DEBARMENT CERTIFICATION

Sanofi-aventis U.S. LLC, a SANOFI COMPANY, as the authorized US Agent for UCB, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

UCB also provided debarment certification in NDA 22-064 in Module 1.3.1.3.

[Signature]
Cynthia Taylor Psaras, PhD
Director
Global Regulatory Affairs
Sanofi US Services Inc.
on behalf of sanofi-aventis U.S. LLC,
A SANOFI COMPANY
DEBARMENT CERTIFICATION

Sanofi-aventis U.S. LLC, A SANOFI COMPANY, as the authorized US Agent for UCB, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

UCB also provided debarment certification in NDA 22-157 in Module 1.3.1.3.

[Signature]
Cynthia Taylor Psaras, PhD
Director
Global Regulatory Affairs
Sanofi US Services Inc.
on behalf of sanofi-aventis U.S. LLC,
A SANOFI COMPANY
ACTION PACKAGE CHECKLIST

APPLICABLE INFORMATION

**NDA #** 209089
**NDA Supplement #**
**BLA #**
**BLA Supplement #**

If NDA, Efficacy Supplement Type:
(an action package is not required for SE8 or SE9 supplements)

Proprietary Name: Xyzal 24 HR
Established/Proper Name: levocetirizine dihydrochloride
Dosage Form: tablet

Applicant: UCB, Inc.
Agent for Applicant (if applicable): Sanofi-aventis U.S., LLC

RPM: Sherry Stewart
Division: Division of Nonprescription Drug Products (DNDP)

NDA Application Type: 505(b)(1) [ ] 505(b)(2) [X]
Efficacy Supplement: 505(b)(1) [ ] 505(b)(2) [X]

BLA Application Type: 351(k) [X] 351(a) [ ]
Efficacy Supplement: 351(k) [X] 351(a) [ ]

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

☐ No changes
☐ New patent/exclusivity (notify CDER OND IO)

Date of check: 

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 January 31, 2017
- Previous actions (specify type and date for each action taken)
  - None

If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain ________________

Application Characteristics ³

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.

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 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.
Review priority: **Standard**  
Chemical classification (new NDAs only): **oral antihistamine Hz receptor antagonist**  

(**confirm chemical classification at time of approval**)

- Fast Track
- Rolling Review
- Orphan drug designation
- 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**)  

### NDAs: Subpart H
- Accelerated approval (21 CFR 314.510)  
- Restricted distribution (21 CFR 314.520)  
- Approval based on animal studies

### BLAs: Subpart E
- Accelerated approval (21 CFR 601.41)  
- Restricted distribution (21 CFR 601.42)  
- Approval based on animal studies

### REMS:
- MedGuide
- Communication Plan
- ETASU
- MedGuide w/o REMS
- REMS not required

#### Comments:
- **BLAs only**: Is the product subject to official FDA lot release per 21 CFR 610.2  
  (approvals only)
- **Public communications (approvals only)**
  - Office of Executive Programs (OEP) liaison has been notified of action  
  - 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)?
  - 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.

### CONTENTS OF ACTION PACKAGE

#### Officer/Employee List
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  - Included

- Documentation of consent/non-consent by officers/employees
  - Included
## Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - AP 1/31/17

## 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)*
    - Included
  - Original applicant-proposed labeling
    - 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)*
    - Included
  - Original applicant-proposed labeling
    - 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))* June 8, 2016
  - Review(s) *(indicate date(s))* May 26, 2016

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

## Administrative / Regulatory Documents

- **RPM Filing Review** / Memo of Filing Meeting *(indicate date of each review)*
  - 5/16/16

- **All NDA 505(b)(2) Actions**
  - Date each action cleared by 505(b)(2) Clearance Committee
  - Not a (b)(2) 1/24/17

- **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](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - Yes ☒  No ☐

---

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

  □ Yes  □ No

- Not an AP action

- Pediatrics *(approvals only)*
  - Date reviewed by PeRC 
    If PeRC review not necessary, explain: 

  Not applicable

- 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)*

  Acknowledgement Letter: 4/14/16
  74 day Letter: 6/13/16
  Information Requests: 5/31/16; 9/1/16; 9/21/16; 12/21/16;
  Labeling PMR/PMC Discussion Comments: 12/28/16

- 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)*

  Memorandum of Informal Teleconference 1/13/16

- Minutes of Meetings

  - If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*
  - Pre-NDA/BLA meeting *(indicate date of mtg)*
  - EOP2 meeting *(indicate date of mtg)*
  - 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)*

  □ N/A or no mtg

  □ No mtg  Pre-IND meeting 10/1/15

  □ No mtg

  □ N/A

  □ N/A

- Advisory Committee Meeting(s)

  □ No AC meeting

- Date(s) of Meeting(s)

<table>
<thead>
<tr>
<th>Decisional and Summary Memos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office Director Decisional Memo <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>□ None</td>
</tr>
<tr>
<td>Division Director Summary Review <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>□ None  1/30/17</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader Review <em>(indicate date for each review)</em></td>
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<tr>
<td>□ None  1/10/17</td>
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<tr>
<td>PMR/PMC Development Templates <em>(indicate total number)</em></td>
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<td>□ None</td>
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</table>

**Clinical**
<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Reviews</strong></td>
<td></td>
</tr>
<tr>
<td>• Clinical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>No separate review</td>
</tr>
</tbody>
</table>
| • Clinical review(s) *(indicate date for each review)* | Wang: 12/12/16  
Gierhart: 11/15/16 |
| • Social scientist review(s) *(if OTC drug)* *(indicate date for each review)* | None  
Pike-McCrudden 12/22/16 |
| • Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)* | Clinical Review (Gierhart) p, 33  
No new studies performed, therefore no new financial disclosure forms. |
| • Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☒ None |
| • Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | N/A |
| **Risk Management** | |
| • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* | None |
| • REMS Memo(s) and letter(s) *(indicate date(s))* | |
| • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | None |
| • OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | ☒ None requested |
| **Clinical Microbiology** | ☒ None |
| • Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | No separate review |
| • Clinical Microbiology Review(s) *(indicate date for each review)* | None |
| **Biostatistics** | ☒ None |
| • Statistical Division Director Review(s) *(indicate date for each review)* | No separate review |
| • Statistical Team Leader Review(s) *(indicate date for each review)* | No separate review |
| • Statistical Review(s) *(indicate date for each review)* | None 12/21/16 |
| **Clinical Pharmacology** | ☒ None |
| • Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | No separate review |
| • Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | No separate review |
| • Clinical Pharmacology review(s) *(indicate date for each review)* | None 12/22/16 |
| • OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | None requested |

