CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203159Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	January 9, 2013
From	Audrey Gassman, MD
NDA #	203159
Applicant name	Bayer Healthcare Pharmaceuticals, Inc
Date of receipt of original submission	December 9, 2012
Original PDUFA goal date	October 9, 2012
Extended PDUFA goal date	January 9, 2013
Proprietary name/established name	Skyla/levonorgestrel-releasing intrauterine system
Dosage Form/strength	Sterile intrauterine system/13.5 mg levonorgestrel
Proposed Indication	Prevention of pregnancy for up to 3 years
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Lisa Soule, MD
Medical Officer Review	Ronald Orleans, MD
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Kimberly Hatfield, PhD Alexander Jordan, PhD
Clinical Pharmacology Review	Li Li, PhD Myong-Jin Kim, PhD
ONDQA Review	Tarun Mehta, PhD Moo-Jhong Rhee, RPh
ONDQA Biopharmaceutics Review	Sandra Suarez Sharp, PhD Angelica Dorantes, PhD
CDRH Division of Enforcement (Device manufacturing facility inspection team)	Steven Kehoe Shirley Zeigler
Product Quality Microbiology Review	Jessica Cole, PhD John Metcalfe, PhD
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CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
CDRH= Center for Devices and Radiologic Health
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPP – Division of Professional Promotion
DDTCP – Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Bayer Healthcare Pharmaceuticals, Inc. submitted NDA 203159 on December 9, 2011, to obtain marketing approval for a new intrauterine system LCS12, for the indication of prevention of pregnancy for up to 3 years. LCS12, also referred to in this review as Skyla, is a levonorgestrel (LNG)-releasing intrauterine system (also referred to as an intrauterine device or IUD). Skyla has an in vitro release rate of 12 µg/24 hours of LNG, which is lower than the current approved LNG-containing IUS, Mirena (NDA 21-225). Intrauterine systems (IUS) are designed to be long acting, reversible, contraceptives. IUS require a healthcare provider to insert and remove the system from the uterus. The first levonorgestrel IUS, Mirena, was initially approved more than 20 years ago and is marketed in over 100 countries.

Levonorgestrel has a long history of use in many approved hormonal products in the US. These indications include both contraception (oral, intrauterine, and implants) and menopausal therapy. The levonorgestrel component of Skyla exerts its contraceptive effect locally in the uterus primarily by:

- thickening the cervical mucus, and
- preventing the proliferation of the endometrium during the menstrual cycle

Skyla is supplied as a T-shaped polyethylene frame with a hormone-elastomer reservoir containing (b) (4) of levonorgestrel. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. (b) (4) polyethylene removal threads with colorant are attached to a loop on the vertical stem. The to-be-marketed Skyla is placed in the uterus with a new preloaded, ready-to-use inserter. A single phase 3 trial (A52238) provided efficacy data and a supportive phase 2 trial (A46796) provided additional safety data for Skyla. The Applicant also supplied safety data from several ongoing protocols that used a new (b) (4) inserter for use with the to-be-marketed Skyla product.

Skyla contains 13.5 mg of levonorgestrel released at an approximate mean rate of 6 mcg/day and is intended for use for up to three years. Compared to an approved IUS

(tradename Mirena), Skyla releases levonorgestrel at a lower daily rate and has a smaller inserter tube, and small T-body frame to facilitate insertion and tolerability. In addition, the Applicant added a silver ring to the upper part of the T-body frame to facilitate localization of the IUD by ultrasound.

Comment: Skyla is regulated as a combination drug-device product. The T-body contains levonorgestrel, a drug, and the components of Skyla and inserter are considered a device. CDRH was consulted to evaluate the functionality of the device portion of this IUS. The findings from CDRH's consults regarding the device portion of Skyla are briefly summarized in section 11 of this review entitled, "Other Relevant Regulatory Issues".

The Applicant is seeking approval of Skyla in reproductive aged women regardless of parity for up to three years of use. To support approval of this NDA, the Applicant conducted a nonclinical and clinical development program. The nonclinical program included acute toxicity, mutagenicity and tolerability studies as well as one 9-month monkey study that evaluated a modified version of the Skyla device. The clinical program included one phase 2 trial (A46796) and one phase 3 trial (A52238) that included a total of 1672 subjects exposed to Skyla.

The phase 3 trial A52238 formed the basis of efficacy for Skyla. Trial A52238 was a multinational randomized, open-label, 2-arm, parallel-group trial conducted in Europe, North and South America. The trial enrolled both nulliparous and parous subjects of reproductive age in good general health who were seeking long-acting contraception. The total treatment duration for subjects who received Skyla was up to 3 years. The primary efficacy variable was the unintended pregnancy rate calculated using the Pearl Index (PI) in women ages 18 to 35 during the first year of use (Year 1 PI) and for the total treatment duration of up to three years (3-year PI). This trial met the Division's recommendation that efficacy evaluation be based on a minimum of 10,000 cycles of exposure in the first year of use (see finalized minutes dated May 1, 2006). Another IUS (LCS16) with an in vitro release rate of 16 μg/24 hours of LNG was also evaluated in the phase 3 study.

Comment: As NDA 203159 only proposed Skyla (LCS12) for approval, therefore efficacy data for LCS16 IUS was not evaluated here. However, safety data from LCS16 obtained from the phase 3 trial was reviewed for comparison purposes, primarily where the progestin dose in the IUS could potentially have impacted the rate or risk of an AE.

The phase 2 and 3 trials (A52238 and A46796) supported the safety of Skyla. The safety database included 1672 women randomized to Skyla, 1697 to LCS16, and 256 to the approved Mirena IUS. Safety data were analyzed by pooling data from phase 2 and 3 trials and also for each trial individually. Safety assessments included evaluation of menstrual bleeding data, insertion and expulsion reports, serious adverse events, deaths, and overall adverse events, endometrial safety data and evaluation of other serious gynecologic adverse events including pelvic inflammatory disease and ectopic pregnancies. Use of a new inserter for Skyla that was not used in the phase 3 trial was

evaluated in the extension trial and determined to be acceptable from a clinical (DRUP) and device (CDRH) perspective for use with Skyla.

