

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021225/S-033

Trade Name: **MIRENA**

Generic Name: **Levonorgestrel Releasing Intrauterine System**

Sponsor: **Bayer HealthCare Pharmaceuticals Inc.**

Approval Date: 05/29/2014

Indications: Mirena is indicated for intrauterine contraception for up to 5 years.

Mirena is also indicated for the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 021225/S-033

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

APPROVAL LETTER



NDA 021225/S-033

APPROVAL LETTER

Bayer HealthCare Pharmaceuticals Inc.
Attention: Joseph Zuccarini
Deputy Director, Global Regulatory Affairs
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915

Dear Mr. Zuccarini:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mirena (levonorgestrel releasing intrauterine system).

We acknowledge receipt of your amendments dated May 29, 30, June 3, August 19, 2013, January 29, and May 28, 2014.

The January 29, 2014, submission constituted a complete response to our August 30, 2013, action letter.

This "Prior Approval Supplement" supplemental new drug application provides for: 1) a modified inserter to replace the current inserter, 2) new packaging materials, 3) changes in polyethylene grade used for the insertion tube and a new pigment for the inserter flange, and 4) corresponding labeling changes.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
05/29/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

OTHER ACTION LETTERS



NDA 021225/S-033

COMPLETE RESPONSE

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Joseph Zuccarini
Deputy Director, Global Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Mr. Zuccarini:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mirena® (levonorgestrel-releasing intrauterine system [IUS]).

We acknowledge receipt of your amendments dated May 29, 30, June 3, and August 19, 2013.

This supplemental new drug application proposes 1) a modified inserter to replace the current inserter and 2) a change in the primary container closure system.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. It is not clear what hazards are associated with the modified inserter. Provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, submit your draft protocol for review prior to conducting the study.
 - Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

- We recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.
 - If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site *Medical Device Human Factors*, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.
2. The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUS. Testing should be conducted to evaluate the ability of the insertion device to deliver the IUS to its target location in its intended shape/configuration. This testing should be conducted in a model that simulates worst-case clinical conditions and should include a statistically valid sample size. Provide a copy of this testing along with the results for review.
 3. Your application referenced the Drug Master File (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on June 27, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

CDRH Office of Compliance Comments:

4. There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls. You must provide information showing that changes in the introducer's design do not affect the safety and effectiveness of the finished product. Similarly, you must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product. You should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, explain why no changes were necessary. Pay particular attention to the requirements for design controls under 21 CFR 820.30(i), (h) and (g).
5. You are adding an additional supplier of the inserter. Provide enough information to demonstrate adequate control over this new supplier and the product provided, as required by 21 CFR 820.50, purchasing controls.

Information about the type of documents to be submitted for review may be found at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>, 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003)

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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

Sincerely,

{See appended electronic signature page}

Audrey Gassman, MD
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
08/30/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

Dosage and Administration (2) 05/2014
Warnings and Precautions (5.6) 02/2013

INDICATIONS AND USAGE

Mirena is a progestin-containing intrauterine system indicated for:

- Intrauterine contraception for up to 5 years (1)
- Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. (1)

It is recommended for women who have had at least one child.

DOSAGE AND ADMINISTRATION

- Initial release rate of levonorgestrel (LNG) is 20 mcg/day; this rate is reduced by about 50% after 5 years; Mirena 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. (2.1)
- Patient should be re-examined and evaluated 4 to 6 weeks after insertion; then, yearly or more often if indicated. (2.2)

DOSAGE FORMS AND STRENGTHS

- One sterile intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing 52 mg levonorgestrel packaged within a sterile inserter (3)

CONTRAINDICATIONS

- Pregnancy or suspicion of pregnancy. Cannot be used for post-coital 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 Mirena (4)

WARNINGS AND PRECAUTIONS

- Remove Mirena if pregnancy occurs with Mirena in place. If 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)
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. (5.3)
- Before using Mirena, consider the risks of PID. (5.4)
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. (5.5)
- Perforation may occur and may reduce contraceptive effectiveness. Risk is increased if inserted in lactating women and may be increased if inserted in women with fixed retroverted uteri and postpartum. (5.6)
- Partial or complete expulsion may occur. (5.7)
- Evaluate persistent enlarged ovarian follicles or ovarian cysts. (5.8)

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials (> 10% users) are uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal/pelvic pain (12.8%) and ovarian cysts (12%). (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

DRUG INTERACTIONS

- Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the serum concentration of progestins. (7)

USE IN SPECIFIC POPULATIONS

- Small amounts of progestins pass into breast milk resulting in detectable steroid levels in infant serum. (8.3)

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

Revised: 5/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Insertion Instructions
- 2.2 Patient Follow-up
- 2.3 Removal of Mirena
- 2.4 Continuation of Contraception after Removal

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Ectopic Pregnancy
- 5.2 Intrauterine Pregnancy
- 5.3 Sepsis
- 5.4 Pelvic Infection
- 5.5 Irregular Bleeding and Amenorrhea
- 5.6 Perforation
- 5.7 Expulsion
- 5.8 Ovarian Cysts
- 5.9 Breast Cancer
- 5.10 Clinical Considerations for Use and Removal

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

11 DESCRIPTION

11.1 Mirena

11.2 Inserter

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Clinical Trials on Contraception

14.2 Clinical Trial on Heavy Menstrual Bleeding

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Mirena is indicated for intrauterine contraception for up to 5 years.
- Mirena is also indicated for the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception.

Mirena is recommended for women who have had at least one child.

The system should be replaced after 5 years if continued use is desired.

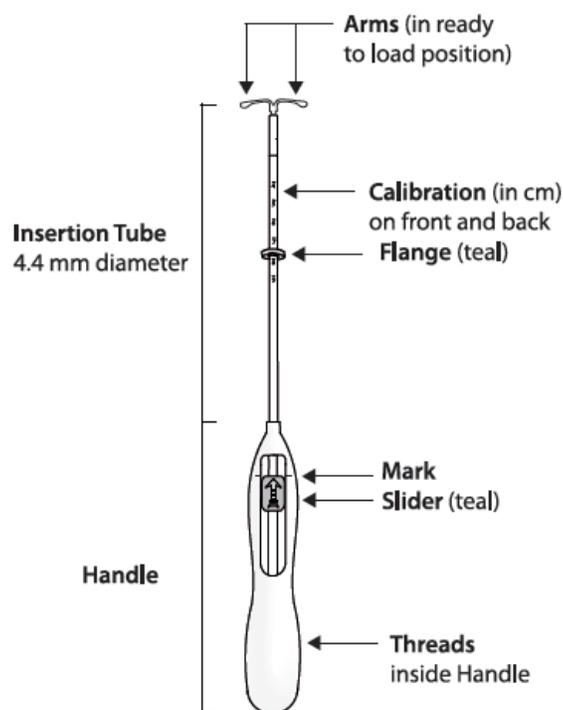
2 DOSAGE AND ADMINISTRATION

Mirena contains 52 mg of levonorgestrel (LNG). Initially, LNG is released at a rate of approximately 20 mcg/day. This rate decreases progressively to half that value after 5 years.

Mirena must be removed by the end of the fifth year and can be replaced at the time of removal with a new Mirena if continued contraceptive protection is desired.

Mirena is supplied within an inserter in a sterile package (see Figure 1) that must not be opened until required for insertion [see Description (11.2)]. Do not use if the seal of the sterile package is broken or appears compromised. Use strict aseptic techniques throughout the insertion procedure [see Warnings and Precautions (5.3)].

Mirena and Inserter



2.1. Insertion Instructions

- A complete medical and social history should be obtained to determine conditions that might influence the selection of a levonorgestrel-releasing intrauterine system (LNG IUS) for contraception. If indicated, perform a physical examination, and appropriate tests for any forms of genital or other sexually transmitted infections. [See Contraindications (4) and Warnings and Precautions (5.10).]
- Follow the insertion instructions exactly as described in order to ensure proper placement and avoid premature release of Mirena from the inserter. Once released, Mirena cannot be re-loaded.

- Mirena should be inserted by a trained healthcare provider. Healthcare providers should become thoroughly familiar with the insertion instructions before attempting insertion of Mirena.
- Insertion may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, bradycardia), or with seizure in an epileptic patient, especially in patients with a predisposition to these symptoms. Consider administering analgesics prior to insertion.

Timing of Insertion

- Insert Mirena into the uterine cavity during the first seven days of the menstrual cycle or immediately after a first trimester abortion. Back up contraception is not needed when Mirena is inserted as directed.
- Postpone postpartum insertion and insertions following second trimester abortions a minimum of six weeks or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion [*see Warnings and Precautions (5.6, 5.7)*].

Tools for Insertion

Preparation

- Gloves
- Speculum
- Sterile uterine sound
- Sterile tenaculum
- Antiseptic solution, applicator

Procedure

- Sterile gloves
- Mirena with inserter in sealed package
- Instruments and anesthesia for paracervical block, if anticipated
- Consider having an unopened backup Mirena available
- Sterile, sharp curved scissors

Preparation for insertion

- Exclude pregnancy and confirm that there are no other contraindications to the use of Mirena.
- Ensure that the patient understands the contents of the Patient Information Booklet and obtain the signed patient informed consent located on the last page of the Patient Information Booklet.
- With the patient comfortably in lithotomy position, do a bimanual exam to establish the size, shape and position of the uterus.
- Gently insert a speculum to visualize the cervix.
- Thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
- Prepare to sound the uterine cavity. Grasp the upper lip of the cervix with a tenaculum forceps and gently apply traction to stabilize and align the cervical canal with the uterine cavity. Perform a paracervical block if needed. If the uterus is retroverted, it may be more appropriate to grasp the lower lip of the cervix. The tenaculum should remain in position and gentle traction on the cervix should be maintained throughout the insertion procedure.
- Gently insert a uterine sound to check the patency of the cervix, measure the depth of the uterine cavity in centimeters, confirm cavity direction, and detect the presence of any uterine anomaly. If you encounter difficulty or cervical stenosis, use dilatation, and not force, to overcome resistance. If cervical dilatation is required, consider using a paracervical block.
- The uterus should sound to a depth of 6 to 10 cm. Insertion of Mirena into a uterine cavity less than 6 cm by sounding may increase the incidence of expulsion, bleeding, pain, perforation, and possibly pregnancy.

Insertion Procedure

Proceed with insertion only after completing the above steps and ascertaining that the patient is appropriate for Mirena. Ensure use of aseptic technique throughout the entire procedure.

Step 1—Opening of the package

- Open the package (Figure 1). The contents of the package are sterile.

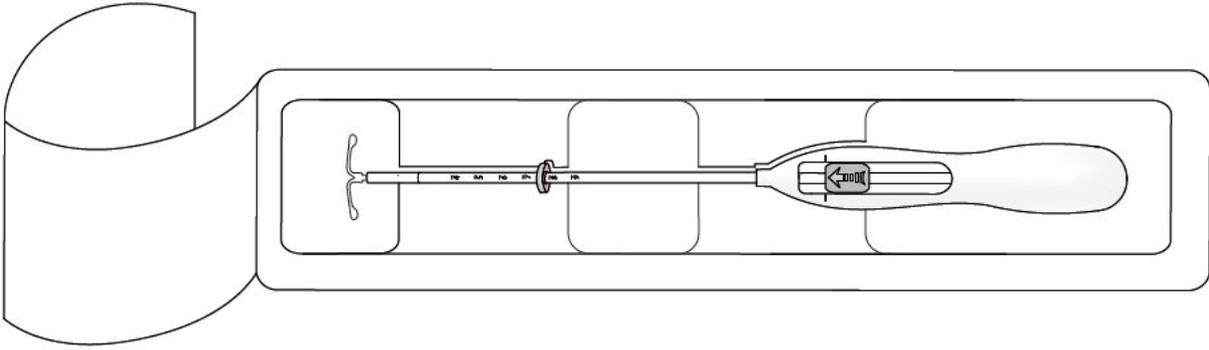


Figure 1. Opening the Mirena Package

- Using sterile gloves lift the handle of the sterile inserter and remove from the sterile package.

Step 2—Load Mirena into the insertion tube

Push the slider forward as far as possible in the direction of the arrow thereby moving the insertion tube over the Mirena T-body to load Mirena into the insertion tube (Figure 2). The tips of the arms will meet to form a rounded end that extends slightly beyond the insertion tube.

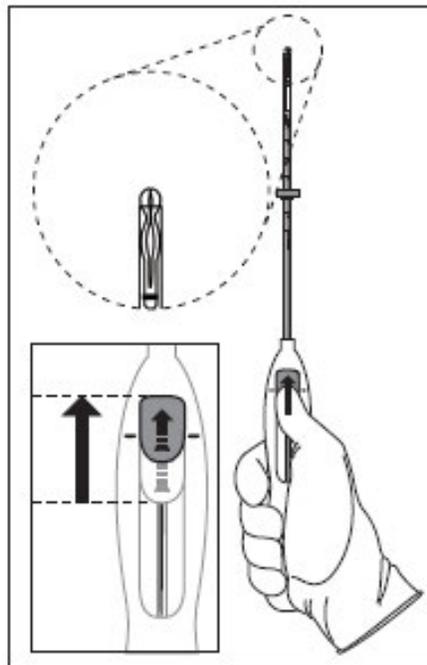


Figure 2. Move slider all the way to the forward position to load Mirena

- Maintain forward pressure with your thumb or forefinger on the slider. DO NOT move the slider downward at this time as this may prematurely release the threads of Mirena. Once the slider is moved below the mark, Mirena cannot be re-loaded.

Step 3—Setting the flange

- Holding the slider in this forward position, set the upper edge of the flange to correspond to the uterine depth (in centimeters) measured during sounding (Figure 3).

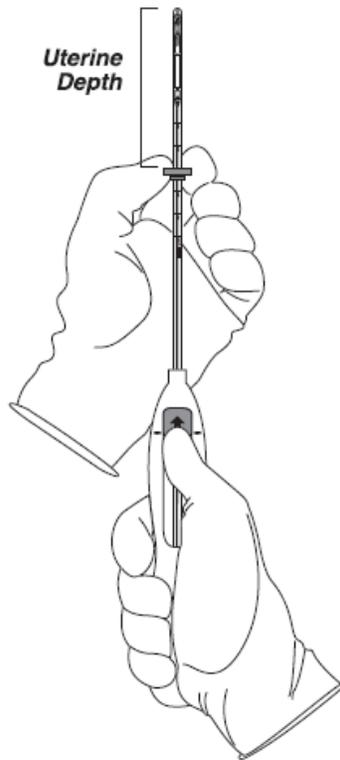


Figure 3. Setting the flange

Step 4—Mirena is now ready to be inserted

- Continue holding the slider in this forward position. Advance the inserter through the cervix until the flange is approximately 1.5–2 cm from the cervix and then pause (Figure 4).

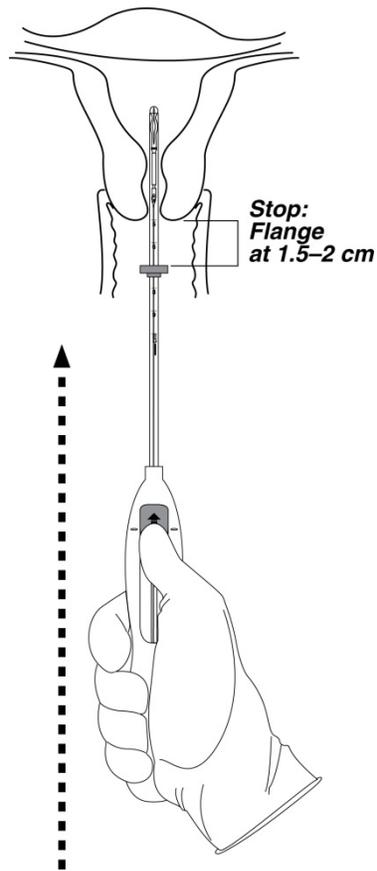


Figure 4. Advancing insertion tube until flange is 1.5 to 2 cm from the cervix

Do not force the inserter. If necessary, dilate the cervical canal.

Step 5—Open the arms

- While holding the inserter steady, move the slider down to the mark to release the arms of Mirena (Figure 5). Wait 10 seconds for the horizontal arms to open completely.

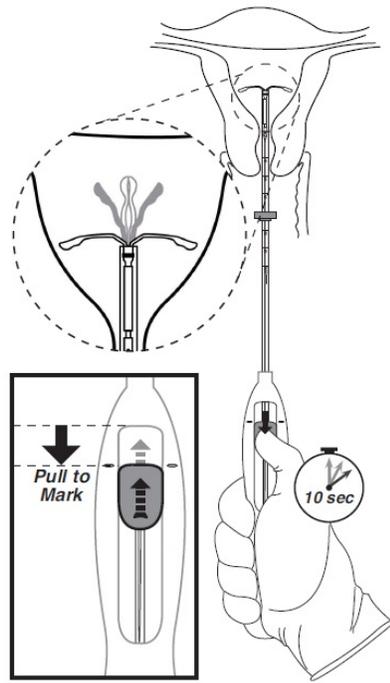


Figure 5. Move the slider back to the mark to release and open the arms

Step 6–Advance to fundal position

- Advance the inserter gently towards the fundus of the uterus until the flange touches the cervix. If you encounter fundal resistance do not continue to advance. Mirena is now in the fundal position (Figure 6). Fundal positioning of Mirena is important to prevent expulsion.

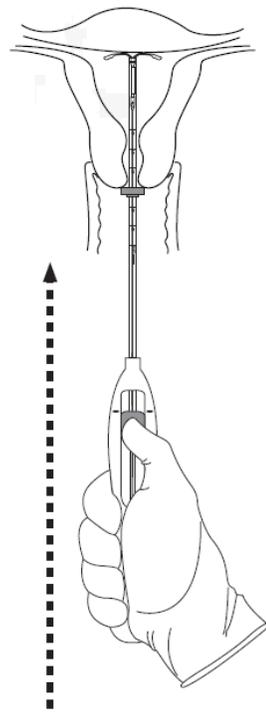


Figure 6. Move Mirena into the fundal position

Step 7—Release Mirena and withdraw the inserter

- Holding the entire inserter firmly in place, release Mirena by moving the slider all the way down (Figure 7).

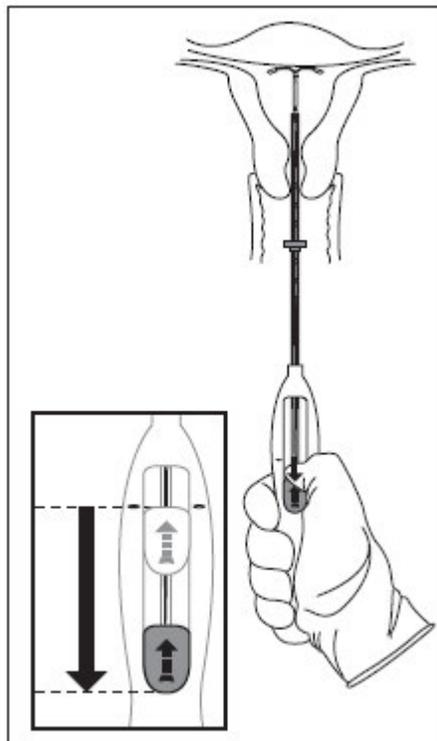


Figure 7. Move the slider all the way down to release Mirena from the insertion tube

- Continue to hold the slider all the way down while you slowly and gently withdraw the inserter from the uterus.

- Using a sharp, curved scissor, cut the threads perpendicular, leaving about 3 cm visible outside of the cervix [cutting threads at an angle may leave sharp ends (Figure 8)]. Do not apply tension or pull on the threads when cutting to prevent displacing Mirena.

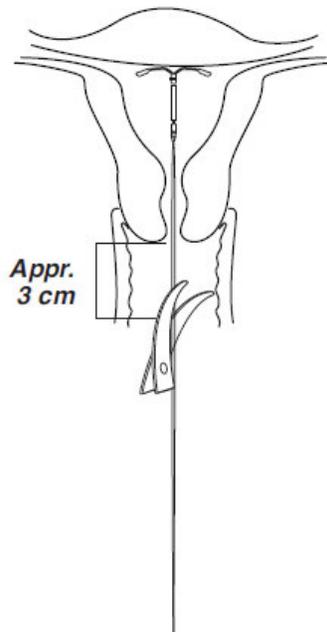


Figure 8. Cutting the threads

Mirena insertion is now complete. Prescribe analgesics, if indicated. Keep a copy of the Consent Form with lot number for your records.

Important information to consider during or after insertion

- If you suspect that Mirena is not in the correct position, check placement (for example, using transvaginal ultrasound). Remove Mirena if it is not positioned completely within the uterus. A removed Mirena must not be re-inserted.
- If there is clinical concern, exceptional pain or bleeding during or after insertion, appropriate steps (such as physical examination and ultrasound) should be taken immediately to exclude perforation.

2.2 Patient Follow-up

- Reexamine and evaluate patients 4 to 6 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

2.3 Removal of Mirena

Timing of Removal

- Mirena should not remain in the uterus after 5 years.
- If pregnancy is not desired, the removal should be carried out during menstruation, provided the woman is still experiencing regular menses. If removal will occur at other times during the cycle, consider starting a new contraceptive method a week prior to removal. If removal occurs at other times during the cycle and the woman has had intercourse in the week prior to removal, she is at risk of pregnancy. [See *Dosage and Administration (2.4).*]

Tools for Removal

Preparation

- Gloves

- Speculum

Procedure

- Sterile forceps

Removal Procedure

- Remove Mirena by applying gentle traction on the threads with forceps. (Figure 9).

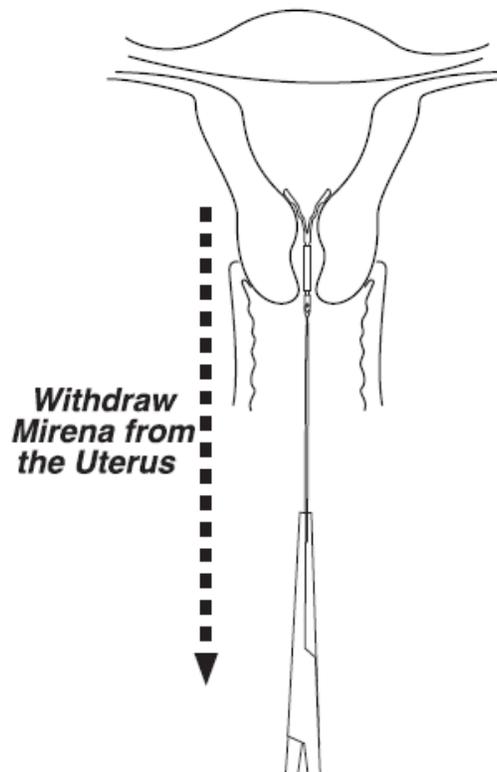


Figure 9. Removal of Mirena

- If the threads are not visible, determine location of Mirena by ultrasound [see *Warnings and Precautions (5.10)*].
- If Mirena is found to be in the uterine cavity on ultrasound exam, it may be removed using a narrow forceps, such as an alligator forceps. This may require dilation of the cervical canal. After removal of Mirena, examine the system to ensure that it is intact.
- Removal may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, or a seizure in an epileptic patient).

2.4 Continuation of Contraception after Removal

- If pregnancy is not desired and if a woman wishes to continue using Mirena, a new system can be inserted immediately after removal any time during the cycle.
- If a patient with regular cycles wants to start a different birth control method, time removal and initiation of new method to ensure continuous contraception. Either remove Mirena during the first 7 days of the menstrual cycle and start the new method immediately thereafter or start the new method at least 7 days prior to removing Mirena if removal is to occur at other times during the cycle.
- If a patient with irregular cycles or amenorrhea wants to start a different birth control method, start the new method at least 7 days before removal.

3 DOSAGE FORMS AND STRENGTHS

Mirena is a LNG-releasing IUS consisting of a T-shaped polyethylene frame with a steroid reservoir containing a total of 52 mg LNG.

4 CONTRAINDICATIONS

The use of Mirena is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspicion of pregnancy; cannot be used for post-coital contraception [*see Warnings and Precautions (5.2)*]
- Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity
- Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy [*see Warnings and Precautions (5.4)*]
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other progestin-sensitive cancer, now or in the past
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled
- Acute liver disease or liver tumor (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections [*see Warnings and Precautions (5.4)*]
- A previously inserted intrauterine device (IUD) that has not been removed
- Hypersensitivity to any component of this product [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Evaluate women for ectopic pregnancy if they become pregnant with Mirena in place because the likelihood of a pregnancy being ectopic is increased with Mirena. Up to half of pregnancies that occur with Mirena in place are likely to be ectopic. Also consider the possibility of ectopic pregnancy in the case of lower abdominal pain, especially in association with missed periods or if an amenorrheic woman starts bleeding.

The incidence of ectopic pregnancy in clinical trials with Mirena, which excluded women with a history of ectopic pregnancy, was approximately 0.1% per year. The risk of ectopic pregnancy, in women who have a history of ectopic pregnancy and use Mirena is unknown. Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. Ectopic pregnancy may result in loss of fertility.

5.2 Intrauterine Pregnancy

If pregnancy occurs while using Mirena, remove Mirena because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of Mirena or probing of the uterus may also result in spontaneous abortion. In the event of an intrauterine pregnancy with Mirena, consider the following:

Septic abortion

In patients becoming pregnant with an IUD in place, septic abortion - with septicemia, septic shock, and death - may occur.

Continuation of pregnancy

If a woman becomes pregnant with Mirena in place and if Mirena cannot be removed or the woman chooses not to have it removed, warn her that failure to remove Mirena increases the risk of miscarriage, sepsis, premature labor and premature delivery. Follow her pregnancy closely and advise her to report immediately any symptom that suggests complications of the pregnancy.

Long-term effects and congenital anomalies

When pregnancy continues with Mirena in place, long-term effects on the offspring are unknown. Congenital anomalies in live births have occurred infrequently. No clear trend towards specific anomalies has been observed. Because of the local exposure of the fetus to LNG, the possibility of teratogenicity following exposure to Mirena cannot be completely excluded. Some observational data support a small increased risk of masculinization of the external genitalia of the female fetus following exposure to progestins at doses greater than those currently used for oral contraception. Whether these data apply to Mirena is unknown.

5.3 Sepsis

Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of Mirena. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of Mirena is essential in order to minimize serious infections such as GAS.

5.4 Pelvic Infection

Pelvic Inflammatory Disease (PID)

Mirena is contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy [see *Contraindications (4)*]. IUDs have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. In clinical trials, total combined upper genital infections were reported in 3.5% of Mirena users. More specifically, endometritis was reported in 2.1%, PID in 0.6%, and all other upper genital infections in $\leq 0.5\%$ of women overall. These infections occurred more frequently within the first year. In a clinical trial with other IUDs¹ and a clinical trial with an IUD similar to Mirena, the highest rate occurred within the first month after insertion.

