CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Review Memorandum

Date: September 12, 2016 addendum to July 29, 2016 memo

To: Charlene Williamson, CDER

From: Terry O. Woods, Ph.D.
OSEL\DAM
301-796-2503

Terry O. Woods -S

Digitally signed by Terry O. Woods -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Terry O. Woods -S, 0.9.2342.19200300.100.1.1=1300085350
Date: 2016.09.12 09:40:13 -04'00'

Re: NDA 208224 Bayer Kyleena IUD, MR testing and labeling

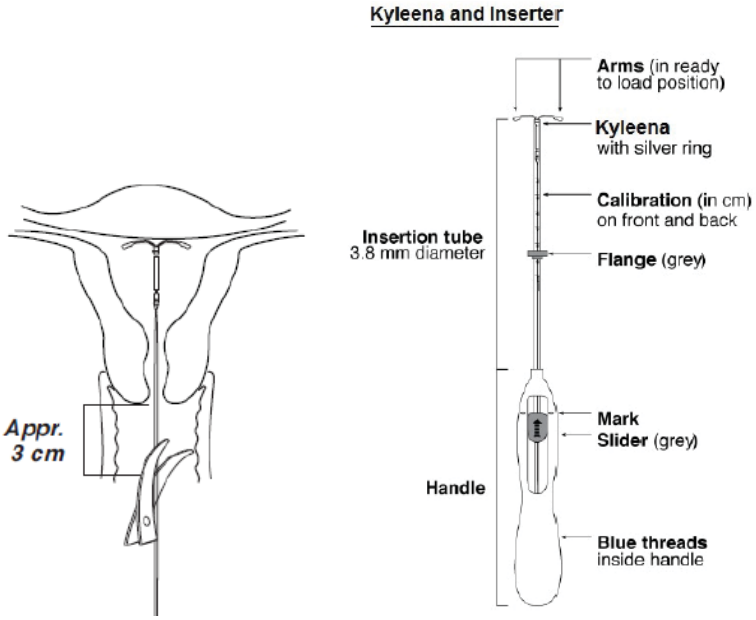
Recommendation: Approval.

SCOPE of REVIEW

I reviewed information related to magnetically induced force, torque RF heating, and artifact testing and labeling.

DEVICE DESCRIPTION

"Kyleena is a LNG-releasing IUS consisting of a T-shaped polyethylene frame with a steroid reservoir containing a total of 19.5 mg LNG." The only metal content is a silver ring shown in the diagram below.



Testing:

(b) (4) performed testing in July 2007 on a device called the IUD LCS Ultra Low Dose Levonorgestrel Contraceptive System. As a reference, he also performed testing on the Skyla IUD in 2012. The Skyla has a

geometry and material composition that is very similar to the Kyleena.

(b) (4)

Company rationale for the LCS system being an acceptable worst case for Kyleena for MRI safety evaluation: "Since the T-body dimensions and silver ring are exactly the same for both products, Levonorgestrel intrauterine delivery system 13.5 mg and Levonorgestrel intrauterine delivery system 19.5 mg, the MRI testing done for Levonorgestrel intrauterine delivery system 13.5 mg is also considered applicable for Levonorgestrel intrauterine delivery system 19.5 mg. Subsequently, Levonorgestrel intrauterine delivery system 19.5 mg can be also considered as MR-conditional and can be scanned with MRI under the conditions established for Levonorgestrel intrauterine delivery system 13.5 mg."

Reviewer comment: The rationale is scientifically sound. The LCS device may be considered worst case for the Kyleena implant for the MRI safety evaluation.

Test results:
They observed a 1° deflection of the test device at a location where the field strength is 2.7T and the spatial field gradient is 720 Gauss/cm for both test reports.

A qualitative torque test showed no torque in both test reports.

Artifact extended about 5 mm from the Skylara at 3T with a gradient echo pulse sequence. Artifact was described as minor for the LCS device.

Testing of the IUD LCS device for heating at 3T showed a temperature increase of 0.6° C at WBSAR of 3.0 W/kg. The Skylara testing for heating at 3T showed a temperature increase of 1.8° Cat WBSAR of 2.9 W/kg

Proposed MR Safety Labeling

The proposed labeling is the same as the labeling that was approved for the Skylara IUD in 2012.

5.11 Magnetic Resonance Imaging (MRI) Information

Non-clinical testing (b) (4) has demonstrated that Kyleena is MR Conditional. Kyleena can be safely scanned (b) (4) conditions:

- Static magnetic field of 3 Tesla or less
- Spatial gradient field of 36,000 Gauss/cm (360 T/m) (b) (4)
- Maximum whole body averaged specific absorption rate (SAR) of 4W/kg in the First Level Controlled mode (b) (4) (b) (4)

In non-clinical testing, the (b) (4) (b) (4)

DEFICIENCY

1. You have provided MRI Safety labeling. Your labeling is inconsistent with our current practice and does not follow our recommendations in the FDA Guidance for Industry and FDA Staff "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment, issued December 11, 2014 and available at http://www fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm107708.pdf. As a result of a request for more clarity and consistency in MRI safety labeling from the MRI user community at a recent FDA workshop on MRI safety, we request that device manufacturers use the format for the MRI safety labeling given in the guidance. Please revise your proposed MRI safety labeling using the format provided in the passive implant guidance document.
    - Please use the heading "MRI Safety Information" for your MRI labeling.
    - Your RF heating testing supports a maximum temperature rise of less than 1º C after 15 minutes of continuous scanning at 4W/kg. We recommend you include that value in your labeling.
    - We would find the following labeling acceptable.

MRI Safety Information

Non-clinical testing has demonstrated the Kyleena is MR Conditional. A patient with Kyleena can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3.0 T or less
- Maximum spatial field gradient of 36,000 gauss/cm (360 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode)

Under the scan conditions defined above, the Kyleena is expected to produce a maximum temperature rise of less than 1º C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extended up to 5 mm from the implant when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

RECOMMENDATION: Additional Information.

The testing is acceptable. They need to alter their MR Conditional labeling to conform to our standard format. I've provided acceptable wording above. I recommend you send them the labeling deficiency included above.

ADDENDUM, September 12, 2016:

Revised labeling:

5.11 Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that Kyleena is MR Conditional. A patient with Kyleena can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 3.0 T or less
- Maximum spatial field gradient of 36,000 gauss/cm (360 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 4W/kg (First Level Controlled Operating Mode)

Under the scan conditions defined above, the Kyleena IUS is expected to produce a maximum temperature rise of less than 2°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the IUS extended up to 5 mm from the IUS when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

FINAL RECOMMENDATION: Approval.

The revised labeling shown above is acceptable. I have no further questions and recommend approval.

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/s/

ZETA-MAE C WILLIAMSON
09/13/2016

Recommendation: *Approval*

NDA 208224
Kyleena
(levonorgestrel-releasing intrauterine system) 19.5 mg

Review #1

Drug Name/Dosage Form	Levonorgestrel; Intrauterine System
Strength	19.5mg
Route of Administration	Intrauterine system
Rx/OTC Dispensed	Rx
Applicant	Bayer Healthcare
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	11/18/2015	All
Amendment SN 0001	12/08/2015	Product
Correspondence SN 0004	03/21/2016	Facilities
Amendment SN 0005	03/21/2016	Product
Amendment SN 0006	03/29/2016	Product
Amendment SN 0007	04/01/2016	Product
Amendment SN 0008	04/22/2016	Product
Amendment SN 0009	05/23/2016	Product
Amendment SN 0010	06/08/2016	Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeff Medwid	Br. II/DNDAPI I/ ONDP
Drug Product	Sarah Ibrahim	Br. V / DNDP II /ONDP
Process	Jessica Liang	Br. V / DPA II / OPF
Microbiology	Elizabeth Bear	Br I / DMA 4 / OPF
Facility	Juandria Williams	Br. III / DIA 5 / OPF
Biopharmaceutics	Hanson Chen	Br. II / DB / ONDP
Regulatory Business Process Manager	Thao Vu	Br I / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	Br. V / DNDP II / ONDP
Laboratory (OTR)	N/A	-
Environmental Analysis (EA)	James Laurenson	EA Team / ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	Adequate	26-Mar-2012	Review by Tarun Mehta
	III			Adequate	26-Mar-2012	Review by Tarun Mehta
4178	II	Bayer Pharma AG	Levonorgestrel	Adequate	26-JUL-2016	Reviewed by Jeff Medwid
(b) (4)	IV		(b) (4)	Adequate	24-July-2012	Review by Tarun Mehta
	III			N/A		
	V			Adequate	27-June-2013	Review by Jean Salemme
	MAF (Device MF)			-	-	*See NDA 203159*