Skyla has not been marketed in any country; therefore, no postmarketing safety information is available. However, postmarketing safety data from Mirena was included in the consideration of the safety of Skyla because of the significant similarity between these products.

No significant safety or efficacy issues were identified during the review of this application. There are no outstanding clinical pharmacology, nonclinical toxicology, or chemistry, manufacturing and control (CMC) issues. Final acceptable product labeling was submitted by the Applicant on January 9. 2013. Both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendations.

2. Background

The Applicant initiated discussions of Skyla for prevention of pregnancy with the Division of Reproductive and Urologic Products (DRUP) in March 2006. The pre-IND discussion on the development program for Skyla was captured in meeting minutes dated May 1, 2006.

IND 73,505 for Skyla (b) (4) was opened on July 30, 2007, with submission of a protocol for Trial A52238 (protocol 310442), entitled: "Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age." Protocol 310442 proposed a multicenter, randomized, open-label, two-arm, parallel group phase 3 trial to evaluate two intrauterine device systems, one that releases LGN at an initial rate of 12 mcg/24 hours (LCS12) and the other at a initial release rate of 16 mcg/24 hours (LCS16). The primary efficacy variable was the pregnancy rate as calculated by the Pearl Index (PI). At the time of the IND submission, a 3-year trial (phase 2 trial A46796) was ongoing in Europe. Trial A46796 evaluated the same levonorgestrel IUS products: LCS12 and LCS16. The Applicant did not request a special protocol assessment (SPA) for protocol 310442.

An EOP2 meeting was held on November 24, 2009, to discuss the recently obtained results of a three-year phase 2 trial A46796 and to obtain Agency concurrence with modification of the clinical development plan and a new in vivo in vitro (IVIVC) correlation plan to bridge the phase 2 and proposed phase 3 trials. At this meeting, plans for IVIVC and pharmacokinetic characterization were agreed to. The clinical and clinical pharmacology team also agreed that no bridging of phase 2 to 3, in terms of a clinical bioequivalence study, would be necessary if an acceptable IVIVC was developed. In addition, the clinical team outlined key recommendations for the phase 3 study as follows, "The Division requests that a minimum of 200 women complete the full duration of treatment for which approval is sought. Review of contraceptive efficacy in years 4

and 5 will be based upon the acceptability of the upper bound of the confidence interval around the Pearl Index. In addition to the Pearl Index and its 95% confidence interval, the life table estimate and its 95% confidence interval should be included in the efficacy analysis. The Division also requests that, at a minimum, pregnancy testing be performed at Month 48, as well as at Months 36 and 60 as proposed." (See IND 73505 – Meeting minutes dated December 17, 2009)

A pre-NDA meeting was held on July 28, 2011, to discuss the content and format of the Applicant's proposed NDA submission. Agreements were reached in regard to the Applicant's proposed NDA and risk management plan. In a post-meeting clinical and statistical comment, the Division provided additional input related to the efficacy analyses and bleeding data, including the following key recommendation:

> "…the Division requests that the Sponsor submit the data expressed in 28-day cycle equivalents, as well as in the manner originally proposed. Given that a month in which back-up contraception was used might span two or more 28-day cycles, the Division recommends that the Sponsor develop an algorithm to assign back-up to a single specific 28-day cycle equivalent in such cases. In addition to providing a Pearl Index based on women-years of exposure, the Sponsor should calculate the Pearl Index based on 28-day cycle equivalents. While the Division acknowledges that the LCS is not a cycle-based method, this analysis will allow for consistency with other hormonal contraceptives in calculating the Pearl Index…..The Pearl Index should be calculated based on women 18 to 35 years of age from the FAS population, the total number of completed 28-day cycles after removing those cycles where another contraceptive method was used, and including all on-treatment pregnancies. The unadjusted 12 month and unadjusted cumulative 3-year Pearl Index will be the basis for demonstrating efficacy." (See IND 73,505 - Meeting Minutes dated August 24, 2011)

The Applicant responded to the Division's post-meeting comments in an amendment (S-0048 received on September 8, 2011) and agreed to provide the 28-day cycle information and use the algorithm used to assign back up contraceptive use to specific 28 day cycles in their Statistical Analysis Plan. The Applicant also agreed to provide unadjusted PIs and bleeding data by 28-day reference periods as requested.

NDA 203159 was submitted on December 9, 2011, to support the efficacy and safety of LCS12 (Skyla) only and not for LCS16.

One issue identified during the review of Skyla was that the to-be-marketed inserter was not the same as the one used in the phase 2 and phase 3 trials. This new inserter (b) (4) was designed with the removal threads prefixed inside the shaft (b) (4) The intent of the new design was to (b) (4) The Applicant provided data on the new inserter through an interim analysis of an ongoing study (Protocol 13362) in their 4-month Safety Update Report (Letter Date April 5,

2012). The interim analysis included data obtained after Skyla insertions and one month post-insertion follow-up visits.

The Division determined that the safety data from the interim analysis of protocol 13362 were insufficient to address whether intrauterine placement was altered by the new inserter. The Division requested the following information on the new inserter in two separate Email communications (both dated July 24, 2012):

- Submit all available data obtained subsequent to the 4-month Safety Update Reporting period ending January 31, 2012 regarding the to-be-marketed inserter.
- All available data regarding IUD-related complication rates using the new inserter such as expulsions, perforations, endometritis, pelvic inflammatory disease, pregnancies and ectopic pregnancy should be submitted from all on-going studies.
- Provide narrative summary data for study subjects in Study 13362 who underwent sonograms to verify appropriate intrauterine placement of the LCS.

On August 10, 2012, the Applicant responded to the Division's aforementioned requests with additional clinical data and information on the new (b) (4) inserter. The Division determined that the August submission constituted a major amendment and informed the Applicant on August 15, 2012, that the extended PDUFA date would be January 9, 2013.

Comment: The Division had requested that at least 10,000 cycles of exposure in the first year of use, of which 45% should be in US subjects. Although the percentage specified was not met, the Applicant provided more than 4,500 evaluable cycles in the US. This number of cycles of exposure in US women was acceptable to the clinical review team for the purposes of safety and efficacy evaluation of Skyla.

