

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208845Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208845	NDA Supplement # (Original NDA)	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zilretta Established/Proper Name: triamcinolone acetonide extended-release Dosage Form: injectable suspension		Applicant: Flexion, Inc. Agent for Applicant (if applicable):
RPM: Kim Compton		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check: 10/5/17</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is _____</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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.

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

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

(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)

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) ( <a href="#">link</a> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees ( <a href="#">link</a> )	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) AP 10/6/17

<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	3/1/17 and 8/9/17 2/28/17 and 8/9/17
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 2/21/17 (PLR format) DMEPA: <input type="checkbox"/> None 7/26/17 and 10/23/17 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 8/26/17 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	10/4/17 (one document)
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 9/26/17
❖ NDAs/NDA supplements only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Completed ( <b>Do not include</b> )
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action

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

❖ Pediatrics ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>9/6/17</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Breakthrough Therapy Designation	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ 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.) ( <i>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</i> )	Various
❖ 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	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/6/17 (also serves as summary memo)
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	2/2/17 (filing) and 8/31/17

<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)</li> </ul>	See page 13 of clinical review dated 8/31/17 and memo dated 10/6/17
<ul style="list-style-type: none"> <li>Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)<sup>5</sup></li> </ul>	<input type="checkbox"/> None DPMH: 8/18/17 DMEP 8/11/17 and 8/14/17
<ul style="list-style-type: none"> <li>Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)</li> </ul>	<input type="checkbox"/> None requested 8/24/17
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Microbiology Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Statistical Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Statistical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Statistical Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 2/23/17 (filing) and 9/1/17
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 2/6/17 (filing) and 8/25/17
<ul style="list-style-type: none"> <li>OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)</li> </ul>	<input checked="" type="checkbox"/> None requested

<sup>5</sup> 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).

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 2/7/17 (filing) and 9/8/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/27/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Biopharm: 8/23/17 Micro: 9/13/17 CDRH: 7/6/17
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See page 90 of IQA dated 9/27/17
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable 7/15/17 (see page 137 of IQA dated 9/27/17) <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY A COMPTON  
10/06/2017

## Compton, Kimberly

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**From:** Compton, Kimberly  
**Sent:** Monday, September 18, 2017 5:03 PM  
**To:** 'Elizabeth Hook'  
**Cc:** Kerry Wentworth  
**Subject:** Labeling recommendations for N 208845/Zilretta  
**Attachments:** N 208-845 working copy of PI --TO FIRM 9-18-17.docx; N 208845 IFU WORD --TO FIRM 9-18-17.docx

Hi Elizabeth,

Thanks for sending this. I will check with the team and let you know.

In the meantime, I finally have the PI and IFU to share with you. They are attached in tracked WORD versions.

We would be most appreciative if your team could review the document and return it to us by next Monday (9/25) at noon at the latest (earlier would be better if possible, and it is fine with us if you separate them too in returning them.)

Please use these WORD versions and using the tracked changes feature, accept the changes that Flexion is OK with (so they then just appear as regular text) and remove any NOTES to SPONSOR you can once you are done with them please, such that the documents you emails me back and WORD attmts are as clean as possible with only items that still require negotiation/work showed in tracked format. (Obviously you should show any Flexion changes or edits in tracked changes as well so we can readily spot those on the next version.) If you like, you can also send us notes back in the Comment bubbles using the "New Comment" feature.

Please let me know if any questions.

Thanks  
Kim

---

**From:** Elizabeth Hook [mailto:ehook@flexiontherapeutics.com]  
**Sent:** Monday, September 18, 2017 4:01 PM  
**To:** Compton, Kimberly  
**Cc:** Kerry Wentworth  
**Subject:** RE: carton and Container labeling recommendations for N 208845/Zilretta

Hi Kim,

We should be able to send you updated draft carton and container labeling tomorrow.

(b) (4)

Also, should we expect comments on the PI and IFU this week? We are okay with receiving comments on these documents separately if they're available at different times.

Best regards,  
Elizabeth

Elizabeth Hook  
Associate Director, Regulatory Affairs  
**Flexion Therapeutics, Inc.**  
10 Mall Road, Suite 301  
Burlington, MA 01803  
Email: [ehook@flexiontherapeutics.com](mailto:ehook@flexiontherapeutics.com)  
Office: 781-305-7750

Follow us:

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**From:** Compton, Kimberly [<mailto:Kimberly.Compton@fda.hhs.gov>]  
**Sent:** Thursday, September 14, 2017 6:23 PM  
**To:** Elizabeth Hook  
**Cc:** Kerry Wentworth  
**Subject:** RE: carton and Container labeling recommendations for N 208845/Zilretta

Hi Elizabeth,

I put your questions to the team and they are fine with your proposals below. We had changed the naming in the PI as well, but you will just need to ensure it is consistent with your below proposal once we are able to send you that too.

Thanks  
Kim

---

**From:** Elizabeth Hook [<mailto:ehook@flexiontherapeutics.com>]  
**Sent:** Thursday, September 14, 2017 1:32 PM  
**To:** Compton, Kimberly  
**Cc:** Kerry Wentworth  
**Subject:** RE: carton and Container labeling recommendations for N 208845/Zilretta

Dear Kim,

We are starting to make changes to our carton and vial labels based on the comments that you sent last night. There are a couple of things that we would like to clarify before we have the vendor make changes to the mock-ups.

- With regard to comment A4 to revise the presentation of the established name, we consider our established name to be "triamcinolone acetonide extended release injectable suspension" and would propose to put parentheses around that entire phrase rather than just "triamcinolone acetonide". This is how we've presented the established name in the PI and is consistent with what we've seen used in other labels of extended release products of non-NME's such as Triesence (triamcinolone acetonide injectable suspension) and Exparel (bupivacaine liposome injectable suspension). Does FDA agree that this will suitably address the comment?

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY A COMPTON  
09/27/2017

## Compton, Kimberly

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**From:** Compton, Kimberly  
**Sent:** Wednesday, September 13, 2017 5:07 PM  
**To:** Elizabeth Hook (ehook@flexiontherapeutics.com)  
**Cc:** Compton, Kimberly; Kerry Wentworth (kwentworth@flexiontherapeutics.com)  
**Subject:** carton and Container labeling recommendations for N 208845/Zilretta

Hi Elizabeth,

Below, please find our comments on the carton and container labeling for Zilretta. We hope to have comments to share with you on the PI and IFU shortly, but hoped you could start working on these in meantime.

We are hopeful that you can turn these around and provide amended drafts (via email initially is fine) no later than COB next wed 9/20/17.

Please let me know if you have any questions.

A. Zilretta Container Label (including Professional Sample)

1. Revise the statement, (b) (4) to read, "Must be reconstituted with the supplied diluent" for clarity and consistency. Furthermore, we recommend you use different colors, boxing, or some other means to increase prominence of this statement. We are aware of post-marketing errors involving other powder products packaged with a diluent where the powder was reconstituted with a diluent other than the supplied diluent.
2. Add the statement, (b) (4) for clarity. Use bold font for this statement to increase the prominence of the storage information and minimize the risk of storage errors.
3. (b) (4)
4. Revise the presentation of the established name so that the established name is included in parenthesis. The established name should be written as follows on all labeling for the product: "(triamcinolone acetonide) for extended release injectable suspension."

B. Diluent Container Label (including Professional Sample)

1. Increase the prominence of the word "DILUENT" by use of different colors, boxing, or some other means to provide adequate differentiation from the Zilretta powder container label. We are aware of post-marketing errors of other powder products packaged with a diluent where the

diluent alone was administered to the patient. To accommodate this change, decrease the size of the “5 mL” statement.

Additionally, use bold font for the statement, “Do not administer directly” and relocate the statement from the side panel to the principal display panel to increase prominence and minimize the risk for errors. To accommodate this change, relocate the statement, “Sterile single-use vial” from the principal display panel to the side panel.

2. See A.3

C. Carton Labeling (including Professional Sample)

1. Revise the statement, “Must be reconstituted” to read, “Must be reconstituted with the supplied diluent” for clarity and consistency. Furthermore, we recommend you use different colors, boxing, or some other means to increase prominence of this statement. We are aware of post-marketing errors involving other powder products packaged with a diluent where the powder was reconstituted with a generic diluent instead of the supplied diluent.

2. Revise the statement, (b) (4) at 2-8°C (36-46°F). (b) (4). Do not freeze. Store vial in carton” to read, (b) (4) at 2-8°C (36-46°F). Do not freeze. Store vials in carton” for clarity. Use bold font for this statement to increase the prominence of the storage information and minimize the risk of storage errors.

3. Include the contents of the carton on the principal display panel. For example: “This carton contains:

- 1 vial of Zilretta microsphere powder
- 1 vial of diluent (5 mL) for Zilretta
- 1 sterile vial adapter”

To accommodate this addition, consider relocating the manufacturer logo from the principal display panel to the side or back panel.

4. Replace the abbreviations IV and ID on the side panel with their full, intended meaning.

5. Add lot # and expiry entries to the carton label.

6. We acknowledge the quantitative inactive ingredient statement on the carton label per 21CFR201.100(b)(5)(iii). Edit this statement to read, “After reconstitution, each dose (b) (4) **will deliver**: 32 mg triamcinolone acetonide with 0.9% (w/w) sodium chloride, 0.5% (w/w) sodium carboxymethylcellulose, and 0.1% (w/w) polysorbate-80 in an aqueous suspension.”