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5 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).
### Nonclinical

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Review Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• ADP/T Review(s) (indicate date for each review)</td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Supervisory Review(s) (indicate date for each review)</td>
<td>☒ No separate review</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)</td>
<td>☐ None 12/2/16</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)</td>
<td>☒ None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies (indicate date for each review)</td>
<td>☒ No carc</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td></td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary (include copies of OSI letters)</td>
<td>☐ None requested</td>
</tr>
</tbody>
</table>

### Product Quality

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Review Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>• Tertiary review (indicate date for each review)</td>
<td>☐ None 12/16/16</td>
</tr>
<tr>
<td>• Secondary review (e.g., Branch Chief) (indicate date for each review)</td>
<td>☐ None 12/16/16</td>
</tr>
<tr>
<td>• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)</td>
<td>☒ None</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)</td>
<td>☒ None</td>
</tr>
<tr>
<td>Environmental Assessment (check one) (original and supplemental applications)</td>
<td></td>
</tr>
<tr>
<td>☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</td>
<td>P. 33 CMC Review</td>
</tr>
<tr>
<td>☐ Review &amp; FONSI (indicate date of review)</td>
<td></td>
</tr>
<tr>
<td>☐ Review &amp; Environmental Impact Statement (indicate date of each review)</td>
<td></td>
</tr>
<tr>
<td>Facilities Review/Inspection</td>
<td></td>
</tr>
</tbody>
</table>

6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>• Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>For Breakthrough Therapy (BT) Designated drugs:</td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>For products that need to be added to the flush list (generally opioids):</td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</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>
</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>
</tr>
<tr>
<td>Ensure Pediatric Record is accurate</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</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/

SHERRY A STEWART
02/07/2017
Hi Cynthia,

Please reply to this email to confirm receipt.

Please refer to original new drug application (NDA) 209089, Xyzal®24HR for the labeling information request below:

Outside Drug Facts label (DFL)
1. Remove "Original Prescription Strength" from PDP on all labels. Per policy, only full switches may use this language. NDA 209089 is a partial-OTC switch and does not qualify for this language.
2. Per §201.61 (c), the statement of identity (SOI) shall be presented in bold face type on principal display panel (PDP). Update SOI to comply with §201.61 (c).
3. Replace all placeholder "Xs" with actual NDC number on cartons and immediate containers to comply with §207.35 (b)(3).
4. Update country of origin to "Switzerland" as these countries are the manufacturers of API.
5. Revise statement, "Clinically proven 24 hour relief" on 10-count carton to comply with drug class labeling for antihistamines.
6. Refer to 45-count Bonus carton. Per non-prescription drug labeling policy, the net quantity statement can reflect the "free" amount by placing a "\" or "X" over the original package size quantity and placing the new quantity on the PDP. Update the 45-count Bonus carton to reflect this policy.
7. Refer to 35-, 45-, 55-and 80-count carton statement, The agency's Division of Pulmonary, Allergy, and Rheumatology cites only three triggers studied. Change listed triggers to "indoor and outdoor allergens" to comply with class labeling for antihistamines.
8. There are ten "X" placeholders on cartons and immediate containers that do not appear to be labeling. Provide explanation for these placeholders.
9. Place statement, "Read directions and warnings before use. Keep this carton. It has important information" on carton as this NDA is not marketed with a consumer information leaflet (CIL).

Drug Facts Label (DFL)
1. In Directions, change "once daily in the evening" to be consistent with prescription labeling.
2. In Inactive ingredients, change "polyethylene glycol" to "polyethylene glycol 400" which states the correct excipient used.
3. In Questions or Comments?, Replace the placeholder Xs with actual telephone number on cartons and immediate container bottles. §201.66 (c)(9) recommends that the label include the days of the week and times that the toll-free number is in operation.

Please make the above revisions to draft labeling and submit revised labeling as an amendment to the application by COB Monday January 6, 2017.

If you have any questions, please let me know.

Thank you and best regards,
Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618
Sherry.Stewart@fda.hhs.gov

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/s/

SHERRY A STEWART
12/28/2016
Hi Cynthia,

Please reply to this email to confirm receipt.

Please refer to original new drug application (NDA) 209090, Children's Xyzal®24HR for the labeling information request below:

**Outside Drug Facts label (DFL)**
1. Per §201.61 (c), the statement of identity (SOI) shall be presented in bold face type on principal display panel (PDP). Update SOI to comply with §201.61 (c).
2. Replace the placeholder "Xs" with actual NDC number to comply with §207.35 (b)(3).
3. Change "ml" to "mL" in statement of identity AND net quantity on carton and immediate container.
4. Change declaration of net quantity to boldface font to comply with §201.62 (g).
5. Update country of origin to "Switzerland and Belgium as these countries are the manufacturers of API."
6. Revise statement, to "Clinically proven 24 hour relief" on 10-count carton to comply with drug class labeling.
7. Recommend placing statement, "Read directions and warnings before use. Keep this carton. It has important information" on carton as this NDA is not marketed with a consumer information leaflet (CIL).
8. Include an image of the dosing cup on the principal display panel of carton labeling. In addition, include an image of the dosing cup on the side panel above the phrase "Use Only With Enclosed Dosing Cup". The image of cup should appear empty with measurement lines visible.

**Drug Facts Label (DFL)**
1. In **Directions**, change to "once daily in the evening" to be consistent with prescription labeling.
2. In **Questions or Comments?**, Replace the placeholder Xs with actual telephone number on cartons and immediate container bottles. We also recommend that the label include the days of the week and times that the toll-free number is in operation.

Please make the above revisions to draft labeling and submit revised labeling as an amendment to the application by COB Friday January 6, 2017.

Thank you and best regards,

*Sherry Stewart, PharmD*

Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618

[Sherry_Stewart@fda.hhs.gov](mailto:Sherry_Stewart@fda.hhs.gov)
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/s/

SHERRY A STEWART
12/28/2016
Hi Swapan,

Karen Livornese, our labeling reviewer has the follow request for information regarding the above mentioned NDAs:

1. The Distributor label states:

   The trade dress of this Xyzal® package is subject to trademark protection.