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND, amendments and associated reviews	IND 73505	Levonorgestrel (LNG) IUS; Bayer
Original NDA, amendments and associated reviews	NDA 21225	Mirena (LNG IUS; 52 mg), Bayer, AP 12/06/2000
Original NDA, amendments and associated reviews	NDA 203159	Skyla (LNG IUS; 13.5 mg, LCS12), Bayer, AP 01/09/2013
Original NDA*, amendments and associated reviews	NDA 206229	Liletta (LNG IUS; 52 mg), Medicines360, AP 02/26/2015

*Not referenced in Bayer NDA 208224

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharm./Tox.	N/A			
CDRH-ODE	Complete	Review of IUS inserter; no deficiencies identified.	08/03/16	Sharon Andrews
CDRH-OC	Complete	As revised, no deficiencies with IUS inserter Quality System (21 CFR 820); acceptable medical device GMP inspection status	08/19/16	Chris Brown
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

Bayer's 505(b)(1) New Drug Application 208224, for Kyleena (levonorgestrel-releasing intrauterine system, 19.5 mg), is recommended for Approval from the OPQ perspective.

Kyleena (levonorgestrel-releasing intrauterine system) is regulated as a drug-device combination product. In accordance with 21 CFR 310.502(a)(8), the intrauterine system (IUS) is considered the new drug. The inserter with which the IUS is placed in the uterus is a 'device' reviewed by CDRH.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the IUS drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The labeling (package insert, container/closure and secondary packaging) is complete, accurate and complies with the labeling requirements under 21 CFR 201.

CDRH Office of Device Evaluation and Office of Compliance reviewers have determined that there are no deficiencies associated with the inserter device from the engineering perspective and from the medical device compliance (21 CFR 820) perspective.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Kyleena (levonorgestrel-releasing intrauterine system) is indicated for the prevention of pregnancy for up to 5 years in women of reproductive age.
Duration of Treatment	The system should be replaced after 5 years if continued use is desired.
Maximum Daily Dose	Not Applicable.
Alternative Methods of Administration	Not Applicable.

Kyleena (levonorgestrel-releasing intrauterine system) consists of T-shaped polyethylene (PE) frame (T-body) with a cylindrical drug reservoir on the vertical stem. Barium sulfate is incorporated into the polyethylene to achieve radio-opacity; a silver ring at the top of the vertical stem enhances detection by ultrasound. A removal thread of medical grade polypropylene pigmented with copper phthalocyanine is attached to the lower end of the vertical stem.

The drug reservoir core contains 19.5 mg levonorgestrel, a progestin, in (b) (4) mg of a silicone elastomer (poly(dimethylsiloxane), PDMS) (b) (4). A silica-(b) (4) PDMS (b) (4) membrane ((b) (4) mg) covers (b) (4) the cylindrical core. (b) (4) (b) (4). This levonorgestrel-releasing intrauterine system (LNG IUS), referred to as LCS16, has an initial *in vitro* release rate of 16 mcg per day. Approximately 17.5 mcg levonorgestrel per day is released *in vivo* after 24 days. The rate declines to 7.4 mcg per day after 5 years, with an average release rate of 9 mcg per day over the 5-year period. An average of (b) (4)% of the initial LNG content remains in the IUS after approximately 5 years.

Except for minor changes to the T-body (b) (4) the to-be-marketed product is the same as the Phase 3 product.

Kyleena is Bayer's third LNG IUS proposed for market in the U.S. Mirena, an LNG IUS containing 52 mg levonorgestrel, was approved in 2000 (see NDA 21225). As currently labeled, the Mirena IUS can be left in place for up to 5 years. It has an initial *in vitro* release rate of 20 mcg per day. Skyla, a smaller LNG IUS developed by Bayer, was approved in 2013 for the prevention of pregnancy for up to 3 years (see NDA 203159). Skyla, or LCS12, has a total levonorgestrel drug load of 13.5 mg and has an initial *in vitro* release rate of 12 mcg per day.

LCS12 and LCS16 were developed in parallel and were evaluated in the same Phase III clinical study (see IND 73505). They are comparable in design, the primary functional difference being a longer cylindrical drug reservoir.

The drug product provides a convenient, long-acting and reversible, and relatively safe method of birth control. Compared to Bayer's Mirena (52 mg LNG IUS), Kyleena delivers a lower daily release rate in a smaller IUS and is inserted with a smaller diameter device. The smaller dimensions make Kyleena (and Skyla) suitable for both nulliparous and parous women, whereas the physically larger Mirena (and inserter) is recommended for use in women who have had at least one child.

B. Quality Assessment Overview

Drug Substance

Levonorgestrel is the optically pure levorotatory form of the synthetic hormone, norgestrel. It occurs as a white or almost white (b) (4) powder with a melting point in the range of 230-240 °C. Levonorgestrel is practically insoluble in water, (b) (4) and slightly soluble in alcohol. There are no known polymorphic forms of levonorgestrel. The drug substance is (b) (4) for the manufacture of the drug product. Control of the drug substance particle size distribution is critical to the performance (release rate) of the drug product.

The chemistry, manufacture and control of the drug substance are documented in Bayer Pharma AG's Type II Drug Master File (DMF) 4178. The DMF was last reviewed and found adequate on July 26, 2016.

The drug substance specification (acceptance criteria and analytical methods) included in the NDA was found adequate to ensure the quality, identity and purity of the drug substance. A retest period of (b) (4) months has been established for levonorgestrel API manufactured by Bayer.

The drug substance information is adequate to support its use in the manufacture of Kyleena. This NDA is therefore recommended for approval from the CMC drug substance perspective.

Drug Product

As described in the Product Overview, Kyleena consists of a drug reservoir (19 mm long x 1.73 mm outside diameter; (b) (4) levonorgestrel in poly(dimethylsiloxane)) with an approximately (b) (4) mm thick (b) (4) membrane (silica (b) (4) poly(dimethylsiloxane)), (b) (4) T-Body ((b) (4) polyethylene containing (b) (4) % barium sulfate), a silver ring, a thin, blue polypropylene removal thread, and an integrated administration device (inserter).

The design of the IUS follows that of Skyla. The suitability of the components of Kyleena for use in an intrauterine system has been demonstrated by a combination of USP, Ph.Eur, ISO and CFR test requirements. Appropriate specifications have been established to ensure the quality of all components of Kyleena (see Module 3.2.P.4 , Control of Excipients).

The manufacture of the drug reservoir consists of: (b) (4)

The regulatory specification for Kyleena includes tests for appearance, identity, assay, content uniformity, sterility, *in vitro* release, (b) (4) , breaking force, recovery of horizontal arms, loading (functional test of loading into inserter), detachment force (functional test of force to remove IUS from the inserter), container closure integrity. A test for impurities is performed only on stability (limit NMT (b) (4) % any individual impurity, limit sum of all impurities NMT (b) (4) %) because degradation products have not been observed at release despite exposure to high temperatures (b) (4)

The complete IUS with inserter is packaged in a [redacted] (b) (4) (tray) with a peelable lid [redacted] (b) (4) The materials comply with indirect food additive regulations (21 CFR 177). The PETG complies with USP<661>. The container closure system is sterilizable with ethylene oxide and is made of suitable materials to maintain sterility. The sealed trays are packaged in white cardboard boxes.

The stability of Kyleena was evaluated under long term conditions (25°C/60% RH and 30°C/75% RH) for 12 months, and under accelerated conditions (40°C/75% RH) for 6 months. Stress [redacted] (b) (4) and photostability tests were also performed. In addition to these tests on pilot scale batches, 3-month data from three production scale batches were provided.