7. See comment A.4 above.

Thanks,  
Kim

*Kimberly Compton*

Kimberly Compton, RPh  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
301-796-1191

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/s/  
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KIMBERLY A COMPTON  
09/15/2017



NDA 208845

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Flexion Therapeutics, Inc.  
10 Mall Road STE 301  
Burlington, MA 01803

ATTENTION: Kerry Wentworth  
Sr. Vice President, Regulatory Affairs and Quality

Dear Ms. Wentworth:

Please refer to your New Drug Application (NDA) dated and received December 8, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Extended Release Injectable Suspension, 32 mg per vial.

We acknowledge receipt of your correspondence, dated and received July 21, 2017, requesting a review of your proposed proprietary name, Zilretta.

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

If any of the proposed product characteristics as stated in your July 21, 2017, 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:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Kimberly A. Compton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1191.

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/  
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TODD D BRIDGES  
08/09/2017

**From:** [Compton, Kimberly](#)  
**To:** [Elizabeth Hook \(ehook@flexiontherapeutics.com\)](mailto:ehook@flexiontherapeutics.com)  
**Cc:** [Kerry Wentworth \(kwentworth@flexiontherapeutics.com\)](mailto:kwentworth@flexiontherapeutics.com)  
**Subject:** Dosing for N 208845 (b) (4) proprietary name  
**Date:** Thursday, July 13, 2017 7:09:04 PM

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Hi Elizabeth,

Based on the data Flexion provided for Zilretta, that show how much triamcinolone is actually delivered, the team has determined that the properly stated dose for the product should be 32 mg, not 40 mg.

(b) (4)

In addition, as stated in our March 1, 2017, letter conditionally granting Zilretta as the tradename for the product, "If any of the proposed product characteristics as stated in your December 8, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review," **we will need a new Proprietary Name Request (PNR) submitted as well.**

Please submit the items (especially the new PNR) as soon as possible to permit full review of the proprietary name with this new dosing characteristic.

Thanks,

Kim

*Kimberly Compton*

Kimberly Compton, RPh

Senior Regulatory Project Manager

Division of Anesthesia, Analgesia, and

Addiction Products

301-796-1191

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/s/  
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KIMBERLY A COMPTON  
07/13/2017

**For Internal Use Only**

**Meeting Request Withdrawn/Meeting Cancellation Form**

Application Type/Number	IND 111325
Meeting Type/Code	B Pre-NDA
DATE Meeting Request Withdrawn by Sponsor	
DATE Meeting Cancelled by Sponsor or FDA (per communication with sponsor)	May 25, 2016
DATE FDA-Initiated Meeting Cancelled (per communication with sponsor)	
Scheduled Meeting Date	May 26, 2016
Reason for Withdrawal/Cancellation	<p>From the Sponsor:</p> <p>Dear Christopher,</p> <p>We have completed our review of the preliminary comments and have made the decision not to proceed with the pre-NDA meeting next week. We found that the written feedback provided excellent clarity for us to move forward with our NDA preparation. We are anticipating submitting the NDA in November 2016 and look forward to further positive interactions with the Agency. Thank you again for providing clear and thoughtful answers in advance.</p> <p>Regards, Elizabeth</p> <p>Elizabeth Hook Sr. Manager, Regulatory Affairs Flexion Therapeutics, Inc. 10 Mall Road, Suite 301 Burlington, MA 01803 Email: <a href="mailto:ehook@flexiontherapeutics.com">ehook@flexiontherapeutics.com</a> Office: 781-305-7750</p>
Project Manager	Christopher Hilfiger

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CHRISTOPHER M HILFIGER  
06/16/2017

## Compton, Kimberly

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**From:** Compton, Kimberly  
**Sent:** Friday, June 09, 2017 1:43 PM  
**To:** Elizabeth Hook (ehook@flexiontherapeutics.com)  
**Cc:** Compton, Kimberly  
**Subject:** IRs for N 208845 from Device reviewer and question

Hi Elizabeth,

I have the following IRs for N 208845 from our Device reviewer:

1. Provide the LOA for (b) (4)
2. We are unable to locate the risk analysis for the vial adapter. Provide risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.

The Device reviewer is requesting a response to the above by 6/13/17.

In addition, I have a clarification request from our nonclinical group.

We note that in your April 14 email correspondence, you stated that “With respect to the questions about impurities (Nonclinical Issue 1) and specifications (Item 5), we do intend to update the impacted Module 3 and 4 sections but we wanted to give the reviewers a chance to review our approach first in case any further discussion is required.”

We received the leachables/extractables data, but are not aware of a response on the impurity issue thus far.

Here is a brief summary of the issues from our 74-day letter and our follow-up t-con:

- Sponsor based their proposed specifications on the maximum daily exposure of triamcinolone acetonide over the intended prolonged release facilitated by the PLGA polymer (b) (4) which Sponsor translated to (b) (4) (Note: administered dose is 40 mg/day).

- However, Agency did not agree with this rationale for establishing degradant specifications without justification that rate of exposure to individual degradants is similar to triamcinolone acetonide.
- Without such data, Agency must assume that the total amount of individual impurities may be exposed on the first day post-injection and specifications must be based on the maximum daily dose of 40 mg.
- Therefore, specifications for specified and unspecified degradants must be reduced, or provide data to justify the safety of the proposed specifications that exceed these thresholds.

We are not aware of receiving Flexion's approach/plan for impurity issues. Please clarify if Flexion is awaiting for input or feedback from the agency on an item in order to permit submission of the required material and if so, please point us to it.

Please let me know if you have any questions.

Thanks  
Kim

*Kimberly Compton*  
Kimberly Compton, RPh  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
301-796-1191

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KIMBERLY A COMPTON  
06/09/2017

## Compton, Kimberly

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**From:** Compton, Kimberly  
**Sent:** Tuesday, April 04, 2017 4:34 PM  
**To:** Kerry Wentworth (kwentworth@flexiontherapeutics.com); Elizabeth Hook (ehook@flexiontherapeutics.com)  
**Cc:** Compton, Kimberly  
**Subject:** N 208845 IR from Clinical portion of team

Hello again Elizabeth and Kerry,

I have the following IR from the clinical portion of our review team:

1. Clarify whether exclusion criterion 23 in study 008 regarding psychiatric disorders was meant to exclude subjects with uncontrolled symptoms of psychosis, mania and depression, or subjects with any chronic psychiatric condition even if their symptoms were in remission and how investigators were instructed to implement this exclusion criterion.
2. Provide the rationale for excluding subjects with BMI to a maximum value of 40 (extreme obesity). NIDDKD data from a 2009-10 survey showed that 6.3% of adults in the U.S. had extreme obesity. If, for example, there were reasons associated with the IA procedure for this exclusionary criterion, please explain.
3. Provide a table summarizing the number of subjects that were screen failures for study 008 by reason for their exclusion as well as a dataset for this data.

After you have a chance to review and discuss with your team, please let me know when you think you will be able to provide a reply.

Thanks  
Kim

---

**From:** Compton, Kimberly  
**Sent:** Monday, April 03, 2017 4:54 PM  
**To:** Kerry Wentworth ([kwentworth@flexiontherapeutics.com](mailto:kwentworth@flexiontherapeutics.com)); Elizabeth Hook ([ehook@flexiontherapeutics.com](mailto:ehook@flexiontherapeutics.com))  
**Cc:** Compton, Kimberly  
**Subject:** N 208845 IR from CDRH portion of team

Hi Kerry and Elizabeth,

The CDRH reviewer working on your application asked me to convey the following:

**You have provided *summary* verification testing in section 3.2.P.7.3. However, we are unable to locate the *complete* testing. Please provide the complete test reports (or specific location) for the following:**

1. **Device description that includes the materials, colorants, dimensions, proof of device compatibility with the off-the-shelf syringes since you will not be including your own syringe)**

2. Specific design specifications (you have not explicitly stated what your specifications are for the vial adapter) along with your lot release specifications for the device constituent
3. Biocompatibility testing for the vial adapter (we have a brief summary, but no complete testing or a summary report of the ISO 10993-1 testing conducted)
4. Testing that evaluates the device function at the end of shelf life for the vial adapter
5. Shipping studies (according to ASTM 4169) for the vial adapter
6. All of the functional verification testing in table 3 of 3.2.P.7.3

You briefly mention the vial adapter is cleared under a 510(k) but there you have not provided that number or included a letter of authorization (LOA) for the 510k. Please either provide that application number or submit an LOA to the 510k you are referencing.

Please provide this information as soon as possible.

Please let me know when you think you can provide a reply and if you have any questions about our request.

Thanks!  
Kim

*Kimberly Compton*  
Kimberly Compton, RPh  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
301-796-1191

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KIMBERLY A COMPTON  
04/04/2017



NDA 208845

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Flexion Therapeutics, Inc.  
10 Mall Road, Suite 301  
Burlington, MA 01803

ATTENTION: Kerry Wentworth  
Senior Vice President, Regulatory Affairs and Quality

Dear Ms. Wentworth:

Please refer to your New Drug Application (NDA) dated and received December 8, 2016, submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Triamcinolone Acetonide Extended-Release Injectable Suspension, 40 mg.

We also refer to your correspondence dated and received December 8, 2016, requesting review of your proposed proprietary name, Zilretta.

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

If any of the proposed product characteristics as stated in your December 8, 2016, 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:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Kimberly Compton, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1191.

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/  
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VIKKI S KINSEY  
03/01/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES  
03/01/2017



NDA 208845

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

Flexion Therapeutics, Inc.  
Suite 301  
10 Mall Road  
Burlington, MA 01803

Attention: Kerry Wentworth  
Sr. Vice President, Regulatory Affairs and Quality

Dear Ms. Wentworth:

Please refer to your New Drug Application (NDA) dated and received December 8, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ZILRETTA (triamcinolone acetonide extended-release) injectable suspension.

