

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208224Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208224

SUPPL #

HFD #

Trade Name Kyleena

Generic Name levonorgestrel-releasing intrauterine system

Applicant Name Bayer Healthcare Pharmaceuticals, Inc.

Approval Date, If Known September 16, 2016

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

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

c) Did the applicant request exclusivity?

YES  NO

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

3 years

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA# 021225 Mirena IUS

NDA# 203159 Skylar IUS

NDA# 206224 Liletta IUS

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

1) CSR PH-37274

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

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

1) CSR PH-37274

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

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

Investigation #1  
IND # 073503      YES       ! NO   
! Explain:

Investigation #2  
YES       ! NO   
! Explain:

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

Investigation #1  
YES   
Explain:      ! NO   
! Explain:

Investigation #2  
!

YES

Explain:

!

! NO

! Explain:

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

YES

NO

If yes, explain:

=====

Name of person completing form: Z. Charlene Williamson  
Title: Regulatory Project Manager  
Date: September 19, 2016

Name of Division Director signing form: Hylton V. Joffe, M.D.  
Title: Division Director



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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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ZETA-MAE C WILLIAMSON  
09/19/2016

HYLTON V JOFFE  
09/20/2016

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>   |  |  |
|--|--|--|
| NDA # 208224<br>BLA #  | NDA Supplement #<br>BLA Supplement #   | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Kyleena<br>Established/Proper Name: levonorgestrel-releasing Dosage Form: intrauterine system  |  | Applicant: Bayer Healthcare Pharmaceuticals, Inc.<br>Agent for Applicant (if applicable):                  |
| RPM: Z Charlene Williamson   |  | Division: Bone, Reproductive and Urologic Products   |
| NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)  | <p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes<br/> <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i><br/>           Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |  |
| ❖ Actions  |  |  |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>September 16, 2016</u></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?<br>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):  
 (*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:

|   |   |
|---|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )  | <input type="checkbox"/> Yes <input type="checkbox"/> No  |
| ❖ Public communications ( <i>approvals only</i> )   |   |
| • Office of Executive Programs (OEP) liaison has been notified of action  | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |
| • Indicate what types (if any) of information were issued   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> FDA Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |
| ❖ Exclusivity   |   |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type          | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes   |
| ❖ Patent Information (NDAs only)  |   |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.                                 | <input checked="" type="checkbox"/> Verified<br><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 ( <i>approvals only</i> ) | <input checked="" type="checkbox"/> Included  |
| Documentation of consent/non-consent by officers/employees  | <input checked="" type="checkbox"/> Included  |

### Action Letters

|   |  |
|---|--|
| ❖ Copies of all action letters ( <i>including approval letter with final labeling</i> ) | Action(s) and date(s) September 16, 2016 |
|---|--|

### Labeling

|  |  |
|--|--|
| ❖ 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<br><input checked="" type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><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>   | 02/20/2016<br>02/17/2016   |
| ❖ Labeling reviews ( <i>indicate dates of reviews</i> )  | RPM: <input checked="" type="checkbox"/> None 02/17/2016<br>DMEPA: <input checked="" type="checkbox"/> None 06/10/2016<br>DMPP/PLT: <input checked="" type="checkbox"/> None 08/19/2016<br>OPDP: <input checked="" type="checkbox"/> None 08/12/2016<br>SEALD: <input type="checkbox"/> None<br>CSS: <input type="checkbox"/> None<br>Product Quality <input checked="" type="checkbox"/> None See<br>CMC Review <input type="checkbox"/> None<br>08/23/2016 |

### Administrative / Regulatory Documents

|  |   |
|--|---|
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )   | 01/29/2016  |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee   | <input checked="" type="checkbox"/> Not a (b)(2)                    |
| ❖ NDAs/NDA supplements only: Exclusivity Summary ( <i>signed by Division Director</i> )  | <input checked="" type="checkbox"/> Completed                       |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><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 |

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

|   |  |
|---|--|
| <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 checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action |
| ❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>N/A</u><br/>If PeRC review not necessary, explain: <u>Application did not trigger PREA</u></li> </ul>  |  |
| ❖ Breakthrough Therapy Designation  | <input checked="" 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> ) | Yes  |
| ❖ 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)   | Yes  |
| ❖ 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 checked="" 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    04/15/2016  |
| <ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input checked="" type="checkbox"/> No mtg   |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>   | <input checked="" type="checkbox"/> N/A  |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input checked="" 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 type="checkbox"/> None    09/16/2016  |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None    09/16/2016  |
| PMR/PMC Development Templates ( <i>indicate total number</i> )  | <input checked="" type="checkbox"/> None   |
| <b>Clinical</b>   |  |

|   |  |  |
|---|--|--|
| ❖ Clinical Reviews  |  |  |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> No separate review |
| • Clinical review(s) ( <i>indicate date for each review</i> )   |  | 09/15/2016   |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> None               |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )  |  | See Clinical Review – Page 18                          |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>  |  | <input checked="" type="checkbox"/> None               |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )  |  | <input checked="" type="checkbox"/> N/A                |
| ❖ 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> |  | <input checked="" type="checkbox"/> None               |
| ❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )   |  | <input type="checkbox"/> None requested 09/15/2016     |
| <b>Clinical Microbiology</b> <input type="checkbox"/> None  |  |  |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None See CMC Review Page 151  |
| <b>Biostatistics</b> <input type="checkbox"/> None  |  |  |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review |
| Statistical Review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None 08/19/2016               |
| <b>Clinical Pharmacology</b> <input type="checkbox"/> None  |  |  |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None 08/19/2016               |
| ❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )  |  | <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 08/02/2016   |
| ❖ 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 type="checkbox"/> None<br>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 08/23/2016   |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )  | <input type="checkbox"/> None CDRH – OCE – 08/03/2016<br>CDRH – OC – 08/19/2016  |
| ❖ 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 CMC Review – 08/23/2016  |
| <input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )  | See CMC Review   |
| <input checked="" type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )  | See CMC Review   |
| ❖ Facilities Review/Inspection   |  |
| <input checked="" type="checkbox"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</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<br>Re-evaluation date:<br><input type="checkbox"/> Withhold recommendation<br><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 type="checkbox"/> No changes<br><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 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<br>( <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 type="checkbox"/> Done  |
| ❖ Send approval email within one business day to CDER-APPROVALS   | <input type="checkbox"/> Done  |