With the exception of some fluctuation in release rate and a slight increase in degradation products, the product is virtually unchanged under the long term and accelerated conditions. Some photodegradation is observed (less than proposed limits for impurities) under ICH Q1B Option 2 photostability test conditions, however the same degradation profile is not observed in control samples or at batch release.

The product is virtually unchanged following [redacted] (b) (4) [redacted] (b) (4)

The proposed expiration dating period of 24 months for product stored at 25°C is supported by the available stability data and is acceptable.

This NDA is recommended for Approval from the Drug Product perspective.

Labeling

From the product quality perspective, the package insert, the immediate container label, and the carton labeling include all information required under 21 CFR 201. The information is accurately presented. See below for 'Special Product Quality Labeling Recommendations' for comments regarding the established name for the drug product, levonorgestrel-releasing intrauterine system.

Product Manufacturing Process

The manufacturing process and controls for the proposed drug product, Kyleena IUS, are very similar to those for the approved Skyla IUS. The applicant has extensive prior manufacturing experience with commercial production of similar IUS (e.g., Skyla IUS) and has successfully manufactured three commercial size (each [redacted] (b) (4) kg, [redacted] (b) (4) units) validation batches for the proposed Kyleena IUS drug product using the same formulation and manufacturing process as used for the clinical (Phase 2&3) and primary stability batches, and at the same manufacturing facility.

Although the manufacturing process is similar to that of Skyla, several concerns with process parameters during the initial process risk assessment (See Attachment I, Risk Assessment / Initial Process Risk Assessment). (b) (4)

The applicant has adequately addressed all the information requests. As a result, this NDA is recommended for APPROVAL from the perspective of drug product manufacturing process.

Product Microbiology

The finished drug product is (b) (4) sterilized with ethylene oxide (ETO) (b) (4) (b) (4) The process has been reviewed in conjunction with both Mirena NDA 21225 and Skyla NDA 203159. The facilities thus have a satisfactory history of sterilizing levonorgestrel-releasing intrauterine systems.

Adequate information regarding the (b) (4) sterilization processes has been provided. Validation of the sterilizers and sterilization cycles provides assurance of the sterility of the drug product. The drug product specification includes a validated test for sterility. Note that endotoxin testing is not required because the drug product is inserted into the intrauterine cavity.

Bayer has provided adequate support for the maintenance of integrity by the proposed container closure system. They have also provided adequate data to support the maintenance of sterility of product on stability.

While the applicant has provided adequate product quality microbiology data to support approval of the NDA, as amended, it is noted that sterilization (b) (4) will need to be adequately qualified, and that any future sterilization site changes could affect microbiological quality.

Biopharmaceutics

Kyleena is designed to release low levels of levonorgestrel over a 5-year period. It is therefore critical to product safety and efficacy that there is batch-to-batch consistency of the release rate. The Biopharmaceutics evaluation of the NDA focused on "the *in vitro* release method development, the discriminatory capabilities of the proposed *in vitro* release method, the *in vitro* release acceptance criteria, and comparison of long-term *in vitro*, *ex vivo*, and *in vivo* release rates of the drug product."

For the purposes of quality control, an *in vitro* release test must be developed that is relatively short (compared to in vivo release) to allow efficient and timely batch release,

yet is sufficiently discriminatory. Levonorgestrel is practically insoluble in water; (b) (4)

Nevertheless, the proposed *in vitro* release method and its acceptance criteria are acceptable.

The long-term *in vitro*, *ex vivo*, and *in vivo* release rates of levonorgestrel from Kyleena were characterized. (b) (4)

Overall, the release rate of levonorgestrel from Kyleena has been well characterized.

From the Biopharmaceutics perspective NDA 208224 is adequate for approval.

Facilities

The drug substance manufacturing facility, Bayer Pharma AG, Bergkamen, Germany, was found acceptable based on CGMP history. The Bayer Berlin, Germany drug substance (b) (4) site was likewise found based on compliance history.

Bayer Oy, Turku, Finland, manufactures the drug product. (b) (4) A general surveillance inspection of Bayer Oy was conducted in April 2016. It was concluded that, "the firm has demonstrated continued ability to maintain a state of control for manufacturing levonorgestrel-based combination products." See comments below under CDRH Device Evaluation for comments on medical device GMPs.

The finished product is sterilized with ethylene oxide by (b) (4). This facility only sterilizes intrauterine systems, and has been doing so for Bayer since 2008. (b) (4) was found acceptable based on compliance history.

The OPF Division of Inspectional Assessment concludes that, "[t]here appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support approval of NDA 208224."

Environmental Analysis

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable. A number of environmental risk factors identified during the review also indicate that additional FDA monitoring of potential cumulative and other impacts from progestins and other hormonally active substances is warranted outside of this subject action.

CDRH Device Evaluation

Kyleena is packaged pre-loaded in an inserter device. CDRH was therefore consulted to evaluate the IUS inserter from the device engineering perspective as well as for evaluation of compliance with 21 CFR 820 (device GMPs) in accordance with 21 CFR subpart 4.

Note that the inserter device is manufactured by (b) (4) ; (b) (4) as documented in Drug Master File (b) (4). The DMF was previously reviewed and found adequate in conjunction with NDA (b) (4).

The inserter for Kyleena is identical to the inserter approved for Skyla except for the slider and flange colorant. The materials of construction are acceptable given the short duration of patient contact. The inserter meets requirements for mechanical performance properties at baseline, following ethylene oxide sterilization and on stability. See the review by Sharon Andrews, CDRH-ODE, dated August 3, 2016 for details. See also CDRH consult reviews associated with NDA 203159 for Skyla.

Although the initial NDA submission was deficient with respect to documentation of compliance with 21 CFR 820, Bayer provided sufficient information to demonstrate compliance with device GMPs. Bayer HealthCare Pharmaceuticals corporate offices in Whippany, NJ was found acceptable based on compliance history. Bayer Oy was found acceptable based on the April 2016 inspection. See the review by Chris Brown, CDRH-OC dated August 19, 2016 for details.

C. Special Product Quality Labeling Recommendations (NDA only)

The established name for Mirena, Skyla, and Liletta (a Medicines360 IUS containing 52 mg LNG approved 02/26/15 under NDA 206229) is 'levonorgestrel-releasing intrauterine system.' This established name appears to have been in use since the approval of Mirena in 2000.

USP General Chapter <1151>, Pharmaceutical Dosage Forms, refers to 'intrauterine [route of administration] systems.' The December 1, 2014 USP Nomenclature

Guidelines (referenced in USP General Chapter <1121>, Nomenclature), gives the general format '[DRUG] Intrauterine System.' Thus Kyleena, and the other products, would have the established name 'levonorgestrel intrauterine system.'

However, given the precedence established for these products and in the absence of a USP monograph title legally recognized under the FD&C Act for the levonorgestrel intrauterine systems, we proposed to continue the use of 'levonorgestrel-releasing intrauterine system' for Kyleena. At such time that a USP monograph becomes official, the nomenclature for all products can be revised. This will minimize the regulatory burden for the current applicant and will minimize product confusion for health care providers and patients.

Note that the lone official USP monograph for an intrauterine system is "Progesterone Intrauterine Contraceptive System," which is inconsistent with the USP-recommended title format.

Dr. Eric Duffy, Division Director for ONDP/DNDP II, concurred with this proposal on August 16, 2016.

D. Final Risk Assessment (see Attachment)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

Mark R. Seggel
CMC Lead (Acting) for DBRUP

Mark R. Seggel -S

Digitally signed by Mark R. Seggel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=1300071539
Date: 2016.08.23 17:46:51 -04'00'

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Analysis

CHAPTER IV: Labeling

CHAPTER V: Process

CHAPTER VI: Facilities

CHAPTER VII: Biopharmaceutics

CHAPTER VIII: Microbiology

CHAPTER IX: Additional Quality Discipline *Not Applicable.*

ATTACHMENT I: Risk Assessment

ATTACHMENT II: Deficiencies *Not Applicable.*

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

ENVIRONMENTAL ANALYSIS

R Regional Information

Environmental Analysis

[Suggested language for executive summary: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable. A number of environmental risk factors identified during the review also indicate that additional FDA monitoring of potential cumulative and other impacts from progestins and other hormonally active substances is warranted outside of this subject action.]

