- Add W/P 5.4 Hypoglycemia Due to Medication Errors to the Highlights section of the label

Thanks,
Callie
planning purposes, can you please confirm the shelf life that would be approved for these presentations is 36 months.

Thanks in advance,
Nilda
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
10/24/2017
NDA 209196

Sanofi-Aventis U.S. LLC
Attention: Nilda Ramos
Associate Director
55 Corporate Drive
Bridgewater, NJ 00807

Dear Ms. Ramos:

We acknowledge receipt on October 11, 2017, of your resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Admelog (insulin lispro injection) U-100.

We consider this a complete, class 1 response to our September 1, 2017, action letter. Therefore, the user fee goal date is December 11, 2017.

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

Sincerely,

Callie Cappel-Lynch, Pharm.D., RAC
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
10/12/2017

Reference ID: 4166617
Hi Nilda,

Please see the attached document with FDA labeling comments for NDA 209196. We ask that you send a revised label by COB today. You may send the revised copy by email and follow up with a formal submission once we have reached full agreement.

Thanks,

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

/s/

CALLIE C CAPPEL-LYNCH
08/30/2017
Hi Nilda,

We would like to clarify our previous labeling comments regarding the NDC numbers for the one Admelog SoloStar pen and the carton for the five Admelog SoloStar pens.

Thanks,

Callie

Callie,  

The revised carton and container labeling is attached. I will schedule these for formal submission to NDA209196.

Best regards,

Nilda

Hi Nilda,

Please see the comment below regarding the carton/container labels for NDA 209196. Please send in revised labels by COB August 25, 2017.

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

/s/

CALLIE C CAPPEL-LYNCH
08/24/2017
Hi Nilda,

Please see our responses below. If you have any further questions, please contact me.

Regarding request #3 d for a revised label that complies with PLLR, Sanofi aligned the label provided in the application with the label for the listed drug Humalog. Sanofi is relying on information from the Humalog label for some sections of the proposed label. We would like to confirm that, if reformating Section 8.1 (to include literature data) causes a deviation from the language in the listed drug label, that this deviation is acceptable to the FDA.

FDA Response: Although your proposed labeling may incorporate relevant data and information from the labeling of the listed drug relied upon, we note that there may be appropriate differences. For example, your proposed labeling should reflect current labeling regulations, guidances, and best practices. In this regard, we note that your proposed labeling must comply with the content and format requirements established by the Pregnancy and Lactation Labeling Rule (PLLR) because your application was submitted on or after June 30, 2015, the effective date of the PLLR.

Thanks,
Callie
Hi Nilda,

This application will not be reviewed under the program. That language was inadvertently left in the letter. I apologize for any confusion. I will get back to you regarding the other two issues as quickly as possible. I look forward to working with you.

Thanks,
Callie

From: Nilda.Ramos@sanofi.com (mailto:Nilda.Ramos@sanofi.com)
Sent: Saturday, January 21, 2017 5:43 AM
To: CappelLynch, Callie
Subject: Sanofi NDA 209196 - Request for Clarification

Dear Callie Cappel-Lynch,

I take this opportunity to introduce myself as Sanofi’s new regulatory contact for NDA 209196. A formal request for change of regulatory contact was submitted to the application on January 19, 2017 (Sequence #0003).

Sanofi is in receipt of the attached NDA filing communication dated January 10, 2017. We are asking for clarification in regards to the information in the filing communication.

Regarding request #3 d for a revised label that complies with PLLR, Sanofi aligned the label provided in the application with the label for the listed drug Humalog. Sanofi is relying on information from the Humalog label for some sections of the proposed label. We would like to confirm that, if reformatting Section 8.1 (to include literature data) causes a deviation from the language in the listed drug label, that this deviation is acceptable to the FDA.

Thank you,

Nilda RAMOS
Assistant Director, Regulatory Affairs
Sanofi
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
08/22/2017
Hi Nilda,

Please see the comment below regarding the carton/container labels for NDA 209196. Please send in revised labels by COB August 25, 2017.

Thanks,

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

/s/

CALLIE C CAPPEL-LYNCH
08/22/2017
NDA 209196

Sanofi-Aventis U.S. LLC
Attention: Nilda Ramos
Associate Director
55 Corporate Drive
Bridgewater, NJ 00807

Dear Ms. Ramos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Admelog (insulin lispro injection) U-100.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
08/21/2017
Hi Nilda,

Please see the comments below regarding the carton and container labels for NDA 209196. We also ask that you add the proprietary name to the revised carton and container labels. Please provide the revised labels within 1 week.

Container Label-SoloStar pen
1. Increase the prominence of “SoloStar” within the proprietary name “TRADE NAME SoloStar” so that the full proprietary name has equal prominence on the label.

2. Remove the abbreviation from the established name so that the name reads as follows: “insulin lispro injection”.

3. Replace the NDC placeholder with the NDC number and submit for Agency review.

4. Move the net quantity statement “3 mL prefilled pen” so that it is not located directly below the product concentration statement “100 units/mL”. We recommend placing the statement “3 mL prefilled pen” where you currently have the statement “501XXXXX” to increase prominence of the quantity statement and placing the statement “501XXXXX” closer to the bottom of the label near the manufacturer information.

5. Add the statement “for subcutaneous use only” directly below the product concentration statement “100 units/mL.” Consider increasing the size of the white area used for text to accommodate the addition of this information on the label.

Carton Labeling-SoloStar pen
1. See comments A.1, A.2, and A.3.

2. Revise the statement to read to clarify that this statement applies to each individual pen. In addition, we recommend placing this statement directly above or below the “Initial Use Date” fillable lines for improved visibility of the pen’s beyond use information.

Container Label-Vial
1. See comments A.2 and A.3.
2. Consider moving the net quantity statement “10 mL vial” so that it is not located directly below the product concentration statement “100 units/mL” to minimize confusion of these numbers.

3. Revise the statement to read “for subcutaneous or intravenous use” to improve clarity.

Carton Labeling-Vial
1. See comments A 2 and A 3.

2. Revise the statement to read “for subcutaneous use” then we recommend revising the statement to “For intravenous infusion after further dilution ONLY under direct medical supervision” for improved clarity of this recommendation.