3. ONDQA

Skyla (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a whitish or pale yellow steroid reservoir (hormone elastomer core) around a vertical stem. The reservoir consists of a mixture of levonorgestrel and dimnethylsiloxane with a silver ring attached to the upper end of the vertical stem. The T-body is (b) (4) The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament removal thread is attached to a loop at the end of the vertical stem of the T-body. The loaded dose in the T-body is 13.5 mg with an initial release rate of levonorgestrel once inserted that is estimated to be 6 mcg/day over the anticipated 3-year period after which it should be removed and may be replaced with a new device.

The Chemistry Review (ONDQA) team evaluated the LNG substance in the core and the excipients and components of the device including the elastomer core, the membrane (b) (4), the T-body, the silver (b) (4) the removal thread and the inserter.

As manufacturing of the drug core is considered the most critical part of the manufacturing process, the chemistry reviewer evaluated changes in the process as compared to those in the approved Mirena product and requested that the applicant revise their critical parameter table for (b) (4) The Chemistry reviewer stated the following in his review dated August 6, 2012, regarding this critical process, "The applicant has agreed in the response dated June 6, 2012 (SN0010) to revise their critical parameter table. The revised process control will include the above mention parameters and are deemed adequate to control the manufacturing process and consistent quality of the drug product."

The Chemistry reviewer also made the following comments on the structural frame in his review dated August 6, 2012, "The structural frame material for T- body is not changed for the proposed NDA. The proposed drug product has less amount of drug substance in the core than the approved Mirena. Additional component, silver profile is added which acts as a single bright spot in ultrasonic examination and facilitates detection of the inserted IUS. Changes made during the phase 2 to phase 3 were considered to be major changes (b) (4)
The applicant has provided the adequate PK data (Bio Pharm review) to support those changes. Changes from phase 3 to phase3b were minor technical changes and do not require any additional study."

After review of the Applicant's submissions for Skyla, on August 6, 2012, the Chemistry review noted the following deficiencies that precluded Approval of Skyla including:

"1. Regarding functionality of the inserter (CDRH Consult Review)

- According to CDRH Consult Review:
  1) Additional details on the functional test study should be provided including an identification of any standards followed, e.g., ASTM F1980-07.
  2) The real time equivalent for the accelerated conditions should be provided.
  3) The tests used along with pass/fail criteria should be provided.

2. Regarding labels/labeling:

- The following labeling issues will be addressed during the labeling discussion with the applicant.
  1. "Description" section of the package insert should be revised by including sterility and therapeutic class information
  2. Established name in the labels should be at least 50% of the tradename.

3. Facility Inspection is still pending."

In an addendum to the August, 2012, ONDQA review, finalized on January 7, 2013, the ONDQA reviewer reported that outstanding issues related to the CDRH consult review and labeling had been addressed. In addition, he noted that the Office of Compliance had issued a final "Acceptable" recommendation for the facilities involved in the NDA had been issued. Based on the resolution of all of the deficiencies, he concluded, "This NDA is now recommended for "Approval" from the ONDQA perspective."

The ONDQA Biopharmaceutics Review team evaluated 1) The acceptability of the in vitro drug release rate method; 2) The acceptability of the in vitro and in vivo drug release rate specifications; 3) The information/data supporting the bridging between the formulations used throughout development, and; 4) The acceptability of the IVIVC model. The Biopharmaceutics team noted that the drug release method and acceptance criteria were agreed upon with the Applicant. The Biopharmaceutics team determined that the IVIVC model was not acceptable. However, upon further internal discussion, the Biopharmaceutics team with the Clinical Pharmacology and Clinical teams concluded that although the IVIVC model was not valid, it was not essential to have an acceptable IVIVC for approval of the NDA. The information/data supporting bridging data through dissolution profiles comparison data was also deemed acceptable. Subsequently, the Biopharmaceutics team concluded on November 26, 2012, that, "From the Biopharmaceutics perspective, NDA 203-159 for Low dose levonorgestrel-releasing intrauterine system, 13.5 mg is recommended for approval."

A preapproval overseas inspection for the site that manufactured the intrauterine device was conducted by the Division of Enforcement in the CDRH Office of Compliance. The final report from this inspection, issued on December 5, 2012, stated that, "CDRH has reclassified the inspection NAI based on the EIR dated September 24, 2012 to October 2, 2012, because there were no supportable violations of 21 CFR part 820." The review stated that the final designation was "Approve PMA".

Comment: There are no outstanding CMC, Device Manufacturing, Biopharmaceutics or Method Validation issues. I concur with the "Approval" recommendation of the ONDQA review team.

4. Nonclinical Pharmacology/Toxicology

The Skyla product was developed based on experience with the approved IUS product Mirena (also owned by the Applicant). From the device perspective, since many of the same materials and components comprising Skyla were studied nonclinically for Mirena, these studies were used to support Skyla. The Applicant authorized cross reference to the currently marketed product Mirena (NDA 21225). To support the new components, acute toxicity, mutagenicity and tolerability studies were performed. In addition, the three components of the inserter were also evaluated for skin sensitization and cytotoxic potential. The Applicant also evaluated the silver component of the T-body after single i.v., i.p. and i.c. administration and after 13 weeks of intrauterine administration and concluded that there were no local tolerance or safety issues.

In her review dated November 23, 2012, the pharmacology/toxicology reviewer noted with respect to the use of silver that, "Since there is no other toxicity, intolerance or mutagenicity noted for the silver component, the use of silver in the LCS12 T-body for ultrasound detection is not a safety concern. Calculations determined that the daily release of silver from LCS12 is at least 3000 times lower than the EPA's established oral

reference dose for silver (an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime)."

In addition, the nonclinical reviewer analyzed toxicokinetic comparisons between clinical and nonclinical use based on values determined in a 9-month intrauterine monkey study with a modified Skyla device and did not identify any new safety signals of concern.

