CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

CHEMISTRY REVIEW(S)

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **January 03, 2013**

From: **Tarun Mehta, M.Sc.**

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: **CMC Review #1 of NDA 203159**

Subject: **Final Recommendation**

The CMC review #1 has noted the following three pending issues:

1. The process control parameters table needed to be revised, excipient (PDMS) specification needed to be revised, the dissolution test was not adequate per Biopharm's Review, and the functionality of inserter was not satisfactorily resolved for CDRH.
2. Final "Acceptable" recommendation from the Office of Compliance was not issued.
3. Label/labeling issues were not resolved.

And because of these deficiencies, this NDA was not recommended for approval from the ONDQA perspective.

On September 28, 2012, the applicant has submitted an amendment SN0022 with the satisfactory revised process control parameter tables and excipients specification (**Attachment-1**).
On September 27, 2012 the Biopharm reviewer, Sandra Suarez, Ph.D., has completed the review and made the "Approval" recommendation (**Attachment-2)**.
On October 24, 2012 the CDRH reviewer Veronica Price, Ph.D. has provided the final review and made the "Approval" recommendation.
On January 7, 2013, the Office of Compliance issued a final "Acceptable" recommendation for the facilities involved in the NDA (**Attachment-3**).
On January 4, 2013, the final label and labeling which were revised satisfactorily from the ONDQA perspective (**Attachment-4**).

Recommendation:

This NDA is **now** recommended for **APPROVAL** from the ONDQA perspective.

Attachments

Attachment-1: Revised Process Control Parameters and Excipients Specification

(b) (4)

[redacted]

PDMS Silica filled:

(b) (4)

Attachment-2: Revised Release Drug Product Specification

Test	Acceptance criterion
Appearance	
Appearance	must comply
Formulation	intrauterine system with silver ring
Surface property	free from visual flaws
Color of drug reservoir	whitish or pale yellow
Identity (HPLC)	must comply
Identity (IR)	must comply with reference spectrum

(b) (4)

[redacted]

Attachment-3: EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203159/000	**Sponsor:**	BAYER HLTHCARE
Org. Code:	580		1000
Priority:	5		MONTVILLE, NJ 070451000
Stamp Date:	09-DEC-2011	**Brand Name:**	LCS12
PDUFA Date:	09-JAN-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	10-AUG-2012	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; INTRAUTERINE DEVICE; LEVONORGESTREL; 13.5MG	

FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	T. MEHTA	Review Chemist	3017961712
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 07-JAN-2013	by S. HERTZ	(HFD-320)	3017963203
	PENDING	on 11-JUL-2012	by EES_PROD		
	PENDING	on 03-JUL-2012	by EES_PROD		
	ACCEPTABLE	on 22-FEB-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 23-DEC-2011	by EES_PROD		
	PENDING	on 23-DEC-2011	by EES_PROD		

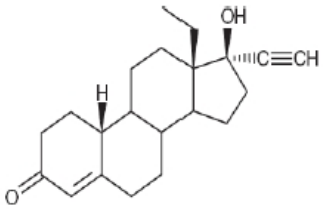
Attachment-4: Final Labeling and Labels

1. Package Insert

#11: Description:

Skyla (levonorgestrel-releasing intrauterine system) contains 13.5 mg of levonorgestrel, a progestin, and is intended to provide an initial release rate of approximately14 mcg/day of levonorgestrel after 24 days.

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Skyla, has a molecular weight of 312.4, a molecular formula of C21H28O2, and the following structural formula:



#16: How Supplied/Storage and Handling

"Skyla (levonorgestrel-releasing intrauterine system), containing a total of 13.5 mg levonorgestrel, is available in a carton of one sterile unit NDC# 50419-422-01
Skyla is supplied sterile. Skyla 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]."

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

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/s/

TARUN D MEHTA
01/07/2013

MOO JHONG RHEE
01/07/2013
Chief, Branch IV

Review Memorandum

To: Charlene Williamson

From: Terry O. Woods, Ph.D.
WO 62-2116

Date: December 20, 2012

Re: NDA 203-159 Bayer Healthcare Pharmaceuticals Skyla (levonorgestrel-releasing intrauterine system), MR induced force, torque, and artifact testing and labeling

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This review covers responses to questions from my memo of October 19 and revised labeling received by e-mail over the last few weeks.