3. Improve the readability of the information currently placed on the colored side panel by making this panel white with black letters. The current white lettering on a background may be difficult for users to distinguish and decrease user readability of this information.

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

/s/

CALLIE C CAPPEL-LYNCH
08/10/2017
Hi Nilda,

Please see IR for NDA 209196 below.

We note that in the analysis of change in insulin dose for study EFC12619 that you report a marked increase in mean basal insulin dose for subjects treated with SAR342434 and that this appears to be due to the subpopulation of SAR342434 subjects that develop treatment-emergent antibodies. In section 9.7.2 of the 12-month study report you attribute this to an error in the basal insulin dose entered for one subject where a dose of 360 U was entered rather than 36 U for weeks 20, 34, 40, and 52, and a dose of 246 was entered rather than 36 U at week 26.

We ask that you provide response to the following:

1. Based on our review of the datasets we were not able to identify the dose of 246 U at week 26. Clarify if this is 360 U or 246 U.
2. Clarify how this was identified and how it was confirmed that this was due to patient error rather than representing a true increase in dose.
3. Provide analyses on change in insulin dose similar to what you have shown for Table 11 and Table 16.2.5.1.2.1 that exclude the data from this patient. Also present this data by treatment-emergent antibody category similar to what is shown in Table 35 and Table 16.2.7.5.2.1.

Please respond by open of business on Friday.

Thanks,

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

/s/

CALLIE C CAPPEL-LYNCH
08/07/2017
Hi Nilda,

Please see the attached document with FDA labeling comments for NDA 209196. Please return a revised label within one week.

If you have any questions, please contact me.

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

/s/

CALLIE C CAPPEL-LYNCH
08/04/2017
Hi Nilda,

Your response to our request for information sent July 27th, 2017 concerning

Please provide your response by Thursday, August 3rd, 2017.

Thanks,
Callie

Callie,

Please find attached our response to your request dated 27 July. It will also be submitted through the gateway tomorrow.

Kind regards,
Nilda

Hi Nilda,

Please see the information request below. We request response by COB next Wednesday, August 2nd.

Please provide the following information to support the proposed labeling concerning

Reference ID: 4133294
Thanks,
Callie
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
08/01/2017

Reference ID: 4133294
Hi Nilda,

Please see the information request below. We request response by COB next Wednesday, August 2nd.

Please provide the following information to support the proposed labeling concerning

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

/s/

CALLIE C CAPPEL-LYNCH
07/27/2017
Hi Nilda and Don,

Please refer to your NDA 209196 submitted pursuant to section 505(b)(2) of the FD&C Act for insulin lispro injection.

We also refer to correspondence dated January 21, 2017, in which you requested clarification about whether identification of Humalog (Product 001) as the listed drug relied upon would be sufficient to support the 505(b)(2) application.

Please contact me if you have any questions.

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

/s/

CALLIE C CAPPEL-LYNCH
07/18/2017
Hi Nilda,

Please see the information request below for NDA 209196.

We note that your safety analyses are primarily presented for the safety population using the on-treatment period. Provide your rationale for selecting this period rather than the on-study period which could include adverse events occurring more than 1 day after discontinuing study drug. Also clarify if inclusion of post-treatment adverse events alters any of the safety conclusions.

We ask that you provide response by COB July 14, 2017.

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

/s/

CALLIE C CAPPEL-LYNCH
06/30/2017
DATE: 4/17/2017

TO: Division of Metabolism and Endocrinology Products
    Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
      Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 209196

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the sites listed below. The insessional outcome from the inspections was classified as No Action Indicated (NAI).

**Inspection Sites**

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Facility Name</th>
<th>Facility Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Clinical</td>
<td>PROFIL Institut für Stoffwechselforschung GmbH</td>
<td>Hellersbergstraße 9, D-41460</td>
</tr>
<tr>
<td></td>
<td>Neuss, Germany</td>
<td></td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
04/17/2017
Hi Nilda,

Please see the information request below for NDA 209196. We ask that you respond within 1 week.

We are interested in comparing your insulin lispro product with the approved insulin lispro by source (i.e., SAR342434 vs. US approved product vs. EU approved product). Provide the following information:

1. Provide the information in the below shell table comparing SAR342434 with US lispro and EU lispro for the 6 month and 12 month period of study EFC12619 and for study EFC13403.

<table>
<thead>
<tr>
<th></th>
<th>EFC12619 – 6 months</th>
<th>EFC12619 – 12 months</th>
<th>EFC13403</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAR342434</td>
<td>US lispro</td>
<td>EU lispro</td>
</tr>
<tr>
<td>N Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hypoglycemias (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemias (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented symptomatic hypoglycemias (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≤70 mg/dL (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt;54 mg/dL (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe and/or confirmed hypoglycemias (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≤70 mg/dL (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt;54 mg/dL (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hypoglycemias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Serious AEs (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Adverse Events (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive AIA tests (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIA titer ≥64 (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Provide a comparison of hypoglycemia event rates (events per patient-year) between SAR342434, US approved lispro, and EU approved lispro. This should include all hypoglycemia, severe hypoglycemia, documented symptomatic hypoglycemia, and severe and/or confirmed hypoglycemia.

3. Generate tables similar to the tables included in the Integrated Summary of Safety for treatment emergent adverse events and serious adverse events (see Table 2.4.3.1 for example) by SOC, HLT and PT with incidence and event rates for SAR342434, US-approved insulin lispro, and EU-approved insulin lispro for each study/study period.

4. Clarify whether datasets include flags which would allow for identification of the source of approved insulin lispro comparator.

In addition, we request the following clarification with regard to the presentation of hypoglycemia:
1. On page 118 of the 6 month study report for Study EFC12619, you state that one patient experienced hypoglycemia with seizure and that this episode was reported in the SAE form but not in the dedicated hypoglycemia case report form. Clarify whether all severe hypoglycemia reported as SAE were incorporated in the total number of severe hypoglycemia reported, including this event of hypoglycemia with seizure. If not, clarify how many hypoglycemia adverse events were reported but not incorporated into your presentation of hypoglycemia in the phase 3 studies.