Promptly examine users with complaints of lower abdominal or pelvic pain, odorous discharge, unexplained bleeding, fever, genital lesions or sores. Remove Mirena in cases of recurrent endometritis or PID, or if an acute pelvic infection is severe or does not respond to treatment.

Women at increased risk for PID

PID is often associated with a sexually transmitted infection, and Mirena does not protect against sexually transmitted infection. The risk of PID is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have had PID are at increased risk for a recurrence or re-infection. In particular, ascertain whether the woman is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome [AIDS], IV drug abuse).

Asymptomatic PID

PID may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID

Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly. Removal of Mirena after initiation of antibiotic therapy is usually appropriate. Guidelines for PID treatment are available from the Centers for Disease Control (CDC), Atlanta, Georgia.

Actinomycosis

Actinomycosis has been associated with IUDs. Symptomatic women should have Mirena removed and should receive antibiotics. The significance of actinomyces-like organisms on Pap smear in an asymptomatic IUD user is unknown, and so this finding alone does not always require Mirena removal and treatment. When possible, confirm a Pap smear diagnosis with cultures.

5.5 Irregular Bleeding and Amenorrhea

Mirena can alter the bleeding pattern and result in spotting, irregular bleeding, heavy bleeding, oligomenorrhea and amenorrhea. During the first three to six months of Mirena use, the number of bleeding and spotting days may be increased and bleeding patterns may be irregular. Thereafter the number of bleeding and spotting days usually decreases but bleeding may remain irregular. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be taken to rule out endometrial pathology.

Amenorrhea develops in approximately 20% of Mirena users by one year. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are generally not necessary in amenorrheic women unless indicated, for example, by other signs of pregnancy or by pelvic pain [see *Clinical Studies (14.1)*].

In most women with heavy menstrual bleeding, the number of bleeding and spotting days may also increase during the initial months of therapy but usually decrease with continued use; the volume of blood loss per cycle progressively becomes reduced [see *Clinical Studies (14.2)*].

5.6 Perforation

Perforation (total or partial, including penetration/embedment of Mirena in the uterine wall or cervix) may occur most often during insertion, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. The incidence of perforation during clinical trials, which excluded breast-feeding women, was < 0.1%.

If perforation occurs, locate and remove Mirena. Surgery may be required. Delayed detection or removal of Mirena in case of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera.

An interim analysis from a large postmarketing safety study shows an increased risk of perforation in lactating women. The risk of perforation may be increased if Mirena is inserted when the uterus is fixed retroverted or not completely involuted during the postpartum period. Delay Mirena insertion a minimum of six weeks or until involution is complete following a delivery or a second trimester abortion.

5.7 Expulsion

Partial or complete expulsion of Mirena may occur resulting in the loss of contraceptive protection. Expulsion may be associated with symptoms of bleeding or pain, or it may be asymptomatic and go unnoticed. Mirena typically decreases menstrual bleeding over time; therefore, an increase of menstrual bleeding may be indicative of an expulsion. The risk of expulsion may be increased when the uterus is not completely involuted. In clinical trials, a 4.5% expulsion rate was reported over the 5-year study duration.

Delay Mirena insertion a minimum of six weeks or until uterine involution is complete following a delivery or a second trimester abortion. Remove a partially expelled Mirena. If expulsion has occurred, Mirena may be replaced within 7 days after the onset of a menstrual period after pregnancy has been ruled out.

5.8 Ovarian Cysts

Because the contraceptive effect of Mirena is mainly due to its local effects within the uterus, ovulatory cycles with follicular rupture usually occur in women of fertile age using Mirena. Sometime atresia of the follicle is delayed and the follicle may continue to grow. Ovarian cysts have been reported in approximately 8% of women using Mirena. Most of these cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases the ovarian cysts disappear spontaneously during two to three months observation. Evaluate persistent ovarian cysts. Surgical intervention is not usually required.

5.9 Breast Cancer

Women who currently have or have had breast cancer, or have a suspicion of breast cancer, should not use hormonal contraception because some breast cancers are hormone-sensitive [*see Contraindications (4)*].

Spontaneous reports of breast cancer have been received during postmarketing experience with Mirena. Two observational studies have not provided evidence of an increased risk of breast cancer during the use of Mirena.

5.10 Clinical Considerations for Use and Removal

Use Mirena with caution after careful assessment if any of the following conditions exist, and consider removal of the system if any of them arise during use:

- Coagulopathy or use of anticoagulants
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Exceptionally severe headache
- Marked increase of blood pressure
- Severe arterial disease such as stroke or myocardial infarction

In addition, consider removing Mirena if any of the following conditions arise during use [*see Contraindications (4)*]:

Uterine or cervical malignancy

Jaundice

If the threads are not visible or are significantly shortened they may have broken or retracted into the cervical canal or uterus. Consider the possibility that the system may have been displaced (for example, expelled or perforated the uterus) [see *Warnings and Precautions* (5.6, 5.7)]. Exclude pregnancy and verify the location of Mirena, for example, by sonography, X-ray, or by gentle exploration of the cervical canal with a suitable instrument. If Mirena is displaced, remove it. A new Mirena may be inserted at that time or during the next menses if it is certain that conception has not occurred. If Mirena is in place with no evidence of perforation, no intervention is indicated.

6 ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are discussed in elsewhere in the labeling:

- Ectopic Pregnancy [see *Warnings and Precautions* (5.1)]
- Intrauterine Pregnancy [see *Warnings and Precautions* (5.2)]
- Group A Streptococcal Sepsis (GAS) [see *Warnings and Precautions* (5.3)]
- Pelvic Inflammatory Disease [see *Warnings and Precautions* (5.4)]
- Alterations of Bleeding Patterns [see *Warnings and Precautions* (5.5)]
- Perforation [see *Warnings and Precautions* (5.6)]
- Expulsion [see *Warnings and Precautions* (5.7)]
- Ovarian Cysts [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience

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

The data provided reflect the experience with the use of Mirena in the adequate and well-controlled studies for contraception (n=2,339) and heavy menstrual bleeding (n=80). For the contraception indication, Mirena was compared to a copper IUD (n=1,855), to another formulation of LNG IUS (n=390) and to a combined oral contraceptive (n=94) in women 18 to 35 years old. The data cover more than 92,000 woman-months of exposure. For the treatment of heavy menstrual bleeding indication (n=80), the subjects included women aged 26 to 50 with confirmed heavy bleeding and exposed for a median of 183 treatment days of Mirena (range 7 to 295 days). The frequencies of reported adverse drug reactions represent crude incidences.

The adverse reactions seen across the two indications overlapped, and are reported using the frequencies from the contraception studies.

The most common adverse reactions ($\geq 5\%$ users) are uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal/pelvic pain (12.8%), ovarian cysts (12%), headache/migraine (7.7%), acne (7.2%), depressed/altered mood (6.4%), menorrhagia (6.3%), breast tenderness/pain (4.9%), vaginal discharge (4.9%) and IUD expulsion (4.9%).

Other relevant adverse reactions occurring in $<5\%$ of subjects include nausea, nervousness, vulvovaginitis, dysmenorrhea, back pain, weight increase, decreased libido, cervicitis/Papanicolaou smear normal/class II, hypertension, dyspareunia, anemia, alopecia, skin disorders including eczema, pruritus, rash and urticaria, abdominal distention, hirsutism and edema.

6.2 Postmarketing Experience

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

- Angioedema
- Device breakage

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with Mirena.

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the serum concentrations of progestins.

Some drugs or herbal products that may decrease the serum concentration of LNG include:

- Barbiturates
- Bosentan
- Carbamazepine
- Efavirenz
- Felbamate
- Griseofulvin
- Nevirapine
- Oxcarbazepine
- Phenytoin
- Rifabutin
- Rifampin
- St. John's wort
- Topiramate

Significant changes (increase or decrease) in the serum concentrations of the progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Consult the labeling of all concurrently used drugs to obtain further information about interactions with Mirena or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The use of Mirena during an existing or suspected pregnancy is contraindicated. Many studies have found no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin-only pills have not demonstrated significant adverse effects. [See *Contraindications (4) and Warnings and Precautions (5.1, 5.2).*]

8.3 Nursing Mothers

In general, no adverse effects of progestin-only contraceptives have been found on breastfeeding performance or on the health, growth, or development of the infant. Isolated postmarketing cases of decreased milk production have been reported. Small amounts of progestins were observed to pass into the breast milk of nursing mothers who used Mirena, resulting in detectable steroid levels in infant serum. [See *Warnings and Precautions (5.6).*]

8.4 Pediatric Use

Safety and efficacy of Mirena have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Mirena has not been studied in women over age 65 and is not approved for use in this population.

8.6 Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of LNG released from Mirena [see *Contraindications (4)*].

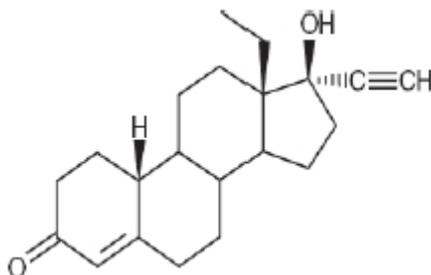
8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of LNG released from Mirena.

11 DESCRIPTION

Mirena (levonorgestrel-releasing intrauterine system) contains 52 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately 20 mcg/day of LNG.

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



11.1 Mirena

Mirena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a white or almost white cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a semi-opaque silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polyethylene of the removal thread contains iron oxide as a colorant (see Figure 10).

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

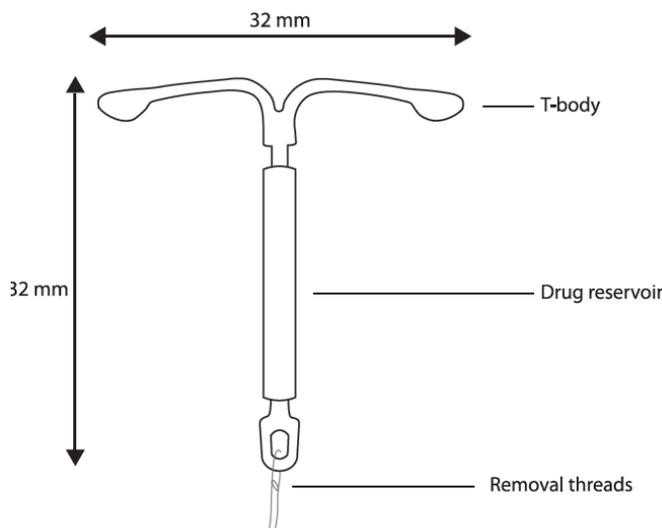


Figure 10. Mirena

11.2 Inserter

Mirena is packaged sterile within an inserter. The inserter (Figure 11), which is used for insertion of Mirena 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 4.4 mm. The vertical stem of Mirena 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 Mirena has been placed, the inserter is discarded.

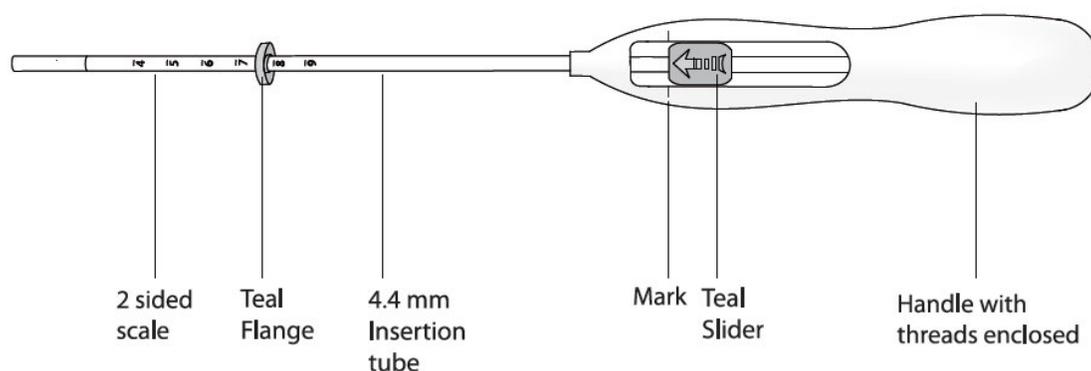


Figure 11: Diagram of Inserter

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The local mechanism by which continuously released LNG enhances contraceptive effectiveness of Mirena has not been conclusively demonstrated. Studies of Mirena and similar LNG IUS prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium.

12.2 Pharmacodynamics

Mirena has mainly local progestogenic effects in the uterine cavity. The high local levels of LNG² lead to morphological changes including stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration and a decrease in glandular and stromal mitoses.

Ovulation is inhibited in some women using Mirena. In a 1-year study, approximately 45% of menstrual cycles were ovulatory, and in another study after 4 years, 75% of cycles were ovulatory.

12.3 Pharmacokinetics

Absorption

Low doses of LNG are administered into the uterine cavity with the Mirena intrauterine delivery system. The initial release rate is approximately 20 mcg/ over the first 3 months tested (day 0 to day 90). It is reduced to approximately 18 mcg/day after 1 year and then decreases progressively to approximately 10 mcg/day after 5 years.

A stable serum concentration, without peaks and troughs, of LNG of 150–200 pg/mL occurs after the first few weeks following insertion of Mirena. LNG concentrations after long-term use of 12, 24, and 60 months were 180±66 pg/mL, 192±140 pg/mL, and 159±59 pg/mL, respectively.

Distribution

The apparent volume of distribution of LNG is reported to be approximately 1.8 L/kg. It is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin.

Metabolism

Following absorption, LNG is conjugated at the 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3α, 5β- tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG-containing contraceptive products. *In vitro* studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

Excretion

About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The elimination half-life of LNG after daily oral doses is approximately 17 hours.

Specific Populations

Pediatric: Safety and efficacy of Mirena have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatric: Mirena has not been studied in women over age 65 and is not currently approved for use in this population.

Race: No studies have evaluated the effect of race on pharmacokinetics of Mirena.

Hepatic Impairment: No studies were conducted to evaluate the effect of hepatic disease on the disposition of Mirena.

Renal Impairment: No formal studies were conducted to evaluate the effect of renal disease on the disposition of Mirena.

Drug-Drug Interactions

No drug-drug interaction studies were conducted with Mirena [see *Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See *Warnings and Precautions (5.9)*]

14 CLINICAL STUDIES

14.1 Clinical Trials on Contraception

Mirena has been studied for safety and efficacy in two large clinical trials in Finland and Sweden. In study sites having verifiable data and informed consent, 1,169 women 18 to 35 years of age at enrollment used Mirena for up to 5 years, for a total of 45,000 women-months of exposure. Subjects had previously been pregnant, had no history of ectopic pregnancy, had no history of pelvic inflammatory disease over the preceding 12 months, were predominantly Caucasian, and over 70% of the participants had previously used IUDs (intrauterine devices). The reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women (0.2%) and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women (0.7%).

About 80% of women wishing to become pregnant conceived within 12 months after removal of Mirena.

14.2 Clinical Trial on Heavy Menstrual Bleeding

The efficacy of Mirena in the treatment of heavy menstrual bleeding was studied in a randomized, open-label, active-control, parallel-group trial comparing Mirena (n=79) to an approved therapy, medroxyprogesterone acetate (MPA) (n=81), over 6 cycles. The subjects included reproductive-aged women in good health, with no contraindications to the drug products and with confirmed heavy menstrual bleeding (≥ 80 mL menstrual blood loss [MBL]) determined using the alkaline hematin method. Excluded were women with organic or systemic conditions that may cause heavy uterine bleeding (except small fibroids, with total volume not > 5 mL). Treatment with Mirena showed a statistically significantly greater reduction in MBL (see Figure 12) and a statistically significantly greater number of subjects with successful treatment (see Figure 13). Successful treatment was defined as proportion of subjects with (1) end-of-study MBL < 80 mL and (2) a $\geq 50\%$ decrease in MBL from baseline to end-of-study.

Figure 12. Median Menstrual Blood Loss (MBL) by Time and Treatment

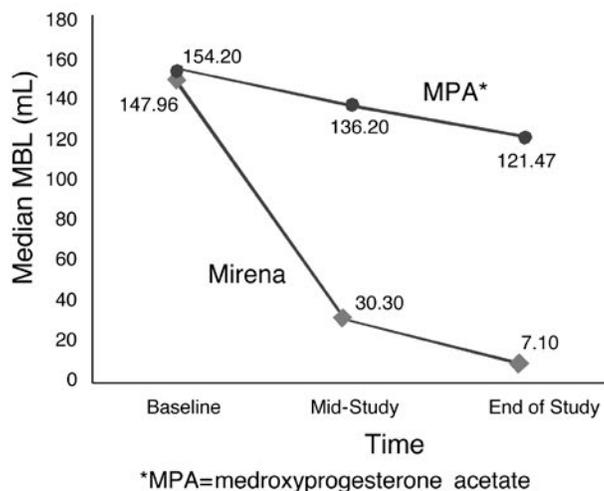
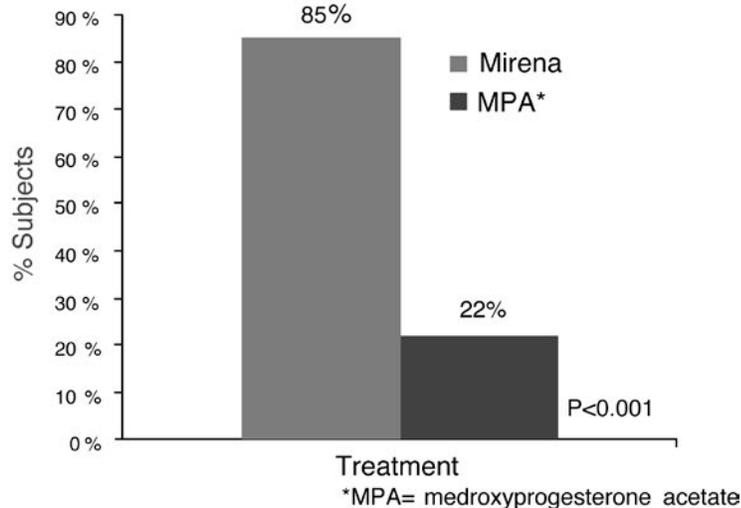


Figure 13. Proportion of Subjects with Successful Treatment



15 REFERENCES

- ¹Farley T M M, Rosenberg M J, Rowe P J, Chen J, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet* 1992; 339:785-788.
- ²Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of LNG in women using a LNG-releasing IUD. *Clinical Endocrinol* 1982;17:529-536.

16 HOW SUPPLIED/STORAGE AND HANDLING

Mirena (levonorgestrel-releasing intrauterine system), containing a total of 52 mg LNG, is available in a carton of one sterile unit NDC# 50419-423-01.

Mirena is supplied sterile. Mirena 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].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Counsel the patient that this product does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).
- Counsel the patient on the benefits, risks, and side effects of Mirena prior to insertion. Provide the Patient Information Booklet and give her the opportunity to read the information and discuss fully any questions she may have concerning Mirena as well as other methods of contraception and therapies for heavy menstrual bleeding. Advise the patient that the Full Prescribing Information is available to her upon request.
- Inform the patient about the risks of ectopic pregnancy, including the loss of fertility. Teach her to recognize and report to her healthcare provider promptly any symptoms of ectopic pregnancy.
- Inform the patient about the possibility of pelvic inflammatory disease (PID) and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death. Teach patients to recognize and report to their healthcare provider promptly any symptoms of PID. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever.
- Counsel the patient that irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her healthcare provider.

- Counsel the patient on how she can check that the threads still protrude from the cervix and caution her not to pull on the threads and displace Mirena. Inform her that there is no contraceptive protection if Mirena is displaced or expelled. *[See Warnings and Precautions (5.6, 5.7).]*
- Instruct the patient to contact her healthcare provider if she experiences any of the following:
 - A stroke or heart attack
 - Very severe or migraine headaches
 - Unexplained fever
 - Yellowing of the skin or whites of the eyes, as these may be signs of serious liver problems
 - Pregnancy or suspected pregnancy
 - Pelvic pain or pain during sex
 - HIV positive seroconversion in herself or her partner
 - Possible exposure to sexually transmitted infections (STIs)
 - Unusual vaginal discharge or genital sores
 - Severe vaginal bleeding or bleeding that lasts a long time, or if she misses a menstrual period
 - Inability to feel Mirena's threads
- Complete the Follow-up Reminder Card and give to the patient.

FDA-Approved Patient Labeling

Patient Information

Mirena® (mur-ā-nah)

(levonorgestrel-releasing intrauterine system)

Mirena does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

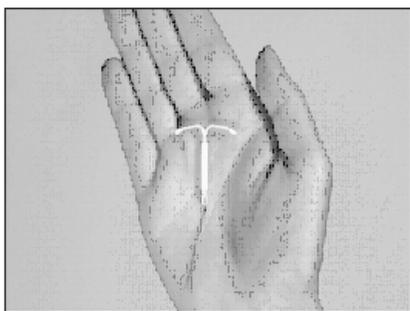
Read this Patient Information carefully before you decide if Mirena is right for you. This information does not take the place of talking with your gynecologist or other healthcare provider who specializes in women's health. If you have any questions about Mirena, ask your healthcare provider. You should also learn about other birth control methods to choose the one that is best for you.

What is Mirena?

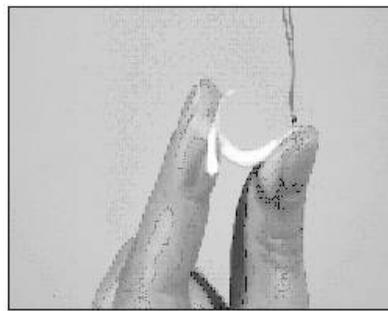
- Mirena is a hormone-releasing system placed in your uterus by your healthcare provider to prevent pregnancy for up to 5 years.
- Mirena can also lessen menstrual blood loss in women who have heavy menstrual flow and who also want to use a birth control method that is placed in the uterus to prevent pregnancy.
- Mirena can be removed by your healthcare provider at any time.
- Mirena is recommended for women who have had at least one child.

Mirena is a small flexible plastic T-shaped system that slowly releases a progestin hormone called levonorgestrel that is often used in birth control pills. Because Mirena releases levonorgestrel into your uterus, only small amounts of the hormone enter your blood. Mirena does not contain estrogen.

Two thin threads are attached to the stem of Mirena. The threads are the only part of Mirena you can feel when Mirena is in your uterus; however, unlike a tampon string, the threads do not extend outside your body.



Mirena is small



and flexible

What if I need birth control for more than 5 years?

Mirena must be removed after 5 years. Your healthcare provider can place a new Mirena during the same office visit if you choose to continue using Mirena.

What if I want to stop using Mirena?

Mirena is intended for long-term use but you can stop using Mirena at any time by asking your healthcare provider to remove it. You could become pregnant as soon as Mirena is removed, so you should use another method of birth control if you do not want to become pregnant.

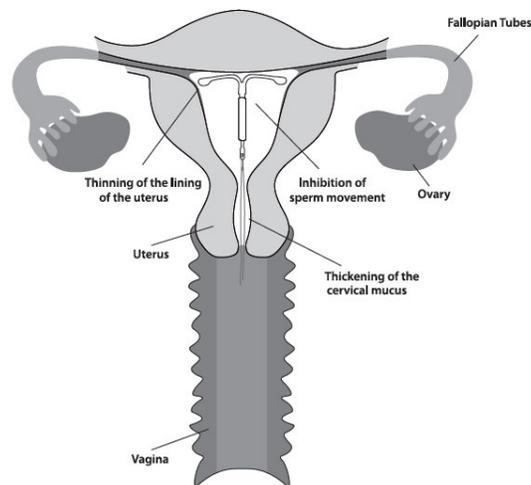
What if I change my mind about birth control and want to become pregnant in less than 5 years?

Your healthcare provider can remove Mirena at any time. You may become pregnant as soon as Mirena is removed. About 8 out of 10 women who want to become pregnant will become pregnant sometime in the first year after Mirena is removed.

How does Mirena work?

Mirena may work in several ways including thickening cervical mucus, inhibiting sperm movement, reducing sperm survival, and thinning the lining of your uterus. It is not known exactly how these actions work together to prevent pregnancy.

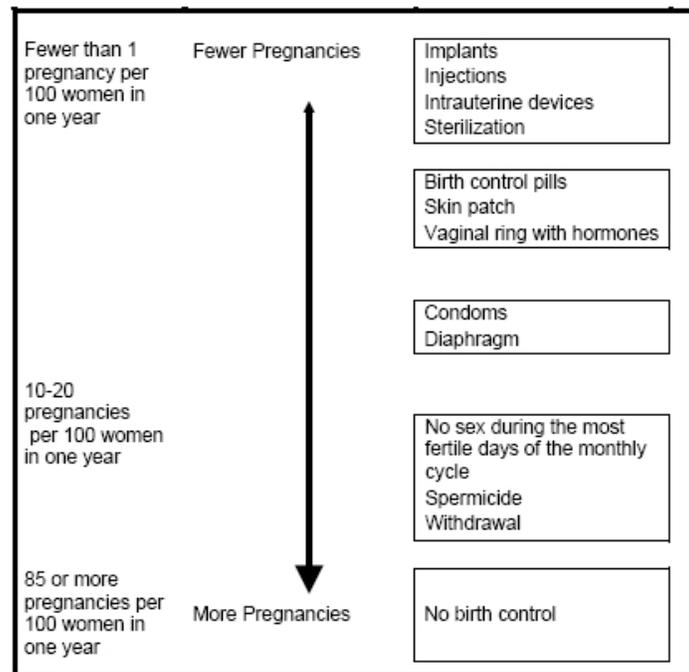
Mirena can cause your menstrual bleeding to be less by thinning the lining of the uterus.



How well does Mirena work for contraception?

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.

Mirena, an intrauterine device (IUD), is in the box at the top of the chart.



How well does Mirena work for heavy menstrual bleeding?

In the clinical trial performed in women with heavy menstrual bleeding and treated with Mirena, almost 9 out of 10 were treated successfully and their blood loss was reduced by more than half.

Who might use Mirena?

You might choose Mirena if you:

- Want long-term birth control that provides a low chance of getting pregnant (less than 1 in 100)
- Want birth control that works continuously for up to 5 years
- Want birth control that is reversible
- Want a birth control method that you do not need to take daily
- Have had at least one child
- Want treatment for heavy periods and are willing to use a birth control method that is placed in the uterus
- Want birth control that does not contain estrogen

Who should not use Mirena?

Do not use Mirena if you:

- Are or might be pregnant; Mirena cannot be used as an emergency contraceptive
- Have had a serious pelvic infection called pelvic inflammatory disease (PID) unless you have had a normal pregnancy after the infection went away
- Have an untreated pelvic infection now
- Have had a serious pelvic infection in the past 3 months after a pregnancy
- Can get infections easily. For example, if you have:
 - Multiple sexual partners or your partner has multiple sexual partners
 - Problems with your immune system
 - Intravenous drug abuse.