From the drug substance and product perspective, levonorgestrel (LNG) has been extensively used in a variety of oral contraceptives, hormone therapies and Mirena. Because of the well-documented safety profile of LNG, no nonclinical studies were conducted by the Applicant to support the safety of LNG. The Applicant did provide published literature and a summary of published literature in the initial IND (73505) to support the LNG component of the device and this information was previously determined to be sufficient (See Pharmacology/Toxicology IND review of 73505/S-006 dated October 1, 2007)

In conclusion, the pharmacology/toxicology review team stated in the final review dated November 23, 2012, that, "Nonclinical data support approval of LCS12, levonorgestrel intrauterine delivery system 13.5 mg, for the prevention of pregnancy for up to 3 years.."

Comment: I concur with the approval recommendation of the pharmacology/toxicology review team that there are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology

Seven clinical study reports were submitted in this NDA submission. Of the 7 submitted reports, 5 reports contained data acquired during Skyla (LCS12) development and were reviewed by the clinical pharmacology team. The team did not review the remaining 2 reports that contained supplementary studies (A229 and A10982) because these studies used an IUS that was not sufficiently identical in formulation to Skyla. In addition, the clinical pharmacology reviewer noted that there were significant modifications to Skyla between the Phase 2 and Phase 3 trials, (b) (4) Therefore, because of the above product differences in Skyla IUS between the Phase 2 and Phase 3 IUS product, the pharmacokinetic characterization obtained in Phase 2 was not reviewed by the clinical pharmacology review team.

The primary pharmacokinetics and pharmacodynamic evaluations for Skyla were based on data obtained from the supportive Phase 2 (A46796) and Phase 3 (A52238) trials. In both trials, pharmacokinetic sampling was conducted in 12 women per treatment arm to determine the non-compartmental pharmacokinetic parameters of serum levonorgestrel during Skyla treatment. These two trials also evaluated Skyla pharmacodynamic effects in a subset of women in each treatment arm by assessing drug effects on ovulation, cervical changes, endometrium and serum silver levels (from the silver ring on the T-body).

Additional supporting clinical pharmacology data reviewed for this submission included a physiology-based pharmacokinetic analysis that compared pharmacokinetics of LNG between adults and adolescents (A57120), an in vitro study evaluating LNG binding protein (A36505), and an in vitro study evaluating the effect of LNG on CYP3A44 activity (A02495). The clinical pharmacology review team also evaluated the modeling of the mean concentration values of total LNG for Skyla at different time points for up to three years post insertion. No drug-drug interaction, renal impairment or hepatic impairment studies were conducted.

Key Clinical Pharmacology findings regarding Skyla included:

- From the Phase 3 study (A52238)
  - Non-compartmental analysis using data from subset population in the Phase 3 study (N=7) indicated that the maximum serum concentration (Cmax) of LNG was 192 ± 105 ng/L, reached after 2 days of LCS12 insertion (median). Thereafter, LNG serum concentrations decreased slowly to the mean value (Cave) of 75 ± 32 ng/L. PK parameters obtained from the noncompartmental analysis were comparable to those derived from the population PK analysis.
  - Serum SHBG concentrations declined slightly during the first 1 to 2 weeks after insertion. Thereafter, nearly plateau-like serum concentrations were observed with a tendency to increase towards the end of the study after 3 years of treatment.
  - Serum silver ion concentrations obtained from a subset of women at baseline and at 1 and 3 years post-insertion revealed levels that were below the lower level of quantification (1 µg/L)
  - No effect on body weight or other covariates on the clearance of LNG was identified in a covariate analysis.
  - The in vivo release of LNG from the LCS12 was calculated from ex vivo residual content data from IUS that were collected in A52238. Release starts immediately after placement in the uterine cavity and the release rate is approximately 14 µg/day after 24 days and reduces to 10 µg/day after 60 days and then decreases progressively to 5 µg/day after 3 years. This downward trend in the release rate of LNG did not translate into higher pregnancy rates in Years 2 and 3, as shown in the efficacy section of this memorandum. The average delivery rate of LNG is approximately 6 µg/day over a period of 3 years.
- From in vitro study (A02495): This study demonstrated that oxidative metabolism of LNG was catalyzed by CYP enzymes, especially CYP3A4.
- Other findings:
  - The Physiology-based pharmacokinetic (PBPK) analysis compared the pharmacokinetics of LNG between female adolescents and adults following insertion (Study A57120). This study noted that there appeared to be no differences in some PK parameters such as C_{max}, C_{365} and $AUC_{0\text{-}365d}$ in girls between 15 and 18, but in girls 10 and 15, up to a 1.6 fold increase in median PK parameters were reported with decreasing age.

- Special populations in women with renal or hepatic impairment. Although it is possible that serum concentrations of LNG could be elevated in these women, as the levels of LNG are 10 times lower than oral contraceptives, no critical concentrations of LNG are expected in these special populations.

Comments:

1. *The Clinical Pharmacology reviewer noted that there is unlikely to be a depot effect of LNG after Skyla removal. I concur that based on data from Mirena, which is a higher dose LNG product, it is unlikely that there will be residual serum LNG that would interfere with a return-to-fertility post-IUS removal.*
2. *Although there was an impact of LNG clearance in women with a BMI over 30 kg/m^2 based on data from the Phase 3 population PK analysis, I concur with the Clinical Pharmacology team that these effects are unlikely to be clinically relevant because the primary effect of LCS12 is local (intrauterine).*
3. *The Clinical Pharmacology reviewer also evaluated the Applicant's PBPK model (Study A57120) to determine whether there were any changes in PK parameters for LNG in adolescents of various age groups. The Clinical Pharmacology reviewer agreed that the Sponsor could extrapolate data for the postmenarchal age group from adults to fulfill PREA. However, she also recommended that the Applicant submit data from a planned multicenter study in Europe that will enroll 300 postmenarchal females under 18 years of age and will collect efficacy and safety data for up to 3 years post-insertion of LCS12. I concur with the CDTL reviewer that the Sponsor should submit efficacy and safety information from this study once it is completed, but that this European data in adolescents is not necessary in terms of requiring a PREA PMR. Extrapolation will be sufficient for the purposes of labeling for use in the adolescent population.*

The Clinical Pharmacology review team made the following recommendation in their review dated December 5, 2012, that, "The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203159 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert."