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

/s/

CALLIE C CAPPEL-LYNCH
04/11/2017
Hi Nilda,

Please see the information request below for NDA 209196. Please respond to this request by COB April 20th.

For Study PDY12704, indicate the location of the following information or submit the information because we were unable to locate the information in Study Report DOH1221 (125084AHEG/AILX):

- Describe how you prepared the standards for the calibration curves and quality control samples to quantify SAR342434, Humalog US, and Humalog EU.
- Describe how you prepared the clinical samples to quantify SAR342434, Humalog US, and Humalog EU.
- State any difference in preparation for the calibration standards, quality control samples, and the clinical samples.
- Provide the recovery results for Humalog US and Humalog EU.

Thanks,

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

/s/

CALLIE C CAPPEL-LYNCH
04/06/2017
DATE: 4/3/2017

TO: Division of Metabolism and Endocrinology Products
   Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
      Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 209196

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Facility Name</th>
<th>Facility Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Clinical</td>
<td>PROFIL Institut für Stoffwechselforschung GmbH</td>
<td>Hellersbergstraße 9, D-41460 Neuss, Germany</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
04/04/2017
Hi Nilda,

Please see the attached information requests for NDA 209196.

Please respond to this request by May 5, 2017. If you have any questions, please contact me.

Thanks,
Callie
The Division believes the analysis should include all randomized patients regardless of whether 1 post-baseline visit was observed. Further, we feel the MMRM is not appropriate for addressing missing data. While, various sensitivity analyses were performed, we are interested in a “Return to Baseline” analysis for active-controlled studies. Since we have moved away from repeated measures analysis, please perform the following multiple imputation analyses:

**Analyses 1:**

All available (on or off treatment) data for patients should be used

For patients (SAR342434 and Humalog) with missing week 26 data, impute the week 26 measurement as follows:

\[
\text{Baseline} + \frac{(y - \text{Baseline})}{\text{Variance}}
\]

In regards to the *variance*, we suggest using \( \frac{1}{n_c} \) is the pooled (SAR342434 and Humalog) variance of HbA1c week 28 measurements among completers, and \( n_c \) is the number of completers from both arms, but feel free to propose a different variance.

**Analyses 2:**

Perform Analyses 1, but for patients on SAR342434, impute the week 26 measurement as follows:

\[
\text{Baseline} + \frac{(y - \text{Baseline})}{\text{Variance}}
\]

**Analyses 3:**

All available (on or off treatment) data for patients should be used

For patients on SAR342434, impute the week 26 measurement as follows:

\[
\text{Baseline} + \frac{(y - \text{Baseline})}{\text{Variance}}
\]

Where *Baseline* and *variance* is the same as in Analyses 1 and 2.
For patients on Humalog, impute week 26 measurements using a model that assumes MAR (e.g., a monotone regression pattern). Or perhaps fit 2 regression models using Humalog completers and impute as follows:

For a Humalog patient with only a baseline value, impute:

\[ \text{Week 26 measurement} = \frac{\text{Baseline value}}{n_{HC}} \]

Where \( n_{HC} \) is the number of Humalog completers.

For a Humalog patient with baseline and week 12 values, impute:

\[ \text{Week 26 measurement} = \frac{\text{Baseline value} + \text{Week 12 value}}{n_{HC}} \]

**Analyses 4:**

Perform Analyses 3, but for patients on SAR342434, impute the week 26 measurement as follows:

For each analyses, generate 10,000 data sets. For each data set, run an ANCOVA with the prespecified factors and covariates (the visit term is not needed). Apply Rubin’s rule to obtain the LS Means and difference in LS Means estimates (with standard errors and confidence intervals).

Please summarize the results and provide code that was used to generate the analyses.

Perform both analyses for studies EFC12619 (6 month) and EFC13403.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
03/30/2017

Reference ID: 4077749
Hello,

Please refer to your Human Factors (HF) Engineering/Usability Report for insulin lispro, NDA 209196, submitted on November 1, 2016. In the results for your HF validation study I, you indicate that a patient chose the correct pen in the first draw but chose incorrectly in a second draw. However, your study methodology does not indicate that study participants completed study tasks more than once. Please provide clarification regarding the methodology used for both validation studies. We request that you respond to this information request by Monday, March 20, 2017. Thanks in advance.

Terrolyn Thomas, MS, MBA
Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Email: terrolyn.thomas@fda.hhs.gov
Office: 240.402.3981
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERROLYN THOMAS
03/14/2017
Hi Nilda,

Please see additional information requests below.

In your clinical study report, PDY13502, you have reported a higher number of infusion set occlusions in the SAR342434 group compared to the Humalog group, particularly in the second treatment period. From the information you have provided, it is unclear whether there may have been other factors that may have contributed to infusion set occlusions. Please provide clarification regarding the following:

1) You have provided information (PDY13502-16-2-7-ae-data, page 21 of 134) that the average interval of infusion set changes (in days) when occlusion occurs due to failure to correct hyperglycemia was a mean of 16.44 days with SAR342434 and 18.73 days with Humalog. This reported interval of infusion set changes is significantly beyond the 3 day intended use period for insulin pump infusion sets. Please provide line data from your study (which includes the duration of wear of each infusion set all subjects in the study and highlight those subjects reporting with any infusion set occlusion; failure to correct or alarm) to help clarify whether utilization of the infusion sets beyond the intended use period may have contributed to the higher number of infusion set occlusions in the SAR342434 group, particularly during the second treatment period. Alternatively the subject’s log/diary can be provided.

You have reported that “The total number of infusion set occlusion events during the on-treatment period was 23, with 14 occurring while receiving SAR342434 and 9 while receiving Humalog (Table 14). Only 1/23 event occurred >3 days (3.13 days) after a previous infusion set change” This statement appears to conflict with the data as presented in which, as stated above, the occlusions appeared to occur after the required period of infusion set change (every 3 days). Please provide clarification of this statement.

2) It is unclear from reviewing your study report as well as relevant appendices, if lower insulin infusion rates may have contributed to the higher number of infusion set occlusions reported in the SAR342434 group, particularly during the second treatment period. Please provide information regarding the (mean) total daily dose of insulin used during each treatment period per subject; identify the insulin used at each period and if an occlusion (failure to correct or alarm) occurred during that period.