Recommendation: I have no further questions on the testing and analysis. I request that they change

(b) (4)

To

Skyla can be safely scanned (b) (4) only under specific conditions.

where it appears in their patient booklet, patient counseling information, and patient labeling.

I have no further changes to request in the labeling.

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/s/

ZETA-MAE C WILLIAMSON
12/21/2012

PMA EIR REVIEW MEMORANDUM

DATE:	December 5, 2012
FROM:	CSO, Obstetrics/Gynecology, Gastroenterology, and Urology Branch, Division of Enforcement A, Office of Compliance, CDRH
THROUGH:	Debra Demeritt, Chief, Gastroenterology, and Urology Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3540
TO:	Tarun Mehta, OMPT/CDER/OPS/ONDQA, WO-22, Room 1463
Cc:	Jennifer Mercier, OMPT/CDER/OND, WO-22, Room 5358 Charlene Williamson, OMPT/CDER/OND/DRUP, WO-22, Room 5395
SUBJECT:	Review of Premarket Approval (PMA) Preapproval Establishment Inspection Report (EIR) and Exhibits
	Applicant: Bayer Oy, Turku Pansionitie 47 20210 Turku Finland FEI/CFN: 1000350927
PMA NUMBER(S):	NDA 203159
DEVICE(S):	SKYLA (levonorgestrel releasing contraceptive system)
ORA RECOMMENDATION:	VAI
INVESTIGATOR(S):	Steven D. Kehoe, KAN-DO
SITE COMPLIANCE DECISION:	NAI – Facility Clearance
FINAL PMA RECOMMENDATION:	Approve PMA-final decision CDER

I. Purpose and Type of Inspection

The purpose for the inspection was to conduct a pre-approval inspection for NDA 203159 SKYLA (levonorgestrel releasing contraceptive system) internally known as LCS 12, which is a combination product.

The current inspection was a comprehensive baseline Level 2 inspection.

II. Background Information

The firm is currently registered for 2012 as a human drug manufacturer which includes several types of intrauterine contraceptive devices and one antiarrythmic tablet. The products are distributed in the United States (US) through Bayer Health Care's US distribution centers.

(b) (4)

(b) (4)

(b) (4) The firm reports that there have been no known adverse issues stemming from this deviation.

III. Regulatory History

December 12, 2011	The last inspection covered operations associated with pharmaceuticals. This inspection was classified NAI.

IV. Current Inspection

The Obstetrics Gynecology, Gastroenterology, and Urology Devices Branch of the Division of Enforcement 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 October 2, 2012 which took place at Bayer OY, Turku Finland facility. The inspection of this firm indicates that it meets the criteria of a Situation II, in Compliance Program, CP 7383.001, Part V, dated March 5, 2012 in that there is minimal probability that the establishment will produce nonconforming and/or defective medical devices and the inspection is being classified NAI.

CDRH does not concur with the classification recommendation and is requesting that the inspection be classified as NAI, for the following reasons because there

are no deficiencies that qualify as major at the moment.

V. Quality System Review

The review of the EIR and exhibits did not disclose any QS regulation violations or objectionable conditions. Although a FDA 483 was not issued and no violations were cited during this inspection, a device Quality System Regulation concern was identified:

1) **Process Validation, 21 CFR 820.75 (c)**

The firm encountered some unexplained deviations during the qualification process for LCS 12 production. Qualification of [redacted] (b) (4) identified failures in dimensional requirements. A new [redacted] (b) (4) was purchased to correct these deficiencies. However, the process qualification (PQ) of the new equipment identified flaws [redacted] (b) (4) These flaws were identified in all three runs, but failed acceptance criteria in only one run. The root cause was identified [redacted] (b) (4) Preventative maintenance [redacted] (b) (4) was implemented. However, only one additional qualification run was performed. A review of Procedure FI00726 "Process Validation of manufacturing and packaging processes" did not state the number of runs to be executed if there were failures of one or multiple runs.

VI. Observations Pertaining To Other Regulations

There are no observations pertaining to other regulations.

VII. Nonsupportable FDA 483 Observations

A FDA 483 was not issued.

VIII. CDRH Recommendation and Follow-up

CDRH has reclassified the inspection NAI, based on the EIR dated September 24, 2012 to October 2, 2012, because there were no supportable violations of 21 CFR part 820.