We also refer to your amendments dated January 24, 27, and 30, 2017.

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 October 8, 2017.

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 September 10, 2017.

During our filing review of your application, we identified the following potential review issues:

**Nonclinical**

1. The proposed drug product specifications of NMT <sup>(b)</sup><sub>(4)</sub>% for individual specified degradants and NMT <sup>(b)</sup><sub>(4)</sub>% for individual unspecified degradants exceed the qualification threshold

(0.5% or 200 mcg Total Daily Intake (TDI), whichever is lower) and identification threshold (0.2% or 2 mg TDI, whichever is lower), respectively, per the ICH Q3B(R2) guidance for industry, *Impurities in New Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>. We acknowledge that you have based your proposed specifications on the maximum daily exposure of triamcinolone acetonide over the intended duration of release facilitated by the PLGA polymer (b) (4); however, we do not agree with this rationale for establishing degradant specifications. Unless the rate of exposure to individual degradants can be demonstrated to be similar to triamcinolone acetonide, you must assume that the total amount of individual impurities may be exposed on the first day post-injection and specifications must be based on the maximum daily dose of 40 mg. Therefore, you must either reduce the specifications for specified and unspecified degradants to be within the ICH Q3B(R2) thresholds outlined above, or provide data to justify the safety of the proposed specifications that exceed these thresholds. Based on submitted data for registration batches on stability testing, the levels of several impurities (b) (4) appear to remain within ICH thresholds and their specifications should be reduced. Another consideration may be to shorten the expiry of your drug product so that the impurity specifications are within the ICH Q3B(R2) qualification threshold. To adequately qualify impurities/degradants in accordance with ICH Q3B(R2), you must provide the following data:

- a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration via an adequate route to support the proposed indication. In this case, duration of 90 days is appropriate.
  - c. You may be able to justify the safety of a drug product degradant via comparative analytical studies demonstrating that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry, *ANDAs: Impurities in Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf>.
2. Based on a preliminary review of your NDA submission, it does not appear that an adequate extractables/leachables evaluation was performed. In the pre-NDA written responses sent on May 25, 2016, we stated that “although a toxicological risk assessment based on the results of the extraction study may be adequate to support the safety assessment during the development, *you should still evaluate at least three batches of your drug product over the course of your stability studies* and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration.” However, only two batches were evaluated (b) (4)

(b) (4) and, only two batches were evaluated for the diluent with only one of these batches (Lot 023C15) evaluated in the inverted position at one time point (b) (4). As the container system consists of a glass vial and rubber stopper, our primary concern is the potential exposure to patients from leachables arising from the rubber stopper of the diluent. To address this issue, we strongly recommend that you provide leachables data, as soon as possible during this review cycle, from at least three batches of the FX006 Diluent placed on stability in the inverted position at multiple time points over the course of your stability studies, preferably at release, an intermediate time point, and towards the proposed expiry, in order to identify trends in leachable levels over time. Establish your Analytical Evaluation Threshold (AET) to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day depending on the duration of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product (b) (4) in order, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
- FDA guidance for industry, *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf>.

The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple time points over the course of your stability studies, as discussed above. Base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.
- Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although they can be potentially useful to identify original source materials, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.
- Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your extractables/leachables. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We additionally request that you submit the following information:

1. You have not adequately addressed the requirement for 21 CFR 820.20, Management Control. Describe the organizational structure of your quality management system (i.e., organization chart) and explain how your firm controls all levels of the product development and manufacturing (i.e., supplier agreements).
2. You have not adequately addressed the requirement for 21 CFR 820.50, Purchasing Controls. Summarize your procedure(s) for purchasing controls, including a description of the supplier evaluation process and the extent of control over suppliers. Also describe how it is ensured that products/services received are acceptable for their intended use and how changes made by subcontractors/suppliers will not affect the final combination product.
3. You may find useful information regarding the types of documents the guidance for industry, *Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff*, available at,

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>.

4. Provide a justification for the applicability of data collected in foreign study sites to the U.S. population. In particular, address differences in body mass index (BMI) between the U.S. population and the countries of the foreign study sites and how this may impact the interpretation of the study results.
5. Provide the data and propose release specifications for the following attributes of PLGA: Identification by (b) (4)
6. Clarify whether the 24-hour in-use stability study included the use of the adapter to add the diluent. If so, provide any data for possible extractables that may have come from the adapter during transfer of the diluent to the powder vial.
7. Submit the particle size distribution (PSD) values for batches used on the in vitro release (IVR) method discriminating ability studies. These data are needed to support the proposed PSD specification for the microspheres.
8. Submit individual and mean IVR data for clinical batches FL1000, FL1100, and FL1101 and three additional good manufacturing (GMP) development batches (FL1022, FL1208, FL1223) used to set IVR acceptance criteria. Note that the acceptance criteria for IVR are set based on batches tested in pivotal clinical trials.
9. Provide a formal biowaiver request with supporting data/justification for the proposed manufacturing changes.
10. Submit the following to support the extended release designation claim for your drug product (refer also to 21 CFR 320.25f)
  - a. A bioavailability (BA) profile established for the drug product that rules out the occurrence of any dose dumping.
  - b. Data supporting that the drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that was approved as an NDA.
  - c. Data supporting that the drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.
  - d. Data supporting that the drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

11. Submit in vitro release profile comparison between the batches tested in Phase 2 trials and Phase 3 trials. These data are needed to establish the bridge between the formulations tested. Alternately, provide data demonstrating that the vehicle volume does not have an impact on the in vitro release of your proposed drug product.
12. Provide detailed information of the scale-up changes implemented from clinical to commercial sites with justification/data supporting the level of change.

## **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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: The margin in the right is less than ½ inch. Increase to ½ inch.

2. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: The four-digit year is not included. Add “1958”, as that is the year the active ingredient (triamcinolone) was first approved in the U.S.

3. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment: You did not include the manufacturer’s U.S., toll-free phone number. Add this number.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 7, 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.

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). 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>).

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SHARON H HERTZ  
02/17/2017



NDA 208845

**NDA ACKNOWLEDGMENT**

Flexion Therapeutics, Inc.  
10 Mall Road  
Suite 301  
Burlington, MA 01803

Attention: Kerry Wentworth  
Sr. Vice President, Regulatory Affairs and Quality

Dear Ms. Wentworth:

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: Zilretta (triamcinolone acetonide for extended-release) injectable suspension

Date of Application: December 8, 2016

Date of Receipt: December 8, 2016

Our Reference Number: NDA 208845

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 February 6, 2017, 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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Addiction 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](mailto: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) 796-1191.

Sincerely,

*{See appended electronic signature page}*

Kimberly Compton, RPh  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY A COMPTON  
01/09/2017



IND 111325

**MEETING PRELIMINARY COMMENTS**

Flexion Therapeutics, Inc.  
10 Mall Road Suite 301  
Burlington, MA 01803

Attention: Kerry Wentworth  
Sr. Vice President, Regulatory Affairs and Quality

Dear Ms. Wentworth:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for FX-006 Triamcinolone Acetonide for Extended Release Injectable Suspension.

We also refer to your February 19, 2016, correspondence, received February 22, 2016, requesting a meeting to discuss, seek guidance, and gain agreement on clinical, nonclinical, regulatory, and labeling matters in support of Flexion's planned 505(b)(2) new drug application (NDA) submission for FX006.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-4131.

Sincerely,

*{See appended electronic signature page}*

Christopher Hilfiger  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** June 2, 2016 4:00 – 5:00 p.m. EDT  
**Meeting Location:** 10903 New Hampshire Ave  
Silver Spring, MD 20993  
White Oak Build 22 Room 1419

**Application Number:** IND 111325  
**Product Name:** FX-006 Triamcinolone Acetonide for Extended Release Injectable Suspension  
**Indication:** osteoarthritis pain (b) (4)  
**Sponsor/Applicant Name:** Flexion Therapeutics, Inc

**FDA ATTENDEES (tentative)**

Sharon Hertz, MD	Division Director, DAAAP
Ellen Fields, MD, MPH	Deputy Division Director, DAAAP
Pamela Horn, MD	Clinical Team Leader, DAAAP
Jacqueline Spaulding, MD	Medical Officer, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Armaghan Emami, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, DAAAP
Wei Qui, PhD	Clinical Pharmacology Reviewer, DAAAP
David Petullo, PhD	Mathematical Statistics Team Leader, DAAAP
Katherine Meaker, MS	Biometrics Reviewer, DAAAP

**SPONSOR ATTENDEES**

Neil Bodick, MD, PhD	Chief Medical Officer
Mittie Doyle, MD	Vice President, Clinical Research & Development
Elizabeth Hook	Sr. Manager, Regulatory Affairs
James Johnson, PhD	Sr. Director, Biostatistics & Data Sciences
Dan Leblanc	Vice President, CMC Operations
Joelle Lufkin	Vice President, Clinical Operations
Kerry Wentworth	Sr. Vice President, Regulatory Affairs & Quality
Toni Williamson, PhD	Sr. Director, Non-Clinical Research

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### **Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 2, 2016, 4:00 – 5:00 p.m. between Flexion Therapeutics, Inc and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

### **BACKGROUND**

The Sponsor requested a meeting to discuss, seek guidance, and gain agreement for a potential NDA submission. FX-006 is an extended release formulation of triamcinolone acetonide in 75:25 poly (D,L-lactic-co-glycolic acid)(PLGA) microspheres. The drug product is designed to maintain a prolonged therapeutic concentration in the joint following intra-articular injection for the management of osteoarthritis pain [REDACTED] (b) (4). In August 2015, the Agency designated FX006 as a Fast Track development program. The submission will rely, in part, on referencing the Agency's previous findings of safety and efficacy for Kenalog 40 injectable suspension (NDA 014901).

