

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208224Orig1s000**

**OTHER REVIEW(S)**

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance, Division of Manufacturing & Quality  
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

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**Date:** August 16, 2016

**To:** Mark Seggel, OMPT/CDER/OPQ/ONDP/DNDPII/NDPBV, WO22 RM1456  
[Mark.Seggel@fda.hhs.gov](mailto:Mark.Seggel@fda.hhs.gov)

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**RPM:** Thao Vu, [thao.vu@fda.hhs.gov](mailto:thao.vu@fda.hhs.gov)

**Through:** Francisco Vicenty, Combination Product Branch Lead, REGO, DMQ, OC, CDRH  
Francisco Vicenty -S  
2016.08.19 09:59:49 -04'00'

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**From:** Christopher J Brown, REGO, DMQ, OC, CDRH, , WO-66, Room 3428

**Applicant:** Bayer HealthCare Pharmaceuticals Inc.  
100 Bayer Blvd., P.O. Box 915  
Whippany, NJ 07981-0915  
FEI #: 3010700165

**Application #** NDA 208224

**Consult #** ICC1500621

**Product Name:** LCS16 (Levonorgestrel-releasing intrauterine system) 19.5 mg

**Pre-Approval Inspection:** Yes (Pre-Approval), **UPDATED 08/11/2016** Pre-Approval Inspection performed -classified VAI

**Documentation Review:** No Additional Information Required

**Final Recommendation:** **APPROVAL**

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The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208224. The consult request is for the inserter portion of the combination product, not the T-body portion of the product.

**PRODUCT DESCRIPTION**

This submission is for LCS16 (Levonorgestrel-releasing intrauterine system) 19.5 mg (Kyleena IUS). LCS16 is a low-dose Levonorgestrel (LNG) intrauterine system (IUS) that has been

developed for use as a long-acting (5-year), reversible contraceptive (LARC). The LCS16 IUS consists of a hormone-elastomer reservoir mounted on the vertical stem of a T-shaped polyethylene frame (T-body). The drug reservoir is composed of a mixture of 19.5 mg LNG (b) (4) and polydimethylsiloxane (PDMS). This reservoir is covered by a PDMS membrane (b) (4). The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica. A ring composed of 99.95% silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. In addition, the polyethylene of the T-body is compounded with barium sulfate to make it radiopaque. A monofilament blue polypropylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polypropylene of the removal thread contains <0.5% phthalocyaninato (2-) copper as a colorant.

The Kyleena IUS is packaged sterile within an inserter. The inserter is used for insertion of the Kyleena IUS into the uterine cavity and consists of a symmetric two-sided body and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. The outer diameter of the insertion tube is 3.8 mm. The vertical stem of Kyleena is loaded in the insertion tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once the Kyleena IUS has been deployed, it cannot be reloaded into the inserter.

The T-Body is considered a drug component and will not be covered by the Quality System or inspectional status review, at the sponsor. The IUD inserter will be the focus of the QS Review. The design of the inserter to be used for LCS16 is the same as the design that is approved for use with Bayer's other LNG IUSs, Skyla (LCS12) and Mirena.

The sponsor firm (referred to hereon as the firm) currently markets two LNG IUS – Mirena and Skyla. Mirena is approved for intrauterine contraception for up to 5 years and for treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception. Skyla is approved for prevention of pregnancy for up to 3 years. The firm developed the Kyleena IUS to combine the “benefits” of the smaller frame size and insertion tube diameter of Skyla with the longer duration of use of Mirena, while delivering a lower daily LNG release rate compared to Mirena.

The inserter components, as shown in Figure 1, are insertion tube, plunger, flange, handle, slider, and thread lock. Note that the inserter for the Kyleena IUS is identical to the inserter for the NDA approved Skyla LNG IUS, with the exception of a gray colorant to the slider and flange.

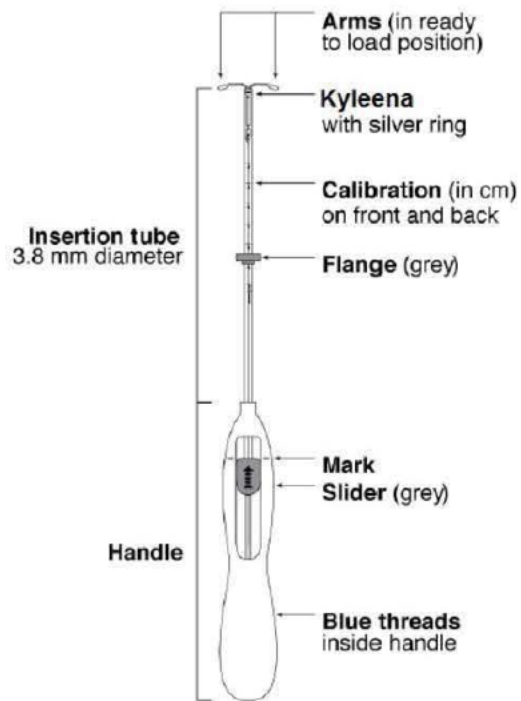
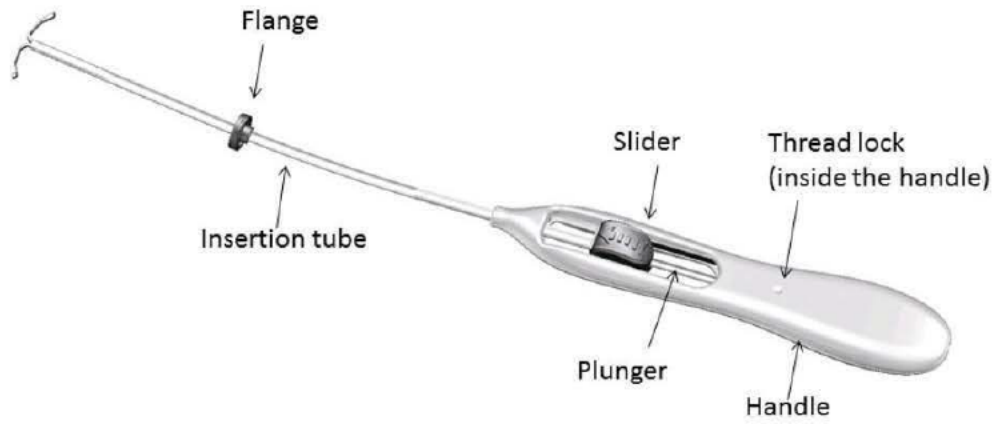


Figure 1. Kyleena IUD inserter

### **REGULATORY HISTORY**

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Bayer HealthCare Pharmaceuticals Inc.  
100 Bayer Blvd., P.O. Box 915  
Whippany, NJ 07981-0915  
FEI Number: 3010700165

Responsibility—Sponsor/applicant, US Agent. The firm appears to be responsible for overall combination product regulatory compliance.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection conducted on 02/22/2016-03/02/2016, 08/26/2015-09/18/2015, and 12/01/2014-12/03/2014. The 2016 and 2014 inspections covered drug GMP were both classified as NAI. The 2015 inspection covered medical device QS requirements and was classified VAI.

- An inspection is not required because a recent inspection of the firm was acceptable.

2. Bayer Oy, Turku  
Pansiontie 47  
20210 Turku, Finland  
FEI Number: 1000350927

Responsibility - Facility responsible for manufacturing, primary packaging, sterilization, secondary packaging, release and stability testing.

Inspectional History – An analysis of the firm’s inspection history showed that an inspection conducted on 09/24/2012-10/02/2012. The inspection covered combination human drug/medical device product (drug GMP and medical device QS requirements) and was classified VAI.

#### **Inspection Recommendation:**

(1) An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent (<2 years) inspection of the firm has not been performed.

### **REGULATORY HISTORY UPDATE AFTER PRE-APPROVAL INSPECTION**

This inspectional review was provided on 12/21/2015 to CDER, and subsequent inspection performed from 4/11/2016-4/15/2016.