   Dist. By: Chattem, Inc., a Sanofi Company, Chattanooga, TN 37409-0219

   ©2017 Origin: Switzerland

   Please confirm origin of foreign country is acceptable.

Please respond via reply all email by 11/23/16.

Let me know if you have any questions,

Thanks,

Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618
Sherry.Stewart@fda.hhs.gov

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Reference ID: 4015333
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERRY A STEWART
11/17/2016
Hi Betsy and Swapan:

The IDS/Labeling Reviewer Karen Livornese has the following request for information with regard to the above mentioned pending NDAs.

1. The PDP displays “(Exempt)” according to the SOP: “We only allow this statement as a flag on the PDP for complete switches (i.e., the prescription product no longer exists because all indications are switched). Exemptions from this policy will be made on a case-by-case basis, and such exemptions will be cleared by ODE IV (e.g., (Exempt)).”

Since this is a partial switch, is this acceptable for these two NDAs?

Please provide your response via reply all email by 11/23/16.

Let me know if you have any questions,

Thanks,

Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618
Sherry.Stewart@fda.hhs.gov

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/s/

SHERRY A STEWART
11/17/2016
Hi Cynthia,

Please reply to this email to acknowledge receipt.

Regarding the above referenced NDA, we have the following request for information.

1. In NDA 209089 SDN2 dated 3/31/16, the “Tabular listing of clinical studies (allergic rhinitis)” (located in Module 5.2 in the NDA 209089 3/31/16 submission) on pg. 29 states that Sanofi was planning on submitting two full complete study reports for A00430 and A00431 in Module 5.3.5.1; however, no such study reports exist in that module. Submit these two study reports in Module 5.3.5.1 for Original NDA 209089.

Submit the requested information to me via email by close of business 9/30/16 and follow up with a formal submission to the NDA.

If you have any questions, please let me know.

Thank you and best regards,

Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618
Sherry.Stewart@fda.hhs.gov

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/s/

SHERRY A STEWART
09/21/2016
Hi Cynthia,

Please reply to this email to acknowledge receipt.

With regard to the above mentioned pending NDA, we have the following request for information:

Of the 62 clinical studies conducted by UCB containing safety information re: levocetirizine dihydrochloride tablet and solution, 13 (21%) of these studies are only linked in the “Tabular listing of all clinical studies” located in Module 2.7.6 to a clinical synopsis. The clinical reviewer is unable to evaluate the safety of these 13 studies based upon a 6 or 7-page synopsis. Please submit final study reports (i.e., clinical study reports) for nine clinical pharmacology studies (i.e., A245, A252, A256, A00280, A00305, A00324, A00331, A00351, and A00373) and four clinical studies (i.e., A00299, A00334, A00348 and A00349).

Please submit the requested information to the applications by close of business September 16, 2016. If you have questions, please let me know.

Thank you and best regards,

Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
301-796-9618
Sherry.Stewart@fda.hhs.gov

The information transmitted in this electronic communication is intended only for the person or entity to whom it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of or taking of any action in reliance upon this information by persons or entities other than the intended recipient is prohibited.
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/s/

SHERRY A STEWART
09/01/2016
FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

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

Dear Dr. Psaras:

Please refer to your New Drug Applications (NDAs) dated and received March 31, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for

- NDA 209089: Xyzal Allergy 24HR (levocetirizine dihydrochloride) tablets, 5 mg
- NDA 209090: Xyzal Allergy 24HR (levocetirizine dihydrochloride) oral solution, 2.5 mg per 5 mL

We have completed our filing reviews and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) these applications are considered filed 60 days after the date we received your applications. The review classification for these applications are Standard. Therefore, the user fee goal date is January 31, 2017.

We are reviewing your applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 3, 2017.

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

If you have any questions, call Sherry Stewart, Regulatory Project Manager, at (301) 796-9618.

Sincerely,

[See appended electronic signature page]

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
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/s/

SHERRY A STEWART
06/13/2016

THERESA M MICHELE
06/13/2016
Dear Dr. Psaras:

Please refer to your New Drug Application (NDA) dated and received March 31, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levocetirizine Dihydrochloride Tablets, 5 mg.

We also refer to your correspondence, dated and received March 31, 2016, requesting review of your proposed proprietary name, Xyzal Allergy 24HR.

We have completed our review of the proposed proprietary name, Xyzal Allergy 24HR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 31, 2016, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Abiola M. Olagundoye-Alawode, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Sherry Stewart, Regulatory Project Manager in the Office of Office of New Drugs, at (301) 796-9618.

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
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/s/

TODD D BRIDGES
06/08/2016
NDA 209090

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

UCB, Inc.
c/o sanofi-aventis U.S. LLC
55 Corporate Drive, Mail Stop: 55D-225A
Bridgewater, NJ 08807

ATTENTION: Cynthia Psaras, PhD
Director, Global Regulatory Affairs

Dear Dr. Psaras:

Please refer to your New Drug Application (NDA) dated and received March 31, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levocetirizine Dihydrochloride Oral Solution, 2.5 mg/5 mL.

We also refer to your correspondence, dated and received April 27, 2016, requesting review of your proposed proprietary name, Children’s Xyzal Allergy 24HR.

We have completed our review of the proposed proprietary name, Children’s Xyzal Allergy 24HR and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 27, 2016, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Abiola M. Olagundoye-Alawode, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Sherry Stewart, Regulatory Project Manager in the Office of Office of New Drugs, at (301) 796-9618.

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
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/s/

----------------------------------------------------
TODD D BRIDGES
06/08/2016
**REQUEST FOR CONSULTATION**

**TO (Division/Office):**
Mail: OSE

**DATE:** June 1, 2016
**IND NO.** 209089 and 209090
**NDA NO.** 209089 and 209090
**TYPE OF DOCUMENT:** New Drug Application
**DATE OF DOCUMENT:** March 31, 2016

**NAME OF DRUG:**
Xyzal Allergy 24 HR (levocetirizine dihydrochloride) tablets, 5 mg and Xyzal Allergy 24 HR (levocetirizine dihydrochloride) oral solution, 2.5 mg/5mL

**PRIORITY CONSIDERATION:** Standard

**CLASSIFICATION OF DRUG:** Antihistamine

**DESIRED COMPLETION DATE:**
12/16/16 (in time for wrap up meeting)

**PDUFA goal date:** 1/31/17

**NAME OF FIRM:** Sanofi

**REASON FOR REQUEST**

**I. GENERAL**
- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

**II. BIOMETRICS**
- STATISTICAL EVALUATION BRANCH
- STATISTICAL APPLICATION BRANCH
- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**
- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

**IV. DRUG EXPERIENCE**
- PHASE IV SURVEILLANCE/EPIEDEMIOLGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

**V. SCIENTIFIC INVESTIGATIONS**
- CLINICAL
- PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**
Review proposed labeling included in the NDA submissions for potential safety issues due to medication errors.