Comment: I concur with the approval recommendation of the Clinical Pharmacology review team. There are no outstanding Clinical Pharmacology issues.

6. Clinical Microbiology

A consult to the Product Quality Microbiology group was requested to provide advice on the Applicant's proposed microbial limits testing. The Microbiology reviewer completed her consult on March 26, 2012. The consult stated that the Applicant's amendment to address microbial limits testing was acceptable and stated, "This application is recommended for approval on the basis of product quality microbiology."

Comment: I concur with the approval recommendation of the Microbiology Review team that there are no outstanding issues related to microbial specifications.

7. Efficacy/Statistics

Contraceptive efficacy data for Skyla was obtained from one open-label, phase 3 clinical trial, Trial A52238, entitled, "Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years." This phase 3 trial was a randomized, open-label study comparing Skyla (LCS12) to a second LNG-IUS containing a different LNG load (LCS16). The trial was conducted at 138 study sites in 11 countries in Europe, Latin America, the US and Canada. The objectives of the trial were to assess the safety, efficacy and pharmacokinetics of the LCS12 system for a maximum of 3 years in women 18 to 35 years of age.

Comment: Since the Applicant is not seeking approval for the LCS16 device at this time, efficacy of this arm of the study will not be addressed in this review.

Trial subjects were women between 18 and 35 years of age, in good general health, and in need of contraception. A full analysis set (FAS) cohort was used for all primary efficacy analyses and included women who were randomized and for whom an IUS was inserted or the insertion of an IUS was attempted. A total of 2884 women were included in the FAS cohort, with 1432 receiving Skyla and 819 completing the maximum treatment duration of 3 years.

Comment: The population studied in this phase 3 trial was determined by the clinical and statistical review teams as similar to the target population of women who would likely use Skyla in the US.

Subjects were to attend 10 study visits, including a screening visit (Visit 1), a baseline visit (Visit 2), seven interim visits (Visits 3-9) and an end-of-study visit (Visit 10). Pregnancy testing was obtained at screening, baseline, and end-of study, as well as any time that pregnancy was suspected. Subjects also could perform home pregnancy tests on an "as needed" basis and results from this testing were recorded by the investigator and collected along with information on concomitant contraceptive methods. In addition, subjects were asked to use a daily diary to assess bleeding patterns and intensity.

Comment: The Applicant did not define "as needed" for home pregnancy testing. However, in my clinical opinion, protocol-specified pregnancy screening in conjunction with the "as needed" home pregnancy testing appeared sufficient to detect on-treatment pregnancy occurrences for this IUS based on supportive pregnancy data available from the phase 2 study.

The primary efficacy endpoint for trial A52238 was the rate of unintended pregnancies during treatment. Efficacy analyses to determine the rate of unintended pregnancies were calculated using the Pearl Index (PI). The formula used for the efficacy analysis (PI calculations) was PI = x/E with x= number of on-treatment pregnancies and E= relevant exposure in 100 woman-years (one women-year is 13 28-day cycles or 365 days of relevant exposure). Relevant exposure (days or 28-day cycles) was equal to the total exposure (days or cycles) minus the following exposure time periods:

- All time periods where additional concomitant contraception or hormones were used for other reasons (data from the concomitant medication form filled out by the investigator at each visit)
- Time periods (in terms of calendar months as documented in the subject diary) of additional contraceptive method use
- The week before removal of Skyla because all subjects were instructed to use condoms for contraception starting at least 7 days prior to removal of LCS unless the removal takes place during the first days of menstruation

Efficacy analyses for Skyla were also performed using life table analysis (Kaplan-Meier method). Both analyses used the FAS population. Additional PI calculations using women-years was done as a sensitivity analysis, with back-up contraception subtracted in terms of 28 day cycles, as well as analyses by age-group, parity and body mass index (BMI). Finally, cumulative failure rates were calculated using the Kaplan-Meier method.

Secondary variables included assessment of menstrual bleeding from subject diaries and subset analyses of ovarian and cervical function (20 subjects in the Skyla treatment group), endometrial histology (31 subjects in the Skyla treatment group), pharmacokinetics of LNG (7 subjects in the Skyla treatment group), and bone mineral density analysis (102 subjects in the Skyla treatment group).

Comments:

1. *Assessments of bleeding patterns and intensities were recorded in subject-kept diaries. The clinical review team has determined that irregular and/or prolonged bleeding significantly affects treatment compliance, and therefore, the reviewer evaluated bleeding parameters as a secondary efficacy parameter. The bleeding profile for Skyla is discussed in a section entitled, "Other Efficacy Issues" below.*
2. *Other pharmacodynamic variables, including ovarian and cervical function markers and endometrial histology were collected in subsets of women in the phase 3 trial. These substudies were reviewed by the Medical Officer and CDTL. The results supported that Skyla has progestogenic actions on the endometrium and cervix, although systemic LNG levels do not appear to be sufficient to block ovulation. (Refer to Medical Officer's review dated December 27, 2012).*

<u>Key entry criteria for the phase 3 trial:</u>

- Age between 18 and 35 years old in good health and requesting contraception
- Has regular menstrual cycles (21-35 days in length without hormonal contraceptive use)
- Had acceptable uterine conditions for inserting the IUS

Women who were parous or nulliparous could be enrolled, although postpartum insertions were postponed until 6 weeks post delivery.

Comment: Eligibility criteria were similar to those of a previously approved IUS product (Mirena) and were acceptable to the clinical team.

Demographics from the phase 3 trial:

A brief summary of key demographics for Skyla treatment is outlined in the table below:

Table 1 – Summary of key demographic and baseline characteristics*:

Variable	**Skyla N=1432**
Ethnicity	
Caucasian	1141 (79.7%)
Black	75 (5.2%)
Hispanic	165 (11.5%)
Asian	11(0.8%)
Other	39 (2.7%)
Mean age in years (range)	27.2 (18-35)
North American Women (number of subjects)	632
Mean weight (kg)	68.7
Mean body mass index (kg/m^2)	25.32
Nulliparous	556 (38.8%)
One birth or more	876 (61.2%)
# of previous births (range)	1.1 (0-6)

*Adapted from Table 6 of the Medical Officer's review dated December 27, 2012.