The applicant asked under IND 073505 whether a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b) would be acceptable under the NDA. Specifically, the expected introduction concentration (EIC) of (b) (4) ppb, or (b) (4) ng/L, for levonorgestrel (LNG) across all uses was noted as approximately three orders of magnitude lower than the 1 ppb categorical exclusion concentration. The claim was accompanied by data indicating that use of the active moiety would not increase, and likely would decrease (see graph for applicant's use of LNG over the next five years). This decrease appears to be due at least in part to substitution of the product for other LNG intrauterine systems (IUSs).

The applicant also noted that a significant amount of the LNG quantities will not enter the aquatic environment but rather end up in municipal trash (landfills, incinerators), as (b) (4) is a patch that retains greater than (b) (4)% of the LNG after use, and Mirena and Skyla each retain greater than (b) (4)% after use.

FDA responded by noting that it appeared that the applicant could claim an exclusion under 21 CFR 25.31(a), which is for actions that do not increase the use of the active moiety. FDA also noted that given the potential for thyroid and other endocrine-related effects noted in the nonclinical data for this active ingredient and given the published literature on potential environmental impacts,[1] and in accordance with new draft FDA guidance, *Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity*, FDA is interested in the environmental impact of LNG and other drugs with similar modes of action (MOAs) more broadly.

The applicant subsequently submitted a claim of a categorical exclusion from an EA under 21 CFR 25.31(a) (no increased use) and provided the required statement regarding no extraordinary circumstances. In response to the Agency request for assistance in assessing the cumulative impacts of LNG and related drugs, the applicant submitted additional information regarding the environmental impact of LNG and two similar acting progestins—dienogest and drospirenone. Key findings from this latter submission for levonorgestral are as follows:

- Environmental fate studies indicate a low degradation potential of LNG, a moderate bioaccumulation potential, and a significant adsorption potential on organic matrices.
- Several ecotoxicity assays have been conducted on levonorgestroal, with the lowest of the no-observed-effects concentrations (NOECs) at < (b) (4) ng/L, the lowest of the lowest-observed-effects concentrations (LOECs) at ≤ (b) (4) ng/L, and a (b) (4)% effects concentration (EC10) at (b) (4) ng/L, all for fecundity in a draft OECD 21-day fathead minnow reproduction screening test for hormonally active compounds. This test had been enhanced by a specific evaluation of the reproductive success including a statistical analysis.

Key findings for drospirenone are as follows:

- Environmental fate studies for drospirenone are similar to those of levenorgestrel in that they indicate a low degradation potential of drospirenone, a moderate bioaccumulation potential, and a significant adsorption potential on organic matrices.
- Several ecotoxicity assays have been conducted on drospirenone, with the lowest NOEC at (b) (4) ng/L and the lowest LOEC at (b) (4) ng/L, based on adult reproduction and histopathological changes in gonads in a chronic life-cycle fish study.

Key findings for dienogest are as follows:

- Environmental fate studies for dienogast show similarities with those of LNG and drospirenone in terms of its low degradation potential, but its bioaccumulation potential and organic matrices adsorption potential are both low too.

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[1] Zeilinger, J., Steger-Hartmann, T., Maser, E., Goller, S., Vonk, R., Länge, R. (2009). Effects of synthetic gestagenes on fish reproduction. Environ. Toxicol. Chem. 28, 2663–2670.

Fick, J., Lindberg, R. H., Parkkonen, J., Arvidsson, B., Tysklind, M., & Larsson, D. J. (2010). Therapeutic levels of LNG detected in blood plasma of fish: results from screening rainbow trout exposed to treated sewage effluents. Environmental science & technology, 44(7), 2661-2666.

- Several ecotoxicity assays have been conducted on dienogest, with the lowest NOEC at (b) (4) ng/L and lowest LOEC at (b) (4) ng/L, based on effects on hatch and survival of fish chronic life-cycle fish study.

The applicant also conducted a review of selected published literature, noting that in summary, the no-effect concentrations for the different synthetic progestins varied from (b) (4) ng/L (EC10, LNG), (b) (4) ng/L (norethindrone), (b) (4) ng/L (dienogest), to (b) (4) ng/L (drospirenone). Effects were primarily seen in decrease in fecundity and, in developmental tests, growth retardation.

Reviewer's Assessment: The applicant's analysis supporting an EIC of (b) (4) ppb, or (b) (4) ng/L, and a decreased release of LNG over time is reasonable based on the data provided, and thus the analysis is consistent with the categorical exclusion claim of no increased use per 21 CFR 25.31(a). The applicant also provided an adequate statement of no extraordinary circumstances, as well as data in response to the FDA request for information on the environmental impact of LNG and other drugs with similar MOAs more broadly. FDA examined the additional data, as described below.

The lowest effects level for LNG noted above was the EC10 of (b) (4) ng/L, which is more than an order of magnitude lower than the EIC of (b) (4) ng/L, thus indicating the need for additional analysis. This additional analysis notes that a significantly lower amount than the EIC of (b) (4) ng/L would actually enter the aquatic environment due to several factors. First, these products retain greater than (b) (4)% of the LNG after use and thus would be disposed with solid waste (e.g., landfills, incinerators) rather than be released into the aquatic environment. In addition, human metabolism would reduce the amount entering wastewater treatment, and degradation during treatment would reduce the amount entering the environment. Dilution and additional degradation in the aquatic environment would reduce concentrations further. These factors are expected to reduce the aquatic environment concentration by more than an order of magnitude, and thus to less than the EC10 of (b) (4) ng/L.

FDA also conducted a limited literature search on LNG to supplement the data provided by the applicant and found that concentrations in the environment are in the low ng/L range (b) (4) which is higher than both the expected aquatic concentration from this applicant (< (b) (4) ng/L) and the EC10 of (b) (4) ng/L. Mixture (or cumulative) effects also are a concern, due in part to other synthetic progestins described by the applicant, to natural progestins, and to other hormonally active chemicals. In addition, the documented persistence of LNG and other synthetic progestins indicate that these substances could accumulate over time.

In summary, while the claim of categorical exclusion from an environmental assessment is acceptable, the above risk factors indicate that additional FDA monitoring of potential cumulative and other impacts from progestins and other hormonally active substances is warranted outside of this subject action, such as through future environmental assessments and/or the requesting of additional data from sponsors.

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[2] Runnalls, T. J., et al. (2015). "From single chemicals to mixtures – reproductive effects of levonorgestrel and ethinylestradiol on the fathead minnow." Aquatic Toxicology 169: 152-167.

Primary EA Reviewer Name and Date: James P. Laurenson, Environmental Officer, CDER/OPQ/ONDP EA Team, 6/14/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): I concur with the above review. M. Scott Furness, Deputy Director, ONDP, 6//29/2016

Michael Furness

Digitally signed by Michael Furness
Date: 8/04/2016 02:06:19PM
GUID: 502e8c7600003dd8331cf6eebf43697a

James Laurenson

Digitally signed by James Laurenson
Date: 8/04/2016 03:26:16PM
GUID: 51dc6bdb0000c62de59b85452e59746f

R Regional Information

1.14 Labeling & Package Insert

A. Package Insert

(a) "Highlights" Section (21CFR 201.57(a)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KYLEENA safely and effectively. See full prescribing information for KYLEENA.