**Link to submissions:**
NDA 209089: \CDSESUB1\evsprod\NDA209089\209089.enx
NDA 209090: \CDSESUB1\evsprod\NDA209090\209090.enx

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06/18/2013

Reference ID: 3939758
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/s/

SHERRY A STEWART
06/01/2016
Hi Cynthia,

Please reply to this email to acknowledge receipt.

Please refer to your new NDA 209089 and 209090 for Xyzal (levocetirizine) received March 31, 2016

We have the following request for information:

The final study report for the pivotal label comprehension study showed that among the 462 subjects who were qualified and scheduled for interviews, 419 subjects completed interviews and 417 subjects were included in the final dataset and analyses. Two subjects were excluded due to missing or incomplete data.

1. Please explain why the study population reduced from 462 to 419. Did the 43 subjects complete any portion of the interview? Were any subject characteristics collected prior to interview or drop out?

2. If some subject characteristics or some interview questions were collected for the missing 43 subjects, please provide that information in an electronic dataset. This will help us evaluate subject disposition and possible reasons for drop out.

Please provide your response to me via email and follow up with an official submission to each of the referenced NDAs by close of business June 10, 2016.

If you have any questions, please let me know.

Thank you and best regards,

Sherry Stewart, PharmD
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
301-796-9618
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/s/

SHERRY A STEWART
05/31/2016
NDA 209089
NDA 209090

NDA ACKNOWLEDGMENT

Sanofi-aventis U.S. LLC  
Attention: Cynthia Psaras, PhD  
Director  
55 Corporate Drive  
Mail Stop 55D-225ª  
Bridgewater, NJ 08807

Dear Dr. Psaras:

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:

NDA Number: 209089
Name of Drug Product: (Proposed) Xyzal Allergy 24HR (levocetirizine dihydrochloride) tablets, 5 mg, and

NDA Number: 209090
Name of Drug Product: (Proposed) Xyzal Allergy 24HR (levocetirazine dihydrochloride) oral solution, 2.5 mg/5mL (0.5 mg/mL)

Date of Application: March 31, 2016
Date of Receipt: March 31, 2016

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 May 30, 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 under 21 CFR 314.101(d)(3).

Reference ID: 3917322
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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:


Additional information regarding Title VIII of FDAAA is available at:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website

When submitting the certification for this application, do not include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 209089 and NDA 209090 submitted on March 31, 2016, and that it contains the FDA Form 3674 that was to accompany those applications.

If you have already submitted the certification for this application, please disregard the above.
The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Nonprescription Drug 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) 796-9618.

Sincerely,

(See appended electronic signature page)

Sherry A. Stewart, PharmD  
Senior Regulatory Project Manager  
Division of Nonprescription Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research
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/s/

SHERRY A STEWART
04/14/2016
NDA 209089, Xyzal Allergy 24HR (levocetirizine dihydrochloride) tablet, 5 mg

This application is not affected by the Application Integrity Policy

Sherry Stewart, PharmD, Regulatory Project Manager, 1/27/16
NDA 209090, Children’s Xyzal Allergy 24HR (levocetirizine dihydrochloride) oral solution 2.5/5 mL

This application is not affected by the Application Integrity Policy

Sherry Stewart, PharmD, Regulatory Project Manager, 1/27/16
MEMORANDUM OF INFORMAL TELECONFERENCE

Sponsor: Sanofi

Product: PIND 126506: Xyzal (levocetirizine dihydrochloride) tablets
        PIND 126507: Xyzal (levocetirizine dihydrochloride) oral solution

Date of teleconference: December 22, 2015, 11:00 AM-11:30 AM

Sponsor Attendees:
Judith Plon, Associate Vice President, Regulatory Affairs, Head CHC US/Chattem
Bernie Simone, Vice President, Project Lead

FDA Attendees:
Office of New Drugs, Office of Drug Evaluation IV, Division of Nonprescription Drug Products
Dan Brum, Chief Project Management Staff
Theresa Michele, Director
Jagjit Grewal, Associate Director of Regulatory Affairs
Brenda Gierhart, Medical Officer
Steven Osborne, Medical Officer
Elizabeth Donohoe, Medical Officer
Barbara Cohen, Social Scientist
Sherry Stewart, RPM

Background:
On October 1, 2015, a Type B meeting was held between Sanofi and FDA to discuss Sanofi’s proposal for a partial Rx-to-OTC switch NDA for Xyzal (levocetirizine dihydrochloride) oral solution and Sanofi’s proposed format and content for a full switch supplemental NDA for Xyzal (levocetirizine dihydrochloride) tablets.

On December 11, 2015, Sanofi submitted a General Correspondence which stated that Sanofi now planned to partially switch both products from Rx-to-OTC [i.e., Xyzal (levocetirizine) oral solution and Xyzal (levocetirizine dihydrochloride) tablets] only supporting the allergy use in March 2016. This submission also included follow-up questions regarding their two planned partial switch applications.

The Division Director, Terri Michele, agreed to an informal teleconference to discuss and respond to the Sanofi’s questions. The teleconference was held on December 22, 2015 at 11:00 AM and lasted approximately 30 minutes.

Summary of Discussion that Occurred During the Teleconference:
Dr. Michele informed Sanofi that this would be considered an informal teleconference, and as such, no formal meeting minutes would be issued.
Sanofi is now planning to initially submit partial switch applications for both of their products from Rx-to-OTC: Xyzal (levocetirizine) oral solution and Xyzal (levocetirizine dihydrochloride) tablets.

For the oral solution, Sanofi plans a partial Rx-to-OTC switch for allergy use in adults and children aged ≥ 2 years, with the hives indication and the dosing and indications for children aged < 2 remaining available only by prescription.

For the tablets, Sanofi plans a partial Rx-to-OTC switch NDA for the allergy indication to be submitted in early 2016.