- Have or suspect you might have cancer of the uterus or cervix
- Have bleeding from the vagina that has not been explained
- Have liver disease or liver tumor
- Have breast cancer or any other cancer that is sensitive to progestin (a female hormone), now or in the past
- Have an intrauterine device in your uterus already
- Have a condition of the uterus that changes the shape of the uterine cavity, such as large fibroid tumors
- Are allergic to levonorgestrel, silicone, polyethylene, silica, barium sulfate or iron oxide

Before having Mirena placed, tell your healthcare provider if you:

- Have had a heart attack
- Have had a stroke
- Were born with heart disease or have problems with your heart valves
- Have problems with blood clotting or take medicine to reduce clotting
- Have high blood pressure
- Recently had a baby or if you are breastfeeding
- Have severe migraine headaches.

How is Mirena placed?

Mirena is placed by your healthcare provider during an in-office visit.

First, your healthcare provider will examine your pelvis to find the exact position of your uterus. Your healthcare provider will then clean your vagina and cervix with an antiseptic solution, and slide a slim plastic tube containing Mirena into your uterus. Your healthcare provider will then remove the plastic tube, and leave Mirena in your uterus. Your healthcare provider will cut the threads to the right length. Placement takes only a few minutes.

You may experience pain, bleeding or dizziness during and after placement. If your symptoms do not pass within 30 minutes after placement, Mirena may not have been placed correctly. Your healthcare provider will examine you to see if Mirena needs to be removed or replaced.

Should I check that Mirena is in place?

Yes, you should check that Mirena is in proper position by feeling the removal threads. It is a good habit to do this once a month. Your healthcare provider should tell you how to check that Mirena is in place. First, wash your hands with soap and water. You can check by reaching up to the top of your vagina with clean fingers to feel the removal threads. Do not pull on the threads. If you feel more than just the threads or if you cannot feel the threads, Mirena may not be in the right position and may not prevent pregnancy. Use non-hormonal back-up birth control (such as condoms and spermicide) and ask your healthcare provider to check that Mirena is still in the right place.

How soon after placement of Mirena should I return to my healthcare provider?

Call your healthcare provider if you have any questions or concerns (see "When should I call my healthcare provider"). Otherwise, you should return to your healthcare provider for a follow-up visit 4 to 6 weeks after Mirena is placed to make sure that Mirena is in the right position.

Can I use tampons with Mirena?

Tampons may be used with Mirena.

What if I become pregnant while using Mirena?

Call your healthcare provider right away if you think you are pregnant. If you get pregnant while using Mirena, you may have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or abdominal pain may be a sign of ectopic pregnancy.

Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.

There are also risks if you get pregnant while using Mirena and the pregnancy is in the uterus. Severe infection, miscarriage, premature delivery, and even death can occur with pregnancies that continue with an intrauterine device (IUD). Because of this, your healthcare provider may try to remove Mirena, even though removing it may cause a miscarriage. If Mirena cannot be removed, talk with your healthcare provider about the benefits and risks of continuing the pregnancy.

If you continue your pregnancy, see your healthcare provider regularly. Call your healthcare provider right away if you get flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge, or fluid leaking from your vagina. These may be signs of infection.

It is not known if Mirena can cause long-term effects on the fetus if it stays in place during a pregnancy.

How will Mirena change my periods?

For the first 3 to 6 months, your period may become irregular and the number of bleeding days may increase. You may also have frequent spotting or light bleeding. Some women have heavy bleeding during this time. After you have used Mirena for a while, the number of bleeding and spotting days is likely to lessen. There is a small chance that your periods will stop altogether.

In some women with heavy bleeding, the total blood loss per cycle progressively decreases with continued use. The number of spotting and bleeding days may initially increase but then typically decreases in the months that follow.

Is it safe to breastfeed while using Mirena?

You may use Mirena when you are breastfeeding if more than six weeks have passed since you had your baby. If you are breastfeeding, Mirena is not likely to affect the quality or amount of your breast milk or the health of your nursing baby. However, isolated cases of decreased milk production have been reported among women using progestin-only birth control pills.

Will Mirena interfere with sexual intercourse?

You and your partner should not feel Mirena during intercourse. Mirena is placed in the uterus, not in the vagina. Sometimes your partner feels the threads. If this occurs, talk with your healthcare provider.

What are the possible side effects of using Mirena?

Mirena can cause serious side effects including:

- **Pelvic inflammatory disease (PID).** Some IUD users get a serious pelvic infection called pelvic inflammatory disease. PID is usually sexually transmitted. You have a higher chance of getting PID if you or your partner have sex with other partners. PID can cause serious problems such as infertility, ectopic pregnancy or pelvic pain that does not go away. PID is usually treated with antibiotics. More serious cases of PID may require surgery. A hysterectomy (removal of the uterus) is sometimes needed. In rare cases, infections that start as PID can even cause death.
- Tell your healthcare provider right away if you have any of these signs of PID: long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal (stomach area) pain, painful sex, chills, or fever.

- **Life-threatening infection.** Life-threatening infection can occur within the first few days after Mirena is placed. Call your healthcare provider immediately if you develop severe pain or fever shortly after Mirena is placed.
- **Perforation.** Mirena may become attached to (embedded) or go through the wall of the uterus. This is called perforation. If this occurs, Mirena may no longer prevent pregnancy. If perforation occurs, Mirena may move outside the uterus and can cause internal scarring, infection, or damage to other organs, and you may need surgery to have Mirena removed. The risk of perforation is increased in breastfeeding women.

Common side effects of Mirena include:

- Pain, bleeding or dizziness during and after placement. If these symptoms do not stop 30 minutes after placement, Mirena may not have been placed correctly. Your healthcare provider will examine you to see if Mirena needs to be removed or replaced.
- Expulsion. Mirena may come out by itself. This is called expulsion. You may become pregnant if Mirena comes out. If you think that Mirena has come out, use a backup birth control method like condoms and spermicide and call your healthcare provider.
- Missed menstrual periods. About 2 out of 10 women stop having periods after 1 year of Mirena use. If you do not have a period for 6 weeks during Mirena use, call your healthcare provider. When Mirena is removed, your menstrual periods will come back.
- Changes in bleeding. You may have bleeding and spotting between menstrual periods, especially during the first 3 to 6 months. Sometimes the bleeding is heavier than usual at first. However, the bleeding usually becomes lighter than usual and may be irregular. Call your healthcare provider if the bleeding remains heavier than usual or increases after it has been light for a while.
- Cysts on the ovary. About 12 out of 100 women using Mirena develop a cyst on the ovary. These cysts usually disappear on their own in a month or two. However, cysts can cause pain and sometimes cysts will need surgery.

This is not a complete list of possible side effects with Mirena. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to the manufacturer at 1-888-842-2937, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

After Mirena has been placed, when should I call my healthcare provider?

Call your healthcare provider if you have any concerns about Mirena. Be sure to call if you:

- Think you are pregnant
- Have pelvic pain or pain during sex
- Have unusual vaginal discharge or genital sores
- Have unexplained fever, flu-like symptoms or chills
- Might be exposed to sexually transmitted infections (STIs)
- Cannot feel Mirena's threads
- Develop very severe or migraine headaches
- Have yellowing of the skin or whites of the eyes. These may be signs of liver problems.
- Have had a stroke or heart attack
- Or your partner becomes HIV positive
- Have severe vaginal bleeding or bleeding that lasts a long time

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet summarizes the most important information about Mirena. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about Mirena that is written for health providers.

For more information, go to www.mirena-us.com or call 1-888-842-2937

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Finland

© 2014, Bayer HealthCare Pharmaceuticals Inc.
All rights reserved.

May 2014

This patient information booklet was updated May 2014.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

MEDICAL REVIEW(S)

Review of Supplemental Labeling Request Division of Bone, Reproductive and Urologic Products

Application #: NDA 21-225/Supplement 033
Name of Drug: Mirena (levonorgestrel-releasing intrauterine system [IUS])
Applicant: Bayer Healthcare Pharmaceuticals, Inc.
Reviewed by: Lisa M. Soule, M.D., Clinical Team Leader, DBRUP
Date: May 28, 2014

The Applicant submitted Supplement 033 on February 27, 2012; this supplement sought approval of a modified inserter to replace the current inserter, new packaging materials, changes in polyethylene grade used for the insertion tube and a new pigment for the inserter flange, and corresponding labeling changes. The new inserter is very similar, but not identical, to that approved for the Skyla Intrauterine System (IUS) under NDA 203-159. The Applicant also provided for minor modifications to the T-body of the IUS (more rounded T-body knobs and slightly larger T-body loop openings).

The ONDQA Filing review determined that the supplement should be managed by OND because it included labeling changes and required review of pharmacology/toxicology information. Reviews were provided by ONDQA, microbiology, pharmacology/toxicology, and CDRH Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD); Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices (DAGRID [human factors]); and Office of Compliance (OC).

Ron Orleans, M.D. reviewed the clinical material, including the proposed minor changes to the T-body of the IUS. He concluded in his review dated August 30, 2013 that the new inserter was adequately supported by clinical data reviewed under NDA 203-159 for a very similar inserter, that changes to the T-body were unlikely to have any clinical impact, and that the submission was approvable from a clinical perspective. Steven Donald, M.S., the Microbiology reviewer recommended approval of the supplement because no deficiencies were identified in his review. Kim Hatfield, Ph.D., the Pharmacology/Toxicology reviewer also recommended approval, as nonclinical data support the safety of the new inserter components; she recommended minor edits to the proposed labeling. The Division of Medication Error Prevention and Analysis reviewed the prescribing information and carton/container labeling and did not recommend any revision. Reviews by CDRH, however, identified a number of deficiencies, leading to a Complete Response action on August 30, 2013. The ONDQA reviewer, Jean Salemmme, Ph.D., concurred in this action, based on the deficiencies identified by CDRH. Deficiencies included:

- Need for a hazard analysis, description of risk mitigation strategies, and methods to validate the effectiveness of these strategies; including determination of whether a Human Factors/Usability study is needed

- Testing in a “worst case” model to ensure successful deployment/delivery of the IUS by the new inserter
- An inadequate DMF (b) (4)
- Documentation that changes to the inserter do not affect safety and effectiveness of the finished product, and that changes to packaging do not affect product integrity
- Sufficient information to demonstrate adequate control over the new supplier of the inserter

The Applicant requested a meeting to discuss the action and the Applicant’s proposal to address the noted deficiencies. The Division responded with a Written Response on January 14, 2014, indicating that the Applicant’s proposed approaches to address the deficiencies appeared acceptable.

The Applicant submitted its Complete Response on January 29, 2014; this supplement has a 4-month clock, with action needed by May 29, 2014.

Reviews have been completed by CDRH’s OC and DRGUD, as well as by ONDQA, and all reviewers found the Applicant’s responses adequate and acceptable. DAGRID concluded that a human factors study was not needed.

Review of labeling was performed at this time; minor edits made by Drs. Hatfield, Salemme and the Office of Prescription Drug Promotion were conveyed to the Applicant. Changes to the following clinical sections of labeling were negotiated:

- (b) (4)
The Division did not consider the justification, (b) (4), sufficient. The Division would reconsider the proposal to remove this language in a future supplement if the Sponsor is able to address the Division’s concerns and provide additional justification.
- The Highlights Warning about removing Mirena in case of pregnancy was revised to clarify that “if pregnancy occurs, there is increased risk of ectopic pregnancy...”
- Updated information was added to Warnings and Precautions sections Intrauterine Pregnancy, Sepsis, Pelvic Infection, Perforation, Expulsion, and Ovarian Cysts.
- Section 6.2, Adverse Reactions, Postmarketing Experience – adverse reactions were bulleted
- Daily release rate information was added to Section 12.3, Pharmacokinetics

Agreement on labeling was reached on May 28, 2014. Therefore, I recommend approval of Supplement 033.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
05/28/2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF SUPPLEMENT
Prior Approval

1. **ORGANIZATION:** ONDQA
2. **NDA/SUPPLEMENT:** 21-225 / S-033
3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 27-Feb-2013
Resubmission: 31-Jan-2014
Goal Date: 31-May-2014 (to OND by 30-Apr)
4. **AMENDMENTS:** None
5. **RECEIVED BY CHEMIST:** March 2013

6. **SPONSOR NAME AND ADDRESS**

Baxter Healthcare Pharmaceuticals
Montville, NJ

7. **SUPPLEMENT PROVIDES FOR:** 1.) a modified inserter (including ergonomic enhancements) to replace the current inserter as an integrated applicator –forming an integral part of the complete levonorgestrel-intrauterine system (LNG-IUS) at the time of application to the patient, and 2.) new packaging materials for the container/closure of the final assembled product.

- | | |
|--|--|
| 8. <u>DRUG PRODUCT NAME:</u> | Mirena |
| 9. <u>NONPROPRIETARY NAME:</u> | Levonorgestrel-releasing Intrauterine Device |
| 10. <u>DRUG SUBSTANCE:</u> | Levonorgestrel |
| 11. <u>DOSAGE FORM/STRENGTH:</u> | Intrauterine system; 52 mg |
| 12. <u>ROUTE OF ADMINISTRATION:</u> | Intrauterine |
| 13. <u>INDICATION:</u> | Contraception |
| 14. <u>HOW DISPENSED:</u> | Rx |
| 15. <u>RELATED IND/NDA/DMF:</u> | NDA 203159, Skyla IUS; DMF (b) (4) DMF (b) (4) |

16. **COMMENTS:**

Mirena, a drug/device combination product, is an intrauterine (IUS) system packaged with an inserter device which delivers the IUS to the uterus. The manufacturing process consists of the following: the intrauterine system (IUS) is manufactured and placed into the inserter, the IUS/inserter is packaged in a blister pack, and the blister pack is sterilized by ethylene-oxide sterilization. The sterilized packaged Mirena system is then aerated, tested, labeled, and packed.

This supplement provides for changes to the inserter device. The proposed inserter is very similar to the inserter approved in the Baxter NDA 203159, Skyla. The proposed inserter will be manufactured by the supplier approved in NDA 203159, (b) (4) and a new supplier, (b) (4). The manufacturing and controls for the inserter were evaluated the CDRH reviewer, V. Price, and deficiencies from the CDRH review were conveyed in the Complete Response action letter issued during the first review cycle.

The responses to the deficiencies have been evaluated by the CDRH reviewer and are acceptable and DMF (b) (4) is now adequate. See review by Ms. V. Price, placed in DARRTS on 13-Mar-2014 by OND Project Manager, Zeta-Mae C Williamson.

17. **CONCLUSIONS AND RECOMMENDATIONS**

The information/data support the use of the new inserter. This supplement, therefore, is recommended for Approval.

18. **REVIEWER NAME**

J. Salemme, Ph.D., Chemistry reviewer, ONDQA

DATE COMPLETED

16-Apr-2014

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN SALEMME
04/16/2014

JOEL S HATHAWAY
04/16/2014
Signed for Thomas Oliver, Div VI Branch Chief, ONDQA

CHEMIST REVIEW
OF SUPPLEMENT
Prior Approval

1. **ORGANIZATION:** ONDQA
2. **NDA/SUPPLEMENT:** 21-225 / S-033 PA
3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 27-Feb-2013
Goal Date: 27-Jun-2013
4. **AMENDMENTS:** None
5. **RECEIVED BY CHEMIST:** March 2013

6. **SPONSOR NAME AND ADDRESS**

Baxter Healthcare Pharmaceuticals
Montville, NJ

7. **SUPPLEMENT PROVIDES FOR:** 1.) a modified inserter (including ergonomic enhancements) to replace the current inserter as an integrated applicator –forming an integral part of the complete levonorgestrel-intrauterine system (LNG-IUS) at the time of application to the patient, and 2.) new packaging materials for the container/closure of the final assembled product.

- | | |
|--|--|
| 8. <u>DRUG PRODUCT NAME:</u> | Mirena |
| 9. <u>NONPROPRIETARY NAME:</u> | Levonorgestrel-releasing Intrauterine Device |
| 10. <u>DRUG SUBSTANCE:</u> | Levonorgestrel |
| 11. <u>DOSAGE FORM/STRENGTH:</u> | Intrauterine system; 52 mg |
| 12. <u>ROUTE OF ADMINISTRATION:</u> | Intrauterine |
| 13. <u>INDICATION:</u> | Contraception |
| 14. <u>HOW DISPENSED:</u> | Rx |
| 15. <u>RELATED IND/NDA/DMF:</u> | NDA 203159, Skyla IUS; (b) (4) |

16. **COMMENTS:**

Mirena, a drug/device combination product, is an intrauterine (IUS) system packaged with an inserter device which delivers the IUS to the uterus. The manufacturing process consists of, the following: the intrauterine system (IUS) is manufactured and placed into the inserter, the IUS/inserter is packaged in a blister pack, and the blister pack is sterilized by ethylene-oxide sterilization. The sterilized packaged Mirena system is then aerated, tested, labeled, and packed.

This supplement provides for changes to the inserter device. The proposed inserter is very similar to the inserter approved in the Baxter NDA 203159, Skyla. The proposed inserter will be manufactured (b) (4)

The manufacturing and controls for the inserter have been evaluated by Ms. Veronica Price, CDRH reviewer, and the FDA/CDRH Office of Compliance has evaluated the manufacturing sites associated with the device.

The CDRH reviewer, Ms. V. Price, finds (b) (4) is adequate and (b) (4) is deficient. Additionally, Ms. Price states in the Consult review:

When compared to the insertion device approved for the Skyla system, NDA 203159, the insertion device proposed for use for Mirena differs with respect to some of the dimensions and the colorant used on the flange/slider. Although the changes in dimensions were necessary to accommodate the larger sized Mirena IUS, there could be some effects on the ease of deployment. Therefore, I recommend that Bayer address the following as part of their NDA:

- The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

These comments regarding the performance of the proposed inserter will be conveyed in a Complete Response action letter.

This supplement also proposes a change in the primary container closure (blister and peelable lid) to a blister polymer used approved in NDA 203159, a change in the polymers used for the inserter tube and flange to those approved in NDA 203159, and a change in the ethylene oxide sterilization process used to sterilize the packaged IUS/inserter. The Pharm-Tox reviewer, Dr. K. Hatfield, has evaluated the polymers and finds them to be acceptable. The Microbiology reviewer, S. Donald, has evaluated the sterilization manufacturing process and has recommended this supplement for approval. All other chemistry, manufacturing and controls information/data evaluated in the submission has been found to be acceptable.

17. CONCLUSIONS AND RECOMMENDATIONS

The information provided is not sufficient to support the use of the proposed inserter. This supplement, therefore, is recommended for a Complete Response action.

Action: Provide the following comments in the CR action letter:

- (1) [REDACTED] ^{(b) (4)} is deficient. The DMF holder has been notified of the deficiencies.
- (2)
 - The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

18. REVIEWER NAME

J. Salemme, Ph.D., Chemistry reviewer, ONDQA

DATE COMPLETED

25-Jun-2013

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN SALEMME
06/27/2013

THOMAS F OLIVER
06/27/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 21225; Supplement 33

Supporting document/s: SD# 697, eCTD# 64

Applicant's letter date: February 27, 2013

CDER stamp date: February 27, 2013

Product: Mirena® (levonorgestrel-releasing intrauterine system)

Indication: 1) Intrauterine contraception for up to 5 years
2) Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.

Applicant: Bayer HealthCare Pharmaceuticals Inc.
PO Box 1000, Montville, NJ 07045-1000

Review Division: Division of Reproductive and Urologic Products

Reviewer: Kimberly Hatfield, PhD

Supervisor/Team Leader: Alexander Jordan, PhD

Division Director: Hylton Joffe, MD, MMSc

Project Manager: Charlene Williamson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21225 are owned by Bayer HealthCare or are data for which Bayer HealthCare has obtained a written right of reference. Any information or data necessary for approval of NDA 21225 that Bayer HealthCare does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Bayer HealthCare does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21225.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	RECOMMENDATIONS.....	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
2	DRUG INFORMATION	4
3	STUDIES SUBMITTED.....	7
10	SPECIAL TOXICOLOGY STUDIES.....	7
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	10

Table of Tables

Table 1: Composition of Mirena IUS	5
--	---

Table of Figures

Figure 1: Schematic illustration of the IUS	5
Figure 2: Schematic illustration of the integrated inserter.....	6

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Nonclinical data support the safety of the two inserter components (LE1005C and LE1004C) of the Mirena® IUS.

1.1.2 Additional Nonclinical Recommendations: None

1.1.3 Labeling

The Sponsor has proposed labeling changes for Mirena based on the approved physician's labeling for Skyla (Bayer is the Sponsor for both Mirena and Skyla). The Sponsor has proposed minor additions of language to Sections 8.1, 8.3 and 8.4, but these are based on clinical knowledge, appear to be appropriate, and there are no objections. In Section 13, the Sponsor has proposed to delete all references to animal studies and retain only a statement referring to the Warnings and Precautions Section 5.9 regarding Breast Cancer, as was done for the Skyla. This is appropriate, and there are no objections. The pharmacologic class, however, is incorrect as currently listed in Highlights of Prescribing Information, and should be edited based on the FDA Established Pharmacologic Class listings, and to match what is listed for Skyla. The word "sterile" should not be used, and the term IUS (intrauterine system) is more appropriate, as this is technically a drug product and not a device. Recommended labeling is shown below, while annotated labeling can be found beginning on page 10 of this review.

Highlights of Prescribing Information Indications and Usage

Mirena is a progestin-containing intrauterine system (IUS) indicated for:

- Intrauterine contraception for up to 5 years (1)
- Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. (1)

It is recommended for women who have had at least one child.

1.2 Brief Discussion of Nonclinical Findings

The two components of the inserter that were tested in the reviewed studies (LE1005C and LE1004C; insertion tube and flange) were well-tolerated following intracutaneous administration, and had no skin sensitization or cytotoxic potential. These inserter components pose no safety concerns for clinical use.

2 Drug Information

2.1 Drug

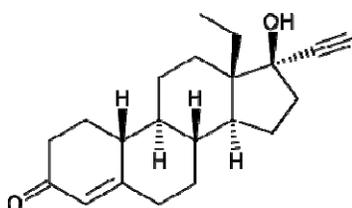
2.1.1 **CAS Registry Number:** 797-63-7

2.1.2 **Generic Name:** Levonorgestrel (LNG) intrauterine system (IUS)

2.1.4 **Chemical Name:** 18,19-Dinorepregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17a)-(-)

2.1.5 **Molecular Formula/Molecular Weight:** C₂₁H₂₈O₂; MW = 312.45 g/mol

2.1.6 Structure



2.1.7 **Pharmacologic class:** Progestin-containing intrauterine system

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 22697: Levonorgestrel Intrauterine Device (Bayer HealthCare Pharmaceuticals Inc; IND for Mirena®)

IND 73505: Levonorgestrel Intrauterine System (Bayer HealthCare Pharmaceuticals Inc; IND for Skyla)

NDA 203159: Skyla (Bayer HealthCare Pharmaceuticals Inc)

DMF 4178: Levonorgestrel (Bayer Pharma AG)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Mirena IUS is an intrauterine drug delivery system consisting of a hormone-elastomer reservoir matrix mounted on a polyethylene T-body. The reservoir consists of a core of (b) (4) levonorgestrel and (b) (4) polydimethylsiloxane elastomer ((b) (4)), covered with polydimethylsiloxane membrane regulating the release of LNG to achieve an initial release rate of 20 µg/day. The T-body is manufactured from pellets containing polyethylene and barium sulphate (b) (4), which is added to render the T-body radiopaque. The removal threads are manufactured from high-density polyethylene and iron oxide (b) (4) (to provide a more visible brown color). The IUS is administered via an integrated inserter, which consists of an insertion tube, plunger, flange, handle, slider and thread lock.

Table 1: Composition of Mirena IUS

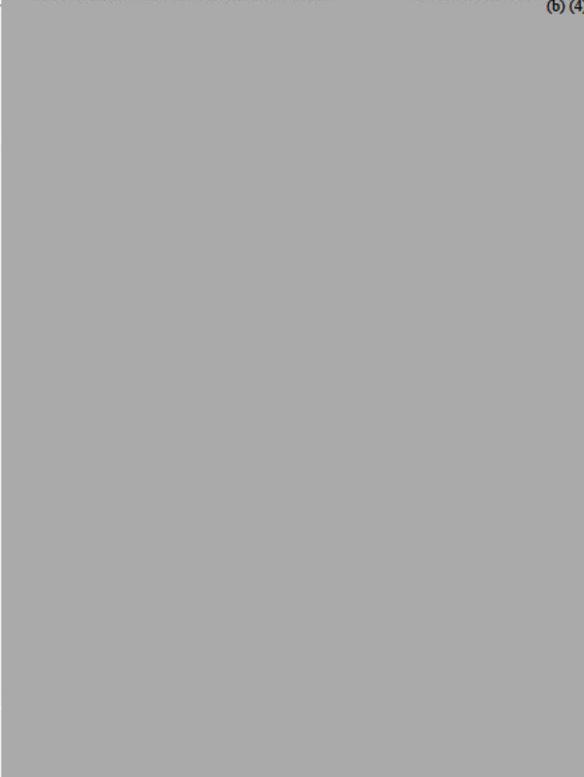
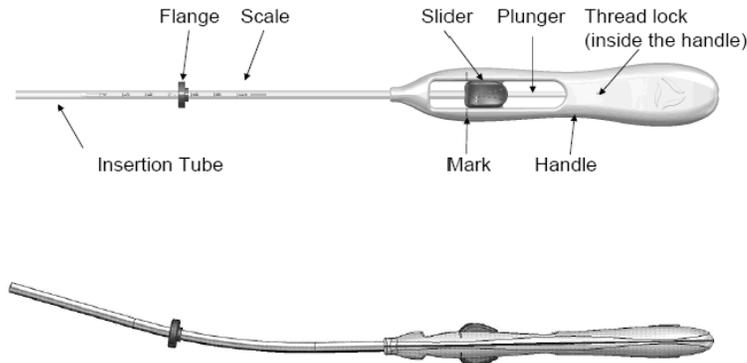
Composition	Reference to Standard	Function	Amount
Drug substance Levonorgestrel micronized		(b) (4)	52 mg
Excipients Poly(dimethylsiloxane) elastomer ^a		(b) (4)	
Poly(dimethylsiloxane) tubing ^b		(b) (4)	
Other components T-body ^c		(b) (4)	
Polyethylene ^c		(b) (4)	
Barium sulphate ^c		(b) (4)	
Thread ^d		(b) (4)	
Polyethylene ^d		(b) (4)	
Iron oxide,  ^{(b) (4)}		(b) (4)	
Integrated administration device Inserter		(b) (4)	
			

Figure 1: Schematic illustration of the IUS



Figure 2: Schematic illustration of the integrated inserter

2.3.2 Comments on Novel Excipients: None

2.3.3 Comments on Impurities/Degradants of Concern: None

2.4 Proposed Clinical Population and Dosing Regimen

This supplement provides no change in clinical population or dosing regimen. The intended clinical population is women who have had at least one child.