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/s/  
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ZETA-MAE C WILLIAMSON  
10/20/2016

**From:** [Williamson, Charlene](#)  
**To:** [Williamson, Charlene](#)  
**Subject:** FW: NDA 208224 - Information Request  
**Date:** Thursday, September 08, 2016 10:20:53 AM

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**From:** Williamson, Charlene  
**Sent:** Monday, June 06, 2016 4:52 PM  
**To:** Jo-Ann Ruane (jo-ann.ruane@bayer.com)  
**Cc:** Williamson, Charlene  
**Subject:** NDA 208224 - Information Request

Jo-Ann,

In the amended analytical study report A01291, you stated that “A long term stability of LNG in human serum sample stored at or below -15°C for at least 4 years is intended to be measured in a partial validation study 2011033 on November 2015.”

We are unable to locate this Study Report 2011033 in the NDA submission.

Please provide us with the location of this report in the NDA.

Thanks  
Charlene

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/s/  
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ZETA-MAE C WILLIAMSON  
09/08/2016

**From:** [Williamson, Charlene](#)  
**To:** [Williamson, Charlene](#)  
**Subject:** FW: NDA 208224 - Information Request  
**Date:** Thursday, September 08, 2016 10:20:23 AM  
**Attachments:** [NDA 208224 Kyleena USPI.docx](#)

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**From:** Williamson, Charlene  
**Sent:** Wednesday, July 27, 2016 9:44 AM  
**To:** Jo-Ann Ruane (jo-ann.ruane@bayer.com)  
**Cc:** carolyn.toves@bayer.com; Sharon Brown; Crisostomo, Nenita; Dao, Jennifer; Williamson, Charlene  
**Subject:** NDA 208224 - Information Request

Jo-Ann,

We are reviewing Section 5.11 (MRI Information) of your labeling for Kyleena IUS. ( Attached)

In order for us to complete our review of your labeling, we need a description of the implanted part of the device giving its dimensions and a list of all of the materials it contains. In addition, I need the test reports you used to generate the MRI information in section 5.11.

I am going on vacation today, I have cc'd two individuals on this email who will be covering for me during my absence.

Can you provide to me, **today**, when you can submit the requested information.

Thanks,

Z. Charlene Williamson  
*Senior Regulatory Project Manager*  
*Food and Drug Administration*  
*Division of Bone, Reproductive and Urologic Products*  
*10903 New Hampshire Avenue, Bldg. 22 Room 5332*  
*Silver Spring, MD 20903*  
*Direct: (301) 796-1025*  
Email: [Charlene.williamson@fda.hhs.gov](mailto:Charlene.williamson@fda.hhs.gov)

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ZETA-MAE C WILLIAMSON  
09/08/2016

**From:** [Williamson, Charlene](#)  
**To:** [Williamson, Charlene](#)  
**Subject:** FW: NDA 208224 - Information Request  
**Date:** Thursday, September 08, 2016 10:18:04 AM

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**From:** Williamson, Charlene  
**Sent:** Wednesday, August 17, 2016 1:17 PM  
**To:** Jo-Ann Ruane (jo-ann.ruane@bayer.com)  
**Cc:** 'Sharon Brown'; Williamson, Charlene  
**Subject:** NDA 208224 - Information Request

Jo-Ann,

We have been informed that Subjects 241140, 246201, and 246221, all receiving LCS16, reported the use of concomitant contraceptives in their diaries, potentially affecting efficacy outcome; however, corresponding source documents indicated that no concomitant contraceptives were used during the respective time periods.

Provide an explanation for these findings, assess whether this situation occurred for other subjects at this site (or other sites) and clarify how these women were handled in the efficacy dataset (i.e., were the cycles in which concomitant back-up may have been used excluded).

Please provide responses by August 24, 2016.

Please acknowledge receipt of this email.

Thanks

Z. Charlene Williamson  
*Senior Regulatory Project Manager*  
*Food and Drug Administration*  
*Division of Bone, Reproductive and Urologic Products*  
*10903 New Hampshire Avenue, Bldg. 22 Room 5332*  
*Silver Spring, MD 20903*  
*Direct: (301) 796-1025*  
Email: [Charlene.williamson@fda.hhs.gov](mailto:Charlene.williamson@fda.hhs.gov)

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ZETA-MAE C WILLIAMSON  
09/08/2016

**From:** [Williamson, Charlene](#)  
**To:** [Williamson, Charlene](#)  
**Subject:** FW: NDA 208224 - Information Request  
**Date:** Thursday, September 08, 2016 10:17:42 AM

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**From:** Williamson, Charlene  
**Sent:** Wednesday, August 24, 2016 4:10 PM  
**To:** Jo-Ann Ruane (jo-ann.ruane@bayer.com)  
**Cc:** 'Sharon Brown'; Williamson, Charlene  
**Subject:** NDA 208224 - Information Request

Jo-Ann,

Another information request:

Subject 246207, if she had a term pregnancy, it appears that she may have conceived on-treatment. Delivery of a 37-week gestation on or before June 2, 2010 would give an estimated date of conception on or before September 30, 2009. It is possible that the pregnancy test on October 12, 2009 (the date of LCS removal) could have been negative with such a date of conception.