The Medical Officer did not identify any concerns related to the demographics or baseline characteristics of subjects in the FAS population. The Medical Officer stated in his review that, "At the pre-IND meeting held April 4, 2006, the Division requested data for a minimum of 10,000 of 28-day equivalent cycles for the first year of use and that a total of 45% of these cycles should be from subjects in North America. The request for 10,000 cycles was successfully met by the Applicant." (See Medical Officer's review dated December 27, 2012). The CDTL reviewer also commented on the demographics of the trials in her review dated January 9, 2013, that, "The racial distribution of the population appears fairly representative of the general US population."

Comments: As previously noted, the Applicant provided a total of 4,500 cycles from women in the US. I agree with the Medical Officer and CDTL that the number of women recruited from the US (38%), although not reaching the requested 45%, was clinically acceptable for an IUS. I also agree with the CDTL that the demographics and baseline characteristics from these trials likely are similar to those in the target population in the US who would choose to use Skyla.

Subject disposition in the phase 3 trial:

For trial A52238, the FAS population consisted of 2884 subjects with 1432 receiving Skyla. The primary reason for discontinuation was adverse events, and other reasons included lost to follow-up, withdrawal of consent, and pregnancy.

The Medical Officer also evaluated discontinuations by parity related to concerns with use of Skyla in nulliparous subjects. His findings are summarized in the table below:

Table 2 – Summary of discontinuations by parity*:

Parity	**Reason for Discontinuation**	**Skyla N=1432**
Nulliparous subjects	**Total**	**556 (100%)**
	Withdrawal of consent or AE	155 (27.9%)
	Progestin side effect	21 (3.8%)
	Bleeding/amenorrhea	29 (5.2%)
Parous subjects	**Total**	**876 (100%)**
	Withdrawal of consent or AE	184 (21%)
	Progestin side effect	27 (3.1%)
	Bleeding/amenorrhea	39 (4.5%)
Total subjects	**Total**	**1432 (100%)**
	Withdrawal of consent or AE	339 (23.7%)
	Progestin side effect	48 (3.4%)
	Bleeding/amenorrhea	68 (4.7%)

*Adapted from Table 6 of the Medical Officer's review dated December 27, 2012.

Comments:

1. *The Medical Officer and Statistical Reviewers evaluated subject disposition and discontinuation rates for the phase 3 trial and did not identify any issues for the overall treatment group (See Medical Officer's review dated December 27, 2012 and Statistical Review dated December 4, 2012).*
2. *The Medical Officer did not identify any concerning differences in discontinuation rates between parous women and nulliparous women. I concur with the Medical Officer that the rates of discontinuation does not signal or show any trend that would suggest that nulliparous women would have a significantly different adverse event profile than parous women.*

Efficacy results from the phase 3 trial:

The statistical review for this NDA was based on the results from a single, uncontrolled, multinational phase 3 trial (A52238). The primary efficacy variable was the pregnancy rate. The primary efficacy analysis was based on the full analysis set (FAS), which included all subjects randomized and who had a successful LCS insertion. As previously mentioned, only women who received the Skyla (LCS12) IUS were evaluated for this submission.

As previously outlined, the primary efficacy endpoint was the pregnancy rate based on the Pearl Index (PI), which was calculated as PI = x/E. The variable x was the number of on-treatment pregnancies and E was the relevant exposure in 100 woman-years (one woman-year was 13 28-day cycles of relevant exposure). Any pregnancy between the day of insertion of Skyla and the seventh day after removal was included in the primary analysis. The upper and lower bounds of a 95% confidence interval (CI) were also calculated, using a Poisson distribution.

The Division asked that exposure time be expressed as 28-day cycles beginning from insertion and that cycles in which back-up contraception was used be nonevaluable; however, the Applicant had collected these data monthly, planning to calculate the Pearl Index based on women-years of exposure. Based on the Division's request, Pearl Index calculations were provided based on both exposure periods, and the Applicant developed an algorithm to attribute back-up to a specific 28-day cycle in cases in which the month in which such use occurred spanned two 28-day cycles. The week prior to removal was also excluded from evaluable exposure because subjects used condoms for contraception during that week.

The Division used a 28-day exposure time for the primary efficacy analysis for the 1swt year of use and therefore, the formula used by the Division was:

> PI = [100 x 13 28-day cycles per year) x number of pregnancies in time period)] / (total number of 28-day cycles excluding cycles where back-up contraception was used)

Comment: The review team considers 28-day cycle PI calculations over the first year as the optimal method to evaluate contraceptives. Although the actual PI calculated using 28-day cycles in this application are similar to the Applicant's which are calculated using exposure based on days, 28-day PI analyses allow cross-comparison to rates reported with other hormonal contraceptives.

The Division asked the Applicant to evaluate efficacy based on 12-month and cumulative 3-year unadjusted Pearl Indices for women 18-35. Cumulative pregnancy rates for Years 2 and 3 were also calculated using the Kaplan Meier method. The statistical reviewer stated in his December 2012 review regarding the Years 2 and 3 calculations that, "The cumulative pregnancy rates based on the PI definition are all less than those based on the Kaplan-Meier method at the end of the second and third years. However, the

corresponding 95% CIs overlap, suggesting there are no significant differences between the two estimates. This reviewer recommends using the Kaplan-Meier estimates for cumulative pregnancy rates beyond the first year because they take into account when, over the course of the study, a pregnancy occurred."

Comment: The Division had requested that a minimum of 200 women complete the full 3 years of treatment and that a minimum of 10,000 women cycles would be included in the primary efficacy analysis to support LCS12. This recommendation was met (See Statistical Review dated December 4, 2012).

Missing concomitant contraceptive use data were considered to be no concomitant use of contraception for this efficacy analysis. Missing information, such as a missing pregnancy, expulsion or removal date was imputed according to the Applicant's statistical analysis plan.