2.5 Regulatory Background

Mirena is a T-shaped intrauterine system (IUS) that has been approved for intrauterine contraception (12-6-2000) and for heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception (10-1-2009).

The current supplement has been submitted to request approval for 1) a modified inserter (including ergonomic enhancements) to replace the current inserter as an integrated applicator – forming an integral part of the complete LNG-IUS at the time of application to the patient, and 2) new packaging materials for the container/closure system of the final assembled product. CMC changes and clinical labeling changes have been submitted, while nonclinical studies to support the change in polyethylene grade used for the insertion tube and pigment used for the inserter flange have also been provided.

The Sponsor notes in the cover letter that the CMC modifications have no clinical impact on the Mirena IUS, and the modified/ergonomically enhanced Mirena inserter has already been approved in NDA 203159 for Skyla™. In addition, the proposed labeling changes will harmonize the Mirena label, where appropriate, with the related information/statements contained the Skyla labeling.

3 Studies Submitted

3.1 Studies Reviewed

A51745: LE1004C (MIRENA Evolution flange) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

A52603: Cytotoxicity assay in vitro: evaluation of materials for medical devices (XTT-test) with LE1004C

PH-36387: Mirena Evolution flange. Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test according to Magnusson and Kligman)

3.2 Studies Not Reviewed

The following submitted studies were previously reviewed for NDA 203159 (Skyla):

A51744: LE1005C (MIRENA Evolution Tube) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

A52604: Cytotoxicity assay in vitro: evaluation of materials for medical devices (XTT-test) with LE1005C

PH-36388: Mirena Evolution Insertion Tube. Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test according to Magnusson and Kligman)

3.3 Previous Reviews Referenced

NDA 203159 (Skyla), SD#1, eCTD #0000; 12/9/2011

IND 73505 (Skyla, LCS12), SD#51, eCTD #0045; 8/31/2011

Both nonclinical reviews conducted by Kimberly Hatfield, PhD

10 Special Toxicology Studies

Submitted studies A51744, A52604 and PH-36388 were reviewed for NDA 203159 (Skyla). In short, LE1005C extracts (LE1005C is the material comprising the insertion tube) were tolerated following intracutaneous administration (A51744), do not possess cytotoxic potential (A52604), and had no skin-sensitization potential (PH-36388).

A new flange material, LE1003C, was reviewed for NDA 203159 (Skyla). However, it appears from the product number that the Mirena flange (LE1004C) has some difference in material from Skyla (likely a pigment color change). Studies supporting the safety of the LE1004C flange material are reviewed here (A51745, A52603, PH-36387).

Study title: LE1004C (MIRENA Evolution flange) [Extract] Local tolerance test after single intracutaneous administration in the rabbit

Study no.: TOXT6082123 (Report #A51745)
 Study report location: NDA 21225; SD #697 (eCTD #64); 2-27-13
 Conducting laboratory and location: Bayer Schering Pharma AG, Nonclinical Drug Safety, 13342 Berlin, Germany
 Date of study initiation: October 26, 2010
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: LE1004C (Batch #C10122) (EtO steril) in aqueous (0.9% NaCl) and oily (sesame oil) extracts. (b) (4)

This study examined the local tolerance of single intracutaneous administration of saline or sesame oil extracts of LE1004C (and controls). Two male and two female New Zealand white rabbits were tested, with each animal receiving 5 injections with 0.2mL of the LE1004C extract in sesame oil on the right side of the spine, and 5 injections with 0.2mL of extraction medium as control. On the left side of the spine, the same animals received the same number and amount of injections with LE1004C extract in 0.9% NaCl, and extraction medium. Reactions were observed immediately and at 4, 24, 48, and 72 hrs post-injection, and from day 5 onwards until alleviation of symptoms (up to day 18). The test article had no effect on body weight. No test-article related findings were observed either with saline extract or sesame oil extract. Reddening or swelling were also observed with control treatment.

Conclusion: LE1004C extracts are tolerated following intracutaneous administration.

Study title: Cytotoxicity assay in vitro: Evaluation of materials for medical devices (XTT-test) with LE1004C

Study no.: T2081652EXT (Report #A52603)
 Study report location: NDA 21225; SD #697 (eCTD #64); 2-27-13
 Conducting laboratory and location: Harlan Cytotest Cell Research GmbH (Harlan CCR), In den Leppsteinswiesen 19, 64380 Rossdorf, Germany
 Date of study initiation: November 24, 2010
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: LE1004C(Batch #C10122) extracted in RPMI 1640 medium, supplemented with 10% FCS (PAA), 1mM sodium pyruvate, 2mM L-glutamine, and 100µg/mL penicillin/streptomycin. (LE1004C is the flange)

This in vitro study was performed to assess the cytotoxic potential of LE1004C using the XTT test with an extract of the test item.

Cell line:	Mouse L929
Negative Control:	RM-C (high density polyethylene) (Lot# C-042) (100% of extract)
Positive Control:	Latex (Lot# 03200694110385) (3-100% of extract)
Medium Control:	Complete medium
Test item:	LE1004C (3-100% of extract)
Incubation time:	24 hours
Cytotox test:	50 μ L XTT mixture added, then absorbance reading at 450 nm

There was no relevant difference in absorbance reading between the negative control and medium control, and the positive control showed a distinct dose-related reduction in cell viability and proliferation (XTT₅₀ = 6.6%). Absorbance readings for LE1004C did not indicate any cytotoxic effect up to the highest concentration of extract, and an XTT₅₀ could not be calculated.

Conclusion: LE1004C does not possess cytotoxic potential.

Study title: LE1004C: Study for the skin sensitization effect in guinea pigs (Guinea Pig Maximization Test according to Magnusson and Kligman)

Study no.: T3081860 (Report #PH-36387)
 Study report location: NDA 21225; SD #697 (eCTD #64); 2-27-13
 Conducting laboratory and location: Bayer Schering Pharma AG, GDD-GED Toxicology, 42096 Wuppertal, Germany
 Date of study initiation: October 26, 2010
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: LE1004C (Batch #C10122) in aqueous (0.9% NaCl) or sesame oil extract (LE1004C is the flange)

This study examined the skin-sensitizing effects of LE1004C in the guinea pig maximization test. Thirty-four female SPF-bred guinea pigs were treated with either control (0.9% (w/v) NaCl-solution (Group 1) or sesame oil (Group 2); 5 animals each) or test-article (LE1004C extract in 0.9% (w/v) NaCl-solution (Group 3) or sesame oil (Group 4); 10 animals each) at 100% concentration. Groups 5 and 6 were dose findings for the challenge concentration/ extract in 0.9% NaCl-solution or sesame oil, respectively.

Methods: Intradermal induction – 6 intradermal injections (0.1mL each), 3 on each side of the neck region, were made according to the following:

Test Groups 3&4	Control Groups 1&2 and Dose-Finding Groups 5&6
a) complete Freund's adjuvant diluted in saline (1:1)	a) complete Freund's adjuvant diluted in saline (1:1)
b) 100% LE1004C	b) undiluted vehicle (saline or sesame oil)
c) 100% LE1004C & complete Freund's adjuvant 1:1	c) 1:1 mixture Freund's adjuvant/vehicle

Topical induction – to provoke the possible sensitizing effect of LE1004C, on day 8, hypoallergenic patches treated with test item (0.5mL 100% LE1004C) or control (0.5mL vehicle) were placed between and on the injection sites for 48 hrs.

Topical challenge – on Day 22 (2 weeks after last epidermal admin), a hypoallergenic patch loaded with 0.5mL 100% test-item or vehicle in saline or sesame oil was placed on the right flank of the animals of respective groups for 24 hrs. Reactions were assessed and graded 48 and 72hrs after the start of the application to induce the challenge. A substance was considered sensitizing if 30% or more of the test group animals reacted positively compared to controls.

Results: The appearance and behavior of the test-item group were not different from controls, and body weights were not different. In control and test-item groups with saline, white wheals with red surrounding were observed, and in control and test-item groups with sesame oil, red wheals and white wheals with red surrounding were observed. Encrustations were observed at the injection site of both control and treated animals after 7 days, with wheals appearing in addition to encrustation in the saline test-item groups. Upon topical challenge, no skin effect was observed in control or test-item groups.

Conclusion: LE1004C exhibits no skin-sensitization potential.

11 Integrated Summary and Safety Evaluation

The two components of the inserter that were tested in the reviewed studies (LE1005C and LE1004C; insertion tube and flange) were well-tolerated following intracutaneous administration, and had no skin sensitization or cytotoxic potential. These inserter components pose no safety concerns for clinical use.

Nonclinical issues regarding labeling:

The Sponsor's proposed labeling changes are based on the recently approved Skyla label (Bayer is the Sponsor for both Mirena and Skyla). This reviewer has reviewed Sections 8 and 13 of the label, along with pharmacologic class in Highlights, and has also compared the Mirena and Skyla labels. The Sponsor has proposed minor additions of language to Sections 8.1, 8.3 and 8.4, but these are based on clinical knowledge. All changes to Section 8 appear appropriate, and there are no objections.

The Sponsor has proposed to delete all references to animal studies in Section 13 and retain only a statement referring to the Warnings and Precautions Section 5.9 regarding Breast Cancer, as was done for the Skyla. This is appropriate, and there are no objections.

The pharmacologic class is incorrect as currently listed in Highlights of Prescribing Information, and should be edited based on the FDA Established Pharmacologic Class listings, and to match what is listed for Skyla.

The following is the Sponsor's proposed labeling for Highlights and Section 13, with recommended annotated edits to the Highlights section (insertions are underlined, deletions are ~~strikethrough~~):

Highlights of Prescribing Information

Indications and Usage

Mirena is a sterile, ~~levonorgestrel-releasing intrauterine system~~ progestin-containing intrauterine system (IUS) indicated for:

- Intrauterine contraception for up to 5 years (1)
- Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. (1)

It is recommended for women who have had at least one child.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.9)]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY P HATFIELD
06/10/2013

ALEXANDER W JORDAN
06/11/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

5/30/2013

NDA: 21225/S-033

Drug Product Name

Proprietary: Mirena

Non-proprietary: Levonorgestrel, USP

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
2/27/2013	2/27/2013	4/2/2013	4/05/2013

Submission History (for 2nd Reviews or higher)

None

Applicant/Sponsor

Name: Bayer HealthCare Pharmaceuticals Inc.

Address: P.O. Box 1000, Montville, NJ 07045-1000

Representative: Joseph Zuccarini,

Telephone: 973 487-2063

Name of Reviewer: Steven P. Donald, M.S.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** PAS
 - 2. SUBMISSION PROVIDES FOR:** Product inserter and packaging changes.
 - 3. MANUFACTURING SITE:** Bayer Oy, Pansionte 47, 20210, Turku, Finland
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** intrauterine system; 52 mg
 - 5. METHOD(S) OF STERILIZATION:** Ethylene oxide
 - 6. PHARMACOLOGICAL CATEGORY:** Contraception
- B. SUPPORTING/RELATED DOCUMENTS:** None
- C. REMARKS:** This PAS provides for modifications to inserter, forming an integral part of the complete levonorgestrel intrauterine system at the time of application to the patient. Materials have changed for the insertion tube, a different polyethylene formulation, and handle, a different (b) (4). Also new packaging materials are used for the container/closure system of the final assembled product: the thermo-formed blister (PETG) with peelable lid (b) (4). New EtO (b) (4) sterilization validation has been performed for two locations and is presented below. An optimized sterilization cycle was developed at (b) (4) (b) (4). This cycle was also transferred to Bayer Oy. Sterilization will be performed at both locations, Bayer, Oy, Pansiontie 47, 20210 Turku, Finland or (b) (4). This submission is in eCTD format.

filename: N21225s33r1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for Approval on the basis of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is terminally sterilized using ethylene oxide gas.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

- A. Reviewer's Signature** _____
Steven P. Donald, M.S.
Microbiology Reviewer
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**
N/A

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN P DONALD
06/03/2013

STEPHEN E LANGILLE
06/03/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

OTHER REVIEW(S)

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 20, 2014

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

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 021225/S-033
Mirena (levonorgestrel-releasing intrauterine system)

Background

This consult review is in response to DBRUP's April 29, 2014, request for OPDP's review of the draft package insert (PI) and carton and container labeling for Mirena (levonorgestrel-releasing intrauterine system). OPDP reviewed the version of the draft PI available in Sharepoint on May 16, 2014, and the draft carton and container labels available in Sharepoint on May 19, 2014. Our comments on the PI are included directly on the attached copy of the labeling. We have no comments on the draft carton and container labels, which are attached for reference.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Lynn Panholzer at 301-796-0616 or lynn.panholzer@fda.hhs.gov.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYNN M PANHOLZER
05/20/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

DATE: April 7, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Charlene Williamson, Regulatory Project Manager, CDER/OND/ODEIII/DBRUP

SUBJECT: [NDA 21225 \(resubmission dated 1/29/2014\)](#)
Applicant: Bayer Healthcare Pharmaceuticals, Inc
Device Constituent: hormone eluting intrauterine system
Drug Constituent: Levonorgestrel
Intended Treatment: prevention of pregnancy
CDRH CTS Tracking No. 1400104

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Contents

CDRH HUMAN FACTORS REVIEW OF NDA SUBMISSION (DATED 1/29/2014)	3
OVERVIEW AND RECOMMENDATION	3
APPENDIX 1: CDRH HF’S INVOLVEMENT HISTORY	5
APPENDIX 2: CDRH HUMAN FACTORS REVIEW OF MEETING PACKAGE (DATED 11/13/2013)	6
OVERVIEW AND RECOMMENDATION	6
APPENDIX 3: PREVIOUS CDRH HUMAN FACTORS REVIEW (6/27/2013)	7
OVERVIEW AND RECOMMENDATIONS	7
APPENDIX 4: DEVICE DESCRIPTION	9

CDRH Human Factors Review of NDA Submission (dated 1/29/2014)

Overview and Recommendation

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review of the NDA submission that contains a use-related risk analysis and a determination of whether a human factors validation study was needed. This was communicated in a meeting package dated 11/13/2014, and in FDA's complete response letter dated 8/30/2013. The complete response includes CDRH HF's question regarding use related risk analysis and a determination for the necessity of a human factors validation study.

FDA Question: Your proposed approach appears to focus on the risks associated with the modified device via a Failure Modes and Effects Analysis. This approach appears reasonable. For ease of review, we ask that you separate the use related risks from the device related risks. Note that your use-related risks analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. Please submit this use-related risk analysis, a determination of the necessity of human factors validation. If you determine that a human factors validation study is necessary, please submit your study protocol for review prior to study initiation. We would like to review the entire human factors study protocol to ensure that the study methodology are acceptable.

Bayer's Response: Bayer indicated that risks associated with the introduction of the proposed Mirena EVO inserter include infection, pain or injury to patient, unplanned pregnancy, environmental risks, and risks including handling steps by the HCP that could affect the outcome of the insertion. These risks have been identified as anticipated risks associated with product use. In addition to identification of these potential risks, Baxter reported that mitigation measures that have been identified and employed in support of the proposed Mirena EVO inserter including material testing, packaging validation, in-process controls, user training, design, and Instructions for Use. In addition, the comparisons of the proposed Mirena EVO inserter to the EVO inserter contained in SKYLA IUS approved on January 9, 2013 and to our current Mirena IUS showed that the EVO Inserter contains minor design changes to facilitate and decrease the steps in physician preparation of the IUS prior to placement. The following table provides an overview of the comparison of the preparatory steps by health care physician:

Current Mirena Inserter	EVO Inserter
<p>Step 1</p> <ul style="list-style-type: none"> • Open the sterile package completely • Release the threads. • Rotate the inserter so that the centimeter scale is upwards • Check that the arms of the system are in horizontal position 	<p>Step 1</p> <ul style="list-style-type: none"> • Open the sterile package completely
<p>Step 2</p> <ul style="list-style-type: none"> • Holding the slider in the furthest position, pull on the threads to draw the IUS into the insertion tube • If the knobs at the ends of the arms do not meet properly, release the arms by pulling the slider back to the mark. • Re-load the IUS by aligning the open arms on a sterile surface. Return the slider to its furthest position and pull on both threads. Check for proper loading. 	<p>Step 2</p> <ul style="list-style-type: none"> • Push the slider upwards, in the direction of the arrow, to the furthest position to load the IUS into the insertion tube
<p>Step 3</p> <ul style="list-style-type: none"> • Fix the threads in the cleft (bottom end of the handle) to keep the product in the loaded position. 	-

As a result, Bayer believes that the introduction of EVO inserter will not introduce any additional risks or user-related hazards.

This consultant reviewed the response along with the use-related risk analysis and determined that a human factors study is not needed because the decrease of manipulation steps associated with the new design and the device will be used by healthcare professionals in hospital setting.

Appendix 1: CDRH HF's Involvement History

- 6/11/2013: CDRH HF was requested to review the sponsor's proposed modifications (ergonomic enhancements) to the inserter device and labeling.
- 6/27/2013: CDRH HF provided a request for use-related risks and determination whether a human factors study is needed
- 12/6/2013: CDRH HF received a request to review a meeting package where the Sponsor provides a proposal to address the request.
- 1/29/2014: CDRH HF was requested to review the Sponsor's use-related risk analysis and determination whether a human factors study is needed
- 4/7/2014: CDRH HF provided a final review memo CDER project manager

Appendix 2: CDRH Human Factors Review of Meeting Package (dated 11/13/2013)

Overview and Recommendation

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of meeting package in response to FDA's complete response letter dated 8/30/2013. The complete response includes CDRH HF's question regarding use related risk analysis and a determination for the necessity of a human factors validation study. The following provides a brief summary of FDA and Sponsor interaction.

FDA Question:

It is not clear what hazards are associated with the modified inserter. Provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if the users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, submit your draft protocol for review prior to conducting the study.

Bayer's Position:

Bayer is developing a Failure Modes and Effects Analyses (FMEA), based on the implementation of the proposed Mirena EVO Inserter, to identify and quantitate any potential risks associated with the minimal changes made to the existing inserter. Similarly, the FMEA will also highlight the mitigation strategies employed to limit/minimize those identified potential risks which include, but are not limited to, proposed labeling instructions, established finished product release and stability testing requirements, physician training materials and results from our proposed *in vitro* bench testing. Where applicable, we also intend to draw correlations to the similarities (i.e., design features) of our proposed Mirena EVO product and SKYLA, a recently approved IUS which also utilizes a significantly similar version of the EVO Inserter. These identified mitigation measures will reference appropriate methods used to validate their effectiveness.

Bayer's Meeting Request Question 1:

Does the Agency agree with our proposed approach in addressing this question?

CDRH HF Proposed Response to Question 1

Your proposed approach appears to focus on the risks associated with the modified device via a Failure Modes and Effects Analysis. This approach appears reasonable.

For ease of review, we ask that you separate the use related risks from the device related risks. Note that your use-related risks analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. Please submit this use-related risk analysis, a determination of the necessity of human factors validation. If you determine that a human factors validation study is necessary, please submit your study protocol for review prior to study initiation. We would like to review the entire human factors study protocol to ensure that the study methodology are acceptable.

Note to CDER: Please issue a new InterCenter Consult when you receive the use-related risk analysis and determination whether a human factors study is needed, and protocol (if needed).

Appendix 3: Previous CDRH Human Factors Review (6/27/2013)

Overview and Recommendations

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of an NDA supplement (sNDA 21225/S33) from Bayer Healthcare Pharm, Inc for modifying the inserter device with “ergonomic enhancements” and associated labeling.

The submission did not provide any information indicating how the Sponsor has evaluated use-related hazards associated with the modified device or how the Sponsor has validated the effectiveness of the mitigations implemented to address the hazards. This device is reviewed by CDRH’s Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD), Obstetrics and Gynecology Devices Branch (OGDB). This reviewer discussed this consult request with OGDB’s branch chief to better understand the use-related hazards. For this type of device, there are known issues such as deployment and detachment that can affect the delivery of the IUD to the target location in its intended shape/configuration. Some of these issues can be associated with how the user interacts with the device. As a result, OGDB has requested human factors data in CDRH premarket review where the sponsor needs to demonstrate the clinicians can correctly use the device.

As a result, the reviewer recommends the following letter-ready comments be transmitted to Bayer Healthcare Pharm:

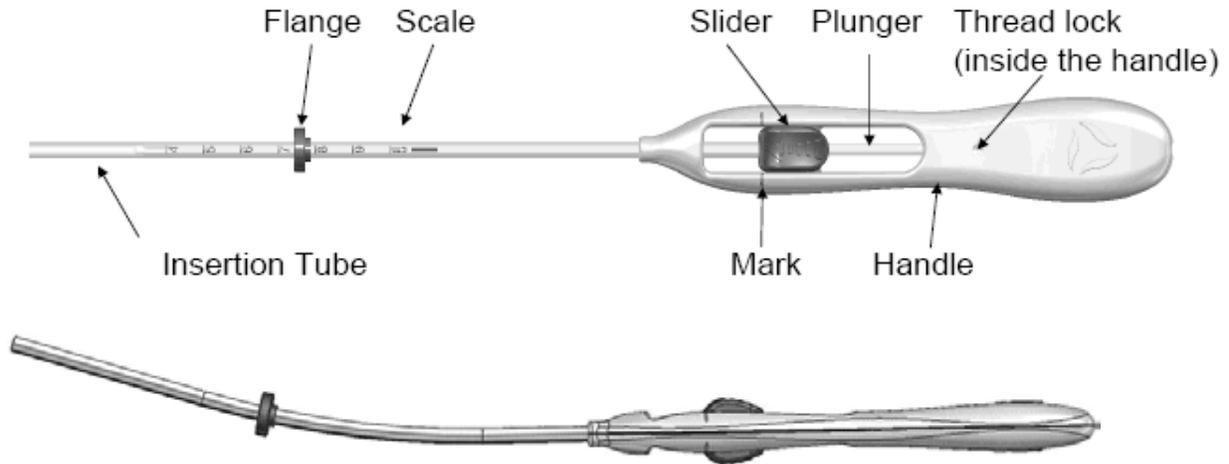
In your cover letter dated February 27, 2013, you requested for approval of a modified inserter including ergonomic enhancements to replace the current inserter. However, it is not clear what hazards are associated with the modified inserter. Please provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, please indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, please submit your draft protocol for review prior to conducting the study.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

Appendix 4: Device Description

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
04/17/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Abdominal and Surgical Devices Branch

DATE: March 31, 2014

TO: Charlene Williamson, Project Manager
CDER/OND/ODEIII
Division of Bone, Reproductive, and Urologic Products
WO22, Room 5395

Cc: Office of combination products at combination@fda.gov

Through: Ronald L. Swann, Chief, Abdominal and Surgical Devices
Branch, Division of Manufacturing and Quality, Office of
Compliance, CDRH, WO-66, Room 3534

From: Felicia Brayboy, CSO, Abdominal and Surgical Devices
Branch, Division of Manufacturing and Quality, Office of
Compliance, CDRH, WO-66, Room 3547

Firm: Bayer Healthcare Pharmaceuticals, Inc.
Pansionitie 47
20210 Turku, Finland
FEI: 1000350927

Application # NDA 21-225, S-033

Product Name: Mirena (Levonorgestrel-releasing intrauterine system)

**Consult
Instructions:** Review response from firm to the Complete Response Letter
issued on August 30, 2013.

The Office of Compliance at CDRH received a consult request from CDER/OND/ODEIII/ Division of Bone, Reproductive, and Urologic Products (DBRUD) to evaluate the adequacy of the firm's response to the Complete Response Letter issued on August 30, 2013.

Product Description

Bayer Healthcare Pharmaceuticals submitted a supplement to its approved NDA 21225, for the Mirena (levonorgestrel-releasing intrauterine system) which is intended for contraception up to 5 years. Mirena is a hormone eluting intrauterine system which, includes an intrauterine device and a plastic insertion device. Bayer indicates that this insertion device is very similar to the one that was recently

approved for the Skyla Intrauterine system (IUS), NDA 203159 (a lower dose IUS marketed by Bayer).

Figure 1. Schematic illustration of the integrated inserter

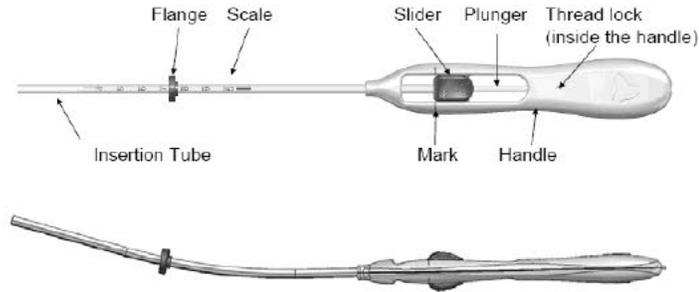


Table 1 - Technical Specifications

Parameter	Current MIRENA (NDA 21-225)	Proposed MIRENA EVO (NDA 21-225, S-033)	SKYLA (NDA 203159) ¹
Indications for Use	MIRENA is a sterile, levonorgestrol-releasing intrauterine system indicated for intrauterine contraception for up to 5 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.	EVO is a sterile, levonorgestrol-releasing intrauterine system indicated for intrauterine contraception for up to 5 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.	SKYLA is a low dose levonorgestrel (LNG) intrauterine system, which has been developed for intrauterine contraception for up to 3 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.
Insertion Tube			
Material	(b) (4) polyethylene (b) (4)	(b) (4) polyethylene (b) (4)	(b) (4)
Diameter	4.75 mm	4.40 mm	3.80 mm
Scale	Markings on one side	Markings on both sides	Markings on both sides
Flange			(b) (4)
Color	(b) (4) Teal	(b) (4) Teal	(b) (4) Pink

Parameter	Current MIRENA (NDA 21-225)	Proposed MIRENA EVO (NDA 21-225, S-033)	SKYLA (NDA 203159) ¹
Plunger			
Material	(b) (4)		
Diameter	3.5 mm	2.9 mm	2.9 mm
Design	Slot	Fork	Fork
Body Contact	Yes	No	No
Handle			
Material	(b) (4)		
Color	(b) (4) White	(b) (4) White	(b) (4) White
Maximum width	21 mm	28 mm	28 mm
Thread lock			
Design	Manually to the thread cleft at the lower end of the handle	Mechanically by a thread lock component inside the handle	Mechanically by a thread lock component inside the handle
Material	(b) (4)		
Slider			
Material	(b) (4)		
Color	(b) (4) Teal	(b) (4) Teal	(b) (4) Pink
Design	Re-loadable	Not re-loadable	Not re-loadable
T-Body			
Material	PE+BaSO4	PE+BaSO4	PE+BaSO4
Dimensions	32 x 32 x 1.5 mm	32 x 32 x 1.5 mm	28 x 30 x 1.5 mm
Removal Thread			
Material	PE: (b) (4)	PE: (b) (4)	PE: (b) (4)
Diameter	0.20 - 0.35 mm (target 0.30 mm)	0.24 - 0.30 mm (target 0.26 - 0.28 mm) Threads are thinner and softer	0.24 - 0.30 mm (target 0.26 - 0.28 mm) Threads are thinner and softer
Total Length	84 cm	56 cm Threads are inside handle	56 cm Threads are inside handle

¹ Skyla (also referred to as LCS12) was approved by the FDA on January 9, 2013

CDRH Office of Compliance Recommendation/Response

The following deficiencies were relayed in the July 10, 2013 memo to CDER and subsequently relayed to the applicant. In a memo to CDER dated December 23, 2013, the firm's approach to satisfy each of the deficiencies was evaluated and deemed acceptable. Below each deficiency is CDRH/OC assessment of the applicant's response.