### **DISCUSSION**

*Question 1: Does the Division agree that the clinical efficacy package from the completed clinical program is sufficient to support NDA submission and potential approval of FX006 40mg as an IA injection for the management of OA pain?*

### **FDA Response:**

**Yes, your plan to submit a 505(b)(2) application relying in part on the Agency's previous finding of safety and efficacy for Kenalog-40 (TCA injection suspension, USP) and data from one positive adequate and well-controlled trial is acceptable to support filing of an NDA submission.**

**According to the 2014 Draft Guidance for Industry *Analgesic Indications: Developing Drugs and Biological Products*, available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, for reformulations of approved analgesics, if an NDA is intended to be submitted as a 505(b)(2) application that references an analgesic listed drug (LD), reliance on the FDA's previous finding of safety and effectiveness for an appropriate LD and one adequate and**

**well-controlled trial (AWC), in addition to comparative BA studies between the product and the LD, may be sufficient to support an application.**

**See also the additional information below entitled 505(b)(2) REGULATORY PATHWAY.**

*Question 2: Does the Division agree that the available safety database from the completed clinical program is sufficient to support an NDA submission and potential approval of FX006 40mg as an IA injection for the management of OA pain?*

**FDA Response:**

**Yes, we agree that the available safety database described in the meeting package appears to be sufficient to support filing of the NDA submission.**

**At the EOP2 meeting on September 24, 2013, you were informed that a minimum of 350 patients exposed to FX006 may be acceptable provided no significant safety concerns arise that would require additional characterization. The safety database number of 350 patients was confirmed by the Division at the Type C meeting on June 26, 2014, with the additional comment that, “the final determination will be made based on the clinical safety profile and nonclinical chronic toxicity profile.”**

**The submission states the total safety database includes 650 patients who received any dose of FX006 and 400 patients who received the to-be marketed dose of 40 mg.**

*Question 3: Does the Division agree with Flexion’s approach to analyzing studies in the Integrated Summary of Efficacy (ISE)? Does the Division have any general comments or recommendations regarding the ISE Statistical Analysis Plan (SAP)?*

**FDA Response:**

**The SAP for the ISE (Appendix 3 of your meeting package) is acceptable.**

*Question 4: Does the Division agree with Flexion’s approach to analyzing studies in the Integrated Summary of Safety (ISS)? Does the Division have any general comments or recommendations regarding the IIS SAP?*

**FDA Response:**

**You propose to have two safety pools; an “all studies pool” and an “efficacy studies pool.” We agree with your approach to pooling the safety data for the purposes of creating the ISS.**

Question 5: *Could the Division please affirm that no additional toxicology studies are needed to support NDA submission?*

**FDA Response:**

The toxicology studies described in your meeting package appear appropriate to support an NDA submission for a single-use (b) (4) indication. However, refer to the following additional comments to determine if additional studies are warranted:

1. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:
  - a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. In addition, you must conduct a single-dose toxicology study to assess both local and systemic safety of the impurity or degradant to support the proposed single-dose indication. Repeat-dose studies may be necessary to support a repeat-dose indication.

Refer to

Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf>

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

- c. Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf>.
2. If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include

justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.

3. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.
4. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: **M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk** for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.
5. **NOTE:** We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds.
6. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for [REDACTED] <sup>(b) (4)</sup> The choice of solvents and conditions for the extraction studies should be justified. The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a toxicological risk assessment based on the results of the extraction studies may be

adequate to support the safety assessment during development, you should still evaluate at least three batches of your drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many (b) (4) are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf> and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf>. Submit a toxicological risk assessment for any leachable that (b) (4). From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 1.5 mcg/day total daily exposure for a chronic indication or 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

*Question 6: Could the Division please affirm the prior agreement that a 505(b)(2) pathway for submission of FX006 NDA is acceptable and provide concurrence that Kenalog<sup>®</sup>-40 is acceptable as the reference LD upon which to rely on FDA's previous findings of safety and effectiveness? Does the Division agree with Flexion's strategy for presenting reference LD information in the label?*

**FDA Response:**

The Agency does not generally advise an Applicant on the selection of a particular listed drug that may be relied upon to support an approval of a NDA. . The proposed FX006 label appears to have been prepared according to the Physician Labeling Rule (PLR) format and using language from the LD, Kenalog-40 and class labeling. Your proposal to reference Kenalog-40 as the LD upon which to rely on the Agency's previous findings of safety and effectiveness appears acceptable.

Your NDA submission must include an annotated label with references to the source of the information, either from the reference LD labeling or to the location of the information in

**your application. This will allow us to provide comment on the appropriateness of the information proposed for inclusion in the label as part of the NDA application review.**

**In addition, the nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**

**See also the additional information below entitled 505(b)(2) REGULATORY PATHWAY.**

**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 that drug and eligible for approval under section 505(j) of the act, we may 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 ANDA that cites the duplicate product as the reference listed drug.**

**Your general strategy to rely on language from the LD label to describe nonclinical data in the relevant sections of your product labeling is appropriate. However, the acceptability of the specific language used to describe this information will be reviewed when the NDA is submitted. Note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at:**

**<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm> .**

*Question 7: Does the Division agree that demonstration of efficacy and safety in the FX006 clinical program, and reliance on FDA's findings of efficacy and safety for Kenalog<sup>®</sup>-40, could be sufficient* (b) (4)

(b) (4)

**FDA Response:**

(b) (4)

*Question 8: Does the Division agree with the elements of the proposed commercial packaging configuration and supporting information?*

**FDA Response:**

**The proposed commercial packaging appears to be acceptable. The evaluation of the packaging configuration will be conducted by CDER and CDRH during the NDA review.**

**The Division of Medication Error Prevention and Analysis finds the proposed packaging configuration acceptable from a medication error perspective. However, you have not submitted labels and labeling for our review; thus, we may have label and labeling recommendations during review of the NDA.**

**The Center for Devices and Radiological Health (CDRH) Office of Compliance (OC) requests that the following items be provided to facilitate our review. To prevent any delays or duplicative information requests during the review of your application, please provide the following information prior to or with your application submission to demonstrate compliance with 21 CFR Part 4:**

**Management Control**

**Specify which manufacturing firm has ultimate responsibility to ensure the combination product is manufactured in compliance with applicable 21 CFR Part 4 requirements at all levels of the organization. Also, provide a description and responsibility of each facility involved at the different levels of the organizational structure.**

**Design Control, General**

**Provide a description of your design control system, which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Provide a summary of the plan used to design the combination product. Explain how you implemented the design control system to develop the combination product under review.**

**Purchasing Controls**

**Provide a summary of the procedure(s) for purchasing controls. The summary should:**

- 1. Describe your supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.**

2. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
3. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier's agreement).

#### **Corrective and Preventive Action**

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of:

1. Sources of quality data to identify existing and potential causes of nonconforming practices and products;
2. Investigation of the cause of nonconformities;
3. Identification of actions needed to correct and prevent recurrence of non-conformances;
4. Verification or validation of the actions.

If you have any questions regarding these requests, please contact the Office of Combination Products [combination@fda.gov](mailto:combination@fda.gov).

*Question 9: Flexion proposes to include case summaries and CRFs in the NDA for all subjects with reported deaths, SAEs, and discontinuations. Does the Division agree?*

#### **FDA Response:**

Yes, we agree that you must include case summaries and CRFs in the NDA for all patients with reported deaths, SAEs and discontinuations due to adverse events. Also include case summaries and CRFs in the NDA for patients with adverse events of special interest (e.g. septic arthritis of target joint and effusion of target joint).

*Question 10: In the Phase 3 Study, FX006-2014-008 (-008), X-ray images were collected at Baseline and End of Study (Week 24) as part of assessing local joint safety. Flexion proposes to provide X-ray images only upon request during the NDA review and not a priori which the original NDA submission. Does the Division agree with this approach?*

#### **FDA Response:**

Include copies of X-ray images in PDF format for patients with discontinuations due to joint adverse events and adverse events involving the target joint with the original NDA submission.

*Question 11: Does the Division agree with Flexion's proposed plan for submitting standardized electronic datasets for data from the clinical development program?*

**FDA Response:**

**Yes, we agree with your proposed plan for submitting electronic datasets for data from the clinical development program. In addition we have the following comments regarding the dataset:**

- 1. The integrated safety dataset must include the following fields/variables:**
  - a. unique patient identifier,**
  - b. study/protocol number,**
  - c. patient's treatment assignment, demographic characteristics, including gender, chronological age (not date of birth), and race,**
  - d. dosing at time of adverse event,**
  - e. dosing prior to event (if different),**
  - f. duration of event (or start and stop dates),**
  - g. days on study drug at time of event,**
  - h. outcome of event (e.g., ongoing, resolved, led to discontinuation),**
  - i. flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment**
  - j. marker for serious adverse events**
  - k. verbatim term**
- 2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the adverse event data set and provide a variable that gives the numeric MedDRA code for each lower level term on the case report form.**
- 3. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**
- 4. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**

- 5. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**
- 6. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**
- 7. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**
- 8. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.**
- 9. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**
- 10. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.**
- 11. All datasets must contain the following variables/fields (in the same format and coding):**
  - a. Each subject must have one unique ID across the entire NDA**
  - b. Study number**
  - c. Treatment assignment**
  - d. Demographic characteristics (age, race, gender, etc.)**
- 12. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.**
- 13. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**

**14. For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**

*Question 12: Does the Division anticipate the need to consult an advisory committee during the review of the NDA for FX006?*

**FDA Response:**

**At this time we do not anticipate the need for an advisory committee. However, we may schedule an advisory committee meeting if during the review of the NDA for FX006 an issue arises that we determine requires the expert input of an advisory committee.**

**Additional Comments:**

**You propose to submit a 505(b)(2) NDA and rely on the Agency’s previous findings on safety of Kenalog-40. To rely on the systemic safety of Kenalog-40, you must demonstrate that the systemic exposure of TCA including  $C_{max}$ ,  $AUC_t$ , and  $AUC_{inf}$  values for your proposed product are not higher than those from Kenalog-40. For analysis of comparative bioavailability of your proposed product and Kenalog-40 in Studies -002 and -005, use the average bioequivalence approach to determine the geometric mean ratios for  $C_{max}$ ,  $AUC_t$ , and  $AUC_{inf}$  and their corresponding 90% confidence intervals.**

**Clarify if the proposed to-be-marketed product has been used in the clinical and clinical pharmacology studies to support your NDA submission.**

**CDRH General Hospital Devices may provide additional comments based on your briefing package in a separate communication.**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our February 29, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

### **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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all

referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf>.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) 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](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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>.

**MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

**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>).

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.

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

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.

**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.

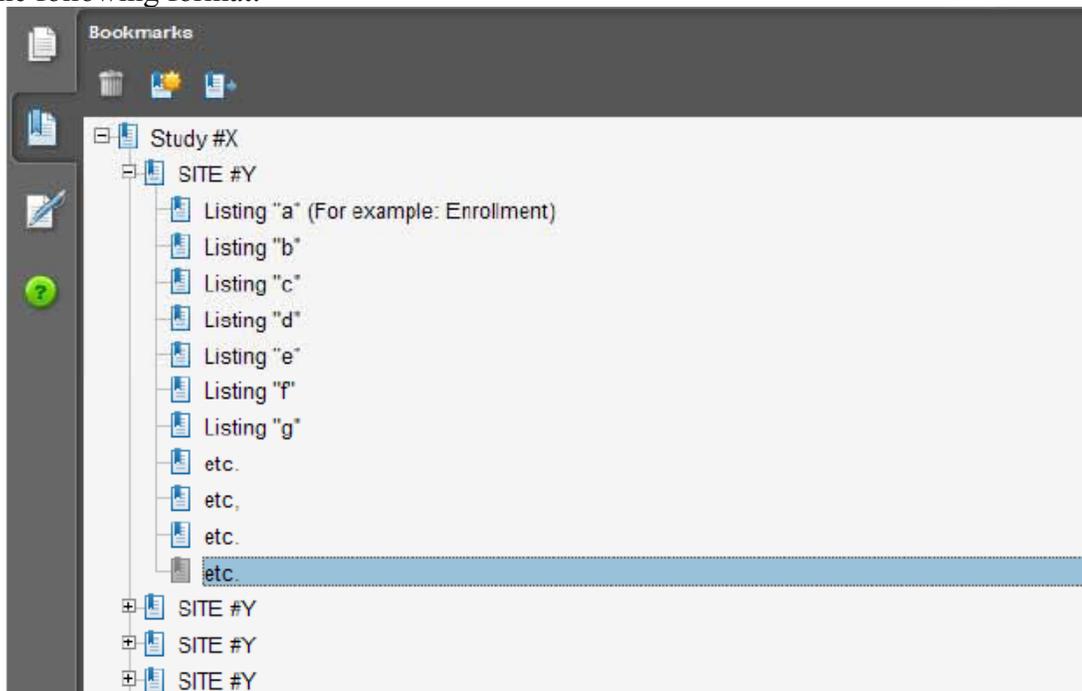
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

**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 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.”

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

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

FDA eCTD web page

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

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## **Attachment 2: Additional Comments for Pre-NDA Stage of Drug Development**

### **Nonclinical Comments**

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.
  
2. We recommend 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 October 1999 draft guidance for industry, *Applications Covered by Section 505(b)(2)*, 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 challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

If you intend to submit a 505(b)(2) application that relies for approval 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). 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 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 is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were

obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

As noted in the document cited above, "the phrase ***new excipients*** means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure, duration of exposure, or route of administration.**" (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.” The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for (b) (4). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many (b) (4) are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents “Container Closure Systems for Packaging Human Drugs and Biologics” and “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation.” Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at [http://www.pqri.org/pdfs/LE\\_Recommendations\\_to\\_FDA\\_09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).
9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

### **Chemistry, Manufacturing and Control (CMC) Comments**

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to

cover the proposed expiry dating.

3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.
4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

**The Abuse Potential section of the NDA is submitted in the eCTD as follows:**

*Module 1: Administrative Information and Prescribing Information*

1.11.4 Multiple Module Information Amendment

This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

*Module 2: Summaries*

2.4 Nonclinical Overview

This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview

This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

*Module 3: Quality*

3.2.P.1 Description and Composition of the Drug Product

This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

#### 3.2.P.2 Description and Composition of the Drug Product

This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

### *Module 4: Nonclinical Study Reports*

#### 4.2.1 Pharmacology

##### 4.2.1.1 Primary Pharmacodynamics

These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

##### 4.2.3.7.4 Dependence

This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

### *Module 5: Clinical Study Reports*

#### 5.3.5.4 Other Study Reports

This section should contain complete study reports of all clinical abuse potential studies.

##### 5.3.6.1 Reports of Postmarketing Experience

This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

### **General Clinical Comments**

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions

7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

### **Sites for Inspection**

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 the inspections (Item I and II).

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

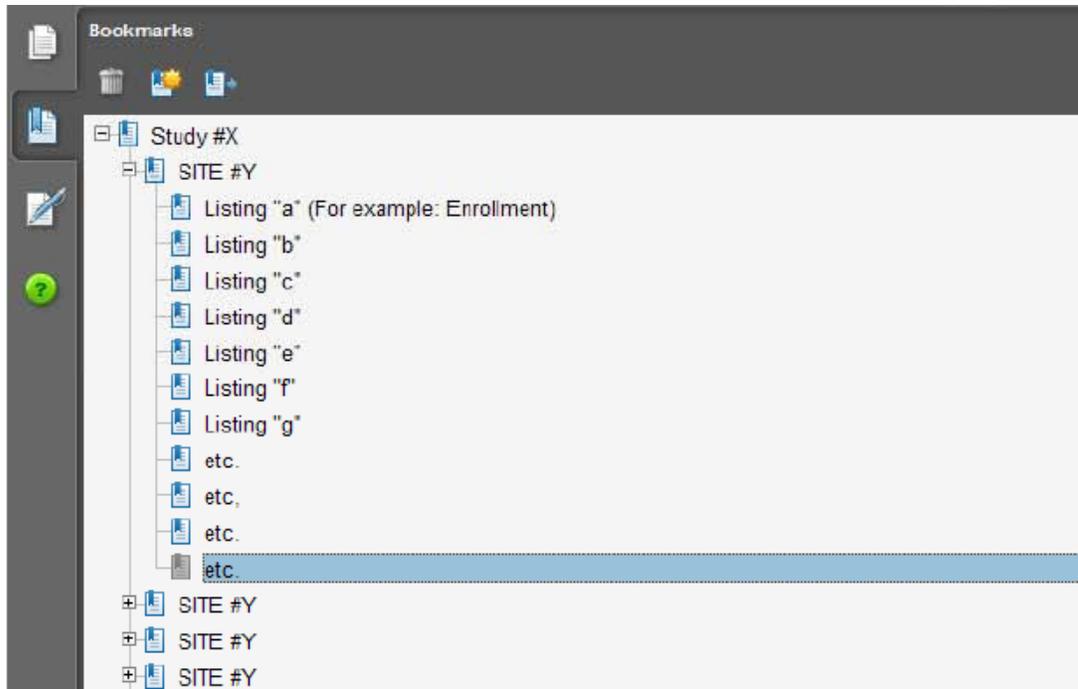
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Subpart 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**
  6. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
    - e. Site number
    - f. Principal investigator
    - g. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    - h. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  7. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
    - d. Number of subjects screened for each site by site
    - e. Number of subjects randomized for each site by site, if appropriate
    - f. Number of subjects treated who prematurely discontinued for each site by site
  8. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
    - d. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    - e. Name, address and contact information of all CROs used in the conduct of the clinical trials
    - f. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies

- g. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
- 9. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
- 10. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

## **II. Request for Subject Level Data Listings by Site**

- 3. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - k. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
  - l. Subject listing for treatment assignment (randomization)
  - m. Subject listing of drop-outs and subjects that discontinued with date and reason
  - n. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - o. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - p. By subject listing, of AEs, SAEs, deaths and dates
  - q. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - r. 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.
  - s. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - t. By subject listing, of laboratory tests performed for safety monitoring
- 4. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



### III. Request for Site Level Dataset

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Subpart 1, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

## Subpart 1

### 1. Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

#### 1.1. Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### 1.2. Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### *Site-Specific Efficacy Results*

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

**Subpart 2**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

C. 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.”

<b>DSI Pre-NDA Request Item<sup>2</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



E. 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.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

FDA eCTD web page

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

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

## Common PLR Labeling Errors

### Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)
7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]

12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]
13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

**Contents (Table of Contents):**

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
24. Do not refer to adverse reactions as “adverse events.” Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].
28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.
30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.
32. If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.
33. For fictitious examples of labeling in the new format, refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices' website, <http://www.ismp.org/Tools/abbreviationslist.pdf>

### **SPL Submission**

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov) for individual assistance.