Bayer Oy, Turku  
Pansiontie 47

20210 Turku, Finland  
FEI Number: 1000350927

The REGO Branch, Division of Manufacturing and Quality in the Office of Compliance has completed its good manufacturing practices review and evaluation under the Quality System regulation of the Establishment Inspection Report (EIR) and exhibits for the inspection which closed on 04/15/2016 which took place at Bayer OY, Turku Finland, facility. Coverage was given to compliance program 7356.002, Drug Manufacturing Inspections, compliance program 7356.002A, Sterile Drug Process Inspections, compliance program 7346.832, Pre-Approval Inspections, and compliance program 7382.845, Inspections of Medical Device Manufacturers. The Quality, Facilities & Equipment, Materials, Production, and Laboratory systems received coverage.

The current inspection found the firm continues to manufacture finished drug and device products for the US market. At the conclusion of the inspection a 6-item FDA 483 was issued including observations for: failure to control issuance and use of forms used to record GMP data; lack of control over electronic records and computer systems; investigations into discrepancies were not thorough; test procedures and specifications were not scientifically sound; laboratory records did not include complete data; and a second person did not verify addition of components and critical steps.

There were no observations associated with the Quality System regulations (21CFR 820). CDRH concurs with the classification recommendation of VAI, based on the information present.

#### **DOCUMENTATION REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Note the FDA correspondence from March 13-March 16, 2015, with Bayer indicates that FDA agreed that certain design information would be sufficient for the device review.

- **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.

### **Management Control, 21 CFR 820.20**

Bayer HealthCare Pharmaceuticals, Inc. is the applicant. However, they state that the manufacturer has control over the management and quality policy for the combination product. In the original application materials, the firm did not appear to provide sufficient Management Control information in the initial application. A deficiency associated with these concerns was sent to the applicant.

Initial Assessment: The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

### **Update 08/02/2016, RESPONSE REVIEW**

#### Deficiency No. 1. Sent 05/16/2016 to Firm

You did not appear to provide information on the firm's Management Responsibility as required by 21CFR 820.20. Provide a detailed summary of the firm's Quality System and management structure with executive responsibility for staff who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm's quality policies are appropriately implemented and followed and the product is appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.

Firm's Response received approximately 05/23/2016.

Updated Assessment: The firm's response has adequately addressed the requirements of 21 CFR 820.20.

Per the firm, the quality, safety and environmental management system and responsibilities are described in the Quality and Health, Safety, Environment (Q&HSE) Manual of Bayer Oy (Q&HSE.FI00179 / 12) and the Site Master File (SMF) of Bayer Oy (SMF.FI04600 / 7). The quality, safety and environmental management system established by Bayer governs a pharmaceutical product, drug/device combination product, or a medical device throughout its life cycle. The firm summarized the Management Responsibility as described below:

#### **Quality policy (Q&HSE Manual, Chapter 2)**

Per the firm, management monitors the implementation and effectiveness of the quality policy as well as the quality of the operations and products. They state that the principles of the Q&HSE system and are designed to ensure:

- adequate personnel and other resources;
- implementation and maintenance of the principles of the Q&HSE system and quality

- policy/HSE policy;
- adherence to the regulations given by authorities and legality of the operations;
- adherence to customer needs;
- continuous development of the Q&HSE system and maintenance of its performance;
- appropriate training and communications.

**Organization (SMF, Chapter 3)**

Organizational charts for Bayer Oy which show the management structure for quality management, production and quality control and are provided below.



**Figure 2. Bayer Oy Production, Quality Management and Quality Control Structure**





**Figure 3. Bayer Oy Quality Control Structure**

The firm described the responsibility for resources and execution of the Quality Policy.

**Responsibility and authority (Q&HSE Manual, Chapter 2.3)**

Per the firm, the responsibilities and authorities are defined in the organizational charts, job descriptions, and standard operating procedures.

**Resources (Q&HSE Manual, Chapter 3)**

Requirements for resources are reviewed as part of the annual planning process by the management, to ensure adequate personnel for management, performance of work, and assessment activities including internal quality audits. The competence of the personnel is maintained by providing training and an initial orientation. Due to changing requirements and to maintain the level of competence, training is continuous and commensurate with the individual's assigned role within the organization. The management responsibilities of the Quality function are described in more detail in Management Responsibilities of the BHC Quality Functions, Global Operating Instruction - GOI 297 / 3 (Local SOP ReferenceDoc.FI02915 / 3).

**Management representative**

The Executive Vice President of Bayer Oy has appointed the Director of Quality Management and HSE to have authority over and be responsible for the Quality Management System of Bayer Oy and for reporting of performance of the quality management system to the management in the form of Quality Reviews (see organizational charts above).

**Management Review (Site Quality Management Reviews Global Standard Operating Procedure - GSOP 208 / 2, Local SOP Toimintaohje.FI00171 /13, Johdon laatukselmukset)**

The Director of Quality Management and HSE is responsible for organizing the review of the Quality Systems. The Quality System reviews are held 4 times a year with attendance by the Board of Supply Center Turku and the Quality Managers of the Bayer Oy site. Meeting minutes

are written and distributed to the participants and the governance functions of Bayer. They are then responsible for communicating the outcome of the reviews to their functions and for execution of any actions from the quality system review meetings.

**Quality planning**

A Quality Plan is compiled for each combination product during the development phase and the plan is updated accordingly throughout the life cycle of the product. The Quality Plan describes the product characteristics, development strategy, distribution of responsibilities, and the quality system and purchasing controls of the combination product.

**Quality system procedures (Q&HSE Manual, Chapter 1.3.1)**

The procedures in the Q&HSE system are based on the Compliance Management System (CMS) that consists of the Q&HSE Manual, global CMS regulations, and local standard operating procedures (SOPs). Global procedures are incorporated into the local SOPs in order to consider the local requirements (e.g. GMP principles). The CMS is organized into Chapters with 5 main headings (see below).

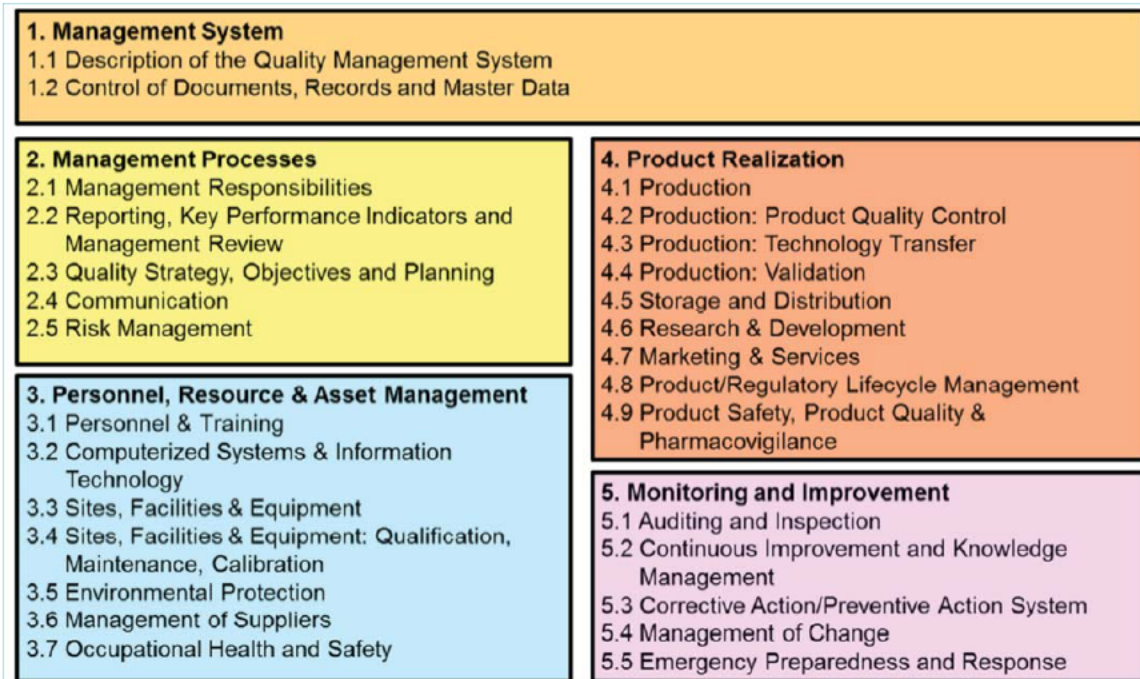


Figure 4. Compliance Management System (CMS) Main headings

**Design Control, General, 21 CFR 820.30**

The firm stated that the inserter for the Kyleena IUS 9(combination product) is identical to the inserter for the NDA approved Skyla LNG IUS (13.5 mg system), with the exception of a gray colorant to the slider and flange. As such, much of the original product design is associated with the legacy product. Per the firm, Risk Management related to device features is controlled though Risk evaluation in compliance with ISO 14971 and identification of use errors per IEC 62366.