1. There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls.

The applicant must provide information showing that changes in the introducer's design do not affect the safety and effectiveness of the finished product. Similarly, the applicant must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product. The applicant should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, the applicant should explain why no changes were necessary. The applicant should pay particular attention to the requirements for design controls under 21 CFR 820.30(i), (h) and (g).

CDRH/OC Assessment of 4a (Design Controls): Standard Operating Procedures (SOPs) or other documentation was provided and addressed all aspects of 21 CFR 820.30. The documentation appeared to be adequate. Below is a list of documents reviewed (this list is not all-inclusive).

Per the firm, development of new products and changes to marketed products are controlled by Bayer Healthcare (b) (4)
Additionally, the following SOPs for Design Validation, Risk Management and Change Management control the design of the device:



(b) (4)

Per the firm, a hazard analysis was performed in accordance with the (b) (4) ISO 14971:2007. The risk assessment showed that all identifiable risks have been reduced to acceptable levels. The Risk Management Report was provided.

CDRH/OC Assessment of 4b (Packaging changes): Per the firm, the following tests were performed on the revised packaging to validate its ability to maintain sterility and integrity of the product:

- (b) (4)
- (b) (4)
- Sterility testing conducted at release
- Stability testing

The changes to the primary packaging of the Mirena inserter were tested according to the following standards:

ASTM F1608-00(2009) Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)

(b) (4)

Data supporting the integrity of the container closure system was provided. Stability data demonstrating sterility over the intended shelf-life were provided as well. Per the firm, the package testing showed that the microbial barrier properties of the materials and the integrity of the seals maintain the sterile barrier system and do not adversely affect the integrity of the product.

The documentation appeared to be adequate.

CDRH/OC Assessment of 4c (Manufacturing changes): Per the firm, design transfer of the modified inserter is controlled by (b) (4). Per the firm, the revised product design did not require manufacturing changes except for the sterilization step.

Due to the design modifications of the inserter, the T-body, and the primary package, some adjustments of the production machines and validation of primary packaging and sterilization process was required.

Validation/re-validation evaluations were referenced and provided.

The documentation appeared to be adequate.

2. The applicant is adding an additional supplier of the inserter. The applicant should provide enough information to demonstrate adequate control over this new supplier and the product provided, as required by 21 CFR 820.50, purchasing controls.

CDRH/OC Assessment

SOPs or other documentation was provided and addressed 21 CFR 820.50. The documentation appeared to be adequate.

Per the firm, suppliers of components or products are controlled by several aspects of the Bayer Quality System. The following procedures cover the evaluation, assessment, qualification and management of suppliers (this list is not all-inclusive):



Per the firm, approval of the additional supplier was based on the following documents:



The supplier was audited on November 26-27, 2009 and a follow-up audit performed in December 7, 2011. No critical or major deficiencies were found.

The QA agreement between  and Bayer Oy was signed in September 7, 2010. The agreement requires that the supplier discuss and reach agreement with Bayer before implementing any changes that may have an effect on the quality of the product.

Deficiencies to be conveyed to the applicant

There are no deficiencies to be relayed to the applicant.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application NDA 21-225, S-033. CDRH will concur with CDER's decision regarding NDA 21-225, S-033 approval. The desk review of the application for compliance with the Medical Device Regulations showed no apparent deficiencies.

Felicia L. Brayboy, CSO

Prepared: FBrayboy: March 28, 2014
Revised: JGomes: 03/31/2014
Reviewed:

CTS No.: ICC1400092

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
04/02/2014



Food and Drug Administration
Office of Device Evaluation

DATE: February 24, 2014

FROM: Veronica Price, Biomedical Engineer
CDRH/ODE/DRGUD/OGDB
301-796-6538

TO: Charlene Williamson
CDER-ODE III
Division of Bone, Reproductive and Urologic Products

RE: NDA 21225/S-033 Response to Complete Response Letter dated 8/30/13
Mirena (levonorgestrel-releasing intrauterine system)
Bayer Healthcare Pharmaceuticals, Inc.

Review Summary:

Bayer Healthcare Pharmaceuticals has submitted a supplement to their approved NDA, 21225/S-033, for Mirena (levonorgestrel-releasing intrauterine system (IUS)) to obtain approval for the use of a modified inserter. Two different suppliers manufacture the modified inserter, (b) (4) and (b) (4)

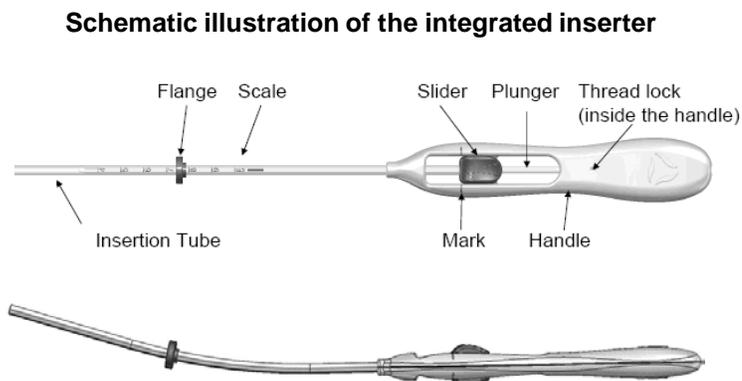
The scope of this consult is limited to the design and performance characteristics of the modified inserter by the two suppliers. There have been several interactions regarding this change. The following is an overview of these interactions:

- Original Consult dated 6/20/13: CDRH requested additional testing to assess the deployment/delivery of the IUS with the modified inserter and additional details on the testing conducted by (b) (4) (DMF (b) (4) on their inserter. FDA included these follow-up items as questions 2 and 3 in an August 30, 2013 letter to Bayer.
- Bayer Request for Meeting dated November 13, 2013: Discussed test protocol provided to address device deployment/delivery and referenced an amendment to DMF (b) (4) provided by (b) (4) on July 9, 2013 to address supplier testing.
- Follow-up Consult dated December 20, 2013: CDRH found that the test protocol is acceptable (following some interaction with the firm 12/19/13 and 12/20/13); and additional information included in (b) (4) DMF is acceptable. CDER issued a complete response letter on 8/30/13.
- Response from Bayer dated 1/29/14: Sponsor provided data on deployment/delivery of IUS with modified inserter (response to question 2) and referenced additional information in (b) (4) DMF (response to question 3).

This review is limited to the responses provided to questions 2 and 3 of the August 30, 2013 Complete Response Letter. The responses are acceptable and there are no outstanding issues related to the modified inserter (“EVO” inserter) for Mirena.

Device Description:

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The focus of this review is limited to the insertion device.



The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings. The following are the key dimensions: overall device length is 279 mm; width at the widest point of the handle (i.e., at the proximal end) is 28 mm; the diameter of the insertion tube is 4.4 mm; and the outer diameter of the flange is 12 mm.

Overview of Principle of Use:

The manufacturer places the intrauterine device within the inserter prior to packaging with the arms extending out from the distal tip of the inserter. After removal from the packaging, the clinician loads the arms of the IUS into the insertion tube by advancing the slider on the handle forward until it clicks into place. He/she sets the flange to the uterine depth determined during sounding. The clinician then advances the inserter through the cervix until the flange is 1.5 to 2 cm from the cervix. (He/she makes this determination based on the depth markings on the outside of the insertion tube.) The physician moves the slider back to a mark on the handle which releases the arms of the IUD within the uterus. (The physician is instructed to wait 10 seconds.) He/she gently pushes the inserter forward until the flange touches the cervix. The IUS arms should now be at the fundus. The physician releases the IUS by moving the slider all the way back until it clicks. With the slider held down, he/she removes the inserter from the patient.

Outstanding Review Issues:

The following is a restatement of the questions included in the August 30, 2013 Complete Response Letter raised during my previous review along with a summary of the firm's response:

Question #2 in CDER letter: The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

Bayer provided a test protocol for review in Attachment 1 of their request for a meeting dated November 13, 2013. As a result of some interaction, a slightly modified version was provided via e-mail on 12/20/13. They proposed to test samples for the following performance characteristics:

- T-body shape recovery following release from inserter
- Force necessary to release device from inserter

In the first test "Recovery of T-body Horizontal Arms Test", 33 samples from 3 different lots of both Mirena with EVO Inserter ("new inserter") (n=99 total) and Mirena with the current inserter (n=99 total) are evaluated. The sponsor loads the T-body into the inserter and keeps it in position for 5 minutes. The lab removes the T-body and allows it to recover its shape for one minute. The sponsor then places it in a test device which measures the angle of the arms. (b) (4)

The firm states that this test and the acceptance criteria are based on ISO 7439:2011 "Copper-bearing contraceptive intrauterine devices –Requirements and tests." Although this device is a hormonal IUD which is not covered by this standard, as noted in the standard, some portions of this standard may be applicable. The test of Visco-elastic property described in section 7.4 is relevant to this product. As such the acceptance criteria called out in section 5.6 of the standard related to this particular test requirement is reasonably applied to this device. However, in contrast to the standard which identifies a maximum residual deformation limit of 5 mm (Section 5.6) the test report provided by the firm sets the limit as (b) (4)

(b) (4)
This test protocol and the acceptance criteria are acceptable.

(b) (4)

(b) (4)
for all

samples tested. There were no noted differences in the mean angles recorded for the arms of the Mirena IUS when deployed with the currently marketed inserter and the EVO inserter. **The results provided demonstrate that the device can recover its intended shape as defined by the test acceptance criteria following deployment with the EVO inserter.**

The purpose of the second test, "IUS Detachment Force," is to verify that the T-body releases from the inserter as intended. In the test set-up, the sponsor pulls the IUS with removal threads out of the EVO Inserter at a constant speed while measuring the detachment force. The sponsor tested 16 samples from 3 batches (n=48 total) of the Mirena with EVO Inserter and 16 samples from 3 batches (n=48 total) of Mirena with Standard Inserter. The acceptance criteria requires a maximum detachment force of (b) (4). In addition, the sponsor compared the results with the Mirena with EVO Inserter to the results with the Mirena with Standard Inserter.

The sponsor derived the acceptance criteria from testing devices in a model simulating worst case conditions. The results of this preliminary testing demonstrated a mean force ranging from (b) (4) to (b) (4) for the Mirena with EVO Inserter and Mirena with Standard Inserter under various test conditions. **The test protocol and acceptance criteria are acceptable.**

In the current submission, the sponsor provided test data. All samples tested met the acceptance criteria of a maximum detachment force < (b) (4). When comparing the mean force required for detaching Mirena from the standard inserter to the mean force required for detaching Mirena from the EVO inserter, less force was required for detachment from the EVO inserter. **The results provided support the ease of removal of the inserter following Mirena deployment.**

The firm's response to Question 2 is acceptable.

Question #3 in CDER letter: Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on June 27, 2013. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

In Bayer's response, they indicate that the DMF holder informed them that the DMF was amended to include the necessary information on July 9, 2013. I reviewed the amendment to DMF (b) (4) to determine whether (b) (4) addressed the outstanding review issues identified with their DMF. The following is a restatement of these issues along with a summary of (b) (4) responses:

(b) (4)





The DMF holder has provided enough information to support the equivalence of their inserter when compared to the one supplied by (b) (4). **There are no outstanding review issues related to the inserter described under DMF (b) (4).**

The firm's response to Question 3 is acceptable.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Director Sign-Off	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
03/13/2014



Food and Drug Administration
Office of Device Evaluation

DATE: December 20, 2013

FROM: Veronica Price, Biomedical Engineer
CDRH/ODE/DRGUD/OGDB
301-796-6538

TO: Charlene Williamson
CDER-ODE III
Division of Bone, Reproductive and Urologic Products

RE: NDA 21225/S-033 with reference to DMF (b) (4) and DMF (b) (4)
Mirena (levonorgestrel-releasing intrauterine system)
Bayer Healthcare Pharmaceuticals, Inc.

Review Summary:

Bayer Healthcare Pharmaceuticals' has submitted a supplement to their approved NDA, 21225/S-033, for the Mirena (levonorgestrel-releasing intrauterine system) to obtain approval for the use of a modified inserter supplied by two different suppliers, (b) (4) and (b) (4). (b) (4) currently supplies an inserter for the approved Skyla IUS marketed by Bayer; however, due to differences in size between the Skyla and Mirena, (b) (4) developed a modified inserter for use with Mirena. A consult related to the use of these inserters with Mirena was originally provided on June 20, 2013. There were follow-up items related to the need for additional testing to assess the deployment/delivery of the IUS with the modified inserter and additional details from (b) (4) on the testing conducted on the inserter. These follow-up items were included as questions 2 and 3 in an August 30, 2013 letter to Bayer.

The firm provided additional information to address these questions in a communication to CDER dated November 13, 2013. As part of the response, they reference an amendment to DMF (b) (4) provided by (b) (4) on July 9, 2013. A consult was issued on December 6, 2013 with a due date of December 20, 2013. The internal CDRH tracking number assigned was ICC1300634.

The firm provided a test protocol to address the request for additional testing on device deployment/delivery. Additional details on the protocol were requested via e-mail on 12/19/13. These details were addressed via return e-mail on 12/20/13. The test protocol provided via e-mail on 12/20/13 is acceptable to address the review concerns cited in my original review.

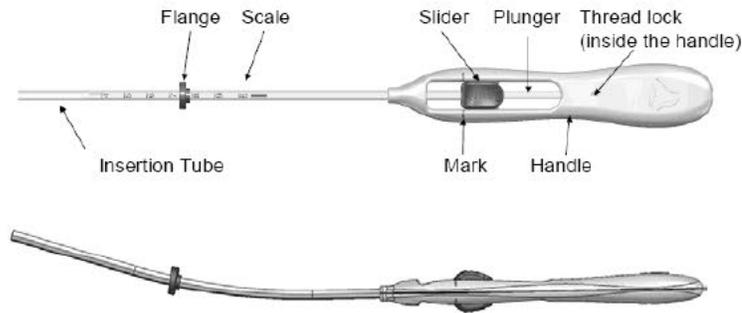
The amendment to the DMF included specific information to address the review concerns cited in my original review. The additional information addresses all of my concerns.

Device Description:

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The focus of this review is limited to the insertion device.

Bayer indicates that this insertion device is very similar to the one that was recently approved for the Skyla IUS, NDA 203159 (a lower dose IUS marketed by Bayer). The following picture from Bayer's application, Description of Product, P.1.01-01, shows the proposed insertion device:

Figure 2 Schematic illustration of the integrated inserter



The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.

Engineering drawings of the insertion device are included in the DMF's. As indicated in these drawings, the overall device length is 279 mm and the width at the widest point of the handle which is proximal end is 28 mm. The diameter of the insertion tube is 4.4 mm and the outer diameter of the flange is 12 mm.

Overview of Principle of Use:

The intrauterine device is placed within the inserter prior to packaging with the arms extending out from the distal tip of the inserter. After removal from the packaging the arms of the IUS are loaded within the insertion tube by advancing the slider on the handle forward until it clicks into place. The flange is then set to the uterine depth determined during sounding. The inserter is advanced through the cervix until the flange is 1.5 to 2 cm from the cervix. (This can be determined based on the depth markings on the outside of the insertion tube.) The slider is then moved back to a mark on the handle which releases the arms of the IUD within the uterus. (The physician is instructed to wait 10 seconds.) The inserter is then gently pushed forward until the flange touches the cervix. The IUS arms should now be at the fundus. The IUS is then released by moving the slider all the way back until it clicks. With the slider held down, the inserter is removed from the patient.

Comparison of Insertion Devices:

(b) (4), Drug Master File, DMF (b) (4) provides the insertion device for the recently approved Skyla IUS, NDA 203159. This master file was reviewed as part of the NDA. (b) (4) amended the file on February 3, 2013, to include information on the Mirena IUS. They state that the components are similar and the manufacturing process is identical for these two products. The product release testing was noted to be identical as well. The following table provides an overview of the differences:

Table 1 Differences between the Mirena Inserter (NDA 21-225) and the Skyla Inserter (NDA 203159)

Component	Mirena (NDA 21-225) Modified Inserter (S-033)	Skyla (NDA 203159)
-----------	--	--------------------

Insertion tube, outer diameter inner diameter ¹ length ²	4.40 mm 3.75 mm 214 mm	3.80 mm 3.10 mm 210 mm
Slider (color)	Teal	Pink
Slider, (design ²)	Dimensions adapted due to the T-body size difference (outer diameter).	Dimensions adapted due to the T-body size difference (outer diameter).
Slider (movement ²)	Approx. 40 mm	Approx. 36 mm
Flange (color)	Teal	Pink
Flange (design)	Same design, inner diameter adapted to outer diameter of insertion tube	Same design, inner diameter adapted to outer diameter of insertion tube
Handle	Same design, however dimensions adapted to different slider movement (length of window approx. 40 mm) and to outer diameter of insertion tube (opening)	Same design, however dimensions adapted to different slider movement (length of window approx. 36 mm) and to outer diameter of insertion tube (opening)
Embossed Handle logo	Embossed Mirena logo	No embossed logo

¹ IUS max. outer diameter 3.65 mm and 2.9 mm for Mirena and Skyla, respectively.

² Due to different T-body dimensions (Skyla 28x30 mm, Mirena 32x32mm)

The differences in dimensions of the Mirena insertion device are minor when compared to the insertion device approved as part of the Skyla. However, these changes in dimensions to accommodate the larger size of the Mirena have the potential to affect the device delivery characteristics; therefore the firm was asked to conduct some additional bench testing to address issues related to IUS deployment. A test protocol was submitted and is discussed below.

Additional Insertion Device Supplier:

In addition to (b) (4) Bayer also proposes use of insertion devices manufactured by (b) (4). A DMF, (b) (4) has been established by this supplier as well. The (b) (4) DMF is limited to the Mirena insertion device. The description of the device including information on the design/function of each of the individual components and the materials is identical to what has been reviewed as part of the (b) (4) DMF. The engineering drawings and final assembly test specifications are identical as well. Additional information on the tests for pull and push strength and distortion were necessary to ensure that they were identical to those applied by (b) (4). This additional information is discussed below.

Review Issues:

The following is a restatement of the issues raised in my original review along with a summary of the responses provided by the firm on November 19, 2013:

Question #2 in CDER letter: The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical

conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

Bayer provided a test protocol for review in Attachment 1 of their request for a meeting dated November 13, 2013. As a result of some interaction, a slightly modified version was provided via e-mail on 12/20/13. They propose to test samples for the following performance characteristics:

- T-body shape recovery following release from inserter
- Force necessary to release device from inserter

In the first test "Recovery of T-body Horizontal Arms Test", 33 samples from 3 different lots of both Mirena with EVO Inserter ("new inserter") (n=99) and Mirena with the current inserter (n=99) are evaluated. The T-body is loaded into the inserter and kept in position for 5 minutes. The T-body is then removed and allowed to recover its shape for one minute. It is then placed in a test device which measures the angle of the arms. The acceptance criteria requires an angle of - (b) (4). The firm states that this test and the acceptance criteria are based on ISO 7439:2011 "Copper-bearing contraceptive intrauterine devices –Requirements and tests." Although this device is a hormonal IUD which is not covered by this standard, as noted in the standard, some portions of this standard may be applicable. The test of Visco-elastic property described in section 7.4 is relevant to this product. As such the acceptance criteria called out in section 5.6 of the standard is this particular test requirement is reasonably applied to this device. However, in contrast to the standard which identifies a maximum residual deformation limit of 5 mm (Section 5.6) the test report provided by the firm sets the limit as a range of degrees. The firm was asked via e-mail on 12/19/13 to demonstrate that their pass criteria equate to 5 mm. This was provided via e-mail on 12/20/13. Based on the calculation provided, the maximum residual deformation of (b) (4). Therefore, the test acceptance criteria are more stringent than required by the standard. **This test protocol and the acceptance criteria are acceptable.**

The following picture was provided via e-mail on 12/20/13 to demonstrate the point along the arm at which the angle is measured. (b) (4)

The second test "IUS Detachment Force" is intended to verify that the T-body releases from the inserter as intended. In the test set-up the IUS with removal threads is pulled out of the EVO Inserter at a constant speed while the detachment force is measured. Sixteen samples from 3 batches (n=48) of the Mirena with EVO Inserter and 16 samples from 3 batches (n=48) of Mirena with Standard Inserter are tested. The acceptance criteria requires a maximum detachment force of < (b) (4). In addition the results obtained with the Mirena with EVO Inserter will be compared to the results with the Mirena with Standard Inserter.

The acceptance criteria was derived from testing conducted on samples of devices used in a model simulating worst case test conditions. The results of this preliminary testing demonstrated a mean force ranging from (b) (4) to (b) (4) for the Mirena with EVO Inserter and Mirena with Standard Inserter under various test conditions. **The acceptance criteria for this test are acceptable.**

Questions from firm regarding the proposed test protocol:

Does the Agency agree that this proposed protocol is adequately designed to address the deployment/delivery concerns highlighted above?

CDRH response: Yes

Does the Agency have any comment(s) on our proposed testing protocol ?

CDRH response: No

Question #3 in CDER letter: Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on June 27, 2013. These deficiencies must be adequately addressed before this application can be

approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

In Bayer's response they indicate that the DMF holder informed them that the DMF was amended to include the necessary information on July 9, 2013. The amendment to DMF (b) (4) was reviewed to determine whether (b) (4) addressed the outstanding review issues identified with their DMF. The following is a restatement of these issues along with a summary of (b) (4) responses:



The DMF holder has provided enough information to support the equivalence of their inserter when compared to the one supplied by (b) (4). **There are no outstanding review issues related to the inserter described under DMF (b) (4).**

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Director Sign-Off	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
01/07/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

DATE: December 19, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Charlene Williamson, Regulatory Project Manager, CDER/OND/ODEIII/DBRUP

SUBJECT: NDA 21225 (meeting package date 11/13/2013)
Applicant: Bayer Healthcare Pharmaceuticals, Inc
Device Constituent: hormone eluting intrauterine system
Drug Constituent: Levonorgestrel
Intended Treatment: prevention of pregnancy
CDRH CTS Tracking No. 1300638

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Contents

CDRH HUMAN FACTORS REVIEW OF MEETING PACKAGE (DATED 11/13/2013)	3
OVERVIEW AND RECOMMENDATION	3
APPENDIX 1: CDRH HF'S INVOLVEMENT HISTORY	4
APPENDIX 2: PREVIOUS CDRH HUMAN FACTORS REVIEW (6/27/2013)	5
OVERVIEW AND RECOMMENDATIONS	5
APPENDIX 3: DEVICE DESCRIPTION	7

CDRH Human Factors Review of Meeting Package (dated 11/13/2013)

Overview and Recommendation

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drug Evaluation and Research requested a Human Factors consultative review of meeting package in response to FDA's complete response letter dated 8/30/2013. The complete response includes CDRH HF's question regarding use related risk analysis and a determination for the necessity of a human factors validation study. The following provides a brief summary of FDA and Sponsor interaction.

FDA Question:

It is not clear what hazards are associated with the modified inserter. Provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if the users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, submit your draft protocol for review prior to conducting the study.

Bayer's Position:

Bayer is developing a Failure Modes and Effects Analyses (FMEA), based on the implementation of the proposed Mirena EVO Inserter, to identify and quantitate any potential risks associated with the minimal changes made to the existing inserter. Similarly, the FMEA will also highlight the mitigation strategies employed to limit/minimize those identified potential risks which include, but are not limited to, proposed labeling instructions, established finished product release and stability testing requirements, physician training materials and results from our proposed *in vitro* bench testing. Where applicable, we also intend to draw correlations to the similarities (i.e., design features) of our proposed Mirena EVO product and SKYLA, a recently approved IUS which also utilizes a significantly similar version of the EVO Inserter. These identified mitigation measures will reference appropriate methods used to validate their effectiveness.

Bayer's Meeting Request Question 1:

Does the Agency agree with our proposed approach in addressing this question?

CDRH HF Proposed Response to Question 1

Your proposed approach appears to focus on the risks associated with the modified device via a Failure Modes and Effects Analysis. This approach appears reasonable.

For ease of review, we ask that you separate the use related risks from the device related risks. Note that your use-related risks analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. Please submit this use-related risk analysis, a determination of the necessity of human factors validation. If you determine that a human factors validation study is necessary, please submit your study protocol for review prior to study initiation. We would like to review the entire human factors study protocol to ensure that the study methodology are acceptable.

Note to CDER: Please issue a new InterCenter Consult when you receive the use-related risk analysis and determination whether a human factors study is needed, and protocol (if needed).

Appendix 1: CDRH HF's Involvement History

- 6/11/2013: CDRH HF was requested to review the sponsor's proposed modifications (ergonomic enhancements) to the inserter device and labeling.
- 6/27/2013: CDRH HF provided a request for use-related risks and determination whether a human factors study is needed
- 12/6/2013: CDRH HF received a request to review a meeting package where the Sponsor provides a proposal to address the request.

Appendix 2: Previous CDRH Human Factors Review (6/27/2013)

Overview and Recommendations

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of an NDA supplement (sNDA 21225/S33) from Bayer Healthcare Pharm, Inc for modifying the inserter device with “ergonomic enhancements” and associated labeling.

The submission did not provide any information indicating how the Sponsor has evaluated use-related hazards associated with the modified device or how the Sponsor has validated the effectiveness of the mitigations implemented to address the hazards. This device is reviewed by CDRH’s Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD), Obstetrics and Gynecology Devices Branch (OGDB). This reviewer discussed this consult request with OGDB’s branch chief to better understand the use-related hazards. For this type of device, there are known issues such as deployment and detachment that can affect the delivery of the IUD to the target location in its intended shape/configuration. Some of these issues can be associated with how the user interacts with the device. As a result, OGDB has requested human factors data in CDRH premarket review where the sponsor needs to demonstrate the clinicians can correctly use the device.