Provide a thorough chronologically-ordered narrative of her IUS location verification, pregnancy testing, IUS removal and reporting of her pregnancy, with calendar dates provided for each interaction. Do not include extraneous background information or discuss unrelated AEs. Justify your conclusion that this should not be considered an on-treatment pregnancy under the "worst case" assumption the Division uses when precise dating information is not available.

Provide all primary calculations of unadjusted PI and KM pregnancy rates including this subject as an on-treatment pregnancy.

Provide us with an update on the status of the EMA review of this LCS, including identification of the Reference Member State, and any approvability concerns of which the Sponsor has been advised by EMA. If they can anticipate the action date/timeframe for EMA, I would like to know that also.

Provide me a response by Monday, August 29, 2016.

Please acknowledge receipt of this email.

Thanks,

Z. Charlene Williamson  
*Senior Regulatory Project Manager*  
*Food and Drug Administration*  
*Division of Bone, Reproductive and Urologic Products*  
*10903 New Hampshire Avenue, Bldg. 22 Room 5332*  
*Silver Spring, MD 20903*



*Direct:* (301) 796-1025

Email: [Charlene.williamson@fda.hhs.gov](mailto:Charlene.williamson@fda.hhs.gov)

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/s/  
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ZETA-MAE C WILLIAMSON  
09/08/2016

**From:** [Williamson, Charlene](#)  
**To:** [Williamson, Charlene](#)  
**Subject:** FW: Kyleena IR -  
**Date:** Thursday, September 08, 2016 10:17:01 AM

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**From:** Williamson, Charlene  
**Sent:** Tuesday, August 30, 2016 12:37 PM  
**To:** Jo-Ann Ruane (jo-ann.ruane@bayer.com)  
**Cc:** Williamson, Charlene  
**Subject:** Kyleena IR -

Jo-Ann,

Another information request:

According to the demographics data you provide in CSR PH-37274, a total of 1.2% of subjects were not sexually active. Clarify why this was not exclusionary, and how such women were accounted for in the evaluation of efficacy, as they clearly would not have been at risk for pregnancy.

Discuss whether or not this assessment was made at baseline, or during the course of the study ; if they were identified as not sexually active at baseline, was there any attempt to ensure that they were indeed sexually active during the study?

Please respond to this request by Friday, September 2, 2016.

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/s/  
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ZETA-MAE C WILLIAMSON  
09/08/2016



NDA 208224

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Bayer Healthcare Pharmaceuticals, Inc.  
100 Bayer Boulevard  
P.O. Box 915  
Whippany, NJ 07981-0915

ATTENTION: Jo-Ann M. Ruane  
Deputy Director, Global Regulatory Affairs

Dear Ms. Ruane:

Please refer to your New Drug Application (NDA), dated and received, November 18, 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel-releasing Intrauterine System, 19.5 mg.

We also refer to your correspondence, dated and received December 8, 2015, requesting review of your proposed proprietary name, Kyleena.

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

If any of the proposed product characteristics as stated in your December 8, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

- 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 Shawnetta Jackson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4952. For any other information regarding this application, contact Charlene Williamson, Regulatory Project Manager in the Office of New Drugs, at 301-796-1025.

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  
02/20/2016



NDA 208224

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Bayer HealthCare Pharmaceuticals Inc.  
Attention: Jo-Ann Ruane  
Deputy Director, Global Regulatory Affairs  
100 Bayer Blvd., P.O. Box 915  
Whippany, NJ 07981

Dear Ms. Ruane:

Please refer to your New Drug Application (NDA) dated and received November 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Kyleena (levonorgestrel-releasing intrauterine system).

We also refer to your amendment dated December 8, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 18, 2016.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 19, 2016.

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



### **Clinical Pharmacology Comments**

1. Effect of race on the Pharmacokinetics (PK) of LCS16:

The PK of levonorgestrel (LNG) following LCS12 insertion was compared between Asian (Study PH-37275) and Caucasian women (Study PH-37274 / Report A52238). Whether a cross-study comparison using LCS12 data will be sufficient to support the potential effect of race on LNG PK following LCS16 insertion will be a review issue.

2. Specific Populations - Pediatric:

The PK of LNG following LCS12 insertion was compared between female adolescents (Study PH-37272) and female adults (Study PH-37274 / Report A52238). Whether a cross-study comparison using LCS12 data will be sufficient to support a labeling claim that “No differences in the pharmacokinetics of adolescents and adults are expected with Kyleena” will be a review issue.

3. Metabolism of LNG:

Whether sufficient evidence is available to support the labeling claim of [REDACTED] <sup>(b) (4)</sup>  
[REDACTED] will be a review issue.

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 request that you submit the following information:

### **Statistical Comments**

1. You mentioned in the Pre-NDA Meeting Information Package page 44 that “... the post-study Pregnancy Forms from the +7-day pregnancies are not part of the study report, they would be provided in a separate subfolder under the study report folder in Module 5.3.5.2.” It appears that case report form (CRF) pages are presented in the CRF folder in Module 5.3.5.2. Clarify:
  - a. Which subjects had post-study pregnancies and the location of the post-study Pregnancy Forms in the NDA package?
  - b. The location and the names of the raw and analysis datasets for the post-study pregnancy information.
2. You mentioned in the Pre-NDA Meeting Information Package page 44 that “... there were 2 pregnancies that were reported after the subjects completed the phase 3 clinical

study in the LCS16 group...these pregnancies will not be included in the PI+7 day calculations. Available information on these pregnancies will be included in the NDA.” Identify the subject IDs for these two pregnancies. Provide the location of available information (CRF, post-study Pregnancies Forms, etc.). If these pregnancies were included in the datasets, clarify the datasets’ name and location.