KYLEENA (levonorgestrel-releasing intrauterine system)
Initial U.S. Approval: 2000

---------- INDICATIONS AND USAGE ----------
Kyleena is a progestin-containing intrauterine system (IUS) indicated for prevention of pregnancy for up to 5 years. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Release rate of levonorgestrel (LNG) is 17.5 mcg/day after 24 days and declines to (b) (4) after 5 years; Kyleena must be removed or replaced after 5 years. (2)
- To be inserted by a trained healthcare provider using strict aseptic technique. Follow insertion instructions exactly as described. (2)
- (b) (4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- One sterile intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing 19.5 mg levonorgestrel packaged within a sterile inserter (3)

---------- CONTRAINDICATIONS ----------
- Pregnancy or suspicion of pregnancy. Cannot be used for post-coital contraception (emergency contraception) (4)
- Congenital or acquired uterine anomaly if it distorts the uterine cavity (4)
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infection (4)
- A previous intrauterine device (IUD) that has not been removed (4)
- Hypersensitivity to any component of Kyleena (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Remove Kyleena if pregnancy occurs with Kyleena in place. If a pregnancy occurs, there is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death), and premature labor and delivery. (5.1, 5.2)
- (b) (4)
- Before using Kyleena, consider the risks of PID. (5.4)
- (b) (4)
- Kyleena can be safely scanned with MRI only under certain conditions. (5.11)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions reported (≥ 5% users) were vulvovaginitis, ovarian cysts, abdominal pain/pelvic pain, headache/migraine, acne/seborrhea, dysmenorrhea/uterine spasm, breast pain/breast discomfort, and increased bleeding. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

(b) (4)

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

Revised: MM/YYYY

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Kyleena levonorgestrel-releasing intrauterine system	Proprietary name is presented correctly. The established name is presented correctly. **Satisfactory.**
Dosage form, route of administration	Dosage: 19.5 mg levonorgestrel Route: Intrauterine	The dosage form "intrauterine" is described adequately. **Satisfactory.**
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Intrauterine: 19.5 mg levonorgestrel	The strength of the intrauterine device is expressed similar to previously approved dosage forms. **Satisfactory.**

Conclusion:

1- Proprietary name Kyleena® has been accepted and package insert includes the correct proprietary name and the proposed labeling.
2- The dosage form is clearly described and adequately summarized.
3- The strength of the dosage form is consistent with similarly approved dosage forms.

This section is **Satisfactory.**

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Kyleena LNG-releasing IUS	Proprietary name is presented correctly. The established name is presented correctly. Satisfactory. **Satisfactory.**
Strengths: in metric system	19.5 mg	The strength of the IUS is expressed similar to previously approved dosage forms. **Satisfactory.**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	LNG-releasing IUS consisting of a T-shaped polyethylene frame with a steroid reservoir containing a total of 19.5 mg LNG.	The description of the IUS is concise and accurate. **Satisfactory.**

Conclusion:

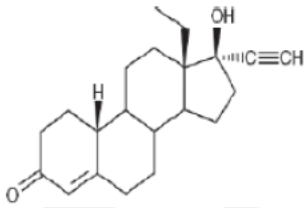
1. The description of the identifying characteristics of the intra-uterine system including container description and consistency is adequately expressed.
2. The strength is expressed as total drug load and is consistent to previously approved dosage forms.

This section is **Satisfactory.**

#11: Description (21CFR 201.57(c)(12))

Kyleena (levonorgestrel-releasing intrauterine system) contains 19.5 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately17.5 mcg/day of LNG after 24 days. [Module 2.5]

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Kyleena, has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:

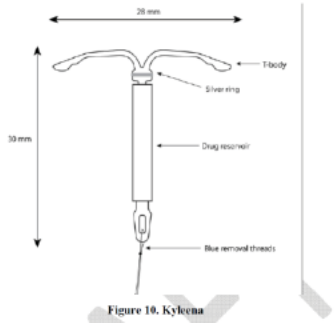
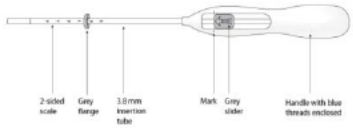


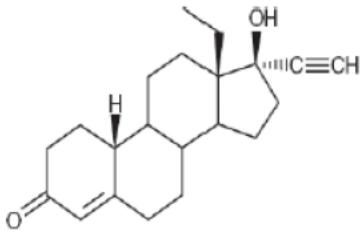
11.1 Kyleena [Module P.2.3 - P.2.3.01]

Kyleena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir consists of a whitish or pale yellow cylinder, 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% pure silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. The polyethylene of the T-body is compounded with barium sulfate, which makes 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 (see Figure 10). [Module 2.5]

The components of Kyleena, including its packaging, are not manufactured using natural rubber latex.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Kyleena (levonorgestrel-releasing intrauterine system) contains 19.5 mg of LNG, a progestin,	Proprietary name is correct. The established name is presented correctly. **Satisfactory.**
Dosage form and route of administration	levonorgestrel-releasing intrauterine system	The dosage form and route are expressed correctly. **Satisfactory.**
Active moiety expression of strength with equivalence statement for salt (if applicable)	19.5 mg LNG	The strength is expressed correctly. **Satisfactory.**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Kyleena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The reservoir consists of a whitish or pale yellow cylinder, 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,	The inactive ingredients information is presented correctly. **Satisfactory.**

	composed of polydimethylsiloxane and colloidal silica. A ring composed of 99.95% pure silver is located at the top of the vertical stem close to the horizontal arms and is visible by ultrasound. The polyethylene of the T-body is compounded with barium sulfate, which makes 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 (see Figure 10).  Figure 10. Kyleena Kyleena is packaged sterile within an inserter. The inserter (Figure 11), which is used for insertion of Kyleena into the uterine cavity, 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 Kyleena has been placed, the inserter is discarded.  Figure 11. Diagram of Inserter	
Statement of being sterile (if	Absent	Sterility should be stated.

applicable)		**Not Satisfactory**
Pharmacological/ therapeutic class	a progestin	This will be determined in the labeling meeting.
Chemical name, structural formula, molecular weight	Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Kyleena, has a molecular weight of 312.4, a molecular formula of C21H28O2, and the following structural formula: 	The chemical names and the structural formula are correct. The molecular weight is included. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	NA

Conclusion:

1. The chemical structures and formula are expressed correctly.
2. The strength of the dosage form is expressed correctly.
3. The molecular weight of the drug substance is included.
4. ***The "Description" section (# 11) should be include sterility, however it is included under section 11.2 and therefore deemed appropriate.***

This section is **Satisfactory.**

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Kyleena (levonorgestrel-releasing intrauterine system), containing a total of 19.5 mg LNG, is available in a carton of one sterile unit. NDC# 50419-424-01

Kyleena is supplied sterile. Kyleena is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

Store at 25°C (77°F); with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	19.5 mg LNG	The information provided is Adequate. **Satisfactory.**
Available units (e.g., bottles of 100 tablets)	Kyleena (levonorgestrel-releasing intrauterine system), containing a total of 19.5 mg LNG, is available in a carton of one sterile unit.	The information provided is Adequate. **Satisfactory.**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC# 50419-424-01	The information provided is Adequate. **Satisfactory.**
Special handling (e.g., protect from light, do not freeze)	Kyleena is supplied sterile. Kyleena is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.	Statement is present. **Satisfactory.**
Storage conditions	Store at 25°C (77°F); with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].	The information provided is Adequate. **Satisfactory.**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ 07981 Manufactured in Finland	**Satisfactory.**