3) You have reported that one patient died during the study – . Please provide the full CRF for this patient, including the patient log/diary. (Or provide information as to where this information is contained within the NDA submission).

4) The protocol stated that the treatment of hyperglycemia involved the subject administering “an insulin bolus via the insulin pump (dose based on the insulin pump instructions), and the plasma glucose was rechecked every 30 minute...”. Please confirm that the pump instructions were the use of the bolus dose calculator in the pump system and based on the
subject’s insulin sensitivity factor. If not, please explain what the pump instructions were. Additionally, please confirm that the subjects obtained and reported blood glucose values at for these evaluations and not CGM data. If the later please provide a line listing of the by subject for all episodes of hyperglycemia and the amount of insulin administered and subsequent glucose value (identifying source as capillary or interstitial).

Thanks,
Callie

From: CappelLynch, Callie
Sent: Wednesday, March 08, 2017 8:14 AM
To: Nilda.Ramos@sanofi.com
Subject: NDA 209196 Information request

Hi Nilda,

Please see the information request below for NDA 209196.

Impurity is described as an in pharmacology reports. However, in the pharmacology written summary (section 2.4) where these studies are summarized, impurity is described as. Please clarify which description is accurate.

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

/s/

CALLIE C CAPPEL-LYNCH
03/10/2017

Reference ID: 4067865
Hi Nilda,

Please see the information request below for NDA 209196.

[Redacted] is described as [Redacted] in pharmacology reports [Redacted]. However, in the pharmacology written summary (section 2.4) where these studies are summarized, impurity [Redacted] is described as [Redacted]. Please clarify which description is accurate.

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

/s/

CALLIE C CAPPEL-LYNCH
03/08/2017
Hi Nilda,

Please see the information requests below for NDA 209196. Please submit a response by COB March 6, 2017.

1. In the document (Disposable Pen Injector_Container Closure System) under 3.2.P.7, you have included table 5- Specifications of the Assembled Insulin Lispro Pen Injector (section 9.2). In document (pen-injector) under 3.2.P.2, you have also included table 1-Essential performance and safety requirements of the insulin lispro pen injector.

   a. Please provide a separate document (signed and dated) of the essential performance requirements of the Insulin Lispro pen-injector.

3. Please provide a traceability matrix for all the essential performance requirements, which should include the location of the verification and/or validation testing documents (see example below).

<table>
<thead>
<tr>
<th>Essential Performance Requirement</th>
<th>Specification</th>
<th>Verification</th>
<th>Validation</th>
<th>Aging / Stability (Y/N)</th>
<th>Shipping/Transportation (Y/N)</th>
<th>Lot Release Testing (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Accuracy</td>
<td></td>
<td>{Insert Document Number}</td>
<td>{Insert Yes if specification was verified after aging the device to the labeled date of expiry}</td>
<td>{Insert Yes if specification was validated after shipping or simulated shipping}</td>
<td>{Insert Yes if specification is a part of the lot release testing of the final finished combination product}</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4060413
5. You have provided dose accuracy testing of the insulin lispro pen injector during your stability study. It is unclear if the shelf-life of any components or subassemblies were considered in this evaluation. Please clarify the maximum age of the various components being assembled into the combination product for stability testing and discuss any impact of the total shelf-life of the combination product.

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

/s/

CALLIE C CAPPEL-LYNCH
02/23/2017
Hello:

Please refer to your Human Factors (HF) Engineering/Usability Report for insulin lispro, NDA 209196, submitted on November 1, 2016. We note that you did not include an updated copy of the moderator script that was used in the study. Please provide an updated copy of the moderator script. We request that you respond to this information request by **Wednesday, February 15, 2017**. Thanks in advance.

**Terrolyn Thomas, MS, MBA**  
Project Management Staff  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Email: terrolyn.thomas@fda.hhs.gov  
Office: 240.402.3981
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERROLYN THOMAS
02/10/2017
Hi Nilda,

Please see the information request below for NDA 209196.

Please refer to your New Drug Application (NDA) dated and received November 1, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin lispro injection U-100.

We also refer to your amendments dated January 10, and February 3, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a “recertification” for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either: 1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate. Your response to this information request must clearly reference your amendments dated January 10, and February 3, 2017.

If you have any questions, please contact me.

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

/s/

CALLIE C CAPPEL-LYNCH
02/13/2017
NDA 209196

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

ATTENTION: Donghui Ni
Associate Director

Dear Mr. Ni:

Please refer to your New Drug Application (NDA) dated November 1, 2016, received November 1, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Insulin Lispro Injection, 100 Units/mL.

We also refer to your November 8, 2016, correspondence, received November 8, 2016, requesting review of your proposed proprietary name, Admelog and Admelog Solostar.

We have completed our review of the proposed proprietary name, Admelog and Admelog Solostar and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

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

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/01/2017
Hi Nilda,

Please see our comments below regarding NDA 209196.

You have provided an NDA to request the use of insulin lispro (SAR342434) with insulin pumps, and have provided data to assess compatibility between lispro insulin (SAR342434) and several PMA sensor-augmented insulin pumps (Medtronic sensor augmented pumps and the Animas Vibe). Please note that insulin pumps both cleared and approved have labeling specifying the insulins for which they have been determined to be compatible. For the use of any new insulin in their pump, the holder of the 510(k) or PMA will need to request a labeling change for their device to specifically identify which insulins can be used with the pump. For the sensor augmented pumps (which are Class III devices) this would be done through the submission of a 180-day PMA supplement requesting a labeling change to add lispro insulin (SAR342434) to the list of compatible insulins. Please note that this will need to be coordinated with at least one of the PMA holders of these pumps in a timely fashion so that at least one pump can be approved with the use of insulin lispro (SAR342434) at the time of the NDA approval. It is advised that you work with one or both of the holders for these PMA devices and the Office of In Vitro Diagnostics and Radiological Health (OIR) to coordinate this process. The point of contact for sensor augmented pumps systems at the FDA is Stayce Beck, Ph.D., M.P.H.

Thanks,
Callie

Callie,
Thanks for your prompt clarifications.
Kind regards,
Nilda

Hi Nilda,

Please see our responses below. If you have any further questions, please contact me.