3. You mentioned in the NDA 208224 Module 1.2 Reviewer’s Guide Section 3.5 that “... Bayer became aware of statistical programming finding that led to the recent amendment of all Phase 3 Clinical Study Reports with LCS16 and/or LCS12 submitted in this application (Module 5.3.5)... All data presented in this submission are current and reflect the results in the amended reports.”

Submit the SAS program BLDWHO.sas used to generate the BLDWHO dataset mentioned in the 310442\_programming\_specs\_d\_bldwho\_v10.doc for study CSR PH-37274 (protocol 91665/310442).

### **Clinical Comments**

1. For Skyla, in the situation where a month in which back-up contraception was used spanned two or more 28-day cycles, you developed an algorithm to assign back-up to a single specific 28-day cycle equivalent. Clarify the plan to address such a situation for LCS16.
2. Provide us with 12 samples of both the to-be marketed LCS16 intrauterine system (IUS) and the marketed Skyla IUS with their respective inserters.

### **PROMOTIONAL MATERIAL**

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

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 patient PI (as applicable), 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Hylton V. Joffe, M.D., M.M.Sc.  
Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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HYLTON V JOFFE  
01/29/2016



NDA 208224

**NDA ACKNOWLEDGMENT**

Bayer HealthCare Pharmaceuticals, Inc.  
Attention: Jo-Ann M. Ruane  
Deputy Director, Global Regulatory Affairs  
P.O. Box 915  
Whippany, NJ 07981

Dear Ms. Ruane:

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

Name of Drug Product: Kyleena intrauterine system

Date of Application: November 18, 2015

Date of Receipt: November 18, 2015

Our Reference Number: NDA 208224

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 January 17, 2016, in accordance with 21 CFR 314.101(a).

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

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

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Bone, Reproductive and Urologic 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) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Z. Charlene Williamson  
Regulatory Project Manager  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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ZETA-MAE C WILLIAMSON  
12/01/2015



IND 073505

**MEETING MINUTES**

Bayer HealthCare Pharmaceuticals Inc.  
Attention: Jo-Ann Ruane  
Deputy Director, Global Regulatory Affairs  
P.O. Box 915  
Whippany, NJ 07981-0915

Dear Ms. Ruane:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCS16, a levonorgestrel-releasing intrauterine contraceptive system.

We refer to the preliminary comments sent to you on March 12, 2015. We also refer to your email dated March 13, 2015, in which you responded to some of our preliminary comments. Your responses included proposals for: 1) the pregnancy case report forms and narratives (Question 10), and 2) the statistical analysis of regional subgroups (Question 12), along with a brief discussion of the proposed draft labeling with respect to the Pregnancy and Lactation Labeling Rule (Question 17). You also requested some minor corrections to the background text in our preliminary responses. We concur in these revisions, and the background section has been updated below (shown with underlining for additions and strikethrough for deletions).

We responded to your proposals on March 16, 2015, and you then requested that the planned pre-NDA meeting scheduled for March 17, 2015, be cancelled based on our feedback.

A copy of the preliminary comments, along with our additional guidance based on your proposals, is enclosed as the official minutes.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
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**

**BACKGROUND**

Bayer Healthcare Pharmaceuticals is developing LCS16, a levonorgestrel-releasing intrauterine contraceptive system for the prevention of pregnancy for up to five years. The Sponsor plans to submit an NDA in Q4/2015.

The LCS16 formulation is similar to other levonorgestrel (LNG) intrauterine systems (IUSs) manufactured by Bayer, which are approved as Mirena (NDA 021225) and Skyla (NDA 203159). Mirena contains 52 mg of LNG and is indicated for prevention of pregnancy for five years; Skyla contains 13.5 mg of LNG and is indicated for prevention of pregnancy for three years. While Mirena is recommended for use in women who have had at least one child, Skyla has smaller dimensions and was studied in both nulliparous and parous women, and is indicated for use without regard to parity. The LCS16 contains 19.5 mg of LNG, has similar dimensions to Skyla (aside from a slightly longer drug reservoir (b) (4)), and was also studied in both nulliparous and parous women. The same phase 3 study that supported approval of Skyla, with an extension phase to collect data out to five years, will be submitted in support of LCS16 marketing approval.

The to-be-marketed inserter was not used in the pivotal phase 3 study. A similar inserter was approved for use with Skyla based on data submitted from several ongoing phase 3b studies that were submitted during the review cycle for Skyla. Subsequently, a similar inserter was approved for use with Mirena product, based primarily on the clinical data submitted for the inserter under NDA 203159, and the absence of significant design differences between the two inserters. The purpose of the meeting is to discuss and reach agreement on the content and organization of Bayer's proposed New Drug Application (NDA) for LCS16.

**SPONSOR'S QUESTIONS AND THE DIVISION'S RESPONSES**

**Chemical, Pharmaceutical and Biological Development**

**Question 1 – Inserter Flange**

(b) (4)

*Does the Division concur that the chosen colorants are appropriate for use in the inserter flange, and that the submission of the proposed supportive information described in this package will be sufficient to support the use of the (b) (4) grey colored flange?*

**FDA Response to Question 1**

No. Provide the following additional supportive information:

- Identification of other US marketed medical devices (by device name, manufacturer and submission number) in which the colorant has been previously used, if known

- Toxicity risk assessment for this colorant, preferably based on the eluted amount of colorant from the flange under intended use, instead of the absolute total amount of the colorant

### **Question 2 – Removal Thread**

*To enable differentiation between LCS12 and LCS16 in situ, Bayer has modified the removal thread of LCS16 from a brown polyethylene thread to a blue polypropylene thread using FDA approved colorants for polypropylene sutures (21 CFR 74.3045 [Phthalocyaninato(2-)] copper). Does the Division concur that the chosen removal thread is appropriate for use in LCS16, and that the submission of the proposed supportive information and justification described in this package will be sufficient to support the use of blue polypropylene thread in the LCS16 product?*