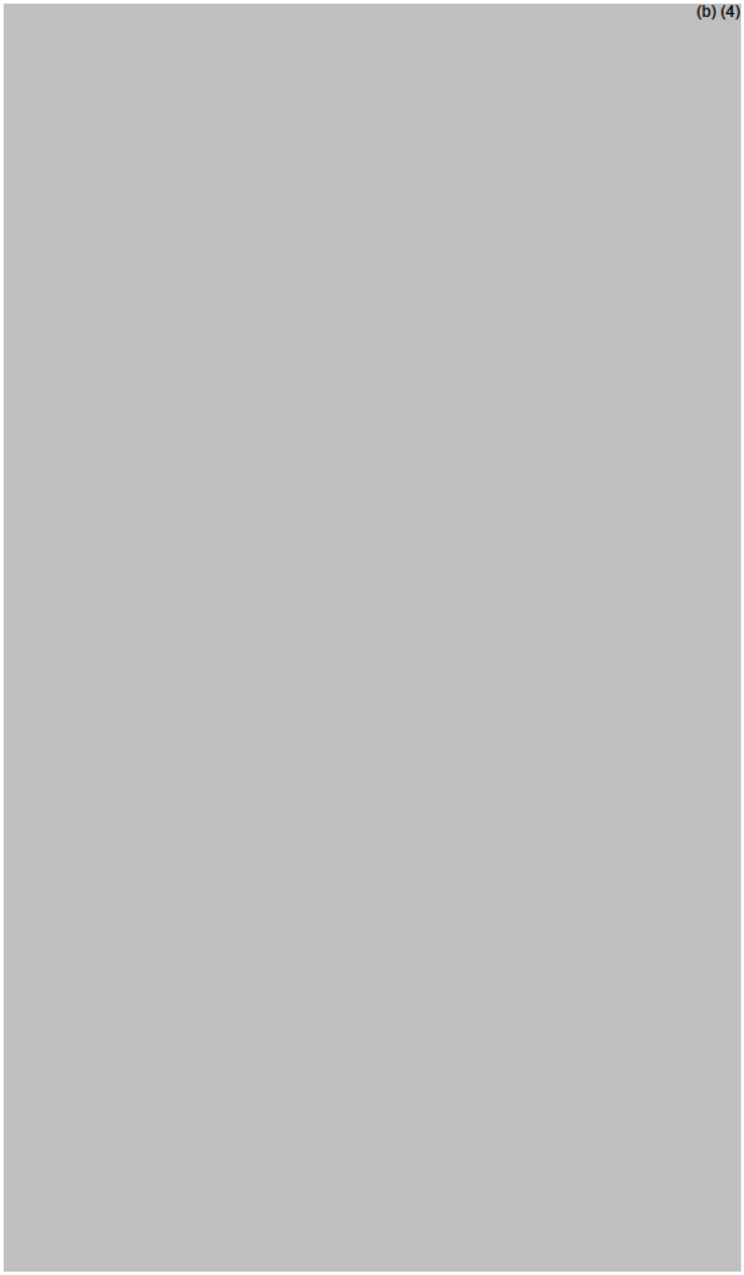
Conclusion:

1. The strength of the dosage form is expressed accurately under section 16.
2. Section 16 includes Available units, NDC number, Special handling and Storage conditions.
3. The package insert section 17 includes the manufacturer/distributor name.

This section is **Satisfactory.**

B. *Immediate Container Label*

(b) (4)



Reviewer's Assessment:

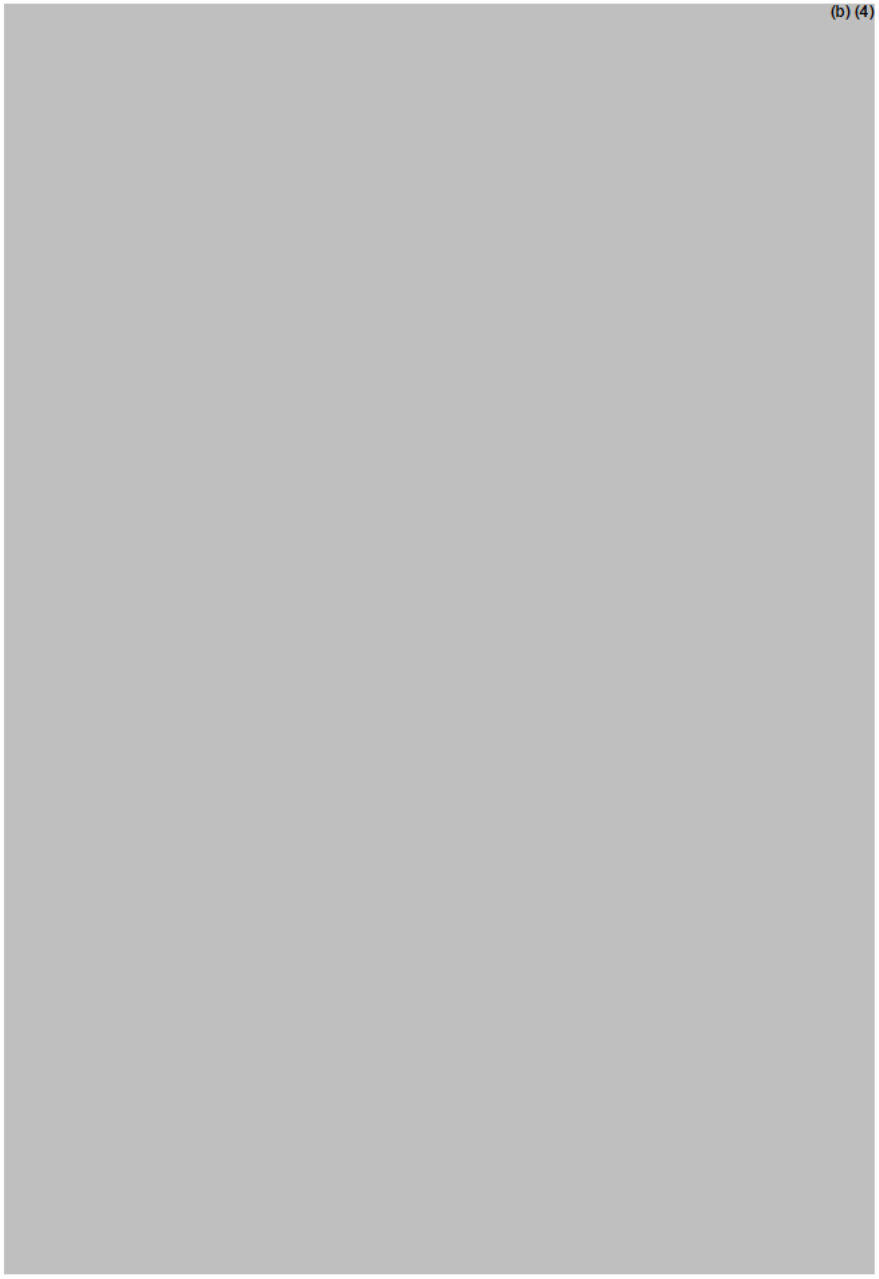
Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Kyleena (Levonorgestrel-releasing intrauterine system)	**Satisfactory.**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	19.5 mg	**Satisfactory.**
Net contents (21 CFR 201.51(a))	One system	**Satisfactory.**
Lot number per 21 CFR 201.18	Displayed	**Satisfactory.**
Expiration date per 21 CFR 201.17	Displayed	**Satisfactory.**
"Rx only" statement per 21 CFR 201.100(b)(1)	Displayed	**Satisfactory.**
Storage (not required)	Displayed	**Satisfactory.**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	**Satisfactory.**
Bar Code per 21 CFR 201.25(c)(2)**	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
Others		

1. The description of the identifying characteristics of the dosage form and strength are adequately expressed.
2. The strength of the IUS is similar to previously approved dosage forms.
3. Net content, lot number, expiration date, manufacturer, and storage conditions are clearly displayed.
4. NDC number and Bar code are adequately displayed.

This section is **Satisfactory**.

C. Carton Labeling

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Kyleena (Levonorgestrel-releasing intrauterine system)	**Satisfactory.**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	19.5 mg	**Satisfactory.**
Net contents (21 CFR 201.51(a))	Displayed	**Satisfactory.**
Lot number per 21 CFR 201.18	Displayed	**Satisfactory.**
Expiration date per 21 CFR 201.17	Displayed	**Satisfactory.**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not Displayed	**Satisfactory.**
Sterility Information (if applicable)	Displayed	**Satisfactory.**
"Rx only" statement per 21 CFR 201.100(b)(1)	Displayed	**Satisfactory.**
Storage Conditions	Displayed	**Satisfactory.**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	**Satisfactory.**
Bar Code per 21 CFR 201.25(c)(2)**	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
"See package insert for dosage information" (21 CFR 201.55)	Displayed	**Satisfactory.**
"Keep out of reach of children" (optional for Rx, required for OTC)	Not Displayed	**Satisfactory.**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Displayed	**Satisfactory.**

1. The Proprietary name, established name and strength are adequately expressed.
2. The strength of the IUS is similar to previously approved dosage forms.
3. Net content, lot number, expiration date, manufacturer, and storage conditions are clearly displayed.

4. NDC number and Bar code are adequately displayed.

This section is **Satisfactory**.

List of Deficiencies:

None.