Reference ID: 4048247
Regarding request #3 for a revised label that complies with PLLR, Sanofi aligned the label provided in the application with the label for the listed drug Humalog. Sanofi is relying on information from the Humalog label for some sections of the proposed label. We would like to confirm that, if reformatting Section 8.1 (to include literature data) causes a deviation from the language in the listed drug label, that this deviation is acceptable to the FDA.

FDA Response: Although your proposed labeling may incorporate relevant data and information from the labeling of the listed drug relied upon, we note that there may be appropriate differences. For example, your proposed labeling should reflect current labeling regulations, guidances, and best practices. In this regard, we note that your proposed labeling must comply with the content and format requirements established by the Pregnancy and Lactation Labeling Rule (PLLR) because your application was submitted on or after June 30, 2015, the effective date of the PLLR.

Thanks,
Callie

From: Nilda.Ramos@sanofi.com [mailto:Nilda.Ramos@sanofi.com]
Sent: Monday, January 23, 2017 9:41 AM
To: CappelLynch, Callie
Subject: RE: Sanofi NDA 209196 - Request for Clarification

Thank you.

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, January 23, 2017 8:57 AM
To: Ramos, Nilda /US
Subject: RE: Sanofi NDA 209196 - Request for Clarification

Hi Nilda,
This application will not be reviewed under the program. That language was inadvertently left in the letter. I apologize for any confusion. I will get back to you regarding the other two issues as quickly as possible. I look forward to working with you.

Thanks,
Callie

From: Nilda.Ramos@sanofi.com [mailto:Nilda.Ramos@sanofi.com]
Sent: Saturday, January 21, 2017 5:43 AM
To: CappelLynch, Callie
Subject: Sanofi NDA 209196 - Request for Clarification

Dear Callie Cappel-Lynch,

I take this opportunity to introduce myself as Sanofi’s new regulatory contact for NDA 209196. A formal request for change of regulatory contact was submitted to the application on January 19, 2017 (Sequence #0003).

Sanofi is in receipt of the attached NDA filing communication dated January 10, 2017. We are asking for clarification in regards to the information in the filing communication.

Regarding request #3 d for a revised label that complies with PLLR, Sanofi aligned the label provided in the application with the label for the listed drug Humalog. Sanofi is relying on information from the Humalog label for some sections of the proposed label. We would like to confirm that, if reformatting Section 8.1 (to include literature data) causes a deviation from the language in the listed drug label, that this deviation is acceptable to the FDA.

Thank you,

Nilda RAMOS
Assistant Director, Regulatory Affairs
Sanofi
55 Corporate Drive
Bridgewater, New Jersey 08807
nilda.ramos@sanofi.com

Reference ID: 4048247
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
01/30/2017
NDA 209196

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Sanofi-Aventis U.S. LLC
Attention: Donghui Ni
Associate Director
55 Corporate Drive
Bridgewater, NJ 00807

Dear Mr. Ni:

Please refer to your New Drug Application (NDA) dated and received November 1, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin lispro injection U-100.

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 September 1, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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 August 4, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. 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:

**Chemistry, Manufacturing, and Controls**

1. Please provide the following:
   
   a. Certificates of analysis for representative lots of excipients used for manufacturing registration stability batches.
   
   b. **An assessment of the extent of**

   c. English translation of the entire executed batch record (EBR) along with numerical data entries for compounding and filling of the drug product

**Device**

2. Provide an assessment of photostability of your drug product per ICH Q1B in the two representative infusion pumps you have previously identified. Testing should be conducted using worst-case delivery settings (i.e. slowest programmable basal delivery rate and longest typically available infusion sets).

**Other**

3. On December 4, 2014, the Food and Drug Administration published the “Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLIR). The PLLIR went into effect on June 30, 2015. According to PLLIR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLIR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).
Submit the following information on insulin lispro use in pregnant and lactating women by February 3, 2017:

a. A review and summary of all available published literature regarding insulin lispro,

b. A review and summary from your pharmacovigilance database,

c. Interim ongoing or final report on a closed pregnancy registry (if applicable),

d. Revised labeling, if appropriate, incorporating the above information (in Microsoft Word format) that complies with PLLR.


We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 3, 2017. The resubmitted labeling will be used for further labeling discussions.

Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

**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. As you develop your proposed PI, we encourage you to review the labeling review resources on the **PLR Requirements for Prescribing Information** and **PLLR Requirements for Prescribing Information** websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
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), patient PI, and instructions for use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf)).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient PI, and instructions for use (IFU), 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](http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm). If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because none of these criteria apply to your application, you are exempt from this requirement.

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

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
01/10/2017
NDA 209196

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

ATTENTION: Donghui Ni
Associate Director

Dear Mr. Ni:

Please refer to your New Drug Application (NDA) dated November 1, 2016, received November 1, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Insulin Lispro Injection, 100 Units/mL.

We acknowledge receipt of your November 8, 2016, correspondence, received November 8, 2016, requesting a review of your proposed proprietary names, Admelog and Admelog Solostar.

If the application is filed, the user fee goal date will be February 6, 2017.

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

Sincerely,

{See appended electronic signature page}

Terrolyn Thomas, MS, MBA
Senior Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERROLYN THOMAS
12/13/2016
NDA 209196

Sanofi-Aventis U.S. LLC
Attention: Donghui Ni
Associate Director
55 Corporate Drive
Bridgewater, NJ 00807

Dear Mr. Ni:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: insulin lispro injection U-100
Date of Application: November 1, 2016
Date of Receipt: November 1, 2016

Our Reference Number: NDA 209196

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 December 31, 2016, 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:

Reference ID: 4009149
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) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D., RAC
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CALLIE C CAPPEL-LYNCH
11/04/2016
IND 120511

MEETING MINUTES

Sanofi US Services Inc.
Attention: Donghui Ni, M.Sc.
Associate Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, NJ 08807

Dear Mr. Ni:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin lispro injection.

We also refer to the meeting between representatives of your firm and the FDA on March 23, 2016. The purpose of the meeting was to discuss the format and content of your proposed marketing application for insulin lispro, including the presentation and acceptability of the data and dataset structure, the presentation of anti-insulin antibody results, and the content of the 4-month safety update.