The firm discussed the product development plan and design as follows. In phase 2 and phase 3 clinical studies, an inserter matching the design that was approved for the marketed product MIRENA at that time was used. This inserter was adapted to the dimensions of Levonorgestrel intrauterine delivery system 19.5 mg and Levonorgestrel intrauterine delivery system 13.5 mg (Skyla).

For phase 3b and the commercial product, the inserter design was modified into an (b) (4) inserter (b) (4)

Per the firm, because the actual insertion procedure remains unchanged, the modifications do not represent a safety concern. Table 1 shows the product differences for each phase.

**Table 1. Comparisons the Approved and Combination Product**

Insertion tube	Phase 3	Phase 3b and LCS12 <sup>a</sup> commercial product	LCS16 <sup>b</sup> commercial product
Scale	(b) (4)	Markings on both sides	Markings on both sides
Diameter	3.80 mm	3.80 mm	3.80 mm
Flange			
Color	(b) (4)	(b) (4)	Grey
Plunger			
Diameter	(b) (4) mm	(b) (4) mm	(b) (4) mm
Tip design	(b) (4)	(b) (4)	
Body contact	(b) (4)	No	No
Handle			
Maximum width	(b) (4) mm	(b) (4) mm	(b) (4) mm
Thread lock system	(b) (4)		
Slider			
Color	(b) (4)		Grey
Design		Ergonomic refinements have been made	Ergonomic refinements have been made <sup>c</sup>

a Levonorgestrel intrauterine delivery system 13.5 mg

b Levonorgestrel intrauterine delivery system 19.5 mg

c Same ergonomic refinements were made as for Levonorgestrel intrauterine delivery system 13.5 mg commercial product

The plunger component is the same as in Levonorgestrel intrauterine delivery system 13.5 mg. The handle of Inserter for LNG IUS 19.5 mg is the same as for Inserter for LNG IUS 13.5 mg. The slider design of Inserter for LNG IUS 19.5 mg is the same as for Inserter for LNG IUS 13.5 mg, but with a grey color rather than the pink used in Inserter for LNG IUS 13.5 mg. After the phase 3 studies, (b) (4) was introduced for the inserter. All development work for the inserter, including the design and production process, has been conducted together with the inserter supplier. Inserter for LNG IUS 19.5 mg used for the

commercial product will be manufactured by the qualified supplier in an (b) (4)

Per the firm, the following global and local SOPs define the design control system at Bayer Oy and how design changes are managed:

- Design Control for Combination Products & Medical Devices GOI 424 / 1
  - Local SOP: ReferenceDoc.FI04402 / 3
- Design Verification for Medical Devices & Combination Products GOI 751/ 1
  - Local SOP: ReferenceDoc.FI05013 / 1
- Design Validation for Combination Products & Medical Devices GOI 919 / 1
  - Local SOP: ReferenceDoc.FI05113 / 1
- Design Transfer for Medical Devices & Combination Products GOI 725 / 1
  - Local SOP: ReferenceDoc.FI05012 / 1
- Risk Management for Medical Devices and Combination products GOI 649 / 1
  - Local SOP: ReferenceDoc. FI04440 / 1
- Change Management Process GOI 503 / 3
  - Toimintaohje.FI04586 / 4 Muutoshallinta Bayer Oy:n tuotekehityksessä (Local change management in development)
  - Toimintaohje.FI00380 / 12 CMC muutosten muutoshallinta (Local change management in production)

Per the firm, the global SOPs have been incorporated into the local (Bayer Oy, Turku) SOPs without changes in the content. Parallel to the design control process, device risk management is performed and reported in the risk management report. Design validation was performed based on technical verification, clinical study data and post-market surveillance data of similar products (MIRENA and SKYLA). Design transfer from development to production at the Bayer Oy site was completed in April 2016. The Design History File (DHF), which documents all the design control activities, is maintained and located at Bayer Oy (Turku, Finland).

No design changes have been initiated to date for LCS16 (Kyleena). Per the firm, in the event a design change may be needed, the change management procedure described in the change management SOPs listed above will be applied.

The firm described the risk management strategy and the information used to support their conclusions and verification, design and validation decisions and is based on the Bayer sales data. There have been (b) (4) units of MIRENA with (b) (4) inserter sold as of July, 2015 and (b) (4) units of SKYLA with (b) (4) inserter have been sold as of July, 2015. Based on a Risk Analyses performed according to the relevant ISO standards, the firm concluded that there are adequate and verified measures in place to mitigate any potential risks and to support the introduction of the Levonorgestrel intrauterine delivery system 19.5 mg. According to the firm, bench testing results evaluating T-body deployment and removal force after IUS placement illustrate no untoward effect, and retrospective analyses of safety data from those markets where MIRENA and SKYLA with (b) (4) inserter is approved, has not shown any signals or trending related to the introduction of the (b) (4) inserter.

The firm provided results and comparisons of the validation and verification testing. The firm provided a summary of detachment force results of loading test of all products (Mirena, Skyla, and the 19.5 mg product)., The firm concluded that the testing was complete and the products fulfill the requirement. The variation in results was clearly explained by the firm and they explained how the detachment force of combination product is well below the specification set for the detachment force. Additionally, the firm provided summaries of breaking force associated with removal treads.

The firm summarized the sterilization process as follows. The ethylene oxide sterilization process includes

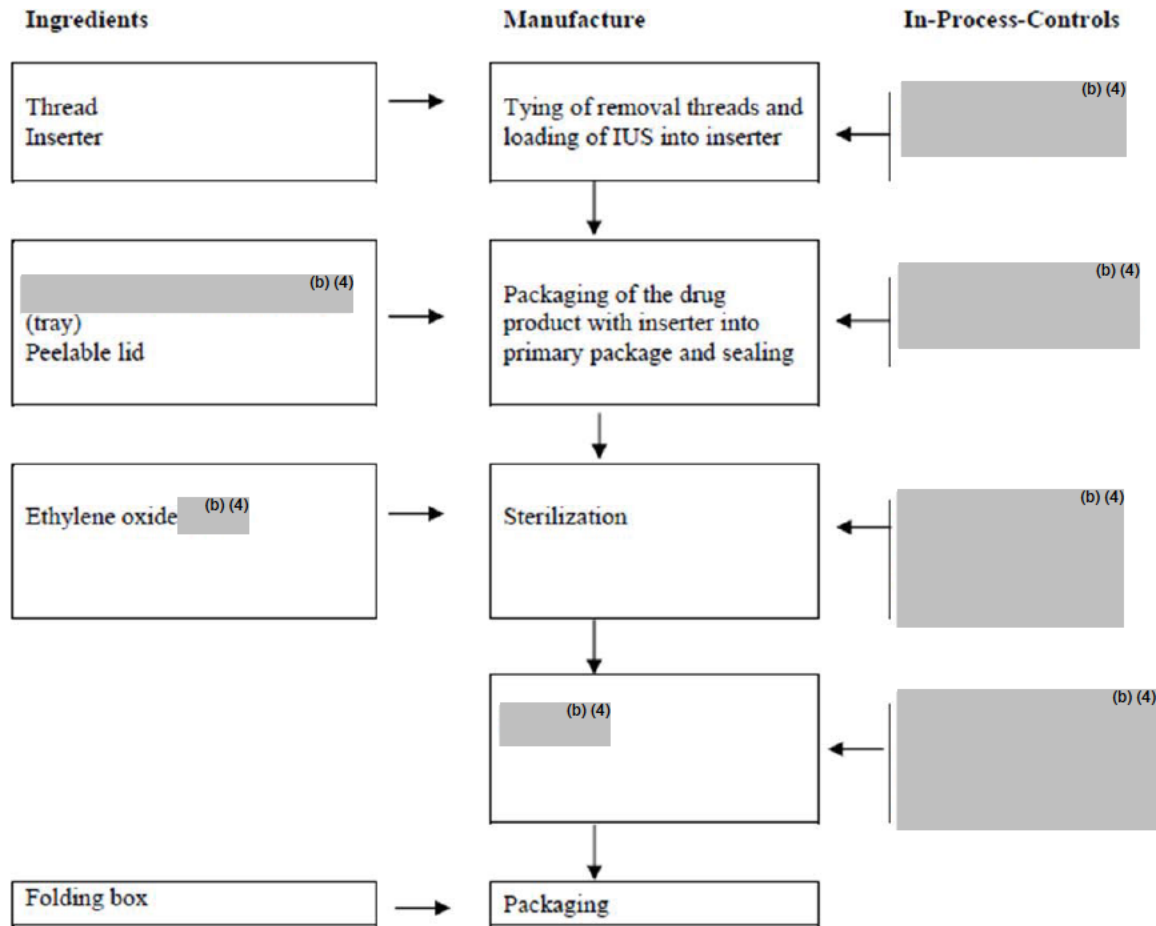
(b) (4)