### **Integrated Summary of Effectiveness**

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

### **CDER Data Standards Reference Guide/Checklist**

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

### **Dataset Comments**

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

The integrated safety dataset that must include the following fields/variables:

- a. A unique patient identifier
- b. Study/protocol number

- c. Patient's treatment assignment
  - d. Demographic characteristics, including gender, chronological age (not date of birth), and race
  - e. Dosing at time of adverse event
  - f. Dosing prior to event (if different)
  - g. Duration of event (or start and stop dates)
  - h. Days on study drug at time of event
  - i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
  - j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
  - k. Marker for serious adverse events
  - l. Verbatim term
2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.
  3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.
  4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.
  5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.
  6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.
  7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.
9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.
10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.
11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.
12. Across all datasets, the same coding must be used for common variables, e.g. “PBO” for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.
13. All datasets must contain the following variables/fields (in the same format and coding):
  - a. Each subject must have one unique ID across the entire NDA
  - b. Study number
  - c. Treatment assignment
  - d. Demographic characteristics (age, race, gender, etc.)
14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.
15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.
16. For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTOPHER M HILFIGER  
05/25/2016



IND111325

**MEETING MINUTES**

Flexion Therapeutic, Inc.  
Attention: Kerry Wentworth, Vice President, Regulatory Affairs  
10 Mall Road  
Suite 301  
Burlington, MA 01803

Dear Ms. Wentworth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for FX006 Triamcinolone Acetonide ER Injectable Suspension.

We also refer to the meeting between representatives of your firm and the FDA on October 14, 2015. The purpose of the meeting was to discuss the adequacy of CMC elements to support FX006 product registration.

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, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

*{See appended electronic signature page}*

Steven Kinsley, Ph.D.  
Regulatory Business Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** Pre-NDA CMC Only

**Meeting Date and Time:** October 14, 2015 9:00:00 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 21, Conference Room: 1539  
Silver Springs, Maryland 20903

**Application Number:** IND 111325  
**Product Name:** FX006 Triamcinolone Acetonide ER Injectable Suspension  
**Indication:** Treatment of pain in osteoarthritis of the knee.  
**Sponsor/Applicant Name:** Flexion Therapeutic, Inc.

**Meeting Chair:** Julia Pinto  
**Meeting Recorder:** Steven Kinsley

**FDA ATTENDEES**

Julia Pinto, Ph.D	Branch Chief, Office of New Drug Products (ONDP)
Haritha Mandula, Ph.D.	Biopharmaceutics Reviewer, ONDP
Kelly Kitchens, Ph.D.	Biopharmaceutics Reviewer, ONDP
Nallaperumal Chidambaram, Ph.D.	Branch Chief, Office of Process and Facilities (OPF)
Peter Krommenhoek, Ph.D.	Process Reviewer, OPF
Yeissa Chabreir-Rosello, Ph.D.	Microbiology Reviewer, OPF
Steven Kinsley, Ph.D.	Regulatory Process Manager, Office of Program and Regulatory Operations

**SPONSOR ATTENDEES**

Elizabeth Hook	Sr. Manager, Regulatory Affairs, Flexion
Derek Jackson	Director, Analytical CMC, Flexion
Dan Leblanc	Vice President, CMC Operations, Flexion
Caitlin Pazzano	Director, Quality Assurance Operations, Flexion
Marco Verwijs, Ph.D.	Director, CMC Operations, Flexion
Kerry Wentworth	Vice President, Regulatory Affairs and Quality
(b) (4)	Consultant, (b) (4)

## 1.0 BACKGROUND

FX006 is an extended-release formulation of triamcinolone acetonide (TCA) for intra-articular (IA) administration that is currently in phase 3 clinical development for the treatment of pain in osteoarthritis of the knee. Flexion intends to submit a New Drug Application (NDA) for FX006 as a 505(b)(2) application with Kenalog®-40 (triamcinolone acetonide, injectable suspension, NDA 014901, USP) as the reference listed drug. The purpose of the Type C meeting was to discuss, seek guidance, and gain agreement on the adequacy of the following CMC elements to support FX006 product registration. Prior to the meeting the Sponsor stated that they will need further clarification on Questions 2,4 and 5.

FDA sent Preliminary Comments to Flexion Therapeutic, Inc. on October 8, 2015. Flexion Therapeutic, Inc. submitted a response via e-mail on October 13, 2015.

For Clarity, the Sponsor's submitted questions and e-mail responses are in *italicized* font, the division's response in **bolded** font and any discussion in normal font.

## 2. DISCUSSION

### *Question 1.*

- a) *Does the Division agree that the proposed IVR method is adequate to support NDA filing and registration?*
- b) *Does the Division agree with the proposed provisional IVR Specification acceptance criteria for the release and stability of FX006 finished product to support NDA filing and registration.*

### **FDA Response to Question 1a:**

**The IVR method development appears reasonable. The agency acknowledges your submission of the dissolution method development. Submit a general correspondence to the IND for a detailed evaluation of the dissolution method by the Agency.**

### **FDA Response to Question 1b:**

**We agree with the proposed approach for establishing acceptance criteria, and the final acceptability of the IVR acceptance criteria will be made during the NDA review process based on the totality of the provided data.**

### *Flexion Response via e-mail October 13, 2015*

*We acknowledge your guidance to submit the general correspondence to the IND and would like to confirm that the Agency will be able to provide an expeditious and detailed review with the opportunity for further dialogue. We do not anticipate the need to discuss this topic any further at the Type C Meeting.*

Discussion:

The sponsor will submit the full IVR method to the IND and requests that the method be reviewed in 30 days. The Agency stated that the cover letter should include a statement requesting the method be reviewed in 30 days.

*Question 2.*

*Does the Division agree that the acceptance criteria and test methods intended for quality control, release and stability of the FX006 drug product (sterile powder) and sterile diluent are adequate to support NDA filing and registration?*

FDA Response to question 2:

**Proposed product testing seems reasonable. Evaluation of the specifications is deferred to the NDA submission, when the data can be evaluated in its totality. Further, we propose the following additional testing to be included at product release :**

- **viscosity**
- **individual impurity specifications set according to ICHQ3B**
- **The amount of free drug included as part of the release specifications**
- **Specifications for the reconstituted product, to include time for reconstitution, (b) (4), assay and impurity testing.**

**From the Biopharmaceutics perspective, refer to our response to Q1b above regarding your proposed in vitro release acceptance criteria.**

**From the Microbiology perspective, the Agency agrees that the following endotoxin and sterility test specifications for the drug product and companion diluent for release and stability, and test methods based on USP<85> and USP<71> respectively are adequate to support NDA filing and registration.**

Drug product:

Endotoxin	USP <85>	NMT (b) (4)EU/mg
Sterility	USP <71>	Sterile, no growth

Companion diluent:

Endotoxin	USP<85>/Ph. Eur. 2.6.14, Kinetic Chromogenic of Gel Clot technique	NMT (b) (4)EU / mL
Sterility	USP<71>/Ph. Eur. 2.6.1	Sterile, no growth

*Flexion Response via e-mail October 13, 2015*

*Flexion is aligned with Agency feedback regarding the additional tests on the FX006 sterile powder. However, we would like to discuss the recommended new tests performed on the reconstituted product as we may not have clearly communicated the reconstitution and administration process that has been used through clinical development and is intended for the commercial setting.*

*FX006 is supplied as a (b) (4) dry powder vial that is reconstituted (b) (4) prior (b) (4) to injection.*

(b) (4)

(b) (4)

Discussion:



*Question 3.*

*Does the Division agree that the proposed plan, including batch selection, for the primary stability program is adequate to support a 24-month shelf-life at the time of NDA filing and registration for the following?*

**FDA Response to question 3:**

**The proposed study protocol, including sterility and endotoxin testing at the initial time point and annually up to 24 months for the drug product and the companion diluent, is acceptable. However, in order to qualify the vials, at least twelve months of stability data for two to three batches of the drug product stored in each container, should be provided, to support use of either vial. Further, provide a comparison of both vials in the NDA as well as a letter of authorization for any associated DMFs.**

*Flexion Response via e-mail October 13, 2015*

*We believe there is alignment between Flexion and FDA on this matter, but to ensure complete clarity Flexion confirms that two lots in each container closure type (stored upright due to the powder nature of FX006) under the full ICH Stability protocol will be provided. This gives a total of four distinct primary lots, each with between 12 and 24 months stability at the time of NDA filing in support of a proposed shelf-life of 24 months. A comparison of the vials and LoAs for their DMFs will be provided in the NDA.*

Discussion:

There was no discussion of this response.

Question 4.

- a) Does the Division agree with the proposed comparability approach for transferring the FX006 drug product manufacturing process to a second site, which includes a manufacturing facility (b) (4) (b) (4) ?
- b) If the comparability plan for these new facilities is met, does the Division agree that these manufacturing facilities, in addition to (b) (4), could be approved concurrently as part of an original NDA filing and review for FX006? If not, please indicate what requirements would need to be met in order for the new facilities to be considered as part of the original NDA.

**FDA Response to question 4a:**

The Agency agrees that a comparability protocol can be submitted for an alternate drug product manufacturing facility (b) (4) (b) (4) at the time of NDA submission. From the manufacturing process perspective, your proposed plan appears to be acceptable. Although the full spectrum of input variability (i.e., of critical process parameters) found in commercial production is not typically known at this stage, the Agency expects that controls include both examination of material quality and equipment monitoring. It is noted that the current approach does not discuss equipment monitoring associated with manufacturing at the current (b) (4) and proposed (b) (4) sites. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or (b) (4) material. The degree of control over those attributes and parameters should be commensurate with their risk to the process and process output.