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

If you have any questions, call Michael White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Wednesday, March 23, 2016; 2:00 PM to 3:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, MD 20903

Application Number: IND 120511
Product Name: insulin lispro injection (SAR342434)
Indication: to improve glycemic control in adults and children with diabetes mellitus
Sponsor/Applicant Name: Sanofi US Services Inc.

Meeting Chair: William Chong, M.D.
Meeting Recorder: Michael G. White, Ph.D.

FDA ATTENDEES
Division of Metabolism and Endocrinology Products
William Chong, M.D., Clinical Team Leader
Lisa Yanoff, M.D., Clinical Team Leader
Mahtab Niiyati, M.D., Clinical Reviewer
Ronald Wange, Ph.D., Supervisory Pharmacologist
Daniel Minck, Ph.D., Nonclinical Reviewer
Jennifer Pippins, M.D., Deputy Director for Safety
Pamela Lucarelli, Chief, Project Management Staff
Michael G. White, Ph.D., Regulatory Project Manager

Division of Clinical Pharmacology II
Manoj Khurana, Ph.D., Clinical Pharmacology Team Leader
Renu Singh, Ph.D., M.S., Clinical Pharmacology Reviewer

Office of Biostatistics
Mark D. Rothmann, Ph.D., Lead Mathematical Statistician
Shuxian Sinks, Ph.D., Statistical Reviewer

Office of Pharmaceutical Quality
Suong Tran, Ph.D., Quality/CMC Lead

Reference ID: 3916750
1.0 BACKGROUND

Sanofi US Services Inc. (Sanofi) has been developing a rapid-acting insulin solution of recombinant DNA origin, insulin lispro injection (SAR342434), for the treatment of diabetes mellitus and seeks to submit marketing applications through the 505(b)(2) regulatory pathway that will rely, in part, on the Agency’s finding of safety and effectiveness for Humalog (NDA 020563). Sanofi states that SAR342434 “has the identical amino acid sequence and structure as the originator’s insulin lispro.” Sanofi also states that “SAR342434 is produced by recombinant DNA technology utilizing a nonpathogenic laboratory strain of Escherichia coli.

Sanofi first obtained Agency feedback on their development program for SAR342434 when they requested a Pre-Investigational New Drug (PIND) meeting for which written responses were issued on February 21, 2014. Sanofi submitted their Investigational New Drug Application (IND) on June 26, 2014, to which the Agency issued non-hold comments on August 28, 2014. An End-of-Phase 2 (EOP2) meeting was held on October 6, 2014, with final minutes issued on November 7, 2014. On July 22, 2015, Sanofi submitted a reply to the Agency’s EOP2 minutes and requested additional comments, to which the Agency issued feedback on September 16, 2015.
Following the EOP2 meeting, Sanofi requested a Type C meeting regarding the use of SAR342434 in pumps for which it received written responses on April 27, 2015. Sanofi replied to the Agency’s responses on June 5, 2015, with the Agency issuing additional comments on September 2, 2015. Sanofi responded to these comments on October 2, 2016, and provided amended clinical trial protocols on November 10, and November 24, 2015, for which the Agency issued comments on February 11, 2016.

Sanofi also submitted a human factors study protocol for Agency comment on October 16, 2015, for which the Agency issued comments on January 27, 2016.

On January 29, 2016, Sanofi requested a Type B, Pre-NDA meeting in anticipation of the submission of their marketing application for SAR342434. The purposes of this meeting was to discuss the format and content of the proposed 505(b)(2) application for insulin lispro, including the presentation and acceptability of the data and dataset structure, the presentation of anti-insulin antibody results, and the content of the 4-month safety update. Preliminary responses to the questions contained in Sanofi’s meeting background package, received February 23, 2015.

The proposed insulin lispro drug product that is to be administered using a prefilled pen injector is a combination product subject under 21 CFR Part 3. As such it is 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.

FDA sent Preliminary Comments to Sanofi on March 21, 2016.

2.0 DISCUSSION

The sponsor’s questions are repeated below in regular text, followed by the FDA’s preliminary responses (bolded), followed by any sponsor’s response (if received) to the FDA preliminary responses (italics), which is followed by the applicable discussion for that question (bolded and italicized, and double indented).

**Question 1:**
Does FDA agree that the CMC, nonclinical, and clinical information to be provided in the Table of Content [in the meeting package] is sufficient for NDA filing and review?

**FDA Response to Question 1:**
For the Combination Product Quality information:

- We remind you to provide data in section 3.2.P.2 Pharmaceutical Development of Module 3 of your new drug application (NDA) to show that your product does not differ in strength from, or its quality or purity does not fall below, the standards set in the USP monographs for “Insulin Lispro” and “Insulin Lispro Injection,” compatibility information on the product when diluted in specific diluents during use (if applicable)
5.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new
dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**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 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf) and [Pregnancy and Lactation Labeling Final Rule](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential;
- 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 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types:
NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, Guidance for Industry Assessment of Abuse Potential of Drugs, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.”
505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

At this time,2 the 505(b)(2) approval pathway may be used for a proposed insulin analog product that is demonstrated to be sufficiently similar to a listed drug to permit reliance, where scientifically justified, on FDA’s finding of safety and/or effectiveness for the listed drug to support approval of an NDA. If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a “bridge” between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. A demonstration of similarity to the listed drug may include, for example, comparative physicochemical tests and bioassay, nonclinical data (which may include bridging toxicology studies),

pharmacokinetic (PK)/pharmacodynamic (PD) data, and clinical data (which may include an assessment of immunogenicity).

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described (e.g., by trade name(s)) in the published literature.