[Redacted]

[Redacted]

(b) (4)

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The firm provided a summary of the process controls, tests, acceptance criterion and procedures. The summary identified the critical parameters that were monitored addressing several parameters within each of the following categories; the drug substance, T-body, the inserter, packaging sterilization and (b) (4). Additionally, the firm provided a description of the Process Control Methods employed within the procedures. The methods summary provides more details on the actual activities associated with the procedures.

#### Acceptance Activities

The firm provided a summary of the release specifications, and acceptance criteria for the drug product. The summary addressed the combination product; drug substance and mechanical devices. The firm provided the acceptance criteria of packaging and other materials. Additionally, the firm provided detailed information on the excipients (i.e. T-body and the inserter). The excipient reports included justifications of specifications, supplier identification, standards for compliance with compendia information and summary release results for batches. Additionally evaluation of for acceptance of excipients included visual inspection, cleanliness review, weighing and spectral analysis.

### **Documentation Review Recommendation**

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

### **RECOMMENDATION**

The application LCS16 (Levonorgestrel-releasing intrauterine system) 19.5 mg – NDA 208224 is approvable from the perspective of the applicable Quality System Requirements.

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
  
- (2) The recommended inspection(s) were conducted and deemed acceptable.

Christopher  
J. Brown -S

Digitally signed by Christopher J. Brown -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=2000986478,  
cn=Christopher J. Brown -S  
Date: 2016.08.19 10:34:06 -04'00'

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Christopher J Brown, P.E.

Prepared: CJBrown: 08/16/2016  
Reviewed: FMLast name: Month/Day/Year

CTS No.: ICC150621  
NDA 208224

Review Cycle Meeting Attendance:  
Various others  
8/15/2016

### **REGULATORY STRATEGY**

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

#### **Primary Contact**

##### **Primary Contact**

Christopher J Brown  
Mechanical Engineer,  
REGO  
DMQ  
Office of Compliance, WO66 RM 3428  
Phone: 301-796-0380

#### **Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Francisco Vicente,  
Branch Chief,  
REGO  
DMQ  
Office of Compliance, WO66 RM 3430  
Phone: 301-796- 5777

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION**



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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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THAO M VU  
08/19/2016  
upload on behalf of CDRH Office of Compliance

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: August 19, 2016

To: Hylton V. Joffe, MD, M.M.Sc.  
Director  
**Division of Bone, Reproductive and Urologic Products (DBRUP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Twanda Scales, MSN/Ed., BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Lynn Panholzer, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): KYLEENA (levonorgestrel-releasing intrauterine system)

Dosage Form and Route: Intrauterine

Application Type/Number: NDA 208224

Applicant: Bayer HealthCare Pharmaceuticals (Bayer)

## 1 INTRODUCTION

On November 18, 2015, Bayer HealthCare Pharmaceuticals, Inc. (BHP) submitted for the Agency's review a New Drug Application for KYLEENA, a levonorgestrel (LNG)-releasing intrauterine system containing 19.5 mg LNG. The proposed indication for KYLEENA (levonorgestrel-releasing intrauterine system) is prevention of pregnancy for up to 5 years.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on February 17, 2016, and February 17, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KYLEENA (levonorgestrel-releasing intrauterine system).

## 2 MATERIAL REVIEWED

- Draft KYLEENA (levonorgestrel-releasing intrauterine system) PPI received on November 18, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on August 10, 2016.
- Draft KYLEENA (levonorgestrel-releasing intrauterine system) PPI received on November 18, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on August 16, 2016.
- Draft KYLEENA (levonorgestrel-releasing intrauterine system) Prescribing Information (PI) received on November 18, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on August 10, 2016.
- Draft KYLEENA (levonorgestrel-releasing intrauterine system) Prescribing Information (PI) received on November 18, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on August 10, 2016.
- Approved MIRENA (levonorgestrel-releasing intrauterine system) comparator labeling dated October 22, 2015.
- Approved SKYLA (levonorgestrel-releasing intrauterine system) comparator labeling dated April 8, 2016.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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TWANDA D SCALES  
08/19/2016

LYNN M PANHOLZER  
08/19/2016

LASHAWN M GRIFFITHS  
08/19/2016

## Clinical Inspection Summary

<b>Date</b>	August 15, 2016
<b>From</b>	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Susan D. Thompson, M.D., Acting Team Leader for Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
<b>To</b>	DBRUP\Project Manager\Charlene Williamson DBRUP\Medical Officer\Ron Orleans DBRUP\Team Leader\Lisa Soule Division of Bone, Reproductive, and Urologic Products
<b>NDA/BLA #</b>	NDA 208224
<b>Applicant</b>	Bayer HealthCare Pharmaceuticals Inc.
<b>Drug</b>	Kyleena (levonorgestrel-releasing intrauterine system)
<b>NME (Yes/No)</b>	No
<b>Therapeutic Classification</b>	Standard Review
<b>Proposed Indication(s)</b>	Prevention of pregnancy for up to 5 years
<b>Consultation Request Date</b>	February 5, 2016
<b>Summary Goal Date</b>	August 17, 2016
<b>Action Goal Date</b>	September 16, 2016
<b>PDUFA Date</b>	September 18, 2016

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Baker, Miranda, and Nyirady were inspected in support of this NDA and the final classification of these inspections was Voluntary Action Indicated (VAI) for the inspection of Dr. Baker and No Action Indicated (NAI) for the inspections of Drs. Miranda and Nyirady.

Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

### 2. BACKGROUND

The Applicant submitted this NDA to support the use of Kyleena (levonorgestrel-releasing intrauterine system) for the prevention of pregnancy for up to five years. Protocol 310442 (also referred to as 91655), entitled “Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years” was inspected in support of this application.

### Protocol 310442

The primary objective of this study was to assess the safety, efficacy and pharmacokinetics of 2 doses of LNG, delivered locally by a new intrauterine contraceptive system for use by women 18-35 years of age.

The study design was a multi-center, open-label, randomized, 2-arm, parallel-group study up to three years, and a single arm, open-label study from 3 years up to 5 years for the LCS16 treatment arm. Subjects were randomized to one of the two treatment arms in a 1:1 ratio. A total of 2820 subjects across 138 centers and 11 countries were planned for recruitment into the study along with as many subjects as were willing to continue after three years of treatment for up to five years of treatment. The primary efficacy variable was the pregnancy rate.

According to the sponsor, the results of this study confirm the contraceptive efficacy of LCS16 and affirm the positive safety profile of LNG-releasing intrauterine systems, with no new or unexpected findings.

Dr. Baker's site was selected for inspection because of its high enrollment.

Dr. Miranda's site was selected because of its relatively high enrollment and the highest overseas discontinuation rate for sites with enrollment over 20 subjects.