For the tablet formulation involving the allergy indication, Sanofi confirmed that they planned to have two distinct OTC products under two distinct Stock Keeping Units (SKUs), with different Drug Facts Labels (DFLs) for each indication.

Sanofi stated that they would be conducting the label comprehension studies (LCS), and that testing of the kidney warning is currently in process, and the /anaphylaxis warnings is currently being researched.

Sanofi stated that it would like to better understand

FDA described possible scenarios for User Fees for submission of the both applications and associated fee implications:

- For the Xyzal solution, Sanofi is considering the following options:
- Option 1: A partial Rx-to-OTC switch for both indications, with the dosing for children aged 6-2 remaining available only by prescription. A new NDA with a ½ user fee would be required.

- Option 2: A partial Rx-to-OTC switch, with the allergy indication.

For the Xyzal tablets, Sanofi is considering the following options:

- Option 1: A full switch from Rx-to-OTC of all indications with no clinical data required. FDA confirmed that an efficacy supplement would be the appropriate regulatory route, and no user fee would be required.

- Option 2: A partial Rx-to-OTC switch for the allergy.
  - FDA confirmed that this would require a new NDA for the partial switch application involving the allergy indication, and a ½ user fee would be incurred.

Sanofi indicated that they understood and agreed with the user fee options as discussed.
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/s/

SHERRY A STEWART
01/13/2016
Sanofi US Services Inc.
Attention: Cynthia Taylor Psaras
Director, Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Psaras:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Xyzal (levocetirizine dihydrochloride) tablets, 5 mg, and Xyzal (levocetirizine dihydrochloride) solution, 2.5 mg/5 mL.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2015. The purpose of the meeting was to discuss the acceptability of your proposal for a partial Rx-to-OTC switch NDA for Xyzal (levocetirizine dihydrochloride) oral solution, and the acceptability of the proposed format and content for Xyzal (levocetirizine dihydrochloride) tablets.

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 Sherry Stewart, Regulatory Project Manager at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-IND

Meeting Date and Time: Thursday, October 1, 2015; 9:00 AM to 10:00 AM

Meeting Location: FDA, White Oak, Building 22, Room 1419

Application Numbers: PIND 126506 and PIND 126507

Product Names: Xyzal (levocetirizine dihydrochloride) tablets, 5 mg, and Xyzal (levocetirizine dihydrochloride) solution, 2.5 mg/5 mL

Proposed Indications: 1) Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
- runny nose
- sneezing
- itchy, watery eyes
- itching of the nose or throat

Sponsor/Applicant Name: Sanofi US Services Inc., authorized US agent on behalf of UCB, Inc.

Meeting Chair: Theresa Michele, MD

Meeting Recorder: Sherry Stewart, PharmD

FDA ATTENDEES
Office of New Drugs, Office of Drug Evaluation IV, Immediate Office
Jagjit Grewal, MPH, Associate Director for Regulatory Affairs

Office of New Drugs, Office of Drug Evaluation IV, Division of Nonprescription Drug Products
Theresa Michele, MD, Director
Daniel Brum, PharmD, MBA, BCPS, RAC Chief, Project Management Staff
Sherry Stewart, PharmD, Regulatory Project Manager

Reference ID: 3844670
1.0 BACKGROUND

As Agent for UCB, Sanofi requested this Pre-IND meeting to discuss the Prescription-to-Over the Counter (Rx-to-OTC) switch of Xyzal (levocetirizine dihydrochloride) tablets (NDA 022064) and oral solution (NDA 022157). UCB has given Sanofi the full right to reference both NDAs in an Appointment of Agent letter submitted by UCB on May 28, 2015.

Xyzal (levocetirizine dihydrochloride) tablets (NDA 022064) were approved by FDA on May 25, 2007 for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children 6 years of age and older and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 years of age and older. Xyzal (levocetirizine) oral solution (NDA 022157) was approved for the same indications on January 28, 2008.
On August 28, 2009, the tablets and oral solution were approved for the relief of symptoms of SAR in children 2 years of age and older and for the relief of symptoms of PAR and the treatment of CIU for children 6 months and older.

The goal of this meeting was to determine the acceptability of Sanofi’s intent to submit a partial Rx-to-OTC switch NDA for Xyzal oral solution, and the acceptability of the proposed format and content for Xyzal tablets.

The sponsor’s targeted submission date is March 16, 2016.

The questions enclosed in the meeting briefing materials are in bold font below; FDA’s preliminary responses are in italics. Discussion that occurred during the meeting is in normal font. For items where no discussion is indicated, no further discussion took place at the meeting.

2.0 DISCUSSION

Question 1
Does the Agency agree that levocetirizine is appropriate to be considered for a switch from prescription to nonprescription use for the specified uses, populations and doses?

FDA Preliminary Response: We agree.

Question 2
Sanofi, as the authorized US agent for UCB, LLC and as Sponsor of the OTC switch dossiers, is planning to submit an sNDA for XYZAL tablets and a new NDA for XYZAL oral solution via submission of 505(b)(2) NDA applications relying upon data from cetirizine (NDA 019835). Does the Agency agree that this is the appropriate regulatory pathway?

FDA Preliminary Response: We agree that submission of an sNDA for Xyzal tablets and a new NDA for Xyzal oral solution via the 505(b)(2) regulatory pathway would be appropriate. See section 8.0 below for additional information regarding the 505(b)(2) regulatory pathway. In addition, see the following comments on each of your specific switch programs.

Xyzal oral solution (partial switch):
An applicant may cross-reference a previously approved 505(b)(2) application for which it is the NDA holder or for which it has right of reference to support approval of its new NDA, if scientifically appropriate. If the cross-referenced portions of the previously approved 505(b)(2) application involve reliance on FDA’s finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that were conducted by or for the applicant or for which the applicant has obtained a right of reference or use), then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. The applicant’s new 505(b)(2) application should identify this/these listed drug(s) as relied upon for its new 505(b)(2) application in accordance with the Agency’s regulations at 21 CFR 314.54.
Note that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.

Furthermore, under § 503(b)(4)(B) of the Act (21 U.S.C. 353(b)(4)(B)), a drug to which the prescription provisions of the Act do not apply (i.e., an OTC drug) shall be deemed to be misbranded if at any time prior to dispensing, the label of the product bears the “Rx only” symbol. The Act does not permit both Rx and OTC versions of the same drug product to be marketed at the same time. § 503(b)(4)(B) of the Act (21 U.S.C. 353(b)(4)(B)). Therefore, a prior approval labeling supplement should be submitted to the Xyzal oral solution prescription application (NDA 022157) at least six months prior to the goal date for the nonprescription NDA to remove from labeling the conditions that will be switched for OTC use.