Although the proposed (b) (4) batches can help provide information that can be used to understand the commercial process, it is unclear if the proposed batch sizes are a representative comparison to the current (b) (4) manufacturing site. The proposed batch size for (b) (4) kg, whereas the batch size at (b) (4) is listed as (b) (4) kg. The batches made at both sites, (b) (4) of the commercial scale, in order to qualify the site. The Agency notes that although comparative information between the two sites may be submitted at the time of NDA submission, the feasibility of the process at all proposed manufacturing sites should be scientifically justified.

The Agency further recommends that comparative information should be provided for the manufacturing process at the alternate manufacturing site, and qualification of the (b) (4) method for the drug product's (b) (4) should be performed at the proposed (b) (4). It is also recommended that additional drug product batches (at least 10) be evaluated at (b) (4) to better

assess the product bioburden levels and the suitability of the (b) (4) approach at this facility.

**Comparative batch analysis and stability data for all batches from both sites should be provided as further support for the addition of the second manufacturing site. Sufficient stability data for the batches made at the second facility must be included in the NDA submission at the time of filing, in order to fully assess the adequacy of the second manufacturing facility.**

**From the Biopharmaceutics perspective, the proposed manufacturing site change could be classified as a level 3 change per the SUPAC-MR Guidance. For additional details, please refer to Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms**

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070640.pdf>

#### **FDA Response Question 4b:**

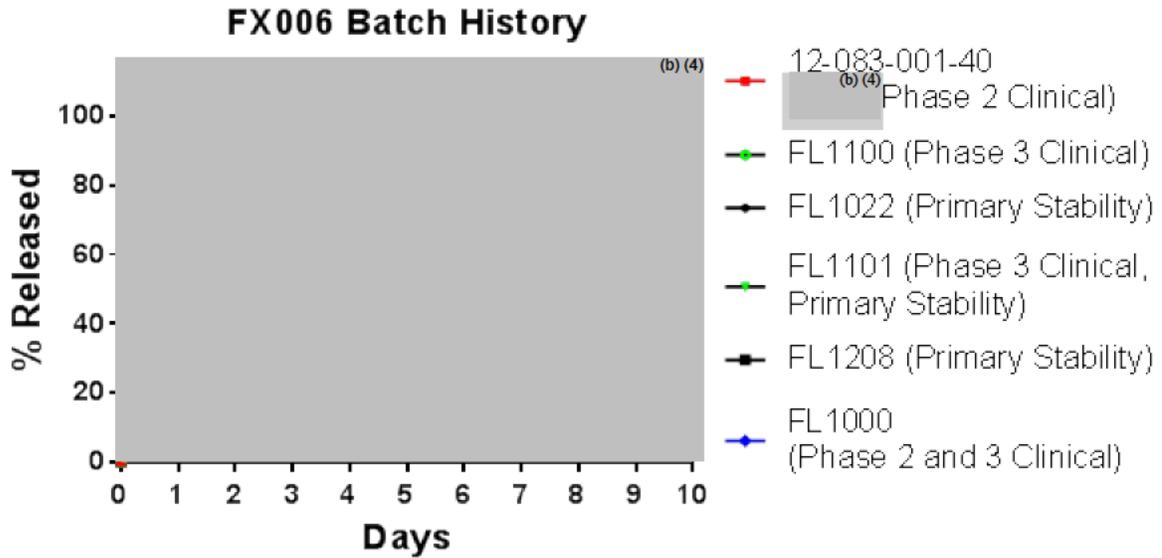
**All facilities may be approved at the time of NDA submission, pending submission of adequate supportive data (see Agency's response to Question 4a) and possible inspections of both facilities.**

*Flexion Response via e-mail October 13, 2015*

*The Agency noted, "From the Biopharmaceutics perspective, the proposed manufacturing site change could be classified as a level 3 change per the SUPAC-MR Guidance." Given that FX006 is an injectable product administered directly into the knee joint, which is the intended site of action, it is unclear how a typical bioequivalence approach as contemplated under this guidance for solid oral dosage forms could be applied. Due to the simplicity of the product, we believe that a physico-chemical comparability package, including the new In Vitro Release (IVR) method, is sufficient to demonstrate comparability. The proposed IVR method is believed to be the most sensitive means of capturing changes in product performance as discussed below.*

*As described in Question 1 in the briefing document, the IVR method has been fully validated to show robustness, precision, accuracy, and discrimination/specificity. The IVR method has demonstrated its ability to measure differences in drug release profiles of batches produced with different process parameter settings both outside of and within the process design space.*

*The IVR method has been employed to evaluate a comprehensive clinical batch history with all batches performing in a range bounded by the (b) (4) clinical batches. This batch history, as shown in the figure below reprinted from the briefing book, was used to set the IVR specifications and is the standard against which all future batches will be measured.*



*We believe our IVR method is significantly more precise and discriminating than either PK or efficacy study data. In vitro profiles in this instance provide the most accurate, sensitive, and reproducible data to determine bioequivalence.*

*Furthermore we believe the site change from (b) (4) for this product does not represent a significant change with respect to product performance. We have taken measures to ensure that there have been no significant process, equipment, material, testing, or container closure changes as demonstrated in the table below. In addition, it should be noted that we have demonstrated an effective tech transfer between (b) (4) during our clinical development which (b) (4)*

**Discussion:**

The sponsor described the basic production process. (b) (4)

(b) (4)

(b) (4)

*Question 5.*

*Does the Division agree with the proposed approach to qualify* [REDACTED] (b) (4)

**FDA Response to question 5:**

(b) (4)

*Flexion Response via e-mail October 13, 2015*

*At the time of submission, we will not have 10 batches produced at either site to include within the NDA submission. We will have at least 6 batches of bioburden data from [REDACTED] (b) (4) and at least 3 batches of bioburden data from [REDACTED] (b) (4)*

*However we will commit to continued generation of bioburden data through at least 10 batches as per guidance.*

*The NDA submission will also contain dose verification and dose mapping data [REDACTED] (b) (4) [REDACTED] Does the Agency agree that this is acceptable for NDA filing?*

**Discussion:**

The sponsor stated that they will not have 10 batches for each facility at the time of submission. The Agency responded that 6 batches from (b) (4) and 3 batches from (b) (4) would be acceptable, provided that the sponsor commit to supplying on at least 10 batches after submission of the NDA. The Agency requests that the sponsor give only one update, preferably before the 74-day letter date. The Agency asked for clarification (b) (4)

(b) (4) The Agency stressed the importance of the inspection status of these sites.

**Additional Discussion during the meeting:**

1) The Agency requests that the sponsor attempt to make a single, rather than multiple submission of CMC data after the original submission of the NDA. The Agency stated that the submission of CMC data should be prior to 74 days after the original submission. The Agency also stated that submissions of data after the 74 day date might not be considered in the review of the NDA.

**3.0 General Comments**

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

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

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

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

Corresponding names and titles of onsite contact:

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

### **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>).

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.

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

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.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion]

#### **5.0 ACTION ITEMS**

[Insert any action items that were identify during the meeting. Include who is responsible to complete the action item and the due date. Responsible party should not be an individual, but either sponsor or FDA. Consider the use of a table to present the information]

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Sponsor will submit a full IVR package to the IND.	Sponsor	Prior to submission of the original NDA.

#### **6.0 ATTACHMENTS AND HANDOUTS**

Flexion Therapeutics, Inc. prepared the following handout for the meeting.

**QUESTIONS AND RESPONSES**  
**Type C Meeting (CMC only)**  
**IND 111,325**

**Flexion Question 1**

- a) Does the Division agree that the proposed IVR method is adequate to support NDA filing and registration?
- b) Does the Division agree with the proposed provisional IVR Specification acceptance criteria for the release and stability of FX006 finished product to support NDA filing and registration?

**FDA Response to Question 1a:**

**The IVR method development appears reasonable. The agency acknowledges your submission of the dissolution method development. Submit a general correspondence to the IND for a detailed evaluation of the dissolution method by the Agency.**

**FDA Response to Question 1b:**

**We agree with the proposed approach for establishing acceptance criteria, and the final acceptability of the IVR acceptance criteria will be made during the NDA review process based on the totality of the provided data.**

**Flexion comment:**

We acknowledge your guidance to submit the general correspondence to the IND and would like to confirm that the Agency will be able to provide an expeditious and detailed review with the opportunity for further dialogue. We do not anticipate the need to discuss this topic any further at the Type C Meeting.

**Flexion Question 2**

Does the Division agree that the acceptance criteria and test methods intended for quality control, release and stability of the FX006 drug product (sterile powder) and sterile diluent are adequate to support NDA filing and registration?

**FDA Response to question 2:**

**Proposed product testing seems reasonable. Evaluation of the specifications is deferred to the NDA submission, when the data can be evaluated in its totality.**

**Further, we propose the following additional testing to be included at product release :**

- **viscosity**
- **individual impurity specifications set according to ICHQ3B**
- **The amount of free drug included as part of the release specifications**
- **Specifications for the reconstituted product, to include time for reconstitution, (b) (4) assay and impurity testing.**

**From the Biopharmaceutics perspective, refer to our response to Q1b above regarding your proposed in vitro release acceptance criteria.**

**From the Microbiology perspective, the Agency agrees that the following endotoxin and sterility test specifications for the drug product and companion diluent for release and stability, and test methods based on USP<85> and USP<71> respectively are adequate to support NDA filing and registration.**

**Flexion comment:**

Flexion is aligned with Agency feedback regarding the additional tests on the FX006 sterile powder. However, we would like to discuss the recommended new tests performed on the reconstituted product as we may not have clearly communicated the reconstitution and administration process that has been used through clinical development and is intended for the commercial setting.