Primary Labeling Reviewer Name and Date:

Sarah Ibrahim, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Moo Jhong Rhee

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Date: 8/19/2016 11:04:27AM
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Sarah Ibrahim

Digitally signed by Sarah Ibrahim
Date: 8/19/2016 12:56:52PM
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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208224

Drug Product Name / Strength: Kyleena LCS16 (Levonorgestrel intrauterine delivery system) 19.5 mg

Route of Administration: Intrauterine

Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Review Summary:

Bayer HealthCare Pharmaceuticals, Inc. developed Kyleena LCS16 (Levonorgestrel intrauterine delivery system) 19.5 mg, which is indicated for the prevention of pregnancy for up to 5 years. The Application was submitted to FDA for review as 505 (b) (1) NDA 208224 on November 18, 2015.

The Biopharmaceutics review focuses on the in vitro release method development, the discriminatory capabilities of the proposed in vitro release method, the in vitro release acceptance criteria, and comparison of long-term in vitro, ex vivo, and in vivo release rates of the drug product.

Following the above review, this Reviewer recommends that NDA 209224 for Kyleena ® (Levonorgestrel intrauterine delivery system (IUS) 19.5 mg) is **ADEQUATE** for approval from the Biopharmaceutics perspective.

List Submissions being reviewed (table):

Application 208224 - Sequence 0000 - 0000 (1) 11/18/2015 ORIG-1 /Multiple Categories/Subcategories

Application 208224 - Sequence 0008 - 0008 (9) 04/22/2016 ORIG-1 /Quality/Response To Information Request

Application 208224 - Sequence 0009 - 0009 (10) 05/23/2016 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: Not reported.

Solubility:

Permeability:

Dissolution:

In Vitro Release Method and Acceptance Criteria

Reviewer's Assessment: The proposed in vitro release method and its acceptance criteria are acceptable.

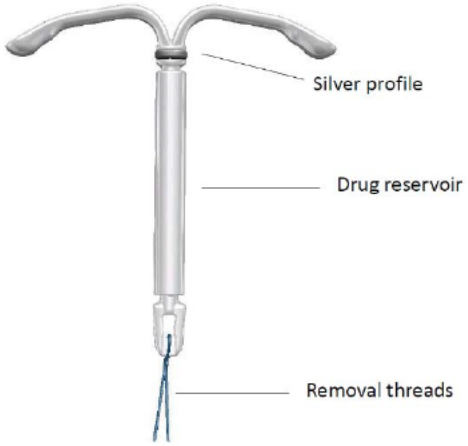
1. Drug Product:

Kyleena LCS16 (Levonorgestrel (LNG) Intrauterine Delivery System (IUS)) 19.5 mg is an intrauterine drug delivery system, which is indicated for the prevention of pregnancy for up to 5 years. This intrauterine delivery system consists of a whitish or pale yellow drug reservoir mounted on the vertical stem of a white T-body. The drug reservoir consists of a core of (b) (4)% levonorgestrel and (b) (4) % poly(dimethylsiloxane) elastomer, covered with a poly(dimethylsiloxane) membrane. The detailed composition of Levonorgestrel intrauterine delivery system 19.5 mg is listed in Table 1.

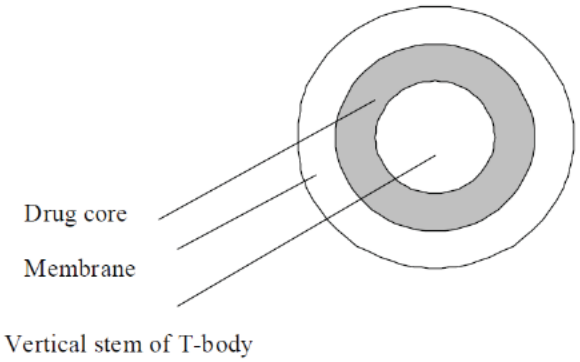
The drug core is covered by a poly(dimethylsiloxane) membrane, (b) (4) A silver ring is attached to the upper part of the vertical stem of the T-body to facilitate ultrasound detection. A removal thread is attached to the loop at the end of the vertical stem of the T-body. The Intrauterine System (IUS) is inserted into the uterus with a preloaded inserter. It is noted that this device should be administered by trained healthcare professionals.

The drug substance is a widely used progestin, which is (b) (4) during the manufacture in order to achieve a (b) (4) mixing of levonorgestrel and poly(dimethylsiloxane) elastomer.

Figure 1. Schematic illustration of the system



T-Body



Cross-section of the drug reservoir

Table 1. Composition of Levonorgestrel intrauterine delivery system 19.5 mg

Composition	Reference to Standard	Function	Amount [mg]
Drug substance			
Levonorgestrel (b) (4)	Ph. Eur., USP	drug substance	19.5 mg
(b) (4)			
Other components			
T-Body for LNG IUS 19.5 mg [b]	specification	structural frame	1 piece
Thread PP blue thin [c]	specification	removal thread	(b) (4) cm
Silver profile (b) (4) mm	specification	facilitates detection by ultrasound	mm
Integrated administration device			
Inserter for LNG IUS 19.5 mg	specification	administration device	1 piece
(b) (4)			

b Polyethylene (Ph. Eur. 3.1.3, USP<661>) containing (b) (4) % barium sulfate (Ph. Eur., USP)
c Polypropylene (Ph. Eur. 3.1.3 and 3.1.6, USP <88>,<661>) pigmented with ≤ (b) (4) % copper phthalocyanine (CI 74160, CAS 147-14-8, 21 CFR 74.3045)

2. Drug Development

Levonorgestrel intrauterine delivery system 19.5 (LCS 16) was developed in parallel with Levonorgestrel intrauterine delivery system 13.5 mg (SKYLA, LCS 12). The former was designated for the use of 5 years, and the latter for 3 years. The development of both LCS 16 and LCS 12 was based on the experience from the marketed product Levonorgestrel intrauterine delivery system 52 mg (Mirena; 20 µg/day levonorgestrel releasing intrauterine system 52 mg) and experimental formulations.

3. In Vitro Release Method

The Applicant developed the following in vitro release method for Levonorgestrel intrauterine delivery system 19.5 mg as a quality control (QC) release test:

Table 2. In vitro release method

Apparatus	Shaking water bath
Agitation speed	70 ± 5 strokes/ min (spm)
Medium	1.0 % 2-hydroxypropyl-β-cyclodextrin (2-HPBCD) solution
Volume	75 mL
Temperature	37 ± 0.5°C
Sampling times	Days 2, 11, and 25

4. In Vitro Release Method Development:

(b) (4)

[redacted]

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(b) (4)

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: N/A

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: N/A

Bridging of Formulations

Reviewer's Assessment:

The formulation used for Phase 3 Clinical Trial is the same as the one used for commercial products. Therefore, no bridging studies are needed.

Biowaiver Request

Reviewer's Assessment: N/A

R Regional Information

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

List of Deficiencies:

N/A

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, 7/11/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Kelly M. Kitchens, Ph.D., July 25, 2016

Kelly Kitchens

Digitally signed by Kelly Kitchens
Date: 8/04/2016 01:57:46PM
GUID: 508da6fd0002849b46320c175775bdfa

Hansong Chen

Digitally signed by Hansong Chen
Date: 8/04/2016 02:06:53PM
GUID: 525d7d660003845a197a2e1682433d0d

MICROBIOLOGY

Product Background: -

NDA/ANDA/BLA: 208224

Drug Product Name / Strength: Kyleena (proposed)/ levonorgestrel-releasing intrauterine system (LCS16)/ intrauterine delivery system containing 19.5 mg of the drug substance.

Route of Administration: intrauterine delivery system

Applicant Name: Bayer Healthcare Pharmaceuticals Inc.