### **FDA Response to Question 2**

Provide the following additional information for the colorant used in the thread:

- Material Safety Data Sheet (MSDS) for the colorant
- Toxicity risk assessment for this colorant, preferably based on the eluted amount of colorant from the thread under intended use, instead of the absolute total amount of the colorant

### **Question 3 – Inserter Design**

*As was the case for Skyla, Bayer intends to use a modified inserter for the commercial formulation compared with the inserter used for phase 3. The modified inserter is the same design and dimensions as that used for Skyla, and it is the same design that is currently used for Mirena (NDA 21-225, Supplement S-033). To support the functionality of the to-be-marketed inserter for LCS16, Bayer intends to submit data comparable to that submitted for Mirena. Specifically, Bayer intends to provide similar bench testing results and device development documentation for LCS16 to demonstrate functionality of the (b) (4) inserter as compared with the Mirena and Skyla (b) (4) inserter. Does the agency agree that this approach is sufficient to support the use of the (b) (4) inserter for LCS16?*

### **FDA Response to Question 3**

The Division agrees that the proposed submission will be sufficient to support review of the (b) (4) inserter for use with LCS16. Submit the information contained in Appendix 2 in the NDA and provide an exact description of any areas in which the to-be-marketed inserter varies from those approved for use with Skyla and with Mirena. For example, clarify whether the (b) (4) design noted in Appendix 2 are identical for the Skyla inserter and for the inserter to be used with LCS16.

## **Nonclinical Development**

### **Question 4 – Proposed Cross-Reference for Nonclinical Information**

*Except for the removal thread and the flange of the inserter, the components of LCS16 IUS and body-contact components of the inserter are the same as those approved for use with Skyla (NDA 203159), including the T-body, core elastomer, membrane elastomer, silver ring, and the insertion tube of the inserter. Does the Division concur that the Skyla NDA may be cross-referenced to incorporate the nonclinical information for these components in the LCS16 NDA?*

**FDA Response to Question 4**

Yes. Provide a tabular listing of titles of studies from NDA 203159 and/or NDA 021225 to be cross-referenced.

**Question 5 – Proposed Testing Strategy for Removal Threads and Flange**

*Does the Division concur that the biocompatibility and genetic toxicology studies to be conducted according to ISO 10993-1 for the new polypropylene removal thread and the (b) (4) inserter flange containing a new grey colorant are appropriate for submission of the LCS16 NDA?*

**FDA Response to Question 5**

Yes.

**Question 6 – Presentation of Nonclinical Data in the LCS16 NDA**

*Nonclinical information related to the components that are unique to LCS16, i.e., the blue polypropylene removal thread and the grey flange of the inserter, will be provided in the LCS16 NDA. Specifically, we plan to prepare a Nonclinical Overview (Module 2.4) summarizing the newly conducted biocompatibility and genetic toxicology studies of the LCS16 PP thread and PE flange. Modules 2.6.6 – 2.6.7 will contain the written and tabulated summaries of the biocompatibility and genotoxicity studies with those PP and PE components. The new reports will be provided in Module 4 (Module 4.2.3). Furthermore, because no new nonclinical studies of the pharmacology or pharmacokinetics of levonorgestrel or the LCS components have been conducted, no written or tabular summaries for pharmacology or pharmacokinetics (Modules 2.6.2, 2.6.3, 2.6.4, 2.6.5) will be prepared for this NDA. Does the Division concur with this submission strategy?*

**FDA Response to Question 6**

Yes.

**Clinical Pharmacology**

**Question 7 – Pharmacodynamic and Pharmacokinetic Characteristics**

*Does the Division concur that the studies/investigations described in the Pre-Meeting Information Package will provide sufficient information on the pharmacodynamic and pharmacokinetic characteristics of levonorgestrel after LCS16 insertion for the LCS16 NDA and that the clinical pharmacology reports previously reviewed for Skyla may be incorporated in the LCS16 NDA by cross-reference to the Skyla NDA?*

**FDA Response to Question 7**

The completed clinical pharmacology studies appear sufficient to support NDA submission, but fileability will be determined after receipt of the complete application. It is acceptable to cross-reference to the information submitted to the Skyla NDA.

**Question 8 – In vivo Release**

*The method for the calculation of the in vivo release from LCS16 is based on residual content measurements of LNG in IUSs obtained from women who prematurely discontinued or completed the study treatment in the pivotal LCS16 Efficacy Study (protocol 91665/310442). A population PK model was used to calculate in vivo release rates over the entire 5 years of use, with representative values provided for 24 days, 60 days, 1 year, 3 years and 5 years after IUS*

*insertion. Additionally, an average release rate over the 5 years of use will be given. This approach is consistent with that used for calculation of the in vivo release rates for approved LCS12 (Skyla). Does the Division concur that the method previously used to determine the in-vivo release for approved LCS12 is also applicable to LCS16 and that calculation of the release rates for the proposed time points is acceptable?*

**FDA Response to Question 8**

Yes.

**Clinical**

**Question 9 – Integrated Summaries of Efficacy and Safety**

*Bayer proposes to provide the narrative portions of the Integrated Summary of Efficacy and the Integrated Summary of Safety by cross-reference to the corresponding Module 2 summaries (2.7.3 and 2.7.4, respectively) and to include the tables, appendices, and datasets in Module 5.3.5.3, following Example 4 of the April 2009 Guidance for Industry entitled "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document." Does the Division concur with Bayer's proposed approach?*

**FDA Response to Question 9**

Yes.