In the primary FAS population of 1432 women 18 to 35 years of age who received Skyla, a total of 10 pregnancies were considered by the clinical and statistical reviewers to be on-treatment pregnancies with Skyla. Of these pregnancies, 5 pregnancies were in Year 1, 3 pregnancies were in Year 2 and 2 pregnancies in Year 3. The Applicant used days of relevant exposure while the Statistical Reviewer focused on exposures of 28-day cycles to calculate the PI as is customary for the Division. The primary efficacy results of the statistical reviewer's analyses of Trial A52238 data using the Pearl Index calculations both by day (Applicant's analysis) and by 28-day cycle (Statistical Reviewer's analysis) from the first year of Skyla use are outlined in the table below:

Table 3: Pearl Index (PI) calculations from the first year use of Skyla*

	N	Total exposure	Back-up contraception exposure	Relevant exposure	Number of pregnancies	PI	95% CI
By Day**	1432	467280	22791	444489	5	0.411	(0.133, 0.958)
By Cycle***	1398	16519	756	15763	5	0.412	(0.134, 0.962)

*Adapted from Table 6 in the Statistical Review dated December 4, 2012
**Statistical Reviewer's analysis based on exposure days from dataset EXPOSUA
***Statistical Reviewer's analysis based on 28 day cycles from dataset EFFCYC

Comment: Efficacy results were similar using the Applicant's calculation based on exposure time in days and the Division's requested calculation based on 28-day cycle.

A supportive analysis was performed using a Kaplan-Meier method. This estimate was calculated by the Applicant using total exposure time based on days and 28 day cycles. In this calculation, subjects were censored at the time of drop out or study end. The censoring of subjects often result in the analysis from Kaplan-Meier method being different from PI calculations. Results of both the Kaplan Meier and PI analyses were multiplied by 100 so that the estimates could be compared to calculations performed using the Pearl Index. Results that compare the Kaplan-Meier method to the PI calculations by year are represented in the table below:

Table 4: Cumulative pregnancy rate from Kaplan-Meier estimate and PI*

	Cycle Analysis** N=1398 women		Day Analysis*** N=1432	
Timeframe	**Kaplan Meier Estimate Per 100 Women**	**PI Definition Estimate**	**Kaplan Meier Estimate Per 100 Women**	**PI Definition Estimate**
End Year 1	0.39 (0.16, 0.94)	0.412 (0.134, 0.962)	0.40 (0.17, 0.97)	0.411 (0.133, 0.958)
End Year 2	0.67 (0.33, 1.34)	0.359 (0.155, 0.708)	0.68 (0.34, 1.37)	0.358 (0.155, 0.706)
End Year 3	0.89 (0.48, 1.66)	0.330 (0.158, 0.607)	0.90 (0.48, 1.69)	0.327 (0.157, 0.601)

*Adapted from Table 7 in the Statistical Review dated December 4, 2012
**Statistical Reviewer's analysis based on 28 day cycles
***Statistical Reviewer's analysis based on exposure days

The Statistical Reviewer preferred use of the Kaplan-Meier analysis for representing cumulative pregnancy rates after the first year because the Kaplan-Meier estimates for cumulative pregnancy beyond the first year take into account when, over the course of the study, a pregnancy occurred. The Statistical and Medical Officer both concurred that the pregnancy rate analysis using the PI and Kaplan Meier for Trial A52238 reported comparable results for Year 1.

In summary, the efficacy results from the phase 3 trial demonstrate:

- The Pearl Index for the first year is 0.41 (95% CI 0.13 to 0.96).
- The corresponding Kaplan-Meier cumulative pregnancy rates per 100 women were similar to those calculated by PI, 0.39 (95% CI is 0.16 to 0.94) at the end of the first year, and was 0.89 (95% CI is 0.48 to 1.66) at the third year.

The Medical Officer concluded that, "The PI and Kaplan-Meier calculations based on data derived from primary Study A55238 strongly support the efficacy of LCS12 over the 3 year time period."

Statistical review of the primary efficacy results from the phase 3 trial:

The statistical review for this NDA was primarily based on the single uncontrolled phase 3 trial (A52238). The statistical reviewer stated that there were no statistical issues identified in this submission. In a review dated December 4, 2012, the statistical reviewer stated that, "From a statistical perspective, this single phase 3 study provides evidence demonstrating the efficacy of LCS12 (13.5 mg levonorgestrel contraceptive intrauterine system) for the prevention of pregnancy for up to 3 years in women 18 to 35 years of age. The Pearl Index at the end of the first year is 0.41 (95% CI is 0.13 to 0.96). Supportive evidence was based on the Kaplan-Meier cumulative pregnancy rate. The cumulative pregnancy rate per 100 women at the end of the first year is 0.39 (95% CI is 0.16 to 0.94) and at the end of the third year is 0.89 (95% CI is 0.48 to 1.66)."

Comment: I concur with the Statistical Reviewer that there are no outstanding statistical issues and that the efficacy data demonstrated the efficacy of Skyla for up to 3 years.

Other efficacy issues:

Statistical and clinical reviews of subgroup analysis of the Pearl Index for Skyla were explored in 4 difference subgroups: age, region, body mass index and parity. After calculating the PI results for the different subgroups, both review groups concluded that there was no evidence of decreased efficacy in the four subgroups compared to the results of the FAS population. The Medical Officer also evaluated the cumulative 3-year failure rate for women by age, parity and BMI and concluded that there were no relevant differences identified in these subgroups compared to the overall FAS population using Skyla.

The percentage of women in the US who were exposed to Skyla in the phase 3 trial (38%) was lower than that previously requested by the Division (45%). After evaluating the statistical reviewer's PI calculations analyzed by region, the CDTL concluded in her review dated January 9, 2013, that, "Unlike typical trends seen when reviewing contraceptive data from US and non-US (European and Canadian) populations, the Pearl Index in the US population is not higher than that in the non-US subjects. This is likely because factors that may be relevant to efficacy differences for other forms of hormonal contraception (greater weight and BMI in American women and improved compliance in non-US women) are not pertinent to this compliance-independent, locally-acting contraceptive."