FX006 is supplied as a (b) (4) dry powder vial that is reconstituted (b) (4) prior to injection. (b) (4)

**Flexion Question 3**

Does the Division agree that the proposed plan, including batch selection, for the primary stability program is adequate to support a 24-month shelf-life at the time of NDA filing and registration for the following?

**FDA Response to question 3:**

**The proposed study protocol, including sterility and endotoxin testing at the initial time point and annually up to 24 months for the drug product and the companion diluent, is acceptable. However, in order to qualify the vials, at least twelve months of stability data for two to three batches of the drug product stored in each container, should be provided, to support use of either vial. Further, provide a comparison of both vials in the NDA as well as a letter of authorization for any associated DMFs.**

**Flexion comment:**

We believe there is alignment between Flexion and FDA on this matter, but to ensure complete clarity Flexion confirms that two lots in each container closure type (stored upright due to the powder nature of FX006) under the full ICH Stability protocol will be provided. This gives a total of four distinct primary lots, each with between 12 and 24 months stability at the time of NDA filing in support of a proposed shelf-life of 24 months. A comparison of the vials and LoAs for their DMFs will be provided in the NDA.

**Flexion Question 4**

a) Does the Division agree with the proposed comparability approach for transferring the FX006 drug product manufacturing process to a second site, which includes a manufacturing facility (b) (4)

b) If the comparability plan for these new facilities is met, does the Division agree that these manufacturing facilities, in addition to (b) (4) could be approved concurrently as part of an original NDA filing and review for FX006? If not, please indicate what requirements would need to be met in order for the new facilities to be considered as part of the original NDA.

**FDA Response to question 4a:**

**The Agency agrees that a comparability protocol can be submitted for an alternate drug product manufacturing facility (b) (4) at the time of NDA submission. From the manufacturing process perspective, your proposed plan appears to be acceptable. Although the full spectrum of input variability (i.e., of critical process parameters) found in commercial production is not typically known at this stage, the Agency expects that controls include both examination of material quality and equipment monitoring. It is noted that the current approach does not discuss equipment monitoring associated with manufacturing at the current (b) (4) and proposed (b) (4) sites. All attributes and parameters should be evaluated in terms of their roles in the process and impact on**

the product or (b) (4) material. The degree of control over those attributes and parameters should be commensurate with their risk to the process and process output.

Although the proposed (b) (4) batches can help provide information that can be used to understand the commercial process, it is unclear if the proposed batch sizes are a representative comparison to the current (b) (4) manufacturing site. The proposed batch size for (b) (4) kg, whereas the batch size at (b) (4) is listed as (b) (4) kg. The batches made at both sites, (b) (4) of the commercial scale, in order to qualify the site. The Agency notes that although comparative information between the two sites may be submitted at the time of NDA submission, the feasibility of the process at all proposed manufacturing sites should be scientifically justified.

The Agency further recommends that comparative information should be provided for the manufacturing process at the alternate manufacturing site, and qualification of the (b) (4) method for the drug product's (b) (4) should be performed at the proposed (b) (4). It is also recommended that additional drug product batches (at least 10) be evaluated at (b) (4) to better assess the product bioburden levels and the suitability of the (b) (4) approach at this facility.

Comparative batch analysis and stability data for all batches from both sites should be provided as further support for the addition of the second manufacturing site. Sufficient stability data for the batches made at the second facility must be included in the NDA submission at the time of filing, in order to fully assess the adequacy of the second manufacturing facility.

From the Biopharmaceutics perspective, the proposed manufacturing site change could be classified as a level 3 change per the SUPAC-MR Guidance. For additional details, please refer to Guidance for Industry:

SUPAC-MR: Modified Release Solid Oral Dosage Forms

<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070640.pdf>

FDA Response Question 4b:

All facilities may be approved at the time of NDA submission, pending submission of adequate supportive data (see Agency's response to Question 4a) and possible inspections of both facilities.

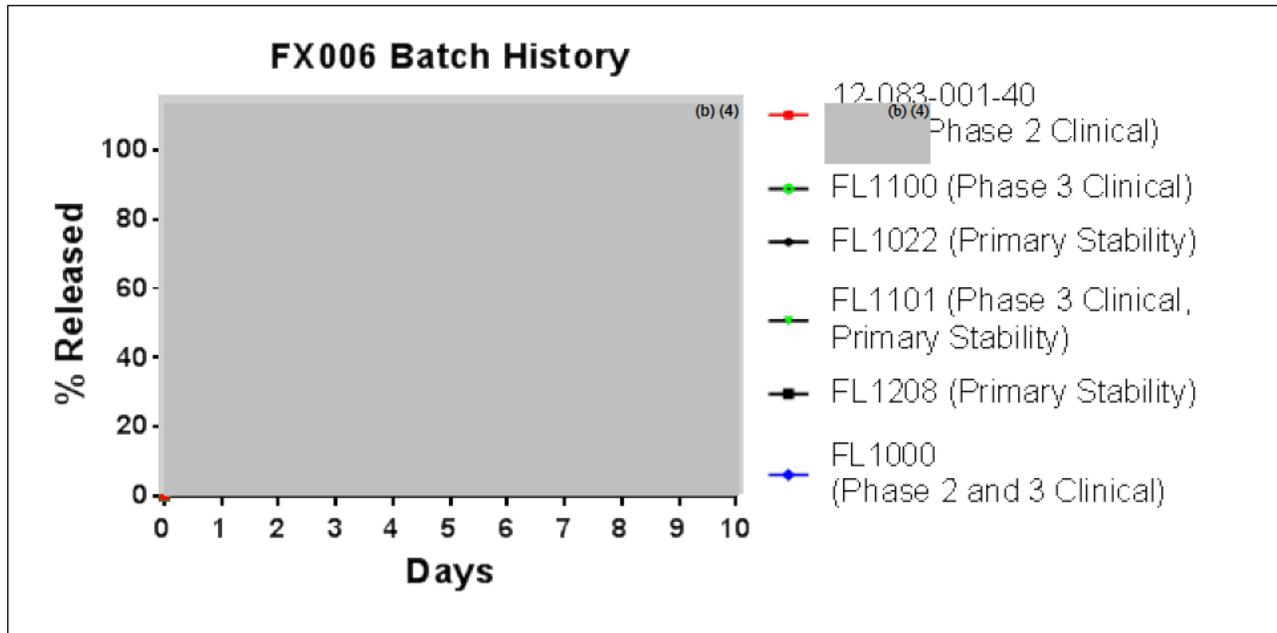
**Flexion comment:**

The Agency noted, "From the Biopharmaceutics perspective, the proposed manufacturing site change could be classified as a level 3 change per the SUPAC-MR Guidance." Given that FX006 is an injectable product administered directly into the knee joint, which is the intended site of action, it is unclear how a typical bioequivalence approach as contemplated under this guidance for solid oral dosage forms could be applied. Due to the simplicity of the product, we believe that a physico-chemical comparability package, including the new In Vitro Release (IVR) method, is sufficient to demonstrate comparability. The proposed IVR method is believed to be the most sensitive means of capturing changes in product performance as discussed below.

As described in Question 1 in the briefing document, the IVR method has been fully validated to show robustness, precision, accuracy, and discrimination/specificity.

The IVR method has demonstrated its ability to measure differences in drug release profiles of batches produced with different process parameter settings both outside of and within the process design space.

The IVR method has been employed to evaluate a comprehensive clinical batch history with all batches performing in a range bounded by the (b) (4) clinical batches. This batch history, as shown in the figure below reprinted from the briefing book, was used to set the IVR specifications and is the standard against which all future batches will be measured.



We believe our IVR method is significantly more precise and discriminating than either PK or efficacy study data. In vitro profiles in this instance provide the most accurate, sensitive, and reproducible data to determine bioequivalence.

Furthermore we believe the site change from (b)(4) for this product does not represent a significant change with respect to product performance. We have taken measures to ensure that there have been no significant process, equipment, material, testing, or container closure changes as demonstrated in the table below. In addition, it should be noted that we have demonstrated an effective tech transfer between (b)(4) during our clinical development which involved much more significant equipment and process changes.

#### Manufacturing Facility Comparison - Equipment and Processing Changes

Parameter	Site Comparison
Facility	(b)(4)
Equipment	
Operational procedures/batch control	
Analytical testing	

Scale	(b) (4)
Raw materials (vendor and grade constant)	
Container Closure (vendor and grade constant)	
“-“ indicates no change from previous site	

The physico-chemical comparability assessment as proposed includes full release testing, additional characterization, comparison of dissolution profiles, and stability. In addition the process will be well controlled through batch record and procedural controls, as well as equipment monitoring. We therefore believe that for FX006, an in vivo bioequivalence approach as outlined in SUPAC-MR is not applicable and a physico-chemical approach is the most scientifically valid. Does the Agency agree? The Agency requested that *“Sufficient stability data for the batches made at the second facility must be included in the NDA submission at the time of filing in order to fully assess the adequacy of the second manufacturing facility.”* Flexion proposes to include (b) (4). Does the Agency agree with this proposal?

**Flexion Question 5**

Does the Division agree with the proposed approach to qualify (b) (4)

**FDA Response to question 5:**

The Agency agrees with the use of (b) (4)

**Flexion comment:**

At the time of submission, we will not have 10 batches produced at either site to include within the NDA submission. We will have at least 6 batches of bioburden data from (b) (4) and at least 3 batches of bioburden data from (b) (4). However we will commit to continued generation of bioburden data through at least 10 batches as per guidance.

The NDA submission will also contain dose verification and dose mapping data (b) (4). Does the Agency agree that this is acceptable for NDA filing?

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEVEN A KINSLEY  
11/06/2015

JULIA C PINTO  
11/06/2015