**Question 10 – Case Report Forms and Narratives**

*The proposed NDA will be based on efficacy and safety data from two studies with LCS16: the pivotal Phase 3 LCS16 Efficacy study (protocol 91665/310442, 5-year CSR PH-37274, and 3-year CSR A52238) and the Phase 2 dose-finding study (protocol 308901, CSR A46796). In the NDA for Skyla (NDA 203159), case report forms (CRFs) and narratives were provided for serious adverse events (SAEs), discontinuations due to AEs, pregnancies (on-treatment and those with an estimate date of conception within 7 days of the removal of the IUS), and deaths reported from Reports A52238 and A46796. Does the Division concur that submission of the same categories of the case report forms (CRFs) and narratives in the LCS16 NDA is acceptable?*

**FDA Response to Question 10**

In general, yes. However, the Sponsor should provide narratives (and CRFs where available) for ALL pregnancies (including those considered to have occurred pre- and post-treatment), as the Division will make its own determination as to which are counted as on-treatment pregnancies.

**The Sponsor's Proposal after Receipt of the Preliminary Comments**

*With respect to the Division's requests for pregnancy CRFs and narratives, Bayer proposes to provide the following for LCS16 treated subjects:*

- 1. Case report forms and narratives for all on-treatment pregnancies;*
- 2. Case report forms, post-treatment pregnancy forms, and narratives for all pregnancies with conception dates within 7 days of removal and with conception dates for which neither the day nor month are known;*
- 3. Post-treatment pregnancy forms for all additional pregnancies that occurred during the 3 month follow up period (all subjects) and the one year follow up period (subjects who discontinued due to a wish for pregnancy).*

*With respect to the Division's request related to pre-treatment pregnancies, it is our understanding that the Division is referring to women who were treated and whose pregnancy was detected shortly after placement (i.e., not to screening failures, where no IUS insertion was attempted). In the LCS16 studies, the earliest conception date recorded was 165 days following LCS16 placement and, therefore, there are no pregnancies that fall into this "pre-treatment" category.*

*Question: Is Bayer's proposal acceptable?*

**FDA Response to the Sponsor's Proposal:**

If there are any post-treatment pregnancies that the Sponsor considers to have been conceived > 7 days post-removal, but for which some information suggests an earlier date of conception (i.e., within the 7-day window), the Division requests Case Report Forms, post-treatment pregnancy forms, and narratives for these pregnancies.

The Division is in agreement with the Sponsor's comments regarding pre-treatment pregnancies.

**Question 11 – Pearl Index Calculation**

*Efficacy data from the pivotal Phase 3 LCS16 Efficacy study (protocol 91665/310442, 5-year CSR PH-37274) will provide the basis for the primary efficacy analysis. As agreed with FDA for the Skyla NDA (NDA 203159), Bayer will perform this efficacy analysis and the supportive efficacy analyses including all pregnancies that have the estimated dates of conception during study treatment or within 7 days after LCS16 removal (referred to as +7-day pregnancies) in the Pearl Index calculation. As for Skyla, pregnancies occurring within 7-days of the removal of the IUS were not recorded on the case report forms for the study and are not included in the study database; therefore, Bayer plans to perform the +7-day pregnancy efficacy analyses for the integrated analysis only. Results of these analyses will be provided in the Integrated Summary of Efficacy. The post-study Pregnancy Forms for the +7-day pregnancies will be provided with the CRFs in a separate subfolder under the study report folder in Module 5. Does the Division agree with this approach?*

**FDA Response to Question 11**

This is acceptable provided that efficacy analyses are conducted for the phase 3 data separately and not solely based upon integrated phase 2 and phase 3 data. As with the Skyla NDA, the Division will rely on the phase 3 study to support the efficacy of the IUS.

**Question 12 – Statistical Analyses**

*The proposed Statistical Analysis Plan (SAP) for the Integrated Analyses of safety and efficacy across the pivotal Phase 3 LCS16 Efficacy study (protocol 91665/310442) and Phase 2 study (protocol 308901) is provided in the Pre-Meeting Information Package. This SAP has been developed based on the Skyla NDA and it incorporates the FDA requests received in conjunction with that application. Also provided in the Pre-Meeting Information Package is a separate proposed SAP for the LCS12 studies in which the (b) (4) Inserter was used. That SAP describes analyses that are planned to support the safety of the (b) (4) inserter for use with LCS16. Does the Division agree with the presented planned analyses as described in the Statistical Analysis Plans?*

### **FDA Response to Question 12**

Yes; the Division also requests the Sponsor to conduct subgroup analysis by region: US (including Canada) versus Non-US.

### **The Sponsor's Proposal after Receipt of the Preliminary Comments:**

*Bayer proposes to address the Division's request for subgroup analysis by region (North America [US and Canada] vs. Non-North America) by providing the following additional efficacy analyses (by study and pooled):*

- *PI based on 28-day cycle equivalents for the subgroup of women between 18 and 35 years by North America vs. non North America*
- *PI (+7 days) based on 28-day cycle equivalents for the subgroup of women between 18 and 35 years by North America vs. non North America*
- *Probability of getting pregnant based on 28-day cycle equivalents for the subgroup of women between 18 and 35 years by North America vs. Non-North America (Kaplan-Meier estimates)*
- *Probability of getting pregnant (+7 days) based on 28-day cycle equivalents for the subgroup of women between 18 and 35 years by North America vs. Non-North America (Kaplan-Meier estimates)*

*In addition, we propose to include the country information in the pregnancy listings.*

*Question: Is Bayer's proposal acceptable?*

### **FDA Response to the Sponsor's Proposal**

Yes.

### **Question 13 – Study Level and Integrated Analysis Datasets**

*Bayer proposes to submit SDTM and Analysis datasets for the Phase 3 LCS16 Efficacy study (protocol 91665/310442, 5-year CSR PH-37274) and Analysis datasets for the integrated analysis of the Phase 3 LCS16 Efficacy study and the 3-year Phase 2 dose-finding study (protocol 308901, CSR A46796). Legacy Analysis datasets from the 3-year analysis of study 91665/310442 (reported in CSR A52238) and from study 308901 were already submitted in NDA 203159 for Skyla and will be included in the LCS16 NDA via cross-reference to NDA 203159. Further details are described in the Pre-Meeting Information Package. Does the Division agree with the proposal regarding scope, format, and documentation of the electronic datasets to be submitted?*

### **FDA Response to Question 13**

Yes.