As a result, the reviewer recommends the following letter-ready comments be transmitted to Bayer Healthcare Pharm:

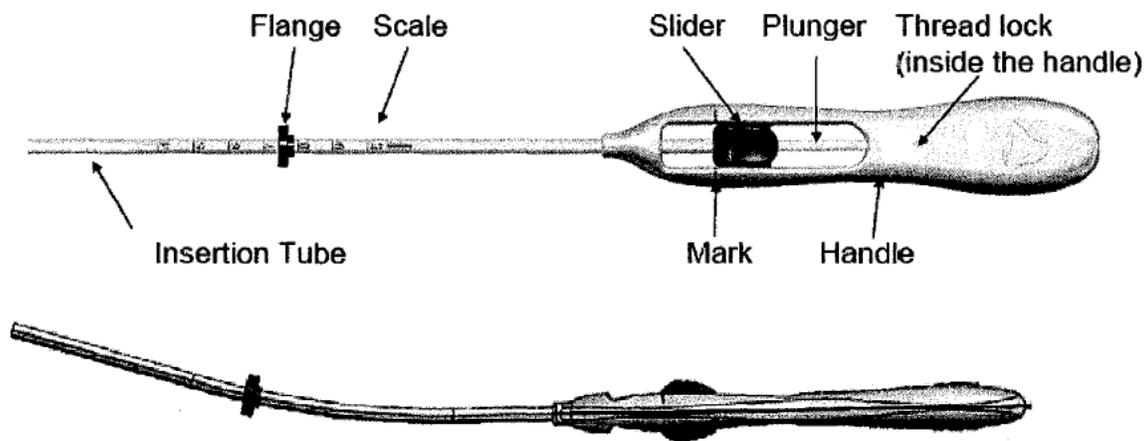
In your cover letter dated February 27, 2013, you requested for approval of a modified inserter including ergonomic enhancements to replace the current inserter. However, it is not clear what hazards are associated with the modified inserter. Please provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, please indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, please submit your draft protocol for review prior to conducting the study.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

Appendix 3: Device Description

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
01/07/2014

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

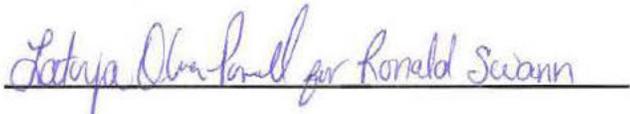
General Hospital Devices Branch

DATE: December 30, 2013

TO: Charlene Williamson, Project Manager
CDER/OND/ODEIII
Division of Bone, Reproductive, and Urologic Products
WO22, Room 5395

Cc: Office of combination products at combination@fda.gov

Through: Ronald L. Swann, Chief, Abdominal and Surgical Devices
Branch, Division of Manufacturing and Quality, Office of
Compliance, CDRH, WO-66, Room 3534



From: Felicia Brayboy, CSO, Abdominal and Surgical Devices
Branch, Division of Manufacturing and Quality, Office of
Compliance, CDRH, WO-66, Room 3547

Firm: Bayer Healthcare Pharmaceuticals, Inc.
Pansionitie 47
20210 Turku, Finland
FEI: 1000350927

Application # NDA 21225

Product Name: Mirena (Levonorgestrel-releasing intrauterine system)

Consult Instructions: Review Type A Meeting Request

The Office of Compliance at CDRH received a consult request from CDER/OND/ODEII/ Division of Bone, Reproductive, and Urologic Products (DBRUD) to evaluate the adequacy of NDA 21225 Type A Meeting request as it applies to the medical device regulations.

Product Description

Bayer Healthcare Pharmaceuticals submitted a supplement to its approved NDA 21225, for the Mirena (levonorgestrel-releasing intrauterine system) which is intended for contraception up to 5 years. Mirena is a hormone eluting intrauterine system which, includes an intrauterine device and a plastic insertion device. Bayer indicates that this insertion device is very similar to the one that was recently approved for the Skyla Intrauterine system (IUS), NDA 203159 (a lower dose IUS marketed by Bayer).

Figure 1. Schematic illustration of the integrated inserter

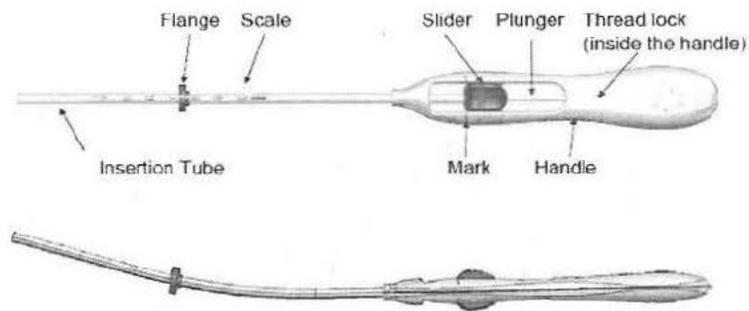


Table 1. Comparison between the Mirena Inserter (NDA 21225) and the Skyla Inserter (NDA 203159) devices.

Component	Mirena (NDA 21-225) Modified Inserter (S-033)	Skyla (NDA 203159)
Insertion tube, outer diameter inner diameter ¹ length ²	4.40 mm 3.75 mm 214 mm	3.80 mm 3.10 mm 210 mm
Slider (color)	Teal	Pink
Slider, (design ²)	Dimensions adapted due to the T-body size difference (outer diameter).	Dimensions adapted due to the T-body size difference (outer diameter).
Slider (movement ²)	Approx. 40 mm	Approx. 36 mm
Flange (color)	Teal	Pink
Flange (design)	Same design, inner diameter adapted to outer diameter of insertion tube	Same design, inner diameter adapted to outer diameter of insertion tube
Handle	Same design, however dimensions adapted to different slider movement (length of window approx. 40 mm) and to outer diameter of insertion tube (opening)	Same design, however dimensions adapted to different slider movement (length of window approx. 36 mm) and to outer diameter of insertion tube (opening)
Embossed Handle logo	Embossed Mirena logo	No embossed logo

1 IUS max. outer diameter 3.65 mm and 2.9 mm for Mirena and Skyla, respectively.

2 Due to different T-body dimensions (Skyla 28x30 mm, Mirena 32x32mm)

CDRH Office of Compliance Recommendation/Response

The following deficiencies were relayed in the July 10, 2013 memo to CDER and subsequently relayed to the applicant. Below each deficiency is CDRH/OC assessment of the applicant's response.

1. There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls.

The applicant must provide information showing that changes in the introducer's design do not affect the safety and effectiveness of the finished product. Similarly, the applicant must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product. The applicant should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, the applicant should explain why no changes were necessary. The applicant should pay particular attention to the requirements for design controls under 21 CFR 820.30(i), (h) and (g).

Applicant Response 4a

Question 4a: (design controls): It is Bayer's intent to provide the required design controls and validation information as cited above. Given the significant similarity in design and functionality between the proposed Mirena EVO inserter and SKYLA (NDA 2013159), Bayer believes it is justified in cross-referencing relevant design data generated with SKYLA. In addition, Bayer will provide reference to existing SOPs related to control of design and process changes.

Does the Agency have any comment on our proposal to use relevant SKYLA data in support of proposed Mirena EVO design changes?

CDRH/OC Assessment

This approach appears to be acceptable however, an additional consult was sent to the Office of Device Evaluation to confirm that the devices are similar enough to site data from the SKYLA.

Applicant Response 4b

Comment 4b (packaging changes): Reference is made to the change in PET grade used in the packaging of the proposed Mirena EVO Inserter and the change in the packaging orientation of the device. Please note Bayer had provided container closure integrity testing and sterilization validation data in support of these packaging changes, respectively, in our original sNDA submission. Bayer will again cross-reference these data in support of this response.

CDRH/OC Assessment

This approach appears to be acceptable.

2. The applicant is adding an additional supplier of the inserter. The applicant should provide enough information to demonstrate adequate control over this new supplier and the product provided, as required by 21 CFR 820.50, purchasing controls.

Applicant Response

Bayer has established processes and procedures in place to qualify and monitor suppliers such as [REDACTED] ^{(b) (4)}, our proposed Mirena EVO Inserter supplier. These include the following:

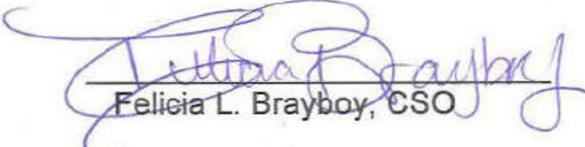
- Various established SOPs concerning assessment and qualification of suppliers and materials;
- Supplier audits;
- Documented QA Agreements; and
- Detailed product delivery specifications and quality control incoming inspection testing requirements.

It is Bayer's intent to further elaborate on these procedures in our final response.

Does the agency concur that this type of information regarding new supplier qualification and monitoring is sufficient to comply with 21 CFR 820.50, purchasing controls?

CDRH/OC Assessment

The type of information outlined above appears to adequately address 21 CFR 820.50, purchasing controls.


Felicia L. Brayboy, CSO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
01/07/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

DATE: December 19, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Charlene Williamson, Regulatory Project Manager, CDER/OND/ODEIII/DBRUP

SUBJECT: [NDA 21225 \(meeting package date 11/13/2013\)](#)
Applicant: Bayer Healthcare Pharmaceuticals, Inc
Device Constituent: hormone eluting intrauterine system
Drug Constituent: Levonorgestrel
Intended Treatment: prevention of pregnancy
CDRH CTS Tracking No. 1300638

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Contents

CDRH HUMAN FACTORS REVIEW OF MEETING PACKAGE (DATED 11/13/2013)	3
OVERVIEW AND RECOMMENDATION	3
APPENDIX 1: CDRH HF'S INVOLVEMENT HISTORY	4
APPENDIX 2: PREVIOUS CDRH HUMAN FACTORS REVIEW (6/27/2013)	5
OVERVIEW AND RECOMMENDATIONS	5
APPENDIX 3: DEVICE DESCRIPTION	7

CDRH Human Factors Review of Meeting Package (dated 11/13/2013)

Overview and Recommendation

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of meeting package in response to FDA's complete response letter dated 8/30/2013. The complete response includes CDRH HF's question regarding use related risk analysis and a determination for the necessity of a human factors validation study. The following provides a brief summary of FDA and Sponsor interaction.

FDA Question:

It is not clear what hazards are associated with the modified inserter. Provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if the users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, submit your draft protocol for review prior to conducting the study.

Bayer's Position:

Bayer is developing a Failure Modes and Effects Analyses (FMEA), based on the implementation of the proposed Mirena EVO Inserter, to identify and quantitate any potential risks associated with the minimal changes made to the existing inserter. Similarly, the FMEA will also highlight the mitigation strategies employed to limit/minimize those identified potential risks which include, but are not limited to, proposed labeling instructions, established finished product release and stability testing requirements, physician training materials and results from our proposed *in vitro* bench testing. Where applicable, we also intend to draw correlations to the similarities (i.e., design features) of our proposed Mirena EVO product and SKYLA, a recently approved IUS which also utilizes a significantly similar version of the EVO Inserter. These identified mitigation measures will reference appropriate methods used to validate their effectiveness.

Bayer's Meeting Request Question 1:

Does the Agency agree with our proposed approach in addressing this question?

CDRH HF Proposed Response to Question 1

Your proposed approach appears to focus on the risks associated with the modified device via a Failure Modes and Effects Analysis. This approach appears reasonable.

For ease of review, we ask that you separate the use related risks from the device related risks. Note that your use-related risks analysis should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. Please submit this use-related risk analysis, a determination of the necessity of human factors validation. If you determine that a human factors validation study is necessary, please submit your study protocol for review prior to study initiation. We would like to review the entire human factors study protocol to ensure that the study methodology are acceptable.

Note to CDER: Please issue a new InterCenter Consult when you receive the use-related risk analysis and determination whether a human factors study is needed, and protocol (if needed).

Appendix 1: CDRH HF's Involvement History

- 6/11/2013: CDRH HF was requested to review the sponsor's proposed modifications (ergonomic enhancements) to the inserter device and labeling.
- 6/27/2013: CDRH HF provided a request for use-related risks and determination whether a human factors study is needed
- 12/6/2013: CDRH HF received a request to review a meeting package where the Sponsor provides a proposal to address the request.

Appendix 2: Previous CDRH Human Factors Review (6/27/2013)

Overview and Recommendations

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of an NDA supplement (sNDA 21225/S33) from Bayer Healthcare Pharm, Inc for modifying the inserter device with “ergonomic enhancements” and associated labeling.

The submission did not provide any information indicating how the Sponsor has evaluated use-related hazards associated with the modified device or how the Sponsor has validated the effectiveness of the mitigations implemented to address the hazards. This device is reviewed by CDRH’s Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD), Obstetrics and Gynecology Devices Branch (OGDB). This reviewer discussed this consult request with OGDB’s branch chief to better understand the use-related hazards. For this type of device, there are known issues such as deployment and detachment that can affect the delivery of the IUD to the target location in its intended shape/configuration. Some of these issues can be associated with how the user interacts with the device. As a result, OGDB has requested human factors data in CDRH premarket review where the sponsor needs to demonstrate the clinicians can correctly use the device.

As a result, the reviewer recommends the following letter-ready comments be transmitted to Bayer Healthcare Pharm:

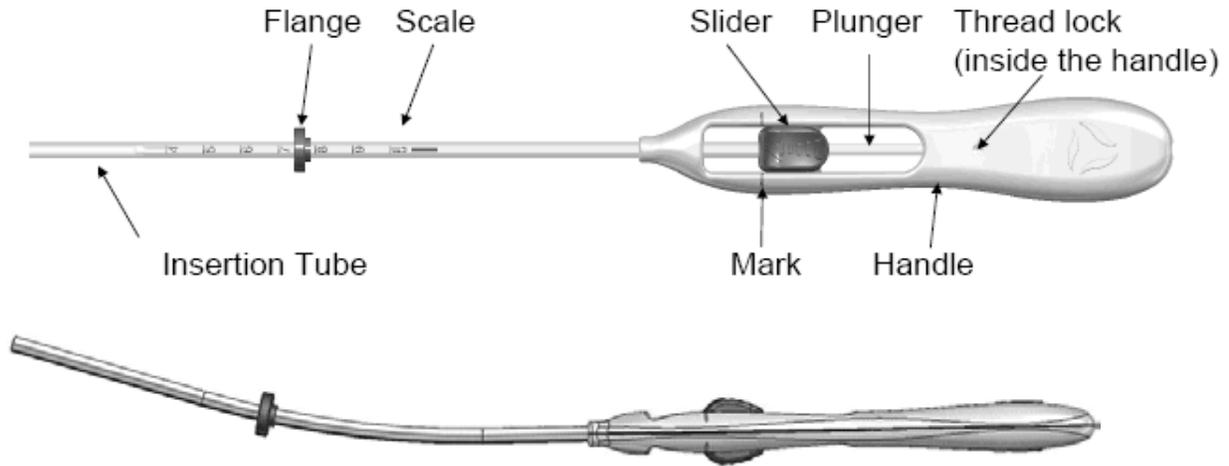
In your cover letter dated February 27, 2013, you requested for approval of a modified inserter including ergonomic enhancements to replace the current inserter. However, it is not clear what hazards are associated with the modified inserter. Please provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, please indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, please submit your draft protocol for review prior to conducting the study.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

Appendix 3: Device Description

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
01/07/2014

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
General Hospital Devices Branch

DATE: July 10, 2013

TO: Charlene Williamson, Regulatory Project Manager
CDER/OND/ODEIII
Division of Bone, Reproductive, and Urologic Products
WO22, Room 5395

Through: Debra Demeritt, Chief, Gastroenterology, and Urology
Devices Branch, Division of Enforcement A, Office of
Compliance, CDRH, WO-66, Room 3540

Debra E. Demeritt -S

From: Shirley Zeigler, CSO, Obstetrics/Gynecology,
Gastroenterology, and Urology Branch, Division of
Enforcement A, Office of Compliance, CDRH
shirley.zeigler@fda.hhs.gov

Firm: Bayer Healthcare Pharmaceuticals, Inc.
Pansionitie 47
20210 Turku, Finland
FEI: 1000350927

Application # NDA 21225/S-033

Product Name: Mirena (Levonorgestrel-releasing intrauterine system)

Consult Instructions: Evaluate the need for an inspection under the Medical
Device Quality System Regulations for 1) (b) (4)
and
2) (b) (4)

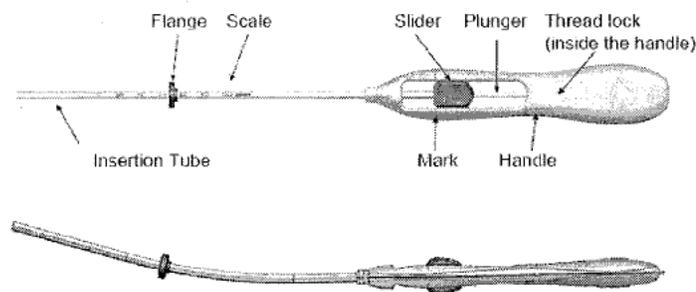
The Office of Compliance at CDRH received a consult request from CDER/OND/ODEIII/ Division of Bone, Reproductive, and Urologic Products (DBRUD) to evaluate the adequacy of NDA 21225/S-033 as it applies to the medical device regulations. The consult included a request to evaluate the need

for an inspection of the 1) (b) (4) and 2) (b) (4) facility sites.

Combination product description

Bayer Healthcare Pharmaceuticals submitted a supplement to their approved NDA, 21225/S-033, for the Mirena (levonorgestrel-releasing intrauterine system) which is intended for contraception up to 3 years. Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. Bayer indicates that this insertion device is very similar to the one that was recently approved for the Skyla Intrauterine system (IUS), NDA 203159 (a lower dose IUS marketed by Bayer). The following picture from Bayer's application, Description of Product, P.1.01-01, shows the proposed insertion device:

Figure 1. Schematic illustration of the integrated inserter



The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.

The firm reports minor changes made on the shape of the T-body for better compatibility with the administration device and reports that the changes have not had any essential effect on the characteristics of the product:

1. The current design of the knobs in the end of the horizontal arm was slightly modified by making the upper surface of the knobs slightly more concave.
2. The loop area on the bottom of the T-body has been slightly modified to fit with the plunger tip of the inserter. This adaptation is reportedly necessary to ensure proper orientation of the IUS in the preloaded inserter.
3. The target diameter of the removal threads have been reduced and adapted to the performance of the administration device with pre-locking feature. See the following table 1 with a complete list of changes in the Mirena device compared to the Skyla device.

Table 1. Comparison between the Mirena Inserter (NDA 21225) and the Skyla Inserter (NDA 203159) devices

Component	Mirena (NDA 21-225) Modified Inserter (S-033)	Skyla (NDA 203159)
Insertion tube, outer diameter inner diameter ¹ length ²	4.40 mm 3.75 mm 214 mm	3.80 mm 3.10 mm 210 mm
Slider (color)	Teal	Pink
Slider, (design ²)	Dimensions adapted due to the T-body size difference (outer diameter).	Dimensions adapted due to the T-body size difference (outer diameter).
Slider (movement ²)	Approx. 40 mm	Approx. 36 mm
Flange (color)	Teal	Pink
Flange (design)	Same design, inner diameter adapted to outer diameter of insertion tube	Same design, inner diameter adapted to outer diameter of insertion tube
Handle	Same design, however dimensions adapted to different slider movement (length of window approx. 40 mm) and to outer diameter of insertion tube (opening)	Same design, however dimensions adapted to different slider movement (length of window approx. 36 mm) and to outer diameter of insertion tube (opening)
Embossed Handle logo	Embossed Mirena logo	No embossed logo

1 IUS max. outer diameter 3.65 mm and 2.9 mm for Mirena and Skyla, respectively.

2 Due to different T-body dimensions (Skyla 28x30 mm, Mirena 32x32mm)

Inspection History evaluation

The following facilities associated with this application have been identified as key facilities regarding the finished combination product from a medical device regulatory perspective:

Sponsor:

Bayer OY
Pansionitie 47
20210 Turku, Finland
FEI: 1000350927

Manufacturing facilities:



(b) (4)

(b) (4)

A compliance status analysis for the past 3 years was conducted for Bayer OY, Turku, Finland. The facility was inspected in September 2012 and the inspection was classified NAI. This was a preapproval inspection for a combination human drug/medical device product covered under NDA 203159 for the production of Skyla (levonorgestrel 13.5 mg intrauterine device) as well as review of process validation activities, validation of ethylene oxide sterilization (b) (4), review of the firm's change management system, and coverage of complaint and adverse event handling. The inspection also covered the firm's Corrective and Preventive Action system, design controls surrounding the Skyla product and review of the firm's purchasing control and acceptance activities. No FDA 483 was issued during the inspection. However, one verbal item regarding the lack of yield specification was discussed with management during the closing discussion. The firm provided a written explanation detailing their plan to obtain a working set of scientific data from future production batches to more accurately set the yield specifications.

A previous inspection of Bayer OY was conducted in December 2011. This inspection covered operations associated with pharmaceuticals and was classified NAI.

Change in container closure system

The container closure system is designed to contain one levonorgestrel intrauterine system with inserter. The package has been redesigned to adapt to the improved design of the inserter. The firm reports that the primary package material of Levonorgestrel intrauterine delivery system 52 mg with inserter (Mirena) comply with (b) (4). Physical tests for container (PETG-film) and the cytotoxicity test.

Additional Insertion Device Supplier

In addition to (b) (4) Bayer also proposes use of insertion devices manufactured by (b) (4). A Drug Master File (DMF) (b) (4) has been established by this supplier as well. The (b) (4) DMF is limited to the Mirena insertion device.

CDRH Office of Compliance Recommendation

The following deficiencies were noticed:

1. There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls.

The applicant must provide information showing that changes in the introducer's design do not affect the safety and effectiveness of the finished product. Similarly, the applicant must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product. The applicant should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, the applicant should explain why no changes were necessary. The applicant should pay particular attention to the requirements for design controls under 21 CFR 820.30(i), (h) and (g).

2. The applicant is adding an additional supplier of the inserter. The applicant should provide enough information to demonstrate adequate control over this new supplier and the product provided, as required by 21 CFR 820.50, purchasing controls.

Information about the type of documents to be submitted for review may be found at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>, 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003).

CDRH recommends CDER to request from the sponsor additional documentation associated with the deficiencies found in the submission regarding design controls. This would allow for a complete desk review of the sponsor's design activities.

Shirley A.
Zeigler -A

Digitally signed by Shirley A. Zeigler -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130019667
1, cn=Shirley A. Zeigler -A
Date: 2013.07.10 12:25:00 -04'00'

Shirley Zeigler, CSO

Prepared: SZeigler: 7/9/2013
Revised: SZeigler: 7/10/2013
Reviewed: DDemeritt: 7/10/2013
Final:

cc:

WO66-3556 (SZeigler)
WO21-2663 (KJennings)
WO21-2648 (JSalemme)

combination@fda.gov (OCP)

CTS No.: ICC1300207

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
07/19/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: June 27, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGRID

TO: Charlene Williamson, Regulatory Project Manager, CDER/OND/ODEIII/DBRUP
Kerri-Ann Jennings, Program Management, CDER/OPS/ONDQA
Please see letter-ready comments in blue text on pages 2 and 3

SUBJECT: sNDA 21225/S33
Applicant: Bayer Healthcare Pharm, Inc.
Drug: Mirena
Device: Inserter Device (part of a Intrauterine Device)
Intended Use: prevention of pregnancy
Review Materials:
\CDSESUB\IEVSPROD\NDA021225\0064
CDRH CTS Tracking: ICC1300278; CON1311740

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2013.06.27 16:30:18 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Martha F. Story
2013.06.27 16:33:12 -04'00'

Molly Story, Human Factors and Accessible Medical Technology Specialist for
Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Overview and Recommendations

The Division of Bone, Reproductive and Urologic Products, Office of Drug Evaluation III, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of an NDA supplement (sNDA 21225/S33) from Bayer Healthcare Pharm, Inc for modifying the inserter device with “ergonomic enhancements” and associated labeling.

The submission did not provide any information indicating how the Sponsor has evaluated use-related hazards associated with the modified device or how the Sponsor has validated the effectiveness of the mitigations implemented to address the hazards. This device is reviewed by CDRH’s Division of Reproductive, Gastro-Renal and Urological Devices (DRGUD), Obstetrics and Gynecology Devices Branch (OGDB). This reviewer discussed this consult request with OGDB’s branch chief to better understand the use-related hazards. For this type of device, there are known issues such as deployment and detachment that can affect the delivery of the IUD to the target location in its intended shape/configuration. Some of these issues can be associated with how the user interacts with the device. As a result, OGDB has requested human factors data in CDRH premarket review where the sponsor needs to demonstrate the clinicians can correctly use the device.

As a result, the reviewer recommends the following letter-ready comments be transmitted to Bayer Healthcare Pharm:

In your cover letter dated February 27, 2013, you requested for approval of a modified inserter including ergonomic enhancements to replace the current inserter. However, it is not clear what hazards are associated with the modified inserter. Please provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, please indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, please submit your draft protocol for review prior to conducting the study.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

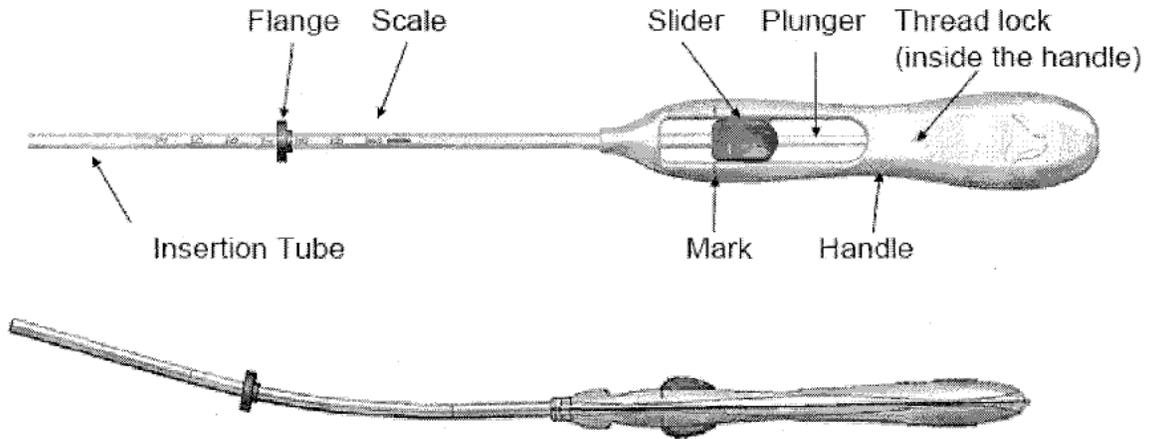
If you need additional information about human factors or assistance to conduct a human factors validation study, we recommend you visit the web site Medical Device Human Factors, at <http://www.medicaldevicehumanfactors.org>. The site offers a number of human factors resources relevant to medical devices, including a directory of consultants that can assist in conducting human factors/usability studies.

CDRH Human Factors Involvement History

Date	Involvements
6/11/2013	CDRH HF was requested to review the sponsor's proposed modifications (ergonomic enhancements) to the inserter device and labeling.