Dr. Nyirady's site was selected because it had the highest overseas enrollment and a relatively high discontinuation rate.

### 3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
2411/ Baker, Jeffrey 2327 Coronado St. Idaho Falls, ID 83404	310442/ 97	4-13 Apr 2016	Pending. (Preliminary Classification VAI)
1501/ Miranda, Maria Jose José Victorino Lastarria #29 Santiago Centro, Santiago Chile	310442/ 56	13-17 Jun 2016	Pending. (Preliminary Classification NAI)
1806/ Nyirady, Tamas Frater Gy. u. 4 Kecskemet, 6000 Hungary	310442/ 82	13-17 Jun 2016	Pending. (Preliminary Classification NAI)

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Jeffrey Baker, M.D.**

At this site for Protocol 310442, 120 subjects were screened, 97 subjects were enrolled, 62 subjects terminated early, and 35 subjects completed the study.

Review of the records of 23 enrolled subjects included, but was not limited to, informed consent, training records, Institutional Review Board (IRB) approvals and correspondence, monitoring records, drug accountability, sponsor and Contract Research Organization (CRO) correspondence, financial disclosures, and FDA Form 1572s, and test article accountability.

Source documents were compared with Case Report Forms (CRFs) and line listings, and several discrepancies were noted.

A Form FDA 483 was issued at the conclusion of the inspection. Observations on the FDA Form 483 included but were not limited to the following:

Numerous documentation discrepancies were noted in the subject records.

For example, for Subjects 241101, 241111, and 241173, source records noted that there were changes to concomitant medications or adverse events; however, review of the records did not indicate the nature of these changes. For Subject 241197, source records indicated regular menstrual cycles while the corresponding CRF indicated irregular menstrual cycles. Follow up communications regarding out-of-window visits and continued study participation for at least two subjects were not documented. Subjects 241140, 246201, and 246221, all receiving LCS16 (16 µg/24 hrs), 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. The review division may wish to consider the significance, if any, of these findings on the evaluation of efficacy. Subjects 241140, 241197, and 246201 were administered Laminaria at Visit 14 for cervical dilation; however, this concomitant medication was not reported.



With respect to inclusion/exclusion criteria:

Subject 241136 (16 µg/24 hrs) presented with chlamydia and gonorrhea at screening, and Subject 246207(16 µg/24 hrs) had a history of herpes simplex and chlamydia and tested positive for chlamydia at screening. There was no documentation to explain why these subjects should not have been considered at high risk for sexually transmitted disease (STDs) and thus have met the relevant exclusion criterion. Neither observation was reported as a protocol deviation.

Subject 241101 (16 µg/24 hrs) was not six weeks post-partum at the time of placement of the IUD, thus meeting an exclusion criterion. There was no documentation to indicate why the subject was enrolled despite meeting an exclusion criterion. This incident was reported as a protocol deviation.

One subject failed to have a Pap smear performed at Visit 6. Subject 241103 had a cyst >3 cm at Visit 2, an exclusion criterion, which was confirmed by a follow up visit; however, the subject was randomized to the study and received the test article.

With respect to adverse event reporting:

Subject 241109 (16 µg/24 hrs) reported lower left pelvic pain at Visit 3 which was not reported as an adverse event. Subject 241111 (16 µg/24 hrs) reported left breast tenderness at Visit 10 which was not reported as an adverse event.

With respect to informed consent, two subjects did not sign the most current consent form in a timely manner. Another subject signed the informed consent document on a specific date; however, there was no documentation that the subject actually visited the site on that date.

With respect to protocol adherence (Out-Of-Window visits):

Additionally, there were 31 subjects whose IUDs were placed out-of-window, specifically beyond the seven day window from start of menses. According to line listings, 25 of these incidents were reported; however, documentation was lacking to explain the large number of out-of-window IUD placements. The review division may wish to consider the potential impact on the evaluation of efficacy given the extent of these findings.

Dr. Baker replied to the inspection findings in a written response dated May 3, 2016. In this response he accepted responsibility for the observations made during the inspection. He alluded to the poor performance of a research coordinator since terminated as being responsible to some degree for those observations. Dr. Baker engaged an outside research consultant and in terms of corrective actions implemented updated SOPs, source document templates, training logs, random chart reviews by research team members, and standardization of tracking logs for informed consent forms.

The inspection revealed numerous examples of inadequate study documentation. Discrepancies between subject diaries and other source documentation were not readily explained. Of potential safety concern was the enrollment of subjects meeting exclusion criteria and the placement of IUDs in subjects outside the protocol-specified time window although no adverse outcomes appear to have resulted from the protocol deviation. Because the number and scope of deficiencies noted are of potential concern, the review division may wish to assess their impact on the evaluation of safety and efficacy. Otherwise, this study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## **2. Jose Maria Miranda, M.D.**

At this site for Protocol 310442, 72 subjects were screened, 56 subjects were enrolled, and 34 subjects completed the three-year study. Of these 34 subjects, 17 entered the extension phase of the study with 10 subjects completing the five-year study. Seven subjects did not complete the extension phase with two subjects reporting adverse events (acne and pelvic pain) four subjects desiring pregnancy and one subject fearing pregnancy.

Review of the records of 18 subjects included, but was not limited to, source documents, case report forms, training documents, financial disclosure, medical histories, inclusion/exclusion criteria, enrollment logs, randomization, concomitant medications, progress notes, the primary efficacy endpoint, adverse events, sponsor, monitor, and IRB correspondence, and test article accountability and storage.

Review of the records of the enrolled subjects for Protocol 310442 indicated that informed consent forms were completed prior to any study-related testing.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

## **3. Tamas Nyirady, M.D.**

At this site for Protocol 310442, 88 subjects were screened, 82 subjects were enrolled, and 50 subjects completed the three-year study. Of these 50 subjects, 23 entered the extension phase of the study with 18 subjects completing the five-year study. Five subjects did not complete the extension phase with one subject desiring pregnancy, one subject becoming pregnant, and three other subjects reporting adverse events (acne, a bleeding disorder, and PID).

The records of 27 subjects in Study 310442 were reviewed. Review of these records included, but was not limited to, informed consent, medical histories, physical examinations, laboratory assessments, endoscopy results, mammography and pap smear results, adverse events, protocol deviations, IRB and monitoring communications, randomization and blinding, and test article storage, administration and disposition.

The review of the informed consent documents indicated that consent forms were completed prior to any study-related testing.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D., for  
Janice Pohlman, M.D., M.P.H.,  
Team Leader,  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CC:

Central Doc. Rm.\NDA 208224  
DBRUP\Division Director\Hylton Joffe  
DBRUP\Team Leader\Lisa Soule  
DBRUP\Medical Officer\Ron Orleans  
DBRUP\Project Manager\Charlene Williamson  
OSI\DCCE\Division Director\Ni Khin  
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew  
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman  
OSI\DCCE\GCPAB\Reviewer\Roy Blay  
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague  
OSI\Database Project Manager\Dana Walters

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ROY A BLAY  
08/15/2016

SUSAN D THOMPSON  
08/15/2016

KASSA AYALEW  
08/15/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** August 12, 2016

**To:** Charlene Williamson  
Regulatory Project Manager  
Division of Bone, Reproductive, and Urologic Products (DBRUP)

**From:** Carrie Newcomer, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA: 208224**  
**KYLEENA (levonorgestrel-releasing intrauterine system)**

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On February 17, 2016, DBRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for KYLEENA (levonorgestrel-releasing intrauterine system).

OPDP has reviewed the proposed PI and carton/container labeling. Our comments are based on the substantially complete version of the draft label dated October 22, 2015, and retrieved from Sharepoint on August 10, 2016.

OPDP's comments on the draft PI are provided directly in the attached copy of the labeling.

OPDP does not have any comments on the carton/container labels, also attached.

The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the PPI in a joint review under separate cover.

Thank you for your consult. If you have any questions on the PI or carton/container labeling, please contact Carrie Newcomer at 6-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov).