### **Question 14 – Scientific Literature and Post-Marketing Information**

*Because LCS16 will not be approved or marketed in any country at the time the LCS16 NDA is submitted, Bayer proposes to address the requirement to provide scientific literature and post-marketing information in the initial LCS16 NDA (as required by CFR 314.50(d)(5)(iv)) by providing the relevant information for Bayer's marketed LNG IUSs, Mirena and Skyla. Specifically, we propose to provide the Executive Summary from the most recently submitted Periodic Benefit-Risk Evaluation Report (PBRE) for Bayer's family of LNG IUSs and to incorporate the complete PBRE by cross-reference to the relevant Mirena/Skyla submissions in*

*which that PBRER can be found. We will update this information in the 4-month Safety Update Report. Does the Division concur with this approach?*

**FDA Response to Question 14**

Yes.

**Risk Management**

**Question 15 – Risk Management Plan**

*Based on the safety and efficacy data for LCS16 and Bayer's experiences with our other marketed LNG IUSs (Mirena and Skyla), Bayer anticipates conducting no risk management activities beyond that of labeling and routine pharmacovigilance. We intend to provide a focused statement of these routine measures in the Risk Management Plan section of the NDA (module 1.16). Does the Division concur that this approach will be acceptable for filing of the application?*

**FDA Response to Question 15**

Yes, the Division agrees that the proposed risk management plan is acceptable for filing, and appears appropriate, provided no unanticipated safety signals are identified during the NDA review.

**Office of Scientific Investigation Information**

**Question 16 – Office of Scientific Investigation Information**

*The pivotal phase 3 study (protocol 91665/310442) for this NDA was also the pivotal phase 3 study for Bayer's NDA 203159 for Skyla (levonorgestrel-releasing intrauterine system) 13.5 mg, which was approved on 9 Jan 2013. The Skyla NDA included 3-year study results for two doses (LCS12 [Skyla] and LCS16), whereas the NDA for LCS16 will incorporate the results of a 2-year extension phase with the LCS16 dose only and, therefore, provide LCS16 results for up to 5 years. Does OSI concur that updated versions of the BIMO information submitted in the Skyla NDA (i.e., for Categories I and III, as described in the Pre-Meeting Package) will be sufficient to address the OSI requests for LCS16 and that Category II need not be submitted?*

**FDA Response to Question 16**

The Office of Science Investigation (OSI) agrees with the Sponsor's plan to submit updated versions of BIMO Category I and III information outlined in its plan. As long as the raw data listings (i.e., those containing information outlined in Category II of the OSI document) submitted to the new application are provided in the same format as those in the previous NDA, OSI will extract necessary data for site inspections. However, OSI requests that for future applications, site-specific data listings requested in Category II of the OSI document be submitted in the outlined format (i.e., a separate pdf folder for each site participating in the study with specified data listings).

**Labeling**

**Question 17 – Pregnancy and Lactation Labeling Rule (PLLR)**

*Bayer is aware that the final Pregnancy and Lactation Labeling Rule (PLLR) will become effective for new NDAs as of June 30, 2015 and, therefore, it will be applicable for LCS16. For Bayer's other marketed levonorgestrel-releasing intrauterine systems, Mirena and Skyla, a 4-year period is permitted for complying with the PLLR requirements, i.e., the Mirena and Skyla*

labels must comply with the requirements by June 30, 2019. Because there is limited pregnancy and lactation data available for LCS16, Bayer anticipates that much of the information needed to comply with the PLLR rule for LCS16 will be based on studies/information related to Mirena and/or Skyla, for which FDA has allocated 4 years for a comprehensive assessment of the data. Therefore, Bayer proposes to submit draft labeling for LCS16 that contains pregnancy and lactation content [REDACTED] <sup>(b) (4)</sup> but in the format established by the PLLR rule. We propose to request a waiver from the remaining content requirements of the PLLR rule and will commit to submitting PLLR labeling supplements for all 3 products within 1 year of approval of LCS16, aiming at harmonized labels. Does the Division concur with this approach?

#### **FDA Response to Question 17**

No agreements on labeling can be made prior to the NDA submission. Labeling should address PLLR requirements and describe known risks if pregnancy were to occur with an IUS in place, and risks related to removing or retaining the IUS during pregnancy. FDA anticipates that the Sponsor will be able to utilize existing information in other IUS labels to discuss these risks. Similarly, existing information on lactation is likely to be useful to inform lactation labeling. Further issues can be discussed during the review cycle.

#### **The Sponsor's Proposal after Receipt of the Preliminary Comments:**

*Bayer will provide draft labeling in the LCS16 NDA in accordance with the FDA comment; we understand that further discussion related to update of the Mirena and Skyla labels can be addressed separately.*

*Question: Is Bayer's understanding as noted above consistent with that of the Division?*

#### **FDA Response to the Sponsor's Proposal:**

Yes.

### **Regulatory**

#### **Question 18 – Financial Disclosure**

*The proposed NDA for LCS16 will include the results of two clinical studies with LCS16, i.e., the pivotal phase 3 study (protocol 91665/310442, 5-year CSR PH-37274, and 3-year CSR A52238) and the 3-year, phase 2 dose-finding study (protocol 308901, CSR A46796). Both of these studies also included a lower investigational dose, LCS12, which was studied up to 3 years, and the 3-year financial disclosure information was included in the LCS12 (Skyla) NDA 203159, which was approved on 9 Jan 2013. For the LCS16 NDA, Bayer proposes to provide updated Financial Disclosure information for the phase 3 study to incorporate the 5-year results for the LCS16 arm; we further propose to incorporate the financial disclosure information for the phase 2 study by reference to the Skyla NDA. Does the Division concur with Bayer's proposed approach?*

#### **FDA Response to Question 18**

Yes.