Xyzal tablets: As a matter of clarification, Sanofi cannot be listed as the applicant for the supplemental application to NDA 022064 for Xyzal tablets. This is because UCB, Inc. is the NDA holder for Xyzal tablets. Sanofi may be listed as the authorized U.S. agent for the sNDA on behalf of UCB, Inc. Furthermore, a supplemental application to a previously approved 505(b)(2) NDA is considered to be inherently relying on the same source(s) of information that the original NDA relied upon for approval. Therefore, such a supplemental application is also to be submitted pursuant to section 505(b)(2) of the FD&C Act and must include an appropriate patent certification or statement to address reliance on the listed drug(s) identified in the original 505(b)(2) NDA.

Discussion: Sanofi inquired as to which sponsor would be the appropriate applicant for the OTC Xyzal oral solution NDA. FDA replied that such a decision is outside of the Agency’s purview and would be determined between Sanofi and UCB. If Sanofi were the applicant for the NDA, it is expected that a letter of authorization from UCB be included providing right of reference to the prescription Xyzal NDAs.

Sanofi requested clarification on the cross-referencing approaches outlined in FDA’s preliminary response. It was noted that approval of the prescription Xyzal tablet 505(b)(2) NDA was based, in part, on reliance upon literature and FDA’s findings of safety and efficacy for the listed drug applications for Zyrtec (cetirizine HCl). The prescription Xyzal oral solution 505(b)(2) NDA also relied upon the listed drug applications for Zyrtec via cross-reference to the Xyzal tablet NDA. FDA explained that for the planned OTC Xyzal tablet supplemental application, the same sources of information that the original NDA relied upon for approval (listed drug applications for Zyrtec and literature) should again be identified as relied upon per the explanation given in the preliminary response. For the planned OTC Xyzal oral solution NDA, it would also be appropriate to identify the listed drug applications for Zyrtec as being relied upon since the OTC NDA will cross-reference the approved prescription Xyzal oral solution NDA. FDA reiterated that both OTC Xyzal applications must include appropriate patent certifications or statements to address reliance on the listed drug applications for Zyrtec.

Sanofi asked if they had to resubmit previously submitted information. FDA stated that it is not necessary to resubmit data but suggested that in the sNDA and NDA submissions, Sanofi
provide a detailed table of contents with hyperlinks so that all information is readily accessible to the review team. FDA noted that a previously established scientific bridge does not need to be re-established, but may be incorporated by cross-reference.

Sanofi asked if new financial disclosure forms would be required. FDA stated that new financial disclosure forms would not be required as long as no new studies were performed and the financial disclosure forms for previous studies performed under the cross-referenced NDAs were readily available.

**Question 3**
Does the Agency agree with the proposal for cross-referencing Modules 2.4, 2.7.1, and 2.7.2 to the previously submitted information for nonclinical safety, biopharmaceutics, clinical pharmacology, and pharmacokinetic data in support of the switch from prescription to nonprescription use?

*FDA Preliminary Response:*
*In general, it is acceptable to cross-reference to previously submitted information; however, we recommend that you include summary documents in the new submission.*

**Question 4**
Sanofi is proposing to provide one comprehensive SCE located in the tablet sNDA (NDA 22-064, Module 2.7.3) in support of the switch of both the levocetirizine tablets and the oral solution formulations. Does the Agency agree with this approach?

*FDA Preliminary Response: We agree.*

**Question 5**
Will the Agency accept a waiver for inclusion of an Integrated Summary of Efficacy (ISE) (Module 5.3.5.3) in both the sNDA for tablets and the new NDA for oral solution submissions?

*FDA Preliminary Response: We agree.*

**Question 6**
Does the Agency agree with Sanofi’s plan to provide one comprehensive SCS and one ISS located in the tablet sNDA (NDA 22-064, Modules 2.7.4 and Module 5.3.5.3, respectively) in support of the switch of both levocetirizine tablets and oral solution to nonprescription status? In addition, does the Agency require any additional safety information in support of the XYZAL nonprescription switch that is not described in the SCS and ISS proposal?

*FDA Preliminary Response:*
It is acceptable to submit one SCS and one ISS that are both located in the tablet sNDA. The submitted 20-pg proposed ISS table of contents appears reasonable. However, when the applications are submitted, include a document that provides the location for each full study report previously submitted. If a full study report has not [been] previously been submitted, submit it with the sNDA for the tablet. It will be a review issue whether the Agency will require any additional safety information in support of the Xyzal Rx-to-OTC switch. Regarding your proposed postmarketing safety data, we expect you will include the following in your application:

1. **Dose-Response Analyses**
   In addition to conducting an analysis of reported adverse events associated with levocetirizine in the UCB’s postmarketing safety databases from the last NDA submission up to 6 months prior to submission of your application, include the adverse events associated with levocetirizine from the following sources: the FDA Adverse Events Reporting System (FAERS) database, World Health Organization (WHO) Vigibase, National Poison Data System (NPDS) from America Association of Poison Control and Drug Abuse Warning Network (DAWN), and medical literature. Analyze the safety data for each database separately by dose from lowest dose to highest dose. Identify the most frequently occurring adverse events for each dose and any serious adverse events for each dose. Compare and contrast the safety profile of each dose with the safety profile of other doses. Compare the dose-responses across the databases and identify differences and similarities across the databases, including the postmarketing safety, the Drug Abuse Warning Network (DAWN) and National Poison Data System (NPDS) data. Identify a biological mechanism of action for the most frequently occurring adverse events and any serious adverse events. Identify the frequently occurring and serious adverse events that are more than likely related to your product based on biological mechanism such as effects on the central nervous system (somnolence, movement disorders, cognitive impairment, psychiatric effects.) Use your analyses to consider the likelihood of these adverse events occurring in the OTC population. Provide a rationale for this decision and any line listings or narratives that support this decision. Provide the data by dose and the associated safety profiles that were utilized in your assessment. Provide a detailed summary of your decisions and the rationale and data supporting those decisions. We expect the review of the medical literature to include a summary of the literature with a risk-benefit assessment.