CDRH recommends followup with the firm to provide updated data for process qualification runs of multiple batches through the [redacted] (b) (4) for the Skyla product (LCS 12).

CDRH leaves to CDER, the lead Center for this inspection, to initiate any follow up actions to the violations found during the inspection and make a final decision on the overall classification of the inspection.

Shirley A. Zeigler

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/s/

ZETA-MAE C WILLIAMSON
12/19/2012

Review Memorandum

To: Veronica Price

From: Terry O. Woods, Ph.D.
WO 62-2116

Date: October 19, 2012

Re: NDA 203-159 Bayer Healthcare Pharmaceuticals Skyla (levonorgestrel-releasing intrauterine system), MR induced force, torque, and artifact testing

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This review covers MR induced force, torque, and artifact testing and labeling. Questions for the company are at the end and are indicated by bullets. Wolfgang Kainz is reviewing the RF heating testing and labeling.

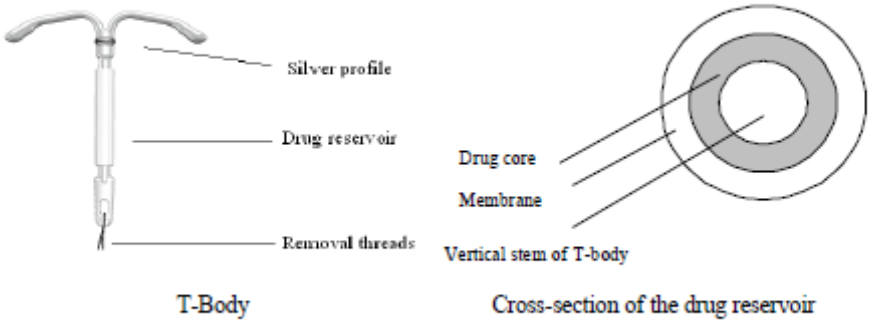
Device Description and intended use: Levonorgestrel intrauterine delivery system 13.5 mg (LCS12) is an intrauterine drug delivery system regulated as medicinal product with device components forming an integral part of the system. Another synonym used in module 3 is LNG IUS.

The intrauterine delivery system consists of a whitish or pale yellow 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 two arms at the other end. Removal threads are attached to the loop.

LCS12 consists of a T-shaped polyethylene frame (T-body) with a cylindrical drug reservoir on the vertical stem. The core is composed of a mixture of 13.5 mg LNG (b) (4) and poly(dimethylsiloxane). The drug core is covered by a poly(dimethylsiloxane) membrane, (b) (4) A silver profile 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.

A detailed discussion of the excipients and components is provided in the module 3 document: Source: P.2.1.01-01 Pharmaceutical Development – Components

Figure 1-1: Schematic illustration of the system



Testing: [redacted] (b) (4) did testing at 3T.

Torque testing:

[redacted] (b) (4) performed a qualitative torque test at 3T that showed no observable torque.

Force testing:

[redacted] (b) (4) did force testing using a method similar to ASTM F2052 using a GE 3T excite scanner. Spatial gradient at the test position is 720 Gauss/cm

He tested one device and measured an average deflection of 1 degree at a location where he indicated the spatial gradient is 720 Gauss/cm. The static field strength at this location was not provided.

Image Artifact Testing

[redacted] (b) (4) did artifact testing using a method similar to F2119. He reports signal void area in mm^2 for a T1 weighted spin echo sequence and a gradient echo sequence. Void extended approximately 5mm from the device in the GRE sequence. Void was greater for the GRE than for the SE sequence.

Proposed labeling from p. 20/36 of the test report

(b) (4)

Questions:

- MRI scanners with maximum spatial gradients approaching 3,000 Gauss/cm are common. This value is substantially greater than the 720 Gauss/cm at the test location for your magnetically induced deflection force testing. Because your device showed a relatively low magnetically induced deflection force in the 720 Gauss/cm spatial gradient used for your testing, we encourage you to perform an additional analysis to determine if there is a larger spatial gradient for which your device can safely be scanned. If this is the case, you would be able to list a larger value of spatial gradient in your labeling and therefore provide your patients with access to MRI scanners with maximum spatial gradient fields greater than the gradient at the location used for your displacement force testing.

In order to perform this analysis, you need to know the values of **both** the spatial gradient and **the magnetic field strength** at the test location. Note that at the test location, the magnetic field strength is less than 3T. The following may be useful if you choose to perform this analysis.