#### **Question 19 – Waiver from the Pediatric Research Equity Act**

*Bayer plans to request a waiver from the Pediatric Research Equity Act (PREA) requirements for pre-menarcheal patients because LCS16 will not be indicated for use in those patients. We*



*plan to request that the PREA requirements for post-menarcheal pediatric patients be deemed fulfilled by extrapolation of adult data. Does the Division concur with this approach?*

**FDA Response to Question 19**

It appears that PREA may not apply to this application. If it is determined to apply, the Division agrees with the proposed approach and reminds the Sponsor to provide justification as to why adult data can be extrapolated to postmenarcheal adolescents.

**Question 20 – Content and Organization of the NDA**

*Based on the summary information provided in this Pre-Meeting Information Package, does the FDA agree that the proposed content and organization of the planned NDA are acceptable and that no barriers to fileability have been identified?*

**FDA Response to Question 20**

Yes, the Division agrees with the proposed content and organization. Fileability will be determined following submission; at this time, no apparent barriers to filing have been identified.

**ADDITIONAL COMMENTS:**

The Sponsor is requested to conduct a comprehensive use-related risk analysis of the proposed LCS16 product. The comprehensive risk analysis must include a comprehensive evaluation of all the steps involved in using the IUS (e.g., based on a task analysis for the device and known problems with similar marketed IUSs), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk mitigation strategies employed to reduce any use errors or failures, and the method of validating the risk mitigation strategies. This information is needed to ensure that all potential risks involved in using the proposed IUS have been considered and adequately mitigated and that all residual risks are acceptable (i.e., are not easily reduced further and are outweighed by the benefits of the product). Based on the comprehensive use-related risk hazard analysis, the Sponsor will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide the Sponsor in the design of a human factors validation protocol study for the IUS if it is warranted based on the risk analysis.

If a validation study is needed to ensure the approach and methodology are acceptable, submit the use-related risk analysis and validation study protocol prior to study implementation for Agency review and comment. Note that DMEPA will need 90 days to review and provide comments under the IND. If the Sponsor determines that no human factors validation study is required, ensure that the use risk analysis and justification for this determination is submitted to the Agency for review.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm>.

Note that FDA has also published three draft guidance documents that, while not yet finalized, might also be useful in understanding the Agency's current thinking and approach to human factors and product design:

- Applying Human Factors and Usability Engineering to Optimize Medical Device Design, available at

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf>

- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>
- Safety Considerations for Product Design to Minimize Medication Errors, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

### **PREA REQUIREMENTS**

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

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

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

Be advised that proposed labeling also would be required to comply with the recently finalized Pregnancy and Lactation Labeling Rule (PLLR). The Sponsor is referred to the December 2014 draft guidance Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format, available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm425398.pdf>

### **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).**

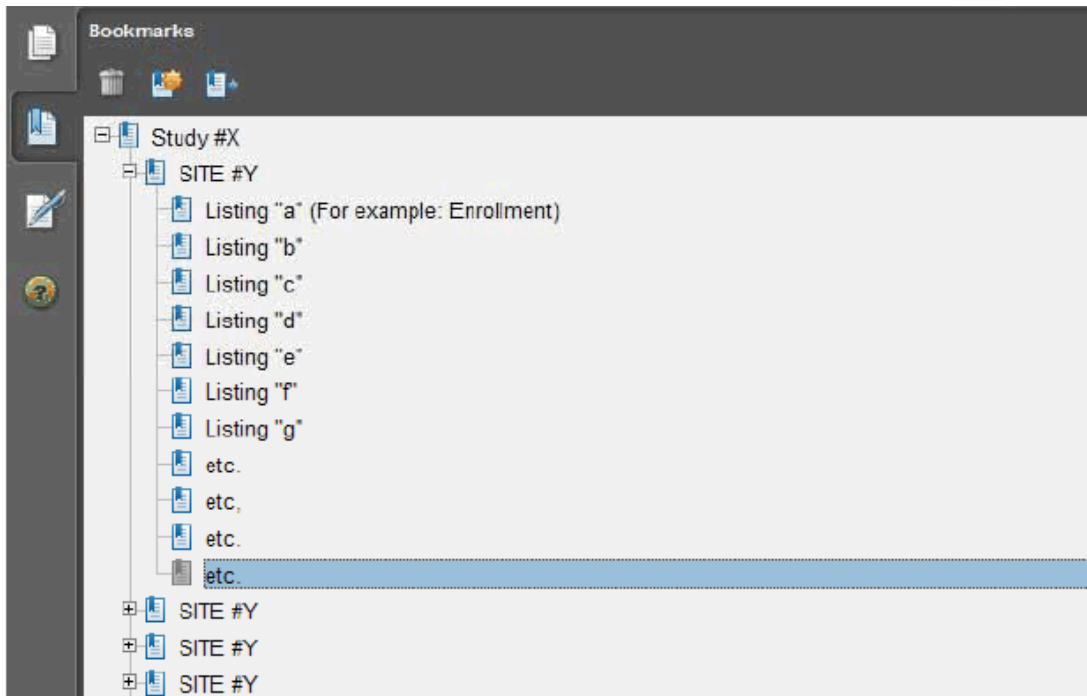
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - 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<br>(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.

<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)

**ACTION ITEMS**

| <b>Action Item/Description</b>     | <b>Owner</b> | <b>Due Date</b> |
|------------------------------------|--------------|-----------------|
| The minutes are due to the Sponsor | FDA          | April 16, 2015  |

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/s/  
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LISA M SOULE  
04/15/2015