Manufacturing Site:
Bayer Oy (Manufacturing (b) (4))
Pansiontie 47, Turku 20210, Finland

(b) (4)

Method of Sterilization: (b) (4) Ethylene Oxide (ETO)

Review Summary: Recommended for Approval

List Submissions being reviewed: 11/18/2015; 03/21/2016; 06/08/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None identified

Supporting/Related Documents: N/A

Remarks Section: This submission is in the eCTD format and the drug product is similar to Mirena and Skyla, which were approved under NDA 21225 and 203159, respectively. The subject drug product and Skyla were developed under the applicant's IND 73,505 for low dose Levonorgestrel Contraceptive System (LCS). Applicant's response dated 03/21/2016 is in response to the Agency's Information Request sent 03/14/2016. Applicant's response dated 06/08/2016 is in response to the Agency's Information Request sent 06/01/2016. Certain tables and figures are copied directly from the submission.

S Drug Substance – Not applicable

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Intrauterine drug delivery system that is designed to release levonorgestrel over a period of 5 years. The system consists of a drug reservoir mounted on the vertical stem of a T-body. The drug reservoir consists of a core of (b) (4)% levonorgestrel and (b) (4)% poly(dimethylsiloxane) elastomer, covered with a poly(dimethylsiloxane) membrane. A silver ring is attached to the upper end of the vertical stem. The T-body has a loop at one end and 2 arms at the other end. Blue polypropylene (PP) removal threads are attached to the loop. An integrated inserter consists of an insertion tube, plunger, flange, handle, slider, and thread lock. Schematics of the system and inserter are copied below (see Section 3.2.P.1, Description of the Drug Product – P.1.01#010263061, p. 3).

Figure 1: Schematic illustration of the system

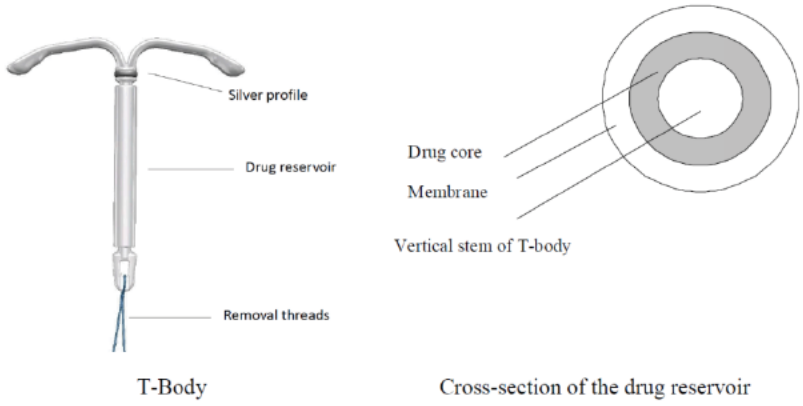
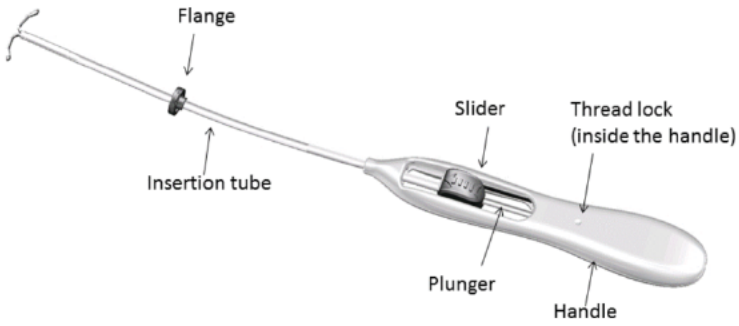


Figure 2: Schematic illustration of the integrated inserter



- **Drug product composition –**

Component	Function	Content
Levonorgestrel (b) (4), Ph. Eur., USP	Drug substance	19.5 mg
(b) (4)		
T-Body for LNG IUS 19.5 mg b	Structural Frame	1 piece
Thread PP blue thin	Removal Thread	(b) (4) cm
Silver profile (b) (4) mm	Facilitates detection by ultrasound	(b) (4) mm
Inserter for LNG IUS 19.5 mg	Administration device	1 piece

- **Description of container closure system –** The drug product is packaged in a (b) (4) package (tray) (b) (4) The applicant states that the primary package was designed to follow the requirements of EN ISO 11607-1. Figure 2-2 below is copied directly from Section 2.3.P, Drug Product, p. 13.

Figure 2-2: Primary package of Levonorgestrel intrauterine delivery system 19.5 mg

(b) (4)

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: The applicant has provided adequate executed batch records (b) (4) [redacted]

Comparability Protocols

Reviewer's Assessment: Not Applicable. No comparability protocol was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Section 1.14.1.3, Draft Labeling Text)

Storage temperature: 25°C (77°F); with excursions permitted between 15–30°C (59–86°F); (b) (4) intrauterine delivery system (b) (4) [redacted]

Reviewer's Assessment: The storage conditions described in the package insert are adequate to maintain product sterility.

Post-Approval Commitments: Not Applicable

Lifecycle Management Considerations

Reviewer's Assessment:

Use of the ETO sterilization process at a facility other than the (b) (4) [redacted] **sites listed in the application could affect microbiological quality.**

List of Deficiencies: None

QUALITY ASSESSMENT

Primary Microbiology Reviewer Name and Date: Elizabeth Bearr, Ph.D. 06/14/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur.

Erika Pfeiler, Ph.D., 14 June 2016

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 7/28/2016 09:05:42AM
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Elizabeth Bearr

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Date: 7/28/2016 09:01:44AM
GUID: 55370d1e00cfd67fc04d8bfbedbf3096

ATTACHMENT I: Risk Assessment

Initial Risk Assessment for NDA 20822, Levonorgestrel-releasing intrauterine system, for the prevention of pregnancy for up to 5 years.

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	• Quality of raw materials • Process parameters • Stability	1	2	1	2	
Identification	• cGMPs	1	5	1	5	
Assay	• Formulation • Raw materials • Process parameters • Scale/Equipment	2	4	3	24	(b)(4) % drug load in core
Impurities / Degradants	• Raw materials • Process parameters • Stability	3	4	5	60	
Uniformity of Dosage Units	• Raw materials • Formulation • Process parameters	2	4	5	40	(b)(4) % drug load in core
Sterility	• Process parameters • Container/closure system (CCS) • Scale/Equipment	3	5	3	45	Ethylene oxide sterilization
Drug Release	• Raw materials • Formulation • Process parameters	3	5	3	45	LNG particle size
Mechanical Properties	• Raw materials • Process parameters	2	5	2	20	Raw material controls; Specification includes several tests for mechanical function

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Appearance	• Quality of raw materials • Process Parameters	2	Automatic on-line inspection is performed during the (b)(4) and IUS assembly steps (= 100 % check).	Acceptable	
Identification	• cGMPs	5	-	Acceptable	
Assay	• Formulation • Raw materials • Process parameters • Scale/Equipment	24	In-process control of (b)(4) drug core dimensions.	Acceptable	
Impurities / Degradants	• Raw materials • Stability • Process	60	(b)(4)	Acceptable	
Uniformity of Dosage Units	• Raw materials • Formulation • Process parameters	40	Drug substance (b)(4) mixing time for LNG/PDMS mixture	Acceptable	

Sterility	• Process parameters • Container/closure system (CCS)	45	Process validation and requalification	Acceptable	See Note 1 below.
Drug Release	• Formulation • Process parameters	45	Control of drug core and (b) (4) drug core weight and dimensions; in vitro release testing	Acceptable	
Mechanical Properties	• Raw materials • Process parameters	20	Raw material controls; Product specficiation	Acceptable	

Note 1. If ethylene oxide (b) (4) sterilization process (b) (4) for production of the subject drug product, then provide requalification data to support that the sterilization process remains valid for the subject drug product in the Annual Report for this application. Reference is made to the outline of requalification studies presented in ANSI/AAMI/ISO 11135.

Use of the ETO sterilization process at a facility other than the (b) (4) sites listed in the application could affect microbiological quality.

Initial Process Risk Assessment (J. Liang)

Product Attribute/ CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Process Risk Assessment						
Physical Stability (Solid state)	(b) (4)	M	H	H	H	(b) (4)
Chemical stability (impurities) an Assay		M	M	H	H	
Dissolution		L	H	M	M	
		M	H	H	H	
Content Uniformity		L	M	M	L	

ATTACHMENT II: List of Deficiencies for Complete Response

Not Applicable.

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