The magnetically induced force on the device is calculated as follows:

$$F_m = \chi \left(\frac{V}{\mu_0} \right) B \nabla B \quad \text{(X3.2)}$$

where:
μ_0 = permeability of free space = $4\pi \times 10^{-7}$ H/m
B = static magnetic field in T
∇B = gradient field in T/m (when on the axis of the MR system bore, ∇B = dB/dz)
χ =dimensionless susceptibility, $M = \chi B$, where B is the background magnetic field present prior to insertion of the device.

The force due to gravity is calculated as follows:

$$F_g = \rho V g \quad \text{(X3.3)}$$

where:

ρ = density in kg/m^3
V = volume
g = acceleration due to gravity

The force ratio is defined as the ratio of the magnetically induced deflection force (F_m) to the weight of the device (F_g). It can be calculated by dividing Eq. X3.2 by Eq. X3.3

$$F_r = \frac{F_m}{F_g} = \frac{\chi}{\rho \mu_0 g} B \nabla B \quad \text{(X3.4)}$$

Considering the measured displacement force from Eq. X2.3,

$$F_r = \frac{F_m}{F_g} = \frac{mg \tan(\alpha)}{\rho V g} = \frac{\rho V g}{\rho V g} \tan(\alpha) = \tan(\alpha) \quad \text{(X3.5)}$$

Equating X3.4 and X3.5 gives

$$\frac{\chi}{\rho \mu_0 g} B \nabla B = \tan(\alpha) \quad \text{(X3.6)}$$

Or

$$\frac{\chi}{\rho\mu_0 g} = \frac{\tan(\alpha)}{B\nabla B} \text{ (X3.7)}$$

Where $\frac{\chi}{\rho\mu_0 g}$ is constant.

Knowing the measured deflection angle, magnetic field strength, and spatial gradient of the magnetic field strength at test location L, it is possible to calculate an acceptable maximum spatial gradient for a different set of field conditions, C.

$$\frac{\tan(\alpha_L)}{B_L \nabla B_L} = \frac{\tan(\alpha_C)}{B_C \nabla B_C} \text{ (X3.8)}$$

And

$$\nabla B_C = \nabla B_L \frac{B_L}{Bc} \frac{\tan(\alpha_C)}{\tan(\alpha_L)} \text{ (X3.9)}$$

For instance, to determine an allowable maximum spatial gradient in a scanner with maximum field strength of 3.0 T, one could assume a field strength of 3.0 T and a force ratio of 1 (where the magnetically induced deflection force equals the device weight and the deflection angle is 45º) and use equation X3.9 together with a suitable safety factor to estimate an allowable maximum spatial gradient.

- In your proposed labeling, please change the header for the MR safety information from [redacted] (b) (4) to "Magnetic Resonance Imaging (MRI) [redacted] (b) (4) Information."

- In your proposed MRI Safety and Compatibility labeling, please add a bullet indicating Normal Operating Mode or First Level Controlled mode, as appropriate.
- In your IFU (p. 263), please also add a statement about the distance the image artifact extends from the device for a particular scan sequence. Suitable language was suggested in your MR consultant's test report.

- Please revise your MR Conditional labeling to conform to the format below. Please include the MR Conditional icon with this section of the labeling. Please also include this information on your implant card.

  Non-clinical testing has demonstrated the (insert device name) is MR Conditional. It can be scanned safely under the following conditions:

  - *static magnetic field of ___ Tesla (or ___ Tesla) only*
  - *spatial gradient field of ___ Gauss/cm (T/m) or less*

- *maximum whole body averaged specific absorption rate (SAR) of 2 or 4W/kg for __ minutes of continuous scanning*
- *Normal Operating Mode or First Level Controlled mode, as appropriate*

In non-clinical testing, the (insert device name) produced a temperature rise of less than __°C at a maximum whole body averaged specific absorption rate (SAR) of 2 or 4W/kg, for ___ minutes of MR scanning in a (field strength__) (model__) (manufacturer__) (software version __) MR scanner.

Also include a statement about extent of image artifact for a specific scan sequence

Recommendation: The testing for force, torque, and artifact is acceptable. The analysis in the long first question should take only a few minutes and will provide the patients access to many more commercial clinical MRI scanners.