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CARRIE A NEWCOMER  
08/12/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Date:** August 3, 2016

**From:** Sharon M. Andrews  
Biomedical Engineer/Branch Chief, CDRH/ODE/DRGUD/OGDB

**Subject:** NDA 208244 – Kyleena LCS16 (Levonorgestrel-releasing intrauterine system, 19.5 mg)  
Bayer Healthcare  
CDRH Engineering Review

**To:** Thao Vu  
Pharmacist, CDER/OPQ/OPRO/DRBPMI/RBPMBI

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**I. Background & Scope of Review**

Bayer Healthcare (hereafter referred to as “the sponsor”) submitted an NDA for LCS16 Levonorgestrel (LNG)-releasing intrauterine system (IUS), 19.5 mg (hereafter referred to by its trade name “Kyleena IUS”).

The sponsor currently markets two LNG IUS – Mirena and Skyla. Mirena is approved for intrauterine contraception for up to 5 years and for treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception. Skyla is approved for prevention of pregnancy for up to 3 years. The sponsor developed the Kyleena IUS to combine the benefits of the smaller frame size and insertion tube diameter of Skyla with the longer duration of use of Mirena, while delivering a lower daily LNG release rate compared to Mirena.

The scope of this CDRH engineering review is limited to a review of the IUS inserter.

**II. Product Description**

The Kyleena IUS consists of a T-shaped polyethylene frame (T-body) with a reservoir (hormone elastomer core) around the vertical stem. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir is made of a mixture of LNG and silicone (polydimethylsiloxane), containing a total of 19.5 mg LNG. The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica. A ring composed of 99.95% silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. In addition, the polyethylene of the T-body is compounded with barium sulfate to make it radiopaque. A monofilament blue polypropylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polypropylene of the removal thread contains <0.5% phthalocyaninato(2-) copper as a colorant.

The Kyleena IUS is packaged sterile within an inserter. The inserter is used for insertion of the Kyleena IUS into the uterine cavity and consists of a symmetric two-sided body and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. The outer diameter of the insertion tube is 3.8 mm. The vertical stem of Kyleena is loaded in the insertion tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once the Kyleena IUS has been deployed, it cannot be reloaded into the inserter.



Figure 1 is an image of the Kyleena IUS in the inserter.

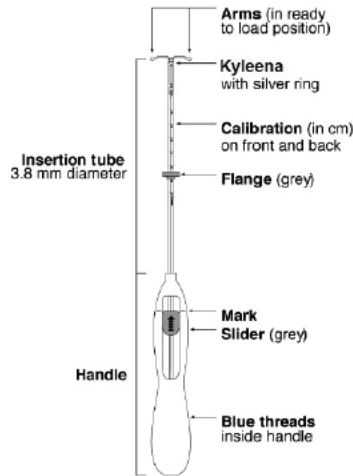


Figure 1 Kyleena IUS in the inserter

LNG is released from the Kyleena IUS in vivo at a rate of approximately 17.5 mcg/day after 24 days. This rate decreases progressively to 9.8 mcg/day after 1 year and to 7.4 mcg/day after 5 years. The average in vivo release rate of LNG is approximately 9 mcg/day over a period of 5 years.

Please note that the inserter for the Kyleena IUS is identical to the inserter for the NDA approved Skyla LNG IUS, with the exception of a gray colorant to the slider and flange.

### III. Intended Use

The Kyleena IUS is indicated for prevention of pregnancy for up to five years.

### IV. Biocompatibility

Table 1 summarizes the material composition of the inserter.

(b) (4)

The table content is redacted with a large grey box.

Table 1 Kyleena IUS inserter material composition

As noted previously, the inserter for the Kyleena IUS is identical to the inserter for the NDA approved Skyla LNG IUS, with the exception of a gray colorant to the slider and flange. The slider is not patient contacting. The flange is patient contacting; however, I do not believe that the addition of gray colorant affects the biocompatibility profile of the flange, due its short duration of patient contact.

**V. Sterilization and Shelf Life**

The Kyleena IUS is provided sterile (EtO sterilization) and is packaged in a (b) (4). I defer to CDER on the acceptability of the sterilization validation for the Kyleena IUS, as the IUS and the inserter are packaged (b) (4) together.

The sponsor proposes a shelf life of (b) (4) months based on the results of an accelerated aging study at 40 °C/75 % RH for 6 months and real time aging at 25 °C/60 % RH and 30 °C/75 % RH on three pilot scale batches. The Kyleena IUS was evaluated for the following at baseline, 3, 6, 9, and 12 months: appearance, formulation, surface property, color of drug reservoir, levonorgestrel related substances, assay of system, release rate, breaking force minimum, recovery of horizontal arms, sealed joint strength, package seal integrity, strength of seal and sterility. The functionality of the inserter was specifically evaluated through loading of IUS and detachment force. (The mechanical performance tests are described in greater detail in Section VI of this review memo.)

The results of the accelerated and real time aging studies demonstrate that the Kyleena IUS maintains its mechanical properties (breaking force minimum, recovery of horizontal arms, and inserter functionality) over the duration of the proposed shelf life.

**VI. Mechanical Testing**

(b) (4)

**VII. Clinical Performance Testing**

I conducted a high level review of the results of the Phase 3 clinical study, and I have no comments specific to the scope of my review.

**VIII. Labeling**

I reviewed the physician labeling for the Kyleena IUS and I have no comments specific to the scope of my review.

**IX. Recommendation**

I have no deficiencies for the sponsor.

Sharon M. Andrews -S  
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THAO M VU  
08/05/2016  
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**USE RISK ANALYSIS, LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** June 10, 2016

**Requesting Office or Division:** Division of Bone, Reproductive, and Urologic Products (DBRUP)

**Application Type and Number:** NDA 208224

**Product Name and Strength:** Kyleena (levonorgestrel-releasing intrauterine system) 19.5 mg

**Product Type:** Combination Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Bayer

**Submission Date:** November 18, 2015

**OSE RCM #:** 2016-383

**DMEPA Primary Reviewer:** Walter Fava, RPh., MEd., Safety Evaluator

**DMEPA Team Leader:** Danielle Harris, PharmD., BCPS

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## 1 REASON FOR REVIEW

This review is in response to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to evaluate the labels and labeling for NDA 208224. This review also includes an evaluation of the use-related risk analysis submitted by Bayer Healthcare Inc. in response to human factors comments previously communicated in a meeting response on March 12, 2015, to assess the need for a human factors validation study.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Risk Hazard Analysis	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the use-related risk analysis and concur with the potential hazards identified as infection, pain or injury to patient, unplanned pregnancy, environmental risks, and usability risks including handling steps by healthcare professionals that could affect the outcome of the insertion. We also concur with the mitigation measures employed to mitigate the potential risks which include material testing, packaging validation, in-process controls, user training, design, and insertion instructions. The external operating principles for Kyleena are identical to those of the currently marketed levonorgestrel-releasing intrauterine system, Skyla (NDA 203159) and no unique risks have been identified for Kyleena. We note the proposed Kyleena, insertion instructions are nearly identical to the approved insertion instructions for Skyla, however a statement instructing the provider to check the product expiration date prior to insertion is not present. The statement "Check expiration date of Skyla prior to initiating insertion" was included in the most recent approved labeling of Skyla NDA 203159/S-005 to mitigate the risk of insertion of expired product. This labeling change to Skyla was made in response to our recommendation in OSE Review RCM #: 2015-150 dated March 30, 2016<sup>1</sup>. We

provide recommendations in section 4.1 for the insertion instructions to mitigate the risk for insertion of expired product.

Our review of the proposed carton labeling and container labels did not identify any vulnerabilities that would cause confusion which could contribute to potential medication errors.

#### 4 CONCLUSION & RECOMMENDATIONS

Based upon our assessment of the risk hazard analysis submitted, we agree with Applicant that a Human Factors validation study is not required. We also find the carton labeling and container label acceptable. We identified one area within the insertion instructions that may be improved upon to promote the safe use of Kyleena.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

We recommend the following be implemented prior to approval of NDA 208224:

- A. To minimize the risk of insertion of expired Kyleena, consider adding the statement “Check expiration date of Kyleena prior to initiating insertion” as the third bullet in the subsection “preparation for insertion” within Section 2.1 *Insertion Instructions* of the prescribing information. This statement was included in the most recent approved labeling of Skyla NDA 203159/S-005 to mitigate the risk of insertion of expired product.

#### APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

##### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kyleena that Bayer Healthcare Inc. submitted on November 18, 2015.

<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	levonorgestrel
<b>Indication</b>	Prevention of pregnancy
<b>Route of Administration</b>	Intrauterine
<b>Dosage Form</b>	Intrauterine system
<b>Strength</b>	19.5 mg
<b>Dose and Frequency</b>	Insert one system into uterus every 5 years as needed.

<sup>1</sup> Baugh, D. Postmarketing Review for Skyla (NDA 203159). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 March 30. RCM No.: 2015-150.

	19.5 mg released in vivo at a rate of approximately 17.5 mcg/day after 24 days. This rate decreases progressively to 9.8 mcg/day after 1 year and to 7.4 mcg/day after 5 years.
<b>How Supplied/Container Closure</b>	Available in a carton of one sterile unit
<b>Storage</b>	25°C (77°F); with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On May 12, 2016, we searched the L:drive and AIMS using the terms, Kyleena to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified one previous proprietary name review<sup>2</sup>.

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<sup>2</sup> Fava, W. Proprietary Name Review for Kyleena NDA 208224. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Feb 16. RCM No.: 2015-2206092.



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/s/  
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WALTER L FAVA  
06/10/2016

DANIELLE M HARRIS  
06/10/2016

**REGULATORY PROJECT MANAGER  
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208224

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** Kyleena (levonorgestrel-releasing intrauterine system) 19.5 mg

**Applicant:** Bayer healthcare Pharmaceuticals, Inc.

**Receipt Date:** November 18, 2015

**Goal Date:** September 18, 2016

### **1. Regulatory History and Applicant's Main Proposals**

### **2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

### **3. Conclusions/Recommendations**

No SRPI format deficiencies were identified in the review of this PI.

## Selected Requirements of Prescribing Information

### 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

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

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- (b) (4)** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

## Selected Requirements of Prescribing Information

• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- (b) (4) 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

**Comment:**

#### Highlights Limitation Statement

- (b) (4) 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- (b) (4) 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- (b) (4) 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- NO** 12. All text in the BW must be **bolded**.

**Comment:**

- NO** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

## Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- NO** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

- NO** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

### Recent Major Changes (RMC) in Highlights

- NO** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:**

- NO** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:**

- NO** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

### Dosage Forms and Strengths in Highlights

- (b) (4)** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:**

### Contraindications in Highlights

- (b) (4)** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

**Comment:**

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- (b) (4) 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

*Comment:*

### Patient Counseling Information Statement in Highlights

- (b) (4) 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

*Comment:*

### Revision Date in Highlights

- (b) (4) 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

(b) (4)

24. The TOC should be in a two-column format.

**Comment:**

(b) (4)

25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.

**Comment:**

**NO**

26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

**Comment:**

(b) (4)

27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

**Comment:**

(b) (4)

28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

**Comment:**

(b) (4)

29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

**Comment:**

(b) (4)

30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”

**Comment:**

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- (b) (4) 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- (b) (4) 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

**Comment:**



## Selected Requirements of Prescribing Information

- NO** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- (b) (4)** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- NO** 35. All text in the BW should be **bolded**.

Comment:

- NO** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

#### CONTRAINDICATIONS Section in the FPI

- (b) (4)** 37. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

- (b) (4)** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- (b) (4)** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- (b) (4)
40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:**

- (b) (4)
41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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ZETA-MAE C WILLIAMSON  
02/17/2016

## DGCPC/OSI CONSULT: Request for Clinical Inspections

**Date:** February 5, 2016

**To:** Ni Khin, M.D., Division Director, DCCE  
Kassa Ayalew, M.D., Branch Chief, GCPAB  
Janice Pohlman, M.D., M.P.H., Team Leader, GCPAB  
CDEROCDSIPMOs@fda.hhs.gov  
Roy A Blay, Ph.D.  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** Ronald Orleans, M.D.  
Lisa Soule, M.D., Clinical Team Leader

**From:** Charlene Williamson

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA #208224

IND#: 73505

Applicant: Bayer HealthCare Pharmaceuticals Inc.

100 Bayer Blvd., P.O. Box 915

Whippany, NJ 07981

Phone: 862-404-3175

Regulatory Point of Contact: Jo-Ann M. Ruane, Deputy Director, Global Regulatory Affairs

Regulatory Point of Contact Phone: 862-404-3668

Regulatory Point of Contact Email: jo-ann.ruane@bayer.com

Drug Proprietary Name: Kyleena

Generic Drug Name: levonorgestrel-releasing intrauterine system

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Prevention of pregnancy for up to 5 years

Submission Date: November 18, 2015

PDUFA: September 18, 2016

DGCPC/OSI Consult

version: 09/28/2011

Action Goal Date: September 16, 2016

Inspection Summary Goal Date: August 1, 2016

**II. Protocol/Site Identification**

<b>(Name,Address, Phone number, email, fax#)</b>	<b>Site #</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
Baker, Jeffrey 2327 Coronado St. Idaho Falls, ID 83404 USA United States phone:(208) 557-2991 fax:(208) 557-2985 email (b) (6)	2411	310442	80	Phase 3 efficacy and safety study of LCS for contraception
Miranda, Maria Jose José Victorino Lastarria #29 Santiago Centro, Santiago CHL Latin America phone:+56-2-6328258 fax:+56-2-6325969 email (b) (6)	1501	310442	56	Phase 3 efficacy and safety study of LCS for contraception
Nyirady, Tamas Frater Gy. u. 4 Kecskemet, 6000 HUN Eastern Europe phone:+36-30-9554703 fax:+36-76-506981 email (b) (6)	1806	310442	82	Phase 3 efficacy and safety study of LCS for contraception

### III. Site Selection/Rationale

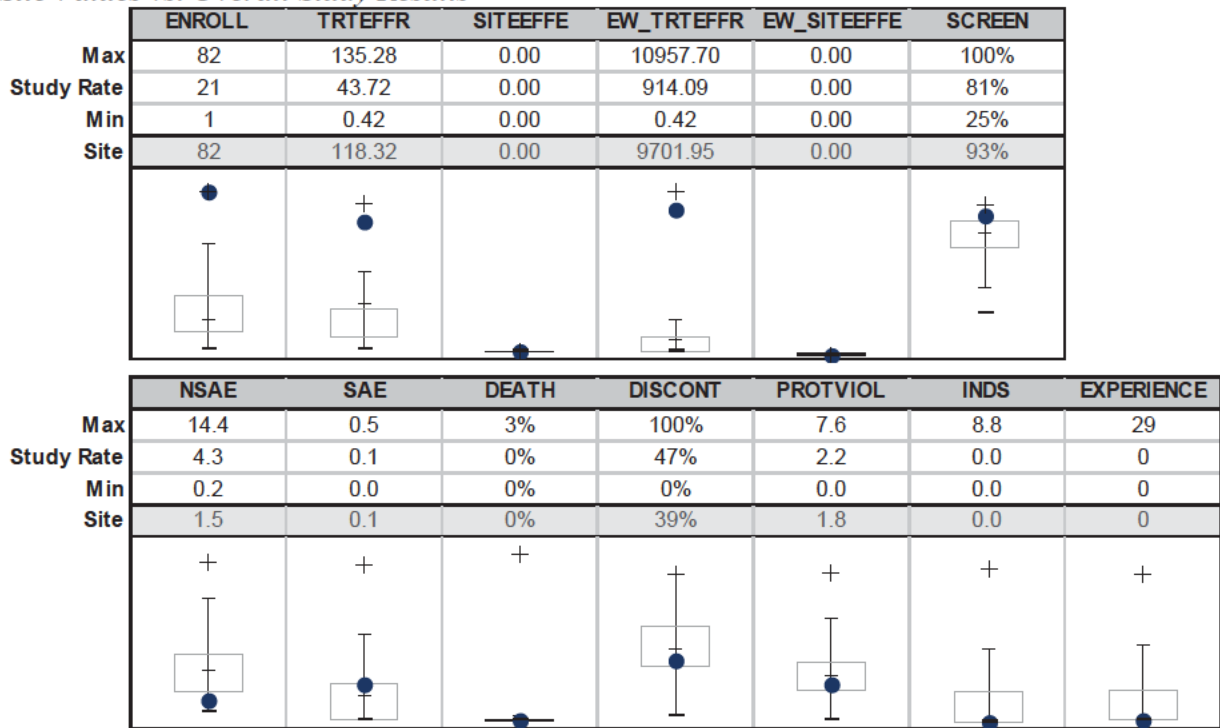
*Site Information*

<b>STUDY:</b>	310442	<b>SITEID:</b>	1806
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<b>NAME</b>	NyirAdy, TamAs
<b>LOCATION</b>	Frater Gy. u. 4 Kecskemet, HUN 6000
<b>PHONE/FAX</b>	+36-30-9554703 / +36-76-506981
<b>EMAIL</b>	(b) (6)