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug or published literature describing a listed drug (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug or on published literature. In your proposed 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.
List the information that may be considered essential to the approval of the proposed drug that is provided by reliance on the FDA’s finding of safety and effectiveness for a listed drug or by reliance on published literature

<table>
<thead>
<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
</tr>
<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
</tr>
<tr>
<td>3. Example: NDA YYYYYY “TRADENAME”</td>
<td>Previous finding of safety for Carcinogenicity, labeling section XXX</td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
</tbody>
</table>

**Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item 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 submission in the format described, the Applicant can describe location or provide a link 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 submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA 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 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 for each site by site

3. Please include the following information in a tabular format in the NDA 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 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 Organization (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 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 line listings for:
   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,
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

Reference ID: 3916750
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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
[m5]
  datasets
    bimo
      site-level
```

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.

---

3 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

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

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

6.0 ATTACHMENTS AND HANDOUTS

Sanofi’s response to FDA preliminary comments as presented at the meeting follows:
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
04/16/2016
IND 120511

Sanofi US Services Inc.
Attention: Donghui Ni, M.Sc.
Senior Manager, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55D-215A
Bridgewater, NJ 08807

Dear Mr. Ni:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin lispro injection.

We also refer to the meeting between representatives of your firm and the FDA on October 6, 2014. The purpose of the meeting was to discuss current data generated to date and the additional studies planned to support submission of a marketing application for insulin lispro.

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

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

Sincerely,

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date and Time: Monday, October 6, 2014; 3:00-4:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903
Application Number: 120511
Product Name: insulin lispro injection (SAR342434)
Indication: to improve glycemic control in adults and children with diabetes mellitus
Sponsor/Applicant Name: Sanofi US Services Inc.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products
Jean Marc Guettier, M.D., Director
William Chong, M.D., Clinical Team Leader (Acting)
Lisa Yanoff, M.D., Clinical Team Leader (Acting)
Valerie Pratt, M.D., Medical Officer
Karen Davis Bruno, Ph.D., Nonclinical Supervisor
Indra Antonipillai, Ph.D., Nonclinical Reviewer
Pamela Lucarelli, Chief, Project Management Staff
Richard Whitehead, M.S., Regulatory Project Manager

Division of Biometrics
Mark Rothmann, Ph.D., Team Leader
Cynthia Liu, Ph.D., Statistics reviewer

Division of Clinical Pharmacology
Manoj Khurana, Ph.D., Team Leader (Acting)

Division of Medication Error Prevention and Analysis
Yelena Maslov, Pharm.D. Team Leader
Sarah Vee, Pharm.D. Reviewer
1.0 BACKGROUND

Insulin lispro (SAR342434) is a human insulin analog, of recombinant DNA origin, which is being developed for the treatment of diabetes mellitus. Sanofi US Services, Inc. (Sanofi) plans to submit a marketing application through the 505(b)(2) regulatory pathway relying, in part, on the Agency’s finding of safety and effectiveness for Humalog (insulin lispro). Sanofi states that the drug substance SAR342434 was therefore designed to have the identical amino acid sequence and structure as the originator’s insulin lispro. Sanofi further states that SAR342434 is produced by recombinant DNA technology utilizing a nonpathogenic laboratory strain of Escherichia coli as the production organism, in the same way as the corresponding RLD. Sanofi describes its plan
to take a multi-step approach to obtain data from physico-chemical analysis, nonclinical studies, and clinical studies including clinical pharmacology, safety, efficacy, and immunogenicity in order to demonstrate the similarity between SAR342434 and Humalog-US (the listed drug relied upon) and to establish an acceptable “bridge” to scientifically justify the relevance of certain data with European Union (EU)-approved insulin lispro.

AR342434 has completed Phase 1 clinical development with start of Phase 3 planned in late 2014. IND 120511 was opened on June 26, 2014.

The purpose of this meeting was to obtain feedback on the data generated to date and the additional studies planned to support a new drug application for SAR342434.

2. DISCUSSION

2.1 Quality

**Question 1:** Does the Agency agree with the evaluation of the applicant and based on available data that the Sanofi product SAR342434, and Humalog-EU and Humalog-US can be considered as similar in terms of product purity notwithstanding minor differences, and that the strategy is suitable to support demonstration of similarity in the NDA?

**FDA Response to Question 1:** The currently available analytical information comparing SAR342434, and Humalog-US and EU-approved insulin lispro is adequate to support the proposed Phase 3 clinical studies. All final analytical reports will be evaluated as part of our review of your proposed 505(b)(2) application and further comments, if any, will be conveyed to you at that time. We remind you to include in your proposed 505(b)(2) application information demonstrating that any difference between your product and Humalog-US has no impact on the safety and/or efficacy of your product.

**Question 2:** In addition to the data submitted in the IND and the data in the Rationale for Question 1, Sanofi plans to provide further comparative data according to a step-wise approach.

a) Does the Agency agree with the sponsor’s strategy and approach for establishing similarity of SAR342434 to the RLD in the NDA?

b) Does the Agency agree on the selected number of batches and drug product presentations for the respective quality attributes to be tested?

c) Does the Agency agree with the selection of one batch of Humalog per market in one presentation (cartridges) and one batch of SAR342434 (cartridges, production-scale), according to the intended study protocol to demonstrate similar degradation pathways of SAR342434, Humalog-EU and Humalog-US?

**FDA Response to Question 2:**

a) We agree with your proposed strategy for the analytical comparison of SAR342434, and Humalog-US and EU-approved insulin lispro.
b) We agree with your proposed number of batches and packaging presentations in the analytical comparison of SAR342434, and Humalog-US and EU approved insulin lispro.

c) We agree with your proposed number of batches and packaging presentations in the degradation pathway comparison of SAR342434, and Humalog-US and EU-approved insulin lispro.

**Question 3:** Does the Agency agree with the sponsor’s proposed primary stability protocol to support the approval of SAR342434 drug product, in particular,

a) Does the Agency agree that in addition to the primary stability data on the SAR342434 drug product in cartridges that will be provided to support registration, the inclusion, in the initial NDA, of at least 6 months stability data on one representative commercial scale batch of cartridges assembled in the final pen device is sufficient to confirm the stability of the drug product in the pen injector presentation?