2. **Age Analyses**
   Analyze the safety data for each database separately by the age grouping provided. Identify the most frequently occurring adverse events for each age group and any serious adverse events. Compare and contrast the safety profile of each age group with the safety profiles of the other age groups. Compare the safety profiles across the databases by comparing and contrasting the most frequently occurring adverse events and serious adverse events. Identify a biological mechanism for the most frequently occurring adverse events and the serious events. Use your analyses to consider the likelihood of these adverse events occurring in the OTC population. Provide a rationale for this decision and any line listings or narratives that support these decisions. Provide the data by age groupings and the associated safety profiles that were utilized in your assessment.
Provide a detailed summary of your decisions and the rationale and data supporting those decisions.

3. Gender Analyses
Analyze the safety data for each database separately by gender. Identify the most frequently occurring adverse events for each gender and any serious adverse events. Compare and contrast the safety profile for each gender. Compare the safety profiles across the databases by comparing and contrasting the most frequently occurring adverse events and serious adverse events. Identify a biological mechanism for the most frequently occurring adverse events and the serious events. Use your analyses to consider the likelihood of these adverse events occurring in the OTC population. Provide a rationale for this decision and any line listings or narratives that support these decisions. Provide the data by gender and the associated safety profiles that were utilized in your assessment. Provide a detailed summary of your decisions and the rationale and data supporting those decisions.

4. Time-to-Onset Analyses
Analyze the safety data by time to onset. Identify the most frequently occurring adverse events for time to onset for the following timeframes: within 48 hours, 49 hours to 14 days, 15-30 days, and 31 days or more. Identify the most frequently occurring adverse events for each timeframe and any serious adverse events. Compare and contrast the safety profile of the timeframes. Compare the safety across the databases by comparing and contrasting the most frequently occurring adverse events and serious adverse events. Identify a biological mechanism for the most frequently occurring adverse events and the serious events. Use your analyses to consider the likelihood of these adverse events occurring in the OTC population. Provide a rationale for this decision and any line listings or narratives that support these decisions. Provide the data by gender and the associated safety profiles that were utilized in your assessment. Provide a detailed summary of your decisions and the rationale and data supporting those decisions.

5. Accidental or Intentional Overdose
Using the prior analyses for dose response, age, gender and time-to-onset together, identify adverse events most likely to occur with accidental or intentional overdose in the OTC population. Provide the rationale for this decision and any line listings, narratives, or safety profiles that support this decision. Provide a detailed summary of the biological mechanism, the dose, and the adverse events.

6. Adverse Events for OTC Population
Using the prior analyses for dose response, age, gender and time to onset together, identify adverse events most likely to occur with the labeled dose and duration in the OTC population. Provide the rationale for this decision and any line listings, narratives, or safety profiles that support this decision. Provide a detailed summary of the biological mechanism, the dose, and the adverse events.

- OTC medications have to provide a wide margin of safety for misuse and abuse. Identify the adverse events most likely to be seen in the OTC population if the duration of use is extended beyond what is labeled. Provide the rationale for this


Decision and a detailed summary of the biological mechanism, and any data supporting this decision.

- Identify the adverse events most likely to occur in the OTC population if the labeled dose is exceeded. Provide the rationale for this decision and a detailed summary of the biological mechanism, and any data supporting this decision.
- Identify the adverse events most likely to occur in the OTC population if the labeled dose AND duration of use are exceeded. Provide the rationale for this decision and a detailed summary of the biological mechanism, and any data supporting this decision.

Discussion: Sanofi proposed an analysis of the above categories using the top five frequently occurring Adverse Events (AEs)/Serious Adverse Events (SAEs). FDA recommended that Sanofi submit an analysis of the top 10 frequently occurring AE/SAEs.

Sanofi asked for clarification about the Time-to-Onset analysis stratified by gender. FDA stated that there is an initiative to evaluate AEs and SAEs in a more comprehensive manner, and this has resulted in a requirement that all new NDAs include an analysis of AEs and SAEs by gender and race. More information on this topic can be found at http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126958.pdf. FDA is also providing consumers with information about who participated in clinical trials that supported the FDA approval of new drugs on our website. For more information see http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

In addition, FDA asked Sanofi to consider AEs that occur when the product is used for an extended period of time that is beyond the labeled duration of use.

Question 7
Does the Agency agree with Sanofi’s proposal not to submit clinical study databases (ie, SAS datasets of the clinical data of either individual studies or pooled studies) in the nonprescription tablet sNDA and oral solution NDA submissions?

FDA Preliminary Response:
Provide in the sNDA and NDA submissions, a listing indicating the location of the SAS datasets of the clinical data for each individual clinical study. If any SAS dataset cannot be easily located, their submission may be requested.

Question 8
Does the Agency accept the cross-referencing of the CMC Drug Substance and Drug Product information in the prescription dossiers in support of the switch from prescription to nonprescription use?

FDA Preliminary Response:
Your approach of cross-referencing the CMC information to the currently approved prescription drug applications are acceptable, provided that the multiple time-points dissolution profiles
comparison shows similarity between your proposed debossed tablets and the original, printed tablet. We expect you will provide the following information in your application:

- Tablets:
  - Provide a visual comparison of the current tablet to the proposed tablet.
  - Provide a comparison of the current packaging presentations to the proposed presentations.
  - In support of the proposed expiry, the tablet count in bottles and in the blister card must be known at the time of submission.

- Oral solution: Submit description, suitability, and quality control data to support the dosing cup.

**Question 9**

Sanofi is seeking feedback on the content of the proposed DFL for allergic rhinitis for XYZAL tablets and oral solution. If the Agency does not agree with any specific statement in Section 10.5.1, please provide your reasons.

**FDA Preliminary Response:**

The appropriateness of the proposed labeling is a review issue. We note that the meeting package states on pg. 13 that Xyzal OTC tablet is “not applicable” for ages 2-5 years; however, your proposed labeling for Xyzal Allergy tablets states “ask a doctor” (instead of “do not use”) for children under age 6 years. We note that prescription Xyzal tablets and solution are both dosed once daily in the evening. No justification for this change was located in the meeting background materials. Include a justification in your submission.

We note that the contraindications included in the current label for patients with end stage renal disease and those undergoing hemodialysis as well as use in children 6 to 11 years with renal impairment have not been adequately captured in the proposed DFL. Generally speaking, contraindications in prescription labeling should be translated into the ‘Do not use’ section of the DFL. Include a justification in your submission for how this information is translated into the DFL for appropriate OTC use.