<b>RANK</b>	2	<b>FINLDISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	13.6	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

High D/C rate

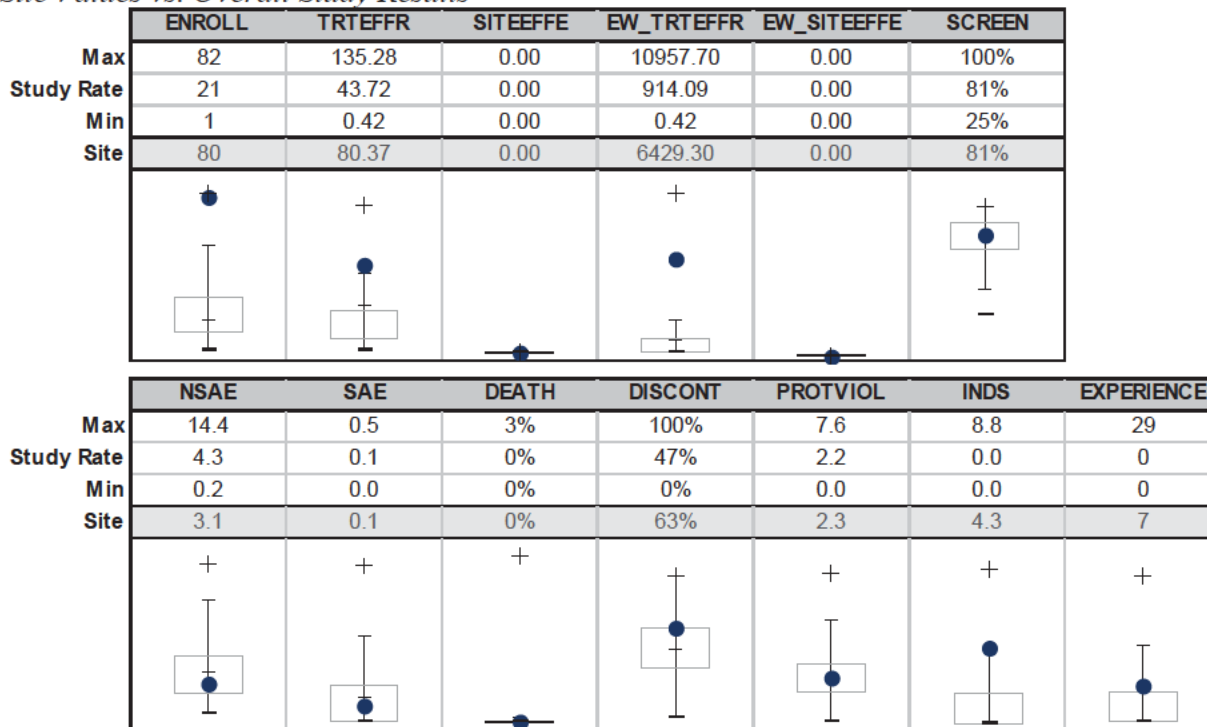
*Site Information*

<b>STUDY:</b>	310442	<b>SITEID:</b>	2411
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<b>NAME</b>	Baker, Jeffrey
<b>LOCATION</b>	2327 Coronado St. Idaho Falls, ID, USA 83404
<b>PHONE/FAX</b>	(208) 557-2991 / (208) 557-2985
<b>EMAIL</b>	(b) (6)

<b>RANK</b>	1	<b>FINLISC</b>	0	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	18.9	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*

Largest Sample/ Check Site # 2462



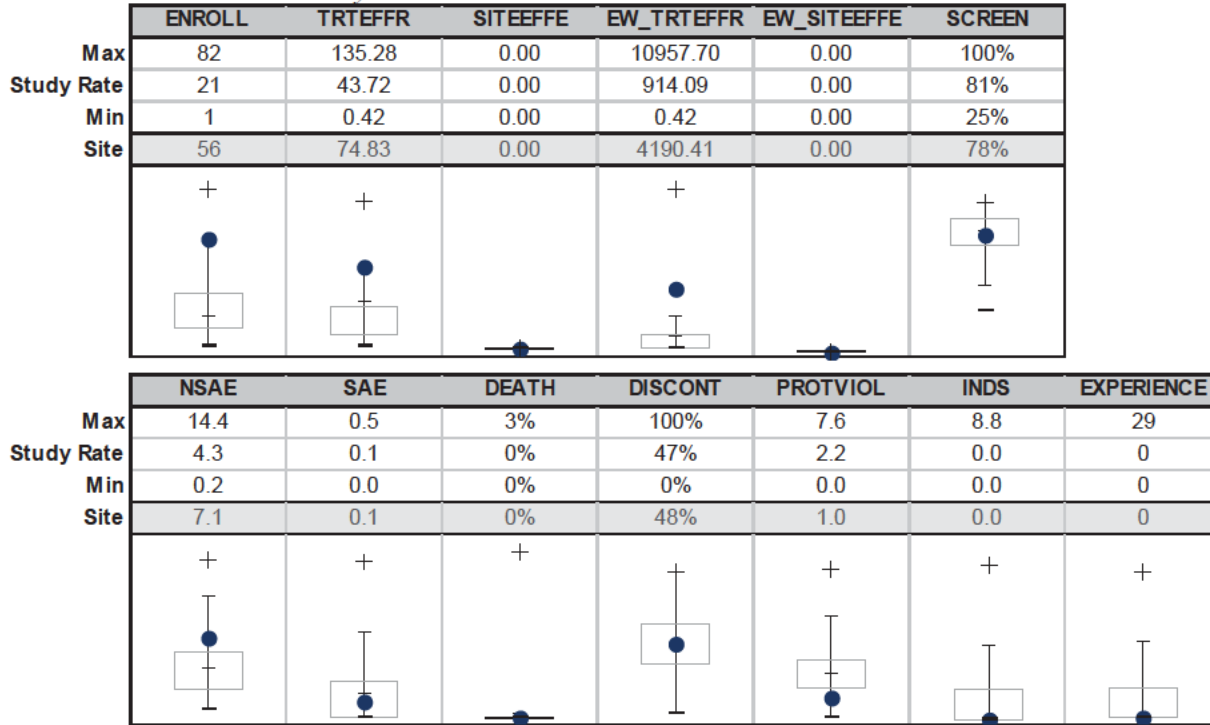
*Site Information*

<b>STUDY:</b>	310442	<b>SITEID:</b>	1501
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<b>NAME</b>	Miranda, Maria JosE
<b>LOCATION</b>	José Victorino Lastarria #29 Santiago Centro, Santiago, CHL
<b>PHONE/FAX</b>	+56-2-6328258 / +56-2-6325969
<b>EMAIL</b>	(b) (6)

<b>RANK</b>	11	<b>FINLISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	9.7	<b>OAI</b>	0	<b>TSLI</b>	3

*Site Values vs. Overall Study Results*



*Site Memo*  
High D/C

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects**
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Large Discontinuation rate**

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Should you require any additional information, please contact Charlene Williamson at 301-796-1025.

Concurrence: (as needed)

- X Medical Team Leader
- X Medical Reviewer
- X OSI Reviewer

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/s/  
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ZETA-MAE C WILLIAMSON  
02/05/2016