I have some requests for changes in the labeling, as well as a request for an implant card, though I don't know if this device is required to have an implant card. Wolfgang will probably also have changes in the labeling to request.

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/s/

ZETA-MAE C WILLIAMSON
11/07/2012

NDA 203-159

Skyla (levonorgestrel-releasing intrauterine system) 13.5 mg

Bayer HealthCare Pharmaceuticals Inc.

Tarun Mehta

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC REVIEW OF NDA 203-159
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 203-159

2. REVIEW #: 1

3. REVIEW DATE: 08-06-2012

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	09-Dec-2011
Amendment SN 0002	22 – Dec - 2011
Amendment SN 0005	12 – Mar - 2012
Amendment SN 0008	16 – Apr - 2012
Amendment SN 0010	06 – June - 2012
Amendment SN 0012	05 – July - 2012
Amendment SN 0017	25 – July - 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer HealthCare Pharmaceuticals Inc.
Address:	PO Box 1000, Montville, NJ 07045-1000
Representative:	Jo-Ann Ruane, Associate Director
Telephone:	(973) 487-2343

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Skyla
b) Non-Proprietary Name: Levonorgestrel-releasing intrauterine system
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Contraception

11. DOSAGE FORM: Intrauterine system

12. STRENGTH/POTENCY: 13.5mg

13. ROUTE OF ADMINISTRATION:

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
4178	II	Bayer Pharma AG	Levonorgestrel	3	Adequate	06-Oct-2011	Adequate Liang Jennifer
(b) (4)	III	(b) (4)		1	Adequate	26-Mar-2012	Review by Tarun Mehta
	III			1	Adequate	26-Mar-2012	Review by Tarun Mehta
				3	Adequate	30-Oct - 2000	Reviewed by R. Agarwal
	IV			1	Adequate	24-July-2012	Reviewed by Tarun Mehta
	V			1	Inadequate*	26-Mar-2012(CMC) 16-May- 2012 (CDRH)	Review by Tarun Mehta/CDRH

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* The DMF (b) (4) for Inserter is still under review by CDRH. The response to the previous IR letter was received on July 25, 2012, and its final review is still pending.

B. Other Documents:

CMC Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73,505	Low Dose Contraceptive system
NDA	21-225	Mirena (levonorgestrel-releasing system)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	Jul 11, 2012	M. Stock
Biopharm	Pending	Feb 10, 2012	Sandra Surez-Sharp
CDRH	Pending	Feb 9, 2012	Jacqueline Ryan / Price Veronica
EA	Adequate	Sep 07, 2012	Tarun Mehta
Microbiology	Adequate	Mar 26, 2012	Jessica Cole

The CMC Review for NDA 203-159

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this submission has ***not*** submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has ***not*** made an overall "Acceptable" recommendation for the facilities involved in this submission.,

Also, the issues on labels/label are ***not*** resolved satisfactorily as of this review date.

Therefore, from the ONDQA perspective, this submission is ***not*** recommended for approval in its present form per 21 CFR 314.125(b)(1),(6), and (13).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance (Levonorgestrel) manufacturer, Bayer Pharma AG, for the proposed NDA is also a supplier for the applicant's marketed product, Mirena IUS (NDA 21-225). The DMF 4178 for the drug substance, levonorgestrel, was found adequate by Liang Jennifer on August 11, 2011. There are no new major amendments submitted by the DMF holder since.

(2) Drug Product

The proposed drug product, Skyla, is a low dose (13.5mg loaded) of levonorgestrel (LNG) intrauterine system, which has been developed for use as a contraceptive. The applicant has similar marketed product, Mirena®, which uses a higher dose (52mg loaded) of LNG. The design and components of the intrauterine system for both the products are very similar with some modification in Skyla. The mean *in vivo* LNG release rate of Skyla is approximately 6 µg/24 hours for over the three-year period while Mirena® has mean *in vivo* release rate of 20 µg/24 hrs and for over five-year period of use. In addition, Skyla is a smaller size system (smaller

insertion tube diameter and T-frame) and contains a silver ring/profile around the vertical stem of the T-frame to facilitate detection during ultrasound examination.

Skyla consists of T-shaped polyethylene frame (T-body) with a cylindrical drug reservoir on the vertical stem. The drug core is composed of a mixture of 13.5 mg LNG (b) (4) and poly (dimethylsiloxane) elastomer. The drug core is covered by a poly(dimethylsiloxane) elastomer membrane, (b) (4)

A modified inserter of Skyla has been developed (b) (4) The proposed indication for Skyla is for the prevention of pregnancy for up to 3 years.