Appendix 1: Device Description

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
07/01/2013



DATE: June 20, 2013

FROM: Veronica Price, Biomedical Engineer
CDRH/ODE/DRGUD/OGDB
301-796-6538

TO: Charlene Williamson
CDER-ODE III
Division of Bone, Reproductive and Urologic Products

RE: NDA 21225/S-033/ (b) (4)
Mirena (levonorgestrel-releasing intrauterine system)
Bayer Healthcare Pharmaceuticals, Inc.

Review Summary:

Bayer Healthcare Pharmaceuticals' has submitted a supplement to their approved NDA, 21225/S-033, for the Mirena (levonorgestrel-releasing intrauterine system) which is intended for contraception up to 3 years. This consult was assigned on 6/10/13 with an internal tracking number of CON1310564. The request was for an evaluation to determine whether the inserter included in this NDA Supplement is identical to the one recently approved as part of the Skyla IUS NDA, 203159.

The inserter approved for Skyla was supplied to Bayer from (b) (4). (b) (4) included information on this device in a Drug Master File, (b) (4). This master file was reviewed as part of the Skyla NDA 203159. (b) (4) amended the DMF on February 3, 2013 to include information specific to the inserter for the Mirena. A review of the DMF, highlighted differences between the insertion device for Skyla and the insertion device for Mirena with respect to some of the dimensions included in the engineering drawings and the colorant used. The DMF supplier, (b) (4) indicates that the manufacturing process is the same. The differences in dimensions were necessary to accommodate the larger size of the Mirena IUS. While these difference are minor they do have the potential to effect the ease of deployment and therefore, confirmatory testing should be conducted to ensure that the performance of the device is not adversely affected.

A request for approval of a second supplier for the inserter is also included in this request. The DMF is (b) (4) and the submitter is (b) (4). This DMF which is limited to the insertion device for Mirena, is similar in content to the DMF from (b) (4). However, (b) (4) fails to include details on the test methods used to assess the insertion devices for pull and push strength and distortion of the insertion tube. This information should be included in the DMF.

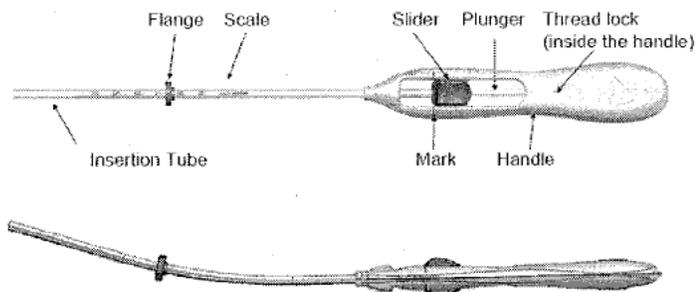
Additional testing information should be provided by Bayer and additional details on the test methods used for final assembly testing should be provided by (b) (4).

Device Description:

Mirena is a hormone eluting intrauterine system which includes an intrauterine device and a plastic insertion device. The focus of this review is limited to the insertion device.

Bayer indicates that this insertion device is very similar to the one that was recently approved for the Skyla IUS, NDA 203159 (a lower dose IUS marketed by Bayer). The following picture from Bayer's application, Description of Product, P.1.01-01, shows the proposed insertion device:

Figure 2 Schematic illustration of the integrated inserter



The inserter components include the following: insertion tube; plunger; flange; handle; slider; and thread lock. The insertion tube includes depth markings.

Engineering drawings of the insertion device are included in the DMF's. As indicated in these drawings, the overall device length is 279 mm and the width at the widest point of the handle which is proximal end is 28 mm. The diameter of the insertion tube is 4.4 mm and the outer diameter of the flange is 12 mm.

Overview of Principle of Use:

The intrauterine device is placed within the inserter prior to packaging with the arms extending out from the distal tip of the inserter. After removal from the packaging the arms of the IUD are loaded within the insertion tube by advancing the slider on the handle forward until it clicks into place. The flange is then set to the uterine depth determined during sounding. The inserter is advanced through the cervix until the flange is 1.5 to 2 cm from the cervix. (This can be determined based on the depth markings on the outside of the insertion tube.) The slider is then moved back to a mark on the handle which releases the arms of the IUD within the uterus. (The physician is instructed to wait 10 seconds.) The inserter is then gently pushed forward until the flange touches the cervix. The IUD arms should now be at the fundus. The IUD is then released by moving the slider all the way back until it clicks. With the slider held down, the inserter is removed from the patient.

Comparison of Insertion Devices:

(b) (4), Drug Master File, DMF (b) (4), provides the insertion device for the recently approved Skyla IUS, NDA 203159. This master file was reviewed as part of the NDA. (b) (4) amended the file on February 3, 2013, to include information on the Mirena IUS. They state that the components are similar and the manufacturing process is identical for these two products. The product release testing was noted to be identical as well. A review of this amended file yields the following differences related to design: change in colorant of the slider and flange from pink to green; and minor dimensional differences.

The following table outlining the differences was provided by Bayer Healthcare to CDER via e-mail on 5/23/13. (It was forwarded to me on 5/29/13.)

Table 1 Differences between the Mirena Inserter (NDA 21-225) and the Skyla Inserter (NDA 203159)

Component	Mirena (NDA 21-225) Modified Inserter (S-033)	Skyla (NDA 203159)
Insertion tube, outer diameter inner diameter ¹ length ²	4.40 mm 3.75 mm 214 mm	3.80 mm 3.10 mm 210 mm
Slider (color)	Teal	Pink
Slider, (design ²)	Dimensions adapted due to the T-body size difference (outer diameter).	Dimensions adapted due to the T-body size difference (outer diameter).
Slider (movement ²)	Approx. 40 mm	Approx. 36 mm
Flange (color)	Teal	Pink
Flange (design)	Same design, inner diameter adapted to outer diameter of insertion tube	Same design, inner diameter adapted to outer diameter of insertion tube
Handle	Same design, however dimensions adapted to different slider movement (length of window approx. 40 mm) and to outer diameter of insertion tube (opening)	Same design, however dimensions adapted to different slider movement (length of window approx. 36 mm) and to outer diameter of insertion tube (opening)
Embossed Handle logo	Embossed Mirena logo	No embossed logo

¹ IUS max. outer diameter 3.65 mm and 2.9 mm for Mirena and Skyla, respectively.

² Due to different T-body dimensions (Skyla 28x30 mm, Mirena 32x32mm)

The differences in dimensions of the Mirena insertion device are minor when compared to the insertion device approved as part of the Skyla. However, these changes in dimensions to accommodate the larger size of the Mirena have the potential to affect the device delivery characteristics. **The firm should conduct some confirmatory testing which ensures that the deployment of the IUS is not adversely impacted by the changes. This is the type of testing which could be conducted on the bench using a test set-up which simulates clinical conditions.**

The change in colorant is not significant from a performance stand point. The firm points out that the color used in the Mirena IUS insertion device is the same that is currently being used in the approved Mirena insertion device; therefore, there should not be any material safety issues for the flange which is a patient contacting component.

Additional Insertion Device Supplier:

In addition to (b) (4) Bayer also proposes use of insertion devices manufactured by (b) (4) (b) (4) A DMF, (b) (4) has been established by this supplier as well. The (b) (4) DMF is limited to the Mirena insertion device. The description of the device including information on the design/function of each of the individual components and the materials is identical to what has been reviewed as part of the (b) (4) DMF. The engineering drawings and final assembly test specifications are identical as well. The submission is deficient, however, with respect to the description of the tests for pull and push

strength as well as distortion. **The DMF should be revised to include the test methods used for each of these tests along with a diagram of the test set-up.**

Review Conclusions:

When compared to the insertion device approved for the Skyla system, NDA 203159, the insertion device proposed for use for Mirena differs with respect to some of the dimensions and the colorant used on the flange/slider. Although the changes in dimensions were necessary to accommodate the larger sized Mirena IUS, there could be some effects on the ease of deployment. Therefore, I recommend that Bayer address the following as part of their NDA:

- The proposed changes to the insertion device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUD. Testing should be conducted which evaluates the ability of the insertion device to deliver the IUD to its target location in its intended shape/configuration. This testing should be conducted in a model which simulates worst case clinical conditions and should include a statistically valid sample size. Please provide a copy of this testing along with the results for review.

Prior to approving (b)(4) as a second supplier for the insertion device for Mirena, additional details on the product release testing should be provided. Therefore, I recommend that (b)(4) address the following as part of their DMF:

- Section 6.4 Test Methods Description of DMF (b)(4) does not contain enough details about the tests that are performed. The following additional information related to this testing should be provided:
 - Section 6.4.1 and 6.4.2 includes pull testing to evaluate detachment force of the tube-slider and push testing to evaluate locking. Although a general description of the test is provided, a diagram of the test set-up should be included.
 - Section 6.4.3 references distortion testing; however, no details are provided on how the test is conducted. Please provide detailed information on the test method along with identification of the pass/fail criteria.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Veronica A. Price -S 2013.06.20 13:17:26 -04'00'
Branch Chief Sign-Off	Elaine H. Blyskun -S 2013.06.20 13:34:24 -04'00'
Division Director Sign-Off	Herbert P. Lerner -S 2013.06.20 13:20:19 -04'00'

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
06/26/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: June 25, 2013

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Mirena (Levonorgestrel-releasing Intrauterine System)
52 mg

Application Type/Number: NDA 021225

Submission Number: 033

Applicant/sponsor: Bayer Healthcare

OSE RCM #: 2013-1437

Contents

1	Introduction.....	1
1.1	Background and Regulatory History.....	1
1.2	Product Information	2
2	Methods and Materials Reviewed.....	2
2.1	Selection of Medication Error Cases.....	3
2.2	Labels and Labeling	3
3	Medication Error Risk Assessment.....	4
3.1	Medication Error Cases.....	4
3.2	Integrated Summary of Medication Error Risk Assessment	6
4	Conclusions and Recommendations	6
5	References.....	7
	Appendices.....	7

1 INTRODUCTION

This review evaluates the proposed revised packaging, container label, carton, and insert labeling, as well as the modified inserter for Mirena NDA 021225/S-033 for areas of vulnerability that could lead to medication errors in response to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP).

1.1 BACKGROUND AND REGULATORY HISTORY

Mirena was approved on December 6, 2000. The current approved label for Mirena was approved by the FDA on October 1, 2009 and was part of the approved NDA 021225 prior approval supplemental application for the treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.

The Applicant, Bayer Healthcare, currently markets another levonorgestrel-releasing intrauterine system in the U.S., Skyla, which was approved under NDA 203159 on January 9, 2013. The Applicant submitted this prior approval CMC supplement (supplement 033) on February 27, 2013, to request approval for a modified inserter (including ergonomic enhancements) to replace the current inserter. The proposed modified inserter for Mirena is the same type of inserter that was approved under the Skyla application. Additionally, this supplement provides for new packaging materials for the container closure system of the final assembled product. The proposed packaging, container labels, carton, and insert labeling for Mirena have been modified to be consistent with those approved for Skyla.

While the Applicant is proposing a new inserter along with modified instructions for use for Mirena, the Applicant did not submit a label comprehension study to demonstrate that the healthcare providers can follow the instructions without confusion that could lead to medication errors. However, a label comprehension study was submitted to NDA 203159 on December 9, 2011, entitled 'Healthcare Professionals User Testing of IUS Insertion Instructions-Mirena' which tested the readability of the instructions for use intended for healthcare professionals only. DMEPA reviewed the label comprehension study as part of the packaging, label, and labeling review in OSE Review #2011-4677 dated September 21, 2012. DMEPA's assessment of the study stated the following:

Although the study concluded that the revised insertion instructions passed the criteria for readability testing (i.e., 80% of subjects were able to locate the information correctly and, of those, 90% understood the meaning of the information based on their responses to interview questions), we note that the test was only performed on previously trained healthcare professionals who were already familiar with Mirena using the previous inserter. Therefore, it does not necessarily represent the full range of practitioners who may be using Mirena or Skyla for the first time. The Applicant states in the December 9, 2011 Risk Management Plan submission, Section 4.1.4.2 External Healthcare Professional Training, that practitioners will receive training from the sponsor concerning the correct insertion technique. However, we do not know the exact extent or effectiveness of this training. Thus, we will need to monitor for wrong technique errors after the approval of Skyla.

Therefore, based on the above recommendation and the fact that the proposed modified inserter is identical to the inserter approved and marketed for Skyla, we will not request another label comprehension study to be submitted, however, we will continue to monitor for wrong technique errors associated with Skyla and Mirena, if approved.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 27, 2013 submission.

- Active Ingredient: Levonorgestrel
- Indication of Use: Prevention of pregnancy for up to 5 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.
- Route of Administration: Intrauterine
- Dosage Form: Intrauterine system designed to deliver levonorgestrel throughout the 5-year period of use.
- Strength: 52 mg levonorgestrel with an initial release rate of 20 mcg/day; this rate is reduced by 50% after 5 years.
- Dose and Frequency: One system is inserted by a healthcare provider and remains in place for up to 5 years.
- How Supplied: One carton of one sterile unit
- Storage: Controlled Room Temperature
- Container and Closure System: An intrauterine drug delivery system consisting of a hormone-elastomer reservoir matrix mounted on a polyethylene T-body. The T-body has a loop at one end and two arms at the other end. Removal threads are attached to the loop. The inserter components are insertion tube, plunger, flange, handle, slider, and thread lock. The drug product mounted on top of the inserter is packed in a thermoformed blister package.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Mirena and Skyla medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the Mirena packaging, labels and package insert labeling submitted by the Applicant. Additionally, we looked at the DMEPA recommendations in OSE Review #2011- 4677, 2011-4677-1, and 2011-4677-2 dated September 21, 2012, November 18, 2012, and December 17, 2012 respectively, as well as the approved Skyla container labels, carton, and insert labeling to ensure consistency between the two products (see Appendix E for Skyla container labels and carton labeling).

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	Skyla: no date range selected Mirena: 1/13/12 to 6/20/13
Drug Names	Trade name: Skyla Trade name: Mirena
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search for Skyla did not retrieve any cases. The FAERS database search for Mirena identified 98 reports. January 13, 2012 was selected as the start date for the search since this was the date of the last search in OSE Review # 2011-4677. Each report was reviewed for relevancy and duplication. After individual review, 51 reports were excluded from further analysis for the following reasons:

- Product quality issues not related to labels and labeling (e.g., device expulsion or dislocation, broken strings)
- Contraceptive failure
- Adverse events not related to medication errors
- Events unrelated to medication errors
- Foreign cases not relevant to this review because foreign labels and labeling may differ from the ones marketed in the United States
- Duplicate cases

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

-  (b) (4)
-  (b) (4)
-  (b) (4)
- Insert and Patient Labeling submitted February 27, 2013 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Mirena labels and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, 47 Mirena medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². The medication errors reported in these 47 cases were similar to the medication errors identified in DMEPA's previous review of Skyla in OSE Review #2011-4677. In general, the cases did not include causality for the errors. Appendix F provides listings of all case numbers for the cases summarized below.

Wrong Duration (n=17)

Seventeen cases involved the use of Mirena beyond the approved five year period. The reported wrong duration errors with Mirena ranged from 5 years plus 6 weeks to up to 9 years in situ. The outcomes included bleeding and heavy periods.

Our review of the revised insert labeling identified that the **Indications and Usage** Section of the insert labeling states 'Intrauterine contraception for up to 5 years' (Highlights and the Full Prescribing Information), 'The system should be replaced after 5 years if continued use is desired.' (Full Prescribing Information), **Dosage and Administration** Section of the insert labeling states 'Mirena must be removed or replaced after 5 years' (Highlights), 'Mirena must be removed by the end of the fifth year and can be replaced at the time of removal with a new Mirena if continued contraceptive protection desired' (Full Prescribing Information). Section **2.3 Removal of Mirena** states 'Mirena should not remain in the uterus after 5 years' (Full Prescribing Information). In the Patient Labeling, under the **What if I need birth control for more than 5 years?**, it is stated that 'Mirena must be removed after 5 years. Your healthcare provider can place a new Mirena during the same office visit if you choose to continue using Mirena.'

Additionally,

(b) (4)

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Expired Drug Use (n=15)

Fifteen cases identified the insertion of Mirena after it had expired or insertion of Mirena which had an expiration date shorter than the 5 year duration of use. Outcomes were not reported in these cases.

The **How Supplied/Storage and Handling** Section of the insert labeling states, 'Insert before the end of the month shown on the label.' (b) (4)

Monitoring Error/Maternal Exposure (n=7)

Seven cases involved a medication error in which Mirena was inserted when the woman was already pregnant. Pregnancy is a contraindication in the use of Mirena as stated in the prescribing information. Of the seven cases, four cases stated that no pregnancy test was performed prior to insertion of Mirena, and the other three cases did not state whether a pregnancy test was or was not performed prior to insertion of Mirena. Reported outcomes of these medication errors included miscarriage, ongoing pregnancy, or delivery by Cesarean Section.

The **Contraindications** Section of the Highlights and the Full Prescribing Information states, 'Pregnancy or suspicion of pregnancy'. The **Warnings and Precautions** Section of the Highlights of the Prescribing Information states, 'Remove Mirena if pregnancy occurs with Mirena in place'. The **Preparation for Insertion** section of Section **2.1 Insertion Instructions** states, 'Exclude pregnancy and confirm that there are no other contraindications to the use of Mirena'. Section **8.1 Pregnancy** in the Full Prescribing Information states, 'The use of Mirena during an existing or suspected pregnancy is contraindicated'.

Wrong Technique (n=8)

Eight cases involved wrong technique errors with Mirena. These errors included insertion of the device on each side of uterus, threads cut too short, wrong placement due to a large uterine fibroid, re-inserting the same Mirena into the patient after removal, and the use of Mirena in women before six weeks postpartum. The reported outcomes were device expulsion or the device left inside past the recommended 5 year period.

Section **5.6 Perforation** of the Full Prescribing Information states, 'Delay Mirena insertion a minimum of six weeks or until involution is complete following a delivery or a second trimester abortion'. Section **2.1 Insertion Instructions** states, 'Follow the insertion instructions exactly as described in order to ensure proper placement and avoid premature release of Mirena from the inserter. Once released, Mirena cannot be re-loaded'. Section **2.1 Insertion Instructions, Timing of Insertion** section states, 'Insert Mirena into the uterine cavity during the first seven days of the menstrual cycle or immediately after a first trimester abortion' and 'Postpone postpartum insertion and insertions following second trimester abortions a minimum of six weeks or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion'. Step 7- Release Mirena and withdraw the inserter/**Insertion Procedure** of Section **2.1 Insertion Instructions** states, Using a sharp, curved scissor, cut the threads

perpendicular, leaving about 3 cm visible outside of the cervix (cutting threads at an angle may leave sharp ends). Do not apply tension or pull on the threads when cutting to prevent displacing Mirena'. Section 4 **Contraindications** states, 'The use of Mirena is contraindicated when one or more of the following conditions exist: Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity'. **Who should not use Mirena** section of the **Patient Labeling** states, 'Have a condition of the uterus that changes the shape of the uterine cavity, such as large fibroid tumors'.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Our June 20, 2013 FAERS search did not retrieve any Skyla medication error cases, but this could be attributed to the fact that this drug has only been in the market for five months and healthcare providers may still be unfamiliar with this new levonorgestrel-releasing intrauterine contraceptive system. Therefore, DMEPA will continue to monitor Skyla and Mirena, post approval, for any medication errors including those associated with the inserter and the insertion instructions which would be relevant to the proposed changes to the Mirena product inserter and the insertion instructions.

DMEPA acknowledges that our recommendations for the container labels and carton labeling from our previous review of Skyla were implemented, (b) (4). Additionally, the revised insert and Patient Labeling address the wrong duration, expired drug use, monitoring errors, and wrong technique medication errors that were retrieved in our June 20, 2013 FAERS search.

Thus, we find the proposed packaging, modified inserter, container labels, carton, and insert labeling for Mirena acceptable.

4 CONCLUSIONS AND RECOMMENDATIONS

Based on this review, DMEPA finds the revised Mirena packaging, labels, and labeling acceptable and we have no further recommendations prior to approval of this NDA supplement.

If you have further questions or need clarifications, please contact Marcus Cato, project manager, at 301-796-3903.

5 REFERENCES

OSE Review #2011-4677, Skyla (Levonorgestrel-releasing Intrauterine System) Label, Labeling, and packaging Review, Park, A. September 21, 2012

OSE Review#2011-4677-2 Skyla (Levonorgestrel-releasing Intrauterine System) Label and Labeling Review, Park, A. December 17, 2012

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

Appendix F: Case numbers discussed in this review

Case #	Vrsn	MFR Ctrl #
8431888	3	FR-BAYER-2012-018072
8433324	1	US-BAYER-2012-017909
8677466	1	US-BAYER-2012-072552
8686856	1	BR-BAYER-2012-073438
8760856	3	US-BAYER-2012-086343
8774684	1	US-BAYER-2012-093410
8811234	1	US-BAYER-2012-099009
8890110	1	US-BAYER-2012-115421
8890189	1	US-BAYER-2012-115822
8890193	1	US-BAYER-2012-116281
8893194	1	US-BAYER-2012-114973
8893700	1	US-BAYER-2012-115408
8893726	1	US-BAYER-2012-116824
8894004	1	US-BAYER-2012-116907
8894377	1	US-BAYER-2012-116825
8914810	1	US-BAYER-2012-118484
8916308	1	US-BAYER-2012-120475
8922714	1	US-BAYER-2012-120665
8923888	1	BR-BAYER-2012-117588
8924093	1	US-BAYER-2012-123644
8924137	1	US-BAYER-2012-123696
8932880	1	US-BAYER-2012-123648
8934474	1	US-BAYER-2012-124910
8936453	1	US-BAYER-2012-125651
8943063	1	US-BAYER-2012-126176
8948650	1	BR-JNJFOC-20121113248
8948697	1	US-BAYER-2012-127897
8950527	1	US-BAYER-2012-126598
8953333	1	US-BAYER-2012-126471
8956383	1	US-BAYER-2012-127826
8960551	1	
8963090	1	US-BAYER-2012-130245
9100951	1	US-BAYER-2013-010811
9124245	1	US-BAYER-2013-005441
9186542	1	US-BAYER-2013-035204
9204105	1	US-BAYER-2013-041144
9204536	1	US-BAYER-2013-038306
9209065	1	US-BAYER-2013-037944
9213306	1	US-BAYER-2013-040415
9216504	1	US-BAYER-2013-039893
9216952	1	US-BAYER-2013-042469
9226882	2	CY-BAYER-2012-108221
9227363	1	US-BAYER-2013-043272
9227543	1	US-BAYER-2013-045173
9244796	1	US-BAYER-2013-045444
9260591	1	US-BAYER-2013-051471
9264814	1	CH-BAYER-2012-120188
9271535	1	US-BAYER-2013-055932
9275158	1	US-BAYER-2013-056420
9321186	1	US-BAYER-2013-066829
9353549	1	US-BAYER-2013-072085
9355634	1	US-BAYER-2013-072534
8886673	2	US-BAYER-2012-113078

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANIZHEH SIAHPOUSHAN
06/25/2013

JAMES H SCHLICK
06/25/2013

Initial Quality Assessment and Triage

ONDQA Branch VI

OND Division: HFD-580 (DRUP)

NDA: 21-225

Supplement: S-033

DARRTS Document Number: SDN697

Applicant: Bayer Health Care Pharmaceuticals

Letter Date: 2-27-2013

Stamp Date: 2-27-2013

ONDQA Receipt Date: delivered to CMC lead on 3-12-2013

ONDQA CMC Lead triage date: 3-13-2013

Application Type: electronic

Proprietary Name: Mirena® (levonorgestrel-releasing intrauterine system)

Established Name: levonorgestrel intrauterine system

Dosage Form: uterine implant

Route of Administration: intrauterine

Submission Type: prior-approval supplement

Recommended submission type: PAS

This prior-approval supplement provides:

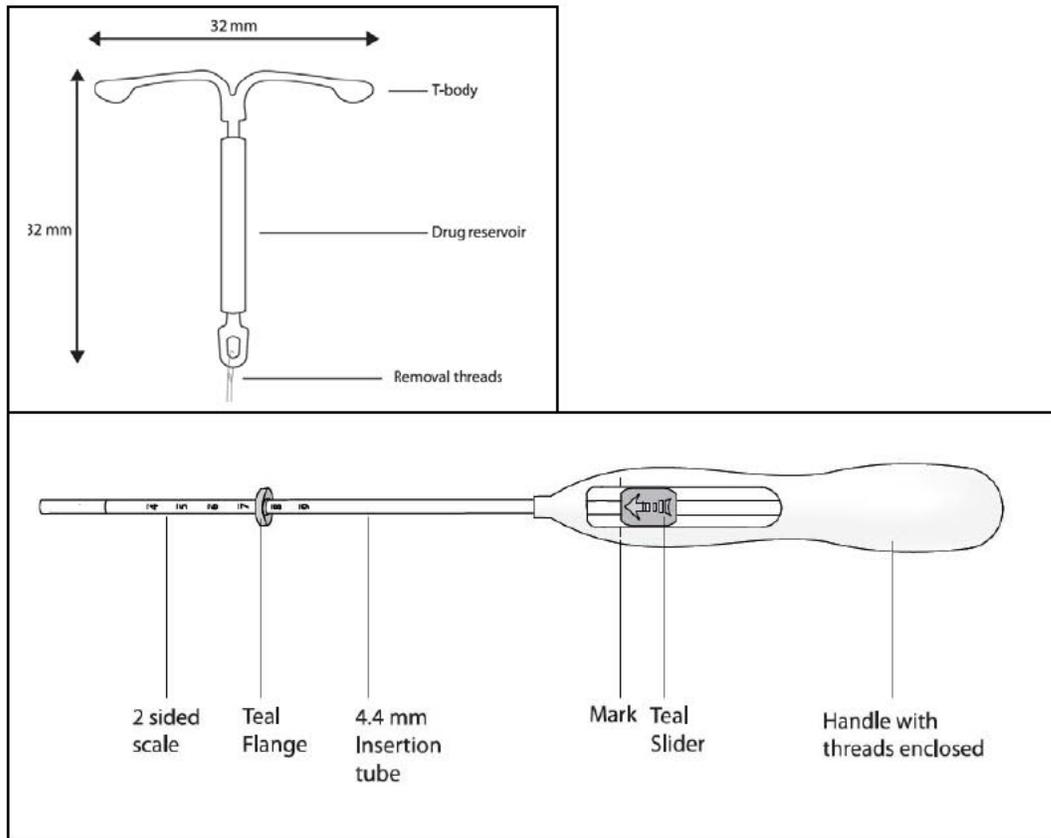
- CMC changes (modified inserter to replace the current inserter as an integrated applicator and new packaging materials for the CCS for the finished product)
- Labeling changes (mainly to reflect use of the new inserter)
- Non-clinical changes (Pharmacology) – to support the change in polyethylene grade used for the new insertion tube, and the new pigment used for the inserter flange

Due to the labeling changes, and maybe due to the Pharmacology/toxicology reports (modules 2.4, 2.6.1, 2.6.6, 2.6.7, and 4), this supplement might have to be managed by OND,

Prior-approval is the correct submission strategy for this post-approval supplement.