Refer to Administrative Comments section for labeling regulations and guidance.

**Discussion:** Sanofi acknowledged FDA’s comments regarding the use of Xyzal in pediatric patients aged 2-5 years. Sanofi will provide justification for their proposed “once daily in the evening.”

Regarding the topic of kidney disease, Sanofi plans to revise the Drug Facts Label (DFL), from “Do not use if you have severe kidney disease.” FDA stated that this appears to be appropriate at this time; however, the content of the DFL will be a matter for review. FDA reminded the sponsor to ensure that statements in the
“Directions” section of the DFL are consistent with statements in the “Do Not Use” section of the DFL.

**Question 10**
Does the Agency agree that no additional consumer studies, such as a label comprehension study, or clinical studies are required to support the switch of levocetirizine tablets and oral solution to nonprescription status are needed to support the content of the proposed DFLs?

**FDA Preliminary Response:**
Label testing may be needed if you introduce changes that vary from existing OTC product labeling. In general, we encourage retesting of significant safety warnings even when they are found in existent labeling.

**Discussion:** The sponsor stated that they had not planned to add new warning...

Given the clinical discussion around the need for a kidney disease warning, it was felt that the “Do Not Use” section would also become more important.

FDA emphasized that a label comprehension study, testing changes that are made to the DFLs could help alleviate concerns and strengthen the case for an Rx-to-OTC switch.

**Question 11**
Does the Agency agree with the content and format of the proposed dossiers for the nonprescription use as a supplement to NDA 022064 for the tablets and the new NDA for oral solution?

**FDA Preliminary Response:**
The proposed content and format of the sNDA for the Xyzal tablet and the new NDA for the Xyzal oral solution appears reasonable, except for postmarketing safety information (see Question 6). The adequacy of each submission will ultimately be a review issue.

**Question 12**
Does the Agency accept a half user fee for the oral solution NDA?

**FDA Preliminary Response:**
Yes. A partial Rx-to-OTC switch of the oral solution would require a new NDA. Contingent that no new clinical data is submitted, and the application will not require a re-analysis of clinical data previously submitted to another application, the NDA for the oral solution would incur half of the PDUFA user fee. Note that the final determination for user fee requirements occurs when the applications are submitted in their entirety to the Agency.

**Question 13**
Can the FDA provide feedback on the appropriate time for Sanofi to request a waiver for quarterly safety updates following the anticipated approval of an Rx-to-OTC switch for the new NDA for XYZAL oral solution?

*FDA Preliminary Response:* Waivers of postmarketing safety reporting requirements (e.g., requirements related to the submission of quarterly and annual periodic safety reports) may be requested at any time after the approval of the application. When a waiver would be granted will depend upon the number and types of safety issues identified post-approval. Plan to submit quarterly safety updates for 3 years post-approval of the new NDA for Xyzal oral solution Rx-to-OTC switch.

**Question 14**
Does the Agency agree that the planned nonprescription sNDA for the tablet dosage form and the NDA for oral solution dosage form do not trigger PREA obligations by Sanofi?

*FDA Preliminary Response:* See Section 3.0 PREA REQUIREMENTS.

*Additional FDA comments:* Biopharmaceutics: When the NDA for the oral solution is submitted, include a biowaiver request with necessary justifications.

**3.0 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 appear to apply to either submission, you would be exempt from these requirements. If there are changes to your development plans that cause either application to trigger PREA, your exempt status will change.
4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (ceder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide
feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

5.0 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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

6.0 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.

7.0 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.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
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<td>1.</td>
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<td>2.</td>
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</tr>
</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
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<td>1.</td>
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<td>2.</td>
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</table>

8.0 **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](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](http://www.regulations.gov)).

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 one or more listed drugs, 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(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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 in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. 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.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

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(s) or on published literature. 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 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 efficacy 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.

<table>
<thead>
<tr>
<th>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source of information</strong> (e.g., published literature, name of listed drug)</td>
</tr>
<tr>
<td>1. Example: Published literature</td>
</tr>
<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
</tr>
</tbody>
</table>
3. Example: NDA YYYYYY
   “TRADE NAME”
   Previous finding of safety for
   Carcinogenicity, labeling section XXX

4. Please be advised that circumstances could change that would render a 505(b)(2) application for
   this product no longer appropriate. For example, if a pharmaceutically equivalent product were
   approved before your application is submitted, such that your proposed product would be a
   “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then
   it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR
   314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug
   Application (ANDA) that cites the duplicate product as the reference listed drug.

9.0 ADDITIONAL ADMINISTRATIVE COMMENTS

LABELING REGULATIONS AND GUIDANCES

As you develop your labeling, we call your attention to the following pertinent labeling
regulations and guidances:

Regulations under the Code of Federal Regulations (CFR)
Include the following in your submission to FDA:

1. All of the proposed labels and labeling (i.e., all count sizes with immediate container and
   carton labeling, including samples, and consumer information leaflet if proposed) as
   required under 21 CFR 314.50.
   a. “clean” labeling and marked up labeling (i.e., annotated) defining the information
      in the summary and technical sections of the application that support the inclusion
      of each statement in the proposed labeling.
   b. font and format specified under 21 CFR 201.66 as part of the annotated labeling
      or detailed in a separate document.

2. In addition to the format and content requirements for over-the-counter (OTC) drug
   product labeling (21 CFR 201.66), we refer you to the following:
   a. 21 CFR, Part 201 Subpart A-General Labeling Provisions and
   b. Subpart C-Labeling Requirements for Over-the-Counter Drugs, which provides
      the labeling required for packaging (Principal Display Panel (PDP)-21 CFR
      201.60 and statement of identity- 21CFR 201.61 etc.).

Guidances
1. See “Guidance for Industry– Labeling OTC Human Drug Products –Questions and
   Answers” (December 2008) for assistance with OTC labeling development.
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guid
   ances/UCM078792.pdf
2. In addition to submitting your label using the Structured Product Labeling (SPL) format, we recommend that you formally submit your proposed labeling in portable document format (PDF) electronically to your NDA.

   a. To ensure electronic storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents (i.e., OTC labeling usually has complex graphics and large file size), follow FDA’s portable document format (PDF) specifications detailed in the document found at the following URL: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf

   b. For complete information on preparing your electronic submissions refer to the following URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

   c. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov.

10.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were distributed at the meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA M MICHELE
11/09/2015