The applicant has successfully manufactured three commercial size (b) (4) validation batches using same formulation and manufacturing process as used for the clinical and the registration batches. The drug product sterility and stability were tested using the proposed commercial packaging. Based on the adequate stability data, the sterile drug product is granted a 24 months of expiration dating period when stored at the room temperature in the proposed packaging.

CDRH was consulted for the concern about the quality of the inserter tube and flange, functionality of the slider and thread lock and overall reproducibility of the device by the device supplier. The consult review is still pending.

B. Description of How the Drug Product is Intended to be Used

The proposed drug product is used for the prevention of pregnancy for over three-year period by inserting the Skyla in uterine cavity. Skyla is supplied within an inserter in a sterile package that should not be open until required for insertion. Skyla is to be inserted by trained health care provider using a strict aseptic technique.

C. Basis for non-approval Recommendation

21CFR 314.125(b)(1)

- Functionality of the inserter in the CDRH Consult Review has not been fully accepted.

21CFR 314.125(b)(6)

- Issues on label/labeling are not resolved satisfactorily yet.

21CFR 314.125(b)(13)

- Preapproval inspection on the site where the inserter is manufacture is pending.

(see the **List of Deficiencies**, p.61)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

CMC Reviewer, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D.

Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

C. CC Block:

(See appended electronic signature page)

Donna F. Christner, Ph.D.

CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

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/s/

TARUN D MEHTA
08/06/2012

MOO JHONG RHEE
08/06/2012
Chief, Branch IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
Obstetrics/Gynecology, Gastroenterology, and Urology Devices Branch

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DATE:	June 13, 2012
TO:	Tarun Mehta, OMPT/CDER/OPS/ONDQA, WO-22, Room 1463
Cc:	Jennifer Mercier, OMPT/CDER/OND, WO-22, Room 5358 Charlene Williamson, OMPT/CDER/OND/DRUP, WO-22, Room 5395 Office of combination products at combination@fda.gov
THRU:	Debra Demerritt, Chief, Gastroenterology, and Urology Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3540
FROM:	Shirley Zeigler, Obstetrics, Gastroenterology, and Urology Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3556
SUBJECT:	Inter-Center consult requested by OMPT/CDER/OPS/ONDQA. This is a premarket consult for NDA 203159, SKYLA (levonorgestrel releasing contraceptive system). The application was submitted by Bayer Healthcare Pharmauceuticals, Inc.
CONSULT INSTRUCTIONS:	Evaluate the manufacturing process for assembly of the T-body drug product into the device inserter to determine what information is necessary for a full review and if an inspection is required to address device issues.

Objective

The Office of Compliance at CDRH received a consult request from CDRH regarding the SKYLA (levonorgestrel releasing contraceptive system) on May 2, 2012. The consult requested CDRH/OC evaluation of the adequacy of the device manufacturing process for assembly of the T-body drug product into the device inserter to determine what information is necessary for a full review and if a device-specific inspection is required to address device issues.

Product Description

The levonorgestrel intrauterine delivery system 13.5 mg (LCS12) is an intrauterine drug delivery system regulated as a medicinal product with device components forming an integral part of the system. LCS12 is designed to release levonorgestrel (LNG) at a constant, predictable rate (initial *invitro* release rate 12 ug/day) with the intended use for prevention of pregnancy. The aim of the development program was to develop a levonorgestrel releasing intrauterine system of smaller size that releases a lower dose of LNG than the Mirena intrauterine delivery system, which is currently marketed in 120 countries.

The intrauterine delivery system consists of a whitish or pale yellow 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 two arms at the other end. Removal threads are attached to the loop. LCS12 is provided with an integrated inserter. The inserter components are the insertion tube, plunger, flange, handle, slider, and thread lock. The drug product, mounted on top of the inserter, is packaged in a (b) (4) package (b) (4) (b) (4) See schematic illustrations in figures 1 and 2.