Need P-Tox consult, microbiology consult, and CDRH consult (modifications have been made to the inserter, which is a device).

NDA 21-225 S-030 covers Mirena®, which is a levonorgestrel-releasing intrauterine system. The drug product consists of an intrauterine system (a T-shaped polyethylene frame with a steroid reservoir containing 52 mg of levonorgestrel). The system is designed to be inserted into the uterus and to release 20 mcg levonorgestrel per day. The Mirena insert is packaged sterile within an inserter, which is comprised of a symmetric two-sided body and slider integrated with flange, lock, pre-bent insertion tube, and plunger. See intrauterine system (on top) and inserter (on bottom).



This prior-approval post-approval supplement proposes the use of a modified inserter to replace the current inserter. There are no qualitative changes proposed for the actual insert (T-body), but the applicant has stated that the design of the knobs at the end of the horizontal arms were “slightly modified”. See QOS, Module 2.3.

Insertion tube: change in formulation of the [REDACTED] (b) (4)
[REDACTED] as well as a decrease in diameter. [REDACTED] (u) (4)

Flange: no change in the dimensions or in the plastic polymer, but the colorant has been changed, due to discontinuation of the current colorant.

Plunger: change in design and diameter of the plunger, from a slotted design to a forked design and a decrease in diameter from 3.5 mm to 2.9 mm; no change noted for materials of fabrication.

Handle: a change in the [REDACTED] (b) (4)
[REDACTED] and an increased width (from 21 to 28 mm).

Slider: a design change is proposed, making the inserter more “ergonomic”.

The T-body is to be fabricated from the same materials, and to the same overall dimensions (32 x 32 x 1.5 mm). the removal thread is proposed to be fabricated from the same PE plastic, but the dimensions of the thread are changed (designed to be thinner and softer). According to the applicant:



This should be evaluated by the clinical review division.

The applicant provides a catalogue of packaging DMF's for the modified inserter.

(b) (4)



This needs to be consulted to HFD-580 Pharmacology & Toxicology staff for review.

The applicant has also modified the CCS for the drug product (the thermoformed blister package with peelable lid). The Mirena device is contained within this CCS and is sterilized by ethylene oxide (EO) treatment.

This applicant needs to be consulted to the Microbiology staff for sterility assurance evaluation because the CCS (in which the Mirena device is sterilized) is modified.

The applicant provides batch analyses for three exhibit batches (new applicator and modified T-body). The current expiration dating period (36 months) is proposed for retention for the product.

This application may also have to be consulted to CDRH. A Device manufacturer certification is provided (Module 3.2.R).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID B LEWIS

03/26/2013

IQA, PAS, need micro, P-Tox, and possibly CDRH consults

THOMAS F OLIVER

03/26/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021225/S-033

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM

FROM: Division of Bone, Reproductive and Urologic Products
Attn: Charlene Williamson

REQUEST DATE
April 22, 2014

IND NO.

NDA/BLA NO.
21225/S-033

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE

Mirena IUS

Priority

(Generally 1 week before the wrap-up meeting)

NAME OF FIRM: Bayer Healthcare Pharmaceuticals, Inc.

PDUFA Date: May 29, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

For OSE USE ONLY

- REMS

EDR link to submission:

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]
Labeling Meetings: [Insert Dates]
Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
04/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Division of Bone, Reproductive and Urologic Products Attn: Charlene Williamson		
DATE April 22, 2014	IND NO.	NDA NO. 21225/S-033	TYPE OF DOCUMENT PAS	DATE OF DOCUMENT
NAME OF DRUG Mirena IUS		PRIORITY CONSIDERATION Priority	CLASSIFICATION OF DRUG progesterone	DESIRED COMPLETION DATE May 2, 2014
NAME OF FIRM: Bayer Healthcare Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review (b) (4) for NDA 21225/S—033 EDR Link: http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=8805468				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

06/18/2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON

04/22/2014

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH

Division:

Mail Code: HF

Consulting Reviewer Name:

Building/Room #:

Phone #:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Bone, Reproductive and U

Mail Code: HF

Requesting Reviewer Name: Charlene Williamson

Building/Room #: 22/5332

Phone#: 6-1025

Fax #:

Email Address:

RPM/CSO Name and Mail Code: Charlene Williamson

Requesting Reviewer's Concurring Supervisor's Name: Lisa Soule

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: January 29, 2014

Requested Completion Date: March 29, 2014

Submission/Application Number: 021225/S-033
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: January 29, 2014

Official Submission Due Date: May 29, 2014

Name of Product: Mirena (levonorgestrel intrauterine system)

Name of Firm: Bayer Healthcare Pharmaceuticals, Inc.

Intended Use: Prevention of pregnancy for up to 5 years.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

See Attached

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Applicant is responding to our Complete Response letter dated August 30, 2013.

Bayer HealthCare Pharmaceuticals Inc. is submitting this response to reply to the Agency's [Complete Response Letter for S-033](#) dated August 30, 2013. The FDA's Comments and information requests (provided in **BOLD**) are followed by the Bayer response.

1. FDA Question 1

It is not clear what hazards are associated with the modified inserter. Provide an analysis of the hazards associated with the aspects of the user interface that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified features of the device. The analysis should also identify the mitigations strategies you employed to control all serious use-related hazards and the methods you used to validate the effectiveness of those mitigations. Based on your analysis, indicate whether a Human Factors/Usability study is necessary to validate that the measures you implemented to control use-related hazards were effective at reducing the risks to acceptable levels. If you determine that it is necessary, submit your draft protocol for review prior to conducting the study.

Response:

Hazard Analysis and Mitigation Summary

The hazards associated with the introduction of the proposed Mirena EVO inserter have been analyzed in a hazard analysis performed in accordance with relevant ISO Standards. The analysis includes the following potential risk categories:

- Infection
- Pain or injury to patient
- Unplanned pregnancy
- Environmental risks
- Usability risks including handling steps by the HCP that could affect the outcome of the insertion

In addition to identification of these potential risks, appropriate mitigation measures have been also identified and are supported by appropriate verifications and/or validations as warranted. The following list highlights those identified mitigation measures that have been employed in support of the proposed Mirena EVO inserter:

- Material testing
- Packaging validation
- In-process controls

- User training
- Design
- Instructions for Use

Please refer to [Attachment 1](#) for the [Risk Analysis](#), [Attachment 2](#) for the [Risk Analysis Plan](#), and [Attachment 3](#) for the [Risk Management Report](#) which have been performed in support of our proposed Mirena EVO Inserter.

The data generated from this Risk Analyses demonstrates the following:

- Bayer has adequately identified all possible risk categories associated with the introduction of the EVO Inserter; and
- Appropriate risk mitigation measures have been identified and verified based on generated data referenced in the analyses.

Product Comparisons

In addition to the conduct of this Risk Analysis, it is important to leverage the comparisons of the proposed Mirena EVO inserter to the EVO inserter contained in our SKYLA IUS approved on January 9, 2013 and to our current Mirena IUS. Although similar in overall design and materials of construction to the original Mirena Inserter, the EVO Inserter contains minor design changes to facilitate physician preparation of the IUS prior to placement. The design advantages are highlighted below:

- Thread release: threads have been relocated inside the handle eliminating the need for physical manipulation of threads to initiate release.
- Horizontal arm check: the IUS system is pre-packaged in the horizontal position thereby eliminating the need for physician adjustment prior to insertion.
- Loading of the IUS System: Elimination of multiple preparatory steps to load the IUS including positioning of the slider device to a preset location, manually manipulating the threads to load the IUS into its desired position, then locking the threads in place. The EVO Inserter achieves the desired loading of the IUS by simply pushing the slider upwards.

A side by side comparison of the inserters is included in [Table 1](#):

Table 1 - Technical Specifications

Parameter	Current MIRENA (NDA 21-225)	Proposed MIRENA EVO (NDA 21-225, S-033)	SKYLA (NDA 203159) ¹
Indications for Use	MIRENA is a sterile, levonorgestrel-releasing intrauterine system indicated for intrauterine contraception for up to 5 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.	EVO is a sterile, levonorgestrel-releasing intrauterine system indicated for intrauterine contraception for up to 5 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.	SKYLA is a low dose levonorgestrel (LNG) intrauterine system, which has been developed for intrauterine contraception for up to 3 years and treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.
Insertion Tube			
Material	(b) (4) polyethylene (b) (4) (b) (4)	(b) (4) polyethylene (b) (4) (b) (4)	(b) (4) (b) (4)
Diameter	4.75 mm	4.40 mm	3.80 mm
Scale	Markings on one side	Markings on both sides	Markings on both sides
Flange			
Material	(b) (4)		
Color	(b) (4) Teal	(b) (4) Teal	(b) (4) Pink
Plunger			
Material	(b) (4)		
Diameter	3.5 mm	2.9 mm	2.9 mm
Design	Slot	Fork	Fork
Body Contact	Yes	No	No
Handle			
Material	(b) (4)		
Color	(b) (4) White	(b) (4) White	(b) (4) White

**Response to Complete Response Letter
 for S-033**

Parameter	Current MIRENA (NDA 21-225)	Proposed MIRENA EVO (NDA 21-225, S-033)	SKYLA (NDA 203159) ¹
Maximum width	21 mm	28 mm	28 mm
Thread lock			
Design	Manually to the thread cleft at the lower end of the handle	Mechanically by a thread lock component inside the handle	Mechanically by a thread lock component inside the handle
Material	(b) (4)		
Slider			
Material	(b) (4)		
Color	(b) (4) Teal	(b) (4) Teal	(b) (4) Pink
Design	Re-loadable	Not re-loadable	Not re-loadable
T-Body			
Material	PE+BaSO4	PE+BaSO4	PE+BaSO4
Dimensions	32 x 32 x 1.5 mm	32 x 32 x 1.5 mm	28 x 30 x 1.5 mm
Removal Thread			
Material	PE: style="background-color: #cccccc;">(b) (4)	PE: style="background-color: #cccccc;">(b) (4)	PE: style="background-color: #cccccc;">(b) (4)
Diameter	0.20 - 0.35 mm (target 0.30 mm)	0.24 - 0.30 mm (target 0.26 - 0.28 mm) Threads are thinner and softer	0.24 - 0.30 mm (target 0.26 - 0.28 mm) Threads are thinner and softer
Total Length	84 cm	56 cm Threads are inside handle	56 cm Threads are inside handle

¹ Skyla (also referred to as LCS12) was approved by the FDA on January 9, 2013

In addition to the product comparisons provided above, Bayer is also providing a side-by-side comparison (Attachment 4) of the preparatory steps required by the Health Care Physician in Table 2, using either the current Mirena Inserter vs. the EVO Inserter, prior to the actual insertion of the IUS:

Table 2 – Preparatory Steps by Health Care Physician

Current Mirena Inserter	EVO Inserter
<p>Step 1</p> <ul style="list-style-type: none"> • Open the sterile package completely • Release the threads. • Rotate the inserter so that the centimeter scale is upwards • Check that the arms of the system are in horizontal position 	<p>Step 1</p> <ul style="list-style-type: none"> • Open the sterile package completely
<p>Step 2</p> <ul style="list-style-type: none"> • Holding the slider in the furthest position, pull on the threads to draw the IUS into the insertion tube • If the knobs at the ends of the arms do not meet properly, release the arms by pulling the slider back to the mark. • Re-load the IUS by aligning the open arms on a sterile surface. Return the slider to its furthest position and pull on both threads. Check for proper loading. 	<p>Step 2</p> <ul style="list-style-type: none"> • Push the slider upwards, in the direction of the arrow, to the furthest position to load the IUS into the insertion tube
<p>Step 3</p> <ul style="list-style-type: none"> • Fix the threads in the cleft (bottom end of the handle) to keep the product in the loaded position. 	-

A complete side by side comparison is provided in [Attachment 4](#).

Given the significant similarities in indications for use, overall design and materials of construction with the above products, and given the minimization of preparatory handling requirements with the EVO Inserter, Bayer considers its implementation for use with Mirena will not introduce any additional risks or user-related hazards.

Readability Study of IFU for EVO Inserter

Additionally, a readability and comprehension study of the [Instructions for Use](#) of the modified inserter has been conducted ([Attachment 5 –User Testing Study](#)). All questions were designed to determine if HCPs could identify key information and demonstrate the understanding that is necessary to ensure safe and effective insertion of the IUS.

Information was located by at least 80% of the HCPs in the study and of those at least 90% gave a correct explanation of the instructions in response to all 13 questions. The ease of use of the inserter was also rated highly (7-10 out of a possible 10).

***In Vitro* Testing Comparisons**

Bayer has developed an *in vitro* testing protocol that evaluates: a) the ability of the T-body component of the IUS to recover to its desired shape following release from the EVO Inserter, and b) demonstrate that there is no force acting upon the T-body during the release of the threads and the removal of the EVO insertion device that would have the potential to alter the T-body positioning post-placement. Reference is made to our response to [Question 2](#) and the data contained therein. These data demonstrate that use of the EVO Inserter does not affect the deployment of the T-Body component, nor does the EVO Inserter have any untoward effect on the positioning during withdrawal of the Inserter component.

Safety Data on Mirena EVO Inserter derived from International Markets

MIRENA Evo Inserter was first launched in Sweden, Norway, Denmark, Finland and Czech Republic in November 2011. To date, the modified inserter has been authorized for use with MIRENA in 97 countries and has been launched in 56 countries. Based on Bayer sales data there have been (b) (4) of MIRENA Evo Inserter sold as of September 30th, 2013.

Bayer reviews and analyzes all safety data including that from spontaneous adverse event reports and prepares Periodic Safety Update Reports (PSURs), summarizing the available safety data at regular intervals both for the PSUR period and cumulatively. A cumulative summary tabulation of all ADRs reported globally to the company until data lock point of the last PSUR can be found in [Module 5.3.6, PBRER/PSUR 28 Mirena, Appendix 3](#) and [Appendix 4](#).

The reporting rates for spontaneous post-marketing cases of uterine perforation with Mirena are under close monitoring by Bayer Global Pharmacovigilance. Based on the analysis of country-specific reports and reporting rates, no signal for an increased reporting rate caused by the use of the EVO Inserter has been identified to date.

Conclusions

Based on the Risk Analyses performed it is concluded that there are adequate and verified mitigation measures in place to support the introduction of the Mirena EVO Inserter. In addition, Bayer has highlighted the significant similarities of the EVO inserter proposed for

use with Mirena to the EVO Inserter in use with our currently approved SKYLA IUS. The significance of the changes between the current Inserter and the EVO Inserter centers on the fact that there are less preparatory steps with the EVO Inserter thereby minimizing physician manipulation with subsequent placement instructions remaining unchanged. In a “Readability Test” conducted with the proposed Mirena EVO Inserter, the accompanying Instructions for Use were rated high with an average score of 87%. Bench testing results evaluating T-body deployment and removal force after IUS placement illustrate no untoward effect and retrospective analyses of safety data from those markets where the Mirena EVO inserter is approved has not shown any signals or trending related to the introduction of the EVO inserter.

Taking into account the conclusions above, Bayer believes that it has provided substantial data to satisfactorily address any potential user-related safety or efficacy concerns with the Mirena EVO inserter and as such, Bayer believes that a Human Factors/Usability Engineering Study is not warranted.

2. FDA Question 2

The proposed changes to the insertions device for Mirena have the potential to affect the ability to successfully deploy/deliver the IUS. Testing should be conducted to evaluate the ability of the insertion device to deliver the IUS to its target location in its intended shape/configuration. This testing should be conducted in a model that simulates worst-case clinical conditions and should include a statistically valid sample size. Provide a copy of this testing along with the results for review.

Response:

Bayer has developed an *in vitro* testing protocol that evaluates: a) the ability of the T-body component of the IUS to recover to its desired shape following release from the EVO Inserter, and b) demonstrate that there is no force acting upon the T-body during the release of the threads and the removal of the EVO insertion device that would have the potential to alter the T-body positioning post-placement. The T-body test used samples from three different lots of Mirena EVO and compared the results against batches using our current Mirena Inserter. Using a removal force specification limit derived from a bench testing apparatus designed to mimic worst-case technical delivery conditions, the release force test compared existing Mirena against our proposed Mirena EVO product. The testing protocol and results from these tests are provided in [Attachment 6](#). The conclusions derived from these results demonstrate there is no impact on IUS deployment, IUS shape, nor placement stability of the IUS following withdrawal of the Mirena EVO Inserter.

3. FDA Question 3

Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on June 27, 2013. These deficiencies must be adequately addressed before tis application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

Response:

The holder, (b) (4) has addressed the deficiencies identified in the DMF Deficiency dated June 27, 2013 (Mirena® inserter) (reference ID 3333286) by filing a DMF Amendment to DMF (b) (4) on July 9, 2013. With this submission, Bayer HealthCare Pharmaceuticals is requesting the Agency to refer to the above DMF submission to address the “Complete Response Letter” issued on August 30, 2013 for the Pending Supplement (S-033) of NDA 21-225.

4. FDA Question 4

There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls. You must provide information showing that changes in the introducer’s design do not affect the safety and effectiveness of the finished product. Similarly, you must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product. You should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, explain why no changes were necessary. Pay particular attention to the requirements for design controls under 21 CFR 820.30(i), (h) and (g).

- A. There were no documents in the application addressing the design changes in the finished combination product as required under 21 CFR 820.30, design controls. You must provide information showing that changes in the introducer’s design do not affect the safety and effectiveness of the finished product.

Response:

Development of new products and changes to marketed products are controlled by (b) (4)

The SOP defines where in the design and development process the device becomes subject to the design control process. It also provides procedures for controlling all phases of the design control process including:



Additionally, the following local SOPs for Design Validation, Risk Management and Change management control the design of the device were utilized:



The modifications to the inserter have been made in compliance with the Design Control requirements. The hazard analysis has been performed in accordance with the  (b) (4) and to ISO 14971:2007. The risk assessment shows that all identifiable risks have been reduced to acceptable levels. ([Attachment 3 – Risk Management Report](#))

Design verification and validation of the modified inserted has been performed as part of the clinical or user trials for the SKYLA Inserter (Reference NDA 203,159 approved 1/9/2013).

The results of the user evaluation showed that > 85% of the insertions were rated as “easy”. More than 70% of the physicians gave the IUS inserter the highest rating for the assessments.

As demonstrated in the response to Comment 1, the modified inserter design for the Mirena device and the SKYLA Inserter are the same except for small dimensional differences to accommodate the respective intrauterine devices and the color of the slider and flange. All other technical aspects of the inserters and the procedure to use the inserter are identical. In addition, both products are manufactured/assembled at Bayer’s facility in Turku, Finland.

Prior to the approval of the SKYLA NDA, an inspection was conducted by FDA of Bayer’s Turku Finland manufacturing facility (September 24-October 2, 2012). The following list of documents was reviewed during the inspection:

Overview of the Design History File for SKYLA:

- (See [Attachment 7](#) for a copy of the Table of Contents from the SKYLA DHF)

List of Design Summary documents reviewed during SKYLA PAI:





Compliance with design controls ensures that the design was developed in accordance with user requirements and verified to meet those requirements. The results of the hazard analysis and the design validation study demonstrate that the modifications to the inserter's design are useful, safe and do not interfere with the intended use of the finished device.

B. Similarly, you must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product.

Response:

The following tests have been performed on the revised packaging to validate its ability to maintain sterility and integrity of the product:



The changes to the primary packaging of the Mirena inserter have been tested according to the following standards:





Compliance with design controls ensures that the design was developed in accordance with user requirements and verified to meet those requirements. The results of the hazard analysis and the design validation study demonstrate that the modifications to the inserter's design are useful, safe and do not interfere with the intended use of the finished device.

B. Similarly, you must provide information showing that the changes made to the packaging for the finished combination product do not affect the integrity of the product.

Response:

The following tests have been performed on the revised packaging to validate its ability to maintain sterility and integrity of the product:



The changes to the primary packaging of the Mirena inserter have been tested according to the following standards:





Data supporting the integrity of the container closure system were provided in the original sNDA for the new inserter in Module 3.2.P.2.5.01 ([P.2.5.01#006997765](#)). Stability data demonstrating sterility over the intended shelf-life were provided in [Module 3.2.P.8](#). The package testing shows that the microbial barrier properties of the materials and the integrity of the seals maintain the sterile barrier system and do not adversely affect the integrity of the product.

- C. You should also provide information regarding any changes in the manufacturing of the finished combination product made as result of these design changes. If no manufacturing changes were implemented, explain why no changes were necessary.**

Response:



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

5. FDA Question 5

You are adding an additional supplier of the inserter. Provide enough information to demonstrate adequate control over this new supplier and the product provided, as required by 21 CFR 820.50, purchasing controls.

Response:



(b) (4)



Approval of the additional supplier is based on following documents:

(b) (4)



The supplier has been audited on November 26-27, 2009 and a follow-up audit performed in December 7, 2011. No critical or major deficiencies were found.

The QA agreement between (b) (4) and Bayer Oy was signed in September 7, 2010. The agreement requires that the supplier discuss and reach agreement with Bayer before implementing any changes that may have an effect on the quality of the product.

Receiving specifications have been identified in the following:

(b) (4)



Acceptance criteria have been defined in the following:

(b) (4)



Based on the established supplier qualification processes and incoming receiving inspections, Bayer has demonstrated that adequate control exists over the addition of the additional supplier for the inserter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
02/07/2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
06/12/2013

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: DRGUD-Human Factor
Mail Code: HF
Consulting Reviewer Name: _____
Building/Room #: _____
Phone #: _____
Fax #: _____
Email Address: _____
RPM/CSO Name and Mail Code: _____

From (Originating Center):

Center: CDER-ODE III
Division: Division of Bone, Reproductive and U
Mail Code: HF
Requesting Reviewer Name: _____
Building/Room #: _____
Phone#: _____
Fax #: _____
Email Address: _____
RPM/CSO Name and Mail Code: _____
Requesting Reviewer's Concurring Supervisor's Name: Charlene Williamson -

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: June 11, 2013

Requested Completion Date: June 25, 2013

Submission/Application Number: NDA 21225/S-033
(Not Barcode Number)

Submission Type: sNDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: February 27, 2013

Official Submission Due Date: _____

Name of Product: Mirena (levonorgestrel-releasing intrauterine s Name of Firm: Bayer Healthcare Pharm., Inc.

Intended Use: Prevention of pregnancy

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Please review the modified insert to replace the current one. There is a design change making the new inserter "ergonomic"

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
06/10/2013

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH

Division: DRGUD-ODE

Mail Code: HF

Consulting Reviewer Name: Veronica Price, M.D.

Building/Room #:

Phone #:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER-ODE III

Division: Division of Bone, Reproductive and U

Mail Code: HF

Requesting Reviewer Name:

Building/Room #:

Phone#:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

Requesting Reviewer's Concurring Supervisor's Name: Charlene Williamson -

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: June 11, 2013

Requested Completion Date: June 25, 2013

Submission/Application Number: NDA 21225/S-033
(Not Barcode Number)

Submission Type: sNDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: February 27, 2013

Official Submission Due Date: _____

Name of Product: Mirena (levonorgestrel-releasing intrauterine s Name of Firm: Bayer Healthcare Pharm., Inc.

Intended Use: Prevention of pregnancy

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Review the functionality of the inserter

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
06/10/2013

MANDATORY: Send a copy of the consult request form to the

Office of Combination Products as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH Office of Compliance

Division:

Mail Code: HF

Consulting Reviewer Name:

Building/Room #:

Phone #:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER Division of Bone, Reproductive

Division:

Mail Code: HF

Requesting Reviewer Name:

Building/Room #:

Phone#:

Fax #:

Email Address:

RPM/CSO Name and Mail Code: Charlene Williamson

Requesting Reviewer's Concurring

Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: May 29, 2013

Requested Completion Date: June 30, 2013

Submission/Application Number: NDA 21225/S-033
(Not Barcode Number)

Submission Type: Supplement
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: February 26, 2013

Official Submission Due Date: June 26, 2013

Name of Product: Mirena

Name of Firm: Bayer Healthcare Pharmaceuticals, Inc.

Intended Use: Prevention of pregnancy

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Labeling supplement with new inserter

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

An EES entry will be submitted to CDER OC for the following sites:

_____^{(b) (4)} AND

_____^{(b) (4)} Finland

The responsibilities of both sites are manufacturers of the inserter device which is used to deliver the IUD. Please evaluate to determine if a device inspection is required for the mentioned facilities.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
05/29/2013



NDA 21225/S-033

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Joseph Zuccarini
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Zuccarini:

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

NDA NUMBER: 21225
SUPPLEMENT NUMBER: 033
PRODUCT NAME: Mirena[®] levonorgestrel (LNG)-releasing intrauterine system (IUS)
DATE OF SUBMISSION: February 27, 2013
DATE OF RECEIPT: February 27, 2013

This supplemental application proposes the following change(s): 1) A modified inserter (including ergonomic enhancements) to replace the current inserter as an integrated applicator--forming an intergral part of the complete LNG-IUS at the time of application to the patient and 2) new packaging materials for the container/closure system of the final assembled product.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 28, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be June 27, 2013.

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

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZETA-MAE C WILLIAMSON
04/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (Division/Office): **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: **Kerri-Ann Jennings- X62919 ONDQA PM**
CMC Reviewer- Jean Saleme

PROJECT MANAGER (if other than sender):

REQUEST DATE
2 APR 2013

IND NO.

NDA NO.
21225/S-33

TYPE OF DOCUMENT
CMC PAS (electronic)

DATE OF DOCUMENT
27 FEB 2013

NAMES OF DRUG
Mirena®

PRIORITY CONSIDERATION

PDUFA DATE
27 JUN 2013

DESIRED COMPLETION DATE
27 MAY 2013

NAME OF APPLICANT OR SPONSOR: **Bayer HealthCare Pharmaceuticals Inc.**

GENERAL PROVISIONS IN APPLICATION

- | | |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED | <input type="checkbox"/> CBE-0 SUPPLEMENT |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT |
| <input type="checkbox"/> BUNDLED | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input type="checkbox"/> DOCUMENT IN EDR | |

COMMENTS / SPECIAL INSTRUCTIONS:

NDA 21225/S-33

This PAS provides for the following:

- 1) modified inserter (including ergonomic enhancements) to replace the current inserter as an integrated applicator---forming an integral part of the complete LNG-IUS at the time of application to the patient and
- 2) new packaging materials for the container/closure system of the final assembled product.

A consult is being requested for sterility assurance evaluation because the CCS (in which the Mirena device is sterilized) is modified.

SIGNATURE OF REQUESTER

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KERRI-ANN JENNINGS
04/02/2013