b) Does the Agency agree with the sponsor’s proposal to test for potency of SAR342434 drug product by performing bioassay testing, according to USP <121> Insulin Assays – Rabbit Blood Sugar method on an annual basis - at start of study, after 1 month storage at +37°C, after 12 months, 24 months, and 36 months at the end of long-term storage conditions (+5°C) - on one representative drug product batch (filled in 3 mL glass cartridges) in an effort to reduce the number of animals tested?

**FDA Response to Question 3:**

a) We agree with your proposal to include in the initial NDA 6 months of stability data on one commercial batch of cartridges assembled in the final pen injector.

b) We agree with your proposed time points for the Rabbit Insulin Assay in the primary stability study.

**Question 4:** Does the Agency agree with the sponsor’s plan to substitute the in vivo bio-identity test by a cell-based bio-identity test for release?

**FDA Response to Question 4:** We agree with your plan to substitute the animal bio-identity test by a cell-based bio-identity test. Method validation and comparability data will be evaluated as part of our review of your NDA and further comments, if any, will be conveyed to you at that time.

2.2 Clinical

**Question 5:** Does the FDA agree that study PDY12704 demonstrated the similarity in PK/PD endpoints between SAR342434 and Humalog?

**FDA Response to Question 5:** Based on the information provided in the background package, it appears that you have provided adequate PK/PD bridging data between SAR342434, Humalog-US, and EU-approved insulin lispro. The final PK/PD study report will be evaluated as part of our review of your proposed 505(b)(2) application, and whether you have demonstrated sufficient similarity to
support reliance on FDA’s finding of safety and effectiveness for Humalog-US and to scientifically justify the relevance of data with EU-approved insulin lispro will be review issues.

Additional Comment:
Please confirm if the SAR342434 formulation proposed for the Phase 3 trials is identical to that used in the PK/PD study, and will be the final to-be-market formulation.

**Question 6:** Does the Agency agree with the methods described in the two protocols for data collection and analysis, in particular regarding the strategy for the missing data?

**FDA Response to Question 6:** We agree

**FDA Meeting Discussion to Question 6:** Refer to Section 3.0 (Attachments and Handouts) for the sponsor’s pre-meeting comments.

After the meeting, the Agency re-reviewed its August 29, 2014, comments to the sponsor and also parts of the FDA response to question 6 above. The Agency noted that the sponsor is still proposing...
Question 7: Does the Agency agree with the sponsor’s approach for assessing the anti-insulin antibodies (AIA) and their clinical relevance?

FDA Response to Question 7: Yes, we agree. In addition to the proposed sampling times, patients with samples that test positive should be followed until anti-drug antibody levels revert to baseline.

FDA Meeting Discussion to Question 7: Refer to Section 3.0 (Attachments and Handouts) for the sponsor’s pre-meeting comments.

Yes, we agree with the sponsor’s approach to follow up the increase of anti-insulin antibodies (AIA) to baseline levels only in patients for which the Allergic Reaction Assessment Committee assesses AIA-mediated hypersensitivity reactions or insulin resistance. We may ask for additional assessment if there is clinical cause.

Question 8: To simplify the anti-insulin antibody sample analysis, Sanofi plans to optimize the AIA assay by performing additional experiments, based on evidence provided by the preliminary data. Does the Agency agree with the plan?

FDA Response to Question 8: Yes, we agree with your plan. However, the final determination on whether it is appropriate to [redacted] will be made after we have reviewed the results of your studies.

FDA Meeting Discussion to Question 8: Refer to Section 3.0 (Attachments and Handouts) for the sponsor’s pre-meeting comments.

Your approach to use either the polyclonal anti-human insulin antibody or the SAR342434-specific antibody, provided the re-validation shows similar drug tolerance and sensitivity of the anti-SAR342434 antibody, to demonstrate the assay is controlled is acceptable.

2.3 Regulatory

Question 9: The sponsor considers that the pre-clinical, CMC and clinical data package that will be generated according to the SAR342434 development program will be adequate to support the NDA using the 505 (b)(2) pathway. Does the Agency agree?
**FDA Response to Question 9:** The proposed development program appears that it will generate data that would support submission of a 505(b)(2) application at this time. The adequacy of the data will be a review issue. However, among other things, it should be noted that if there are any additional changes to the SAR342434 formulation, additional physiochemical analyses and/or bridging animal studies may be required.
Regarding Human Factors, you stated that the proposed drug product (SAR342434) will be made available in vials and disposable prefilled pen devices, which will be identical to the marketed SoloStar pen with modifications in colors and label. In addition, you stated that a human factors validation study protocol along with a use-related risk analysis will be submitted for Agency review prior to conducting the study. We find this approach reasonable.

ADDITIONAL DISCUSSION

Refer to Section 3.0 (Attachments and Handouts) for the sponsor’s pre-meeting comments.

The Sponsor requested an update on the review status of the Pediatric Study Plan. The Agency stated that it would provide comments in separate correspondence at a later time.

Post-Meeting Note:

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. Further, section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended PREA, to set forth a process for reaching agreement between applicants and FDA on initial pediatric study plans (PSPs)

On February 21, 2014, we incorrectly informed you that your proposed 505(b)(2) application for SAR342434 is subject to PREA and requires a PSP. Upon further consideration, we have determined that none of the criteria apply at this time to your proposed 505(b)(2) application, and thus your proposed 505(b)(2) application does not trigger PREA. A PSP is therefore not required at this time.

COMBINATION PRODUCT REQUIREMENTS

Your proposed insulin lispro injection systems are drug-device combination products 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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and 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 clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).
ADDITIONAL REGULATORY COMMENTS (505(B)(2) PATHWAY)

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at:
In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a “bridge” between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that your proposed product is sufficiently similar to the listed drug such that reliance is scientifically justified. A demonstration of similarity to the listed drug may include, for example, comparative physico-chemical tests and bioassay, nonclinical data (which may include bridging toxicology studies), pharmacokinetic (PK)/pharmacodynamic (PD) data, and clinical data (which may include an assessment of immunogenicity).

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described (e.g., by trade name(s)) in the published literature.

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug or published literature describing a listed drug (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA’s finding of safety and/or effectiveness for a listed drug or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.
In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

<table>
<thead>
<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
</tr>
<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
</tr>
<tr>
<td>3. Example: NDA YYYYYY “TRADENAME”</td>
<td>Previous finding of safety for Carcinogenicity, labeling section XXX</td>
</tr>
</tbody>
</table>

### 3.0 ATTACHMENTS AND HANDOUTS

The sponsor provided pre-meeting response to FDA Preliminary Comments with topics for discussion on October 6, 2014.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
11/07/2014