Figure 1. Schematic illustration of the integrated inserter

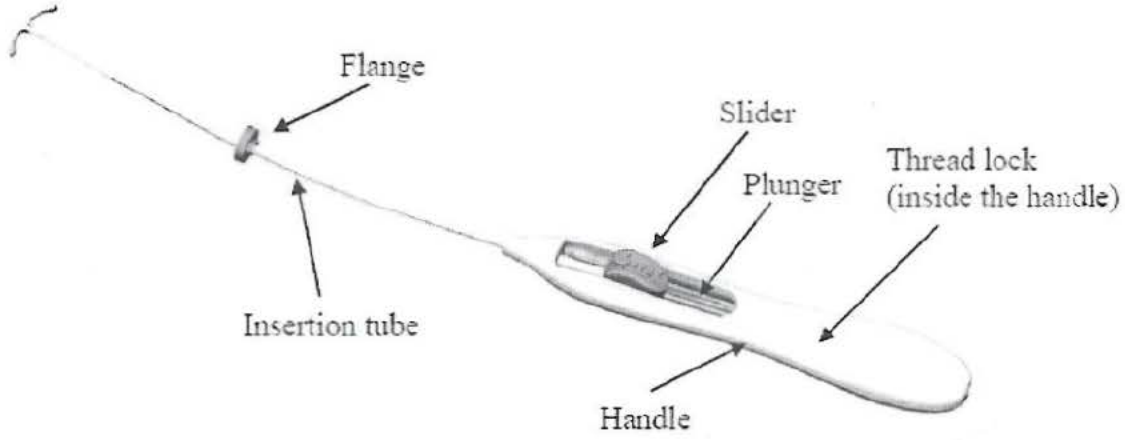
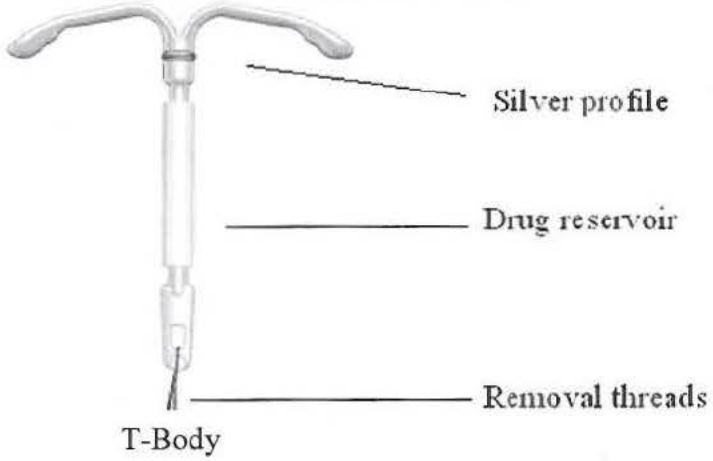


Figure 2. Schematic illustration of the system



The Levonorgestrel intrauterine deliver system 13.5 mg is manufactured in a dedicated production area at Bayer Oy, Turku plant:

Bayer Oy, Turku
Pansionitie 47
20210 Turku
Finland

Consult Evaluation

During the CDRH review of NDA-203159, we identified areas where either the data was missing or incompletely developed. Upon review of the records provided, CDRH Office of Compliance has established that Bayer Oy, located in Torku, Finland is responsible for the finished SKYLA (levonorgestrel intrauterine delivery system) 13.5 mg. The firm's contact information is:

Bayer Oy, Turku
Pansionitie 47
20210 Turku
Finland
FEI: 1000350927

Note: This firm was last inspected December 12, 2011, covering operations associated with pharmaceuticals. The inspection was classified NAI.

CDRH Recommendation

CDRH recommends that the approval of NDA 203159 is deferred until the time when satisfactory pre-approval inspection has been conducted at the site mentioned above. Attached to this review is an inspection guidance document with inspectional suggestions CDRH recommends to be inspected.

Shirley A. Zeigler

Prepared/typed: SZeigler: 06/11/2012 SZ
Revised: SZeigler: 6/13/2012 SZ
Reviewed/approved: DDemerritt:06/13/12 DD 6/13/12
Reviewed/revised: SZeigler: 06/13/2012 SZ
Finalized: [ABFinal:XX/XX/XX] GKroehling 13JUNE2012

cc:
WO66-3515 (DOE-A Firm File)
WO66-3515 (Division Chron File)
WO66-3556 (SZeigler)

CTS No.: ICC1200060
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/s/

ZETA-MAE C WILLIAMSON
10/18/2012
CDRH Review