Finally, a concern was raised about the success of IUS insertions in the phase 2 and 3 studies. In the pooled data containing both phase 2 and 3 trial subjects, Skyla insertion was attempted in 1672 subjects (100%). Of those subjects, 1617 had successful IUS insertion on the first attempt (96.7%). Of the 55 subjects who did not have a successful insertion (3.3%), 48 of the 55 subjects (92.3%) had a successful insertion on the second attempt. The reasons for the failed first insertion in the 55 Skyla subjects included:

- Malfunction of the inserter in 16 subjects (29.1%)
- IUS came out immediately after the insertion in 15 subjects (27.3%)
- Inserter became unsterile in 1 subject (1.8%)

Comments:

1. *I concur with the Medical Officer, Statistical Reviewer and CDTL that the subgroup analysis, although exploratory, do not identify a concerning trend regarding reduced efficacy in the 4 subgroups or in US women.*
2. *The Medical Officer believed that the number of failed first insertions as a result of IUS-related issues likely contributed to the Applicant's decision to change the IUS inserter after Trial A52238 was completed. The issues related to the new* (b) (4) *Inserter are discussed in the Safety section (8.0) in the subsection entitled, "Data on the new "* (b) (4) *inserter" below.*

Bleeding profile:

Analyses of the bleeding profile for Skyla was included in the efficacy assessment of Skyla and submitted by the Applicant using the agreed to definitions and analyses. Subjects completed a daily diary that recorded occurrence and intensity of bleeding or spotting. The following bleeding definitions were used:

- No: no vaginal bleeding
- Spotting: less than the subject's normal menses, with no need for sanitary protection (except panty liners)
- Light: less than the subject's normal menses, but requiring use of sanitary protection
- Normal: like the subject's normal menses
- Heavy: more than the subject's normal menses

A bleeding episode was defined as the number of days of bleeding that were preceded and followed by at least two bleeding-free days; a similar definition was utilized for a spotting episode. A bleeding- (or spotting-) free interval was defined as at least two days free of bleeding or spotting, and followed by at least one bleeding/spotting day. Amenorrhea was defined as the absence of bleeding throughout the reference period being assessed.

The Applicant provided bleeding data using a 90-day reference period and also provided the first year of bleeding data based on 28 day cycles as requested by the Division. The Applicant and the Division also agreed that it was not possible to divide the bleeding periods into "scheduled" and "unscheduled" because there are no hormone free intervals with Skyla use.

The Medical Officer and CDTL both noted that although frequent and irregular bleeding was reported with Skyla use, it appeared to decrease throughout treatment. In addition, the rate of amenorrhea increased over the treatment period. The clinical team looked at both the rate of discontinuation for bleeding (including amenorrhea) with Skyla as well as changes in bleeding patterns, intensity and amenorrhea rates. The CDTL's findings in subjects with at least one day of bleeding using a 28 day reference period is outlined in the table below:

Table 5: Bleeding days per 28-day cycle (First 12 cycles)*

Cycle	N	Mean (SD)	Min	Median	Max
1	1357	7.5 (5.7)	0	6.0	28
2	1347	5.5 (4.8)	0	5.0	28
3	1330	4.3 (4.1)	0	4.0	28
4	1307	3.7 (3.5)	0	3.0	24
5	1290	3.3 (3.4)	0	3.0	28
6	1275	3.1 (3.3)	0	3.0	28
7	1244	2.9 (3.2)	0	2.0	24
8	1216	2.6 (2.9)	0	2.0	22
9	1208	2.4 (3.0)	0	2.0	24
10	1182	2.4 (3.0)	0	1.0	22
11	1154	2.3 (2.7)	0	1.0	18
12	1144	2.2 (2.9)	0	1.0	28

*Adapted from Table 8 of the CDTL's review dated January 9, 2013

After review of the bleeding data above as well as data on spotting days during the first 12 cycles, the CDTL concluded that, "Undesirable categories, such as frequent, irregular and prolonged bleeding/spotting, also decreased throughout treatment.

Comment: The bleeding and spotting data both indicate that the number of bleeding and spotting days decreased during the first year of treatment. I concur with the CDTL that the bleeding profile from these data is acceptable as undesirable bleeding during use will decrease with time.

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate that Skyla (levonorgestrel intrauterine system) was effective for prevention of pregnancy for up to 3 years of use. The Medical Officer summarized efficacy results in his December 27, 2012, review as follows, "Proof of efficacy of LCS12 is based on data from the phase 3 clinical trial A52238. Based on the data from this study, the unadjusted PI of LCS12 for Year 1 is 0.41 (0.13, 0.96). The 3-Year unadjusted PI is 0.33 (0.16, 0.60). The cumulative pregnancy rate estimated by the Kaplan-Meier method per 100 women at the end of the first year is 0.39 (0.16, 0.94) and at the end of the third year is 0.89 (0.48, 1.66). These PIs provide adequate evidence to support the efficacy of LCS12 in the population targeted for marketing."

In her review dated, January 9, 2013, the CDTL further concluded that, "The contraceptive efficacy study conducted by the Applicant provides evidence of an acceptable level of efficacy for the LCS12 (Skyla) in the prevention of pregnancy. The PI showed no increase with successive years of treatment (0.41, 0.30, 0.25 in Years 1, 2 and 3, respectively), and the overall pregnancy rate over the three-year course of treatment by Kaplan-Meier analysis was 0.89."

I agree with the Medical Officer, Statistical Reviewer and CDTL that Skyla is efficacious for prevention of pregnancy for up to 3 years. I also agree with the CDTL that undesirable bleeding conditions decrease with time, which will likely result in acceptable compliance once Skyla is inserted. Therefore, I concur with the recommendations of the Medical Officer, Statistical Reviewer and Cross-Discipline Team Leader that no outstanding efficacy concerns for Skyla remain.

8. Safety

The safety database supporting the use of Skyla for the prevention of pregnancy for up to three years were derived from a pooled analysis of the phase 3 (A52238) and phase 2 (A46796) trials. The phase 3 trial randomized a total of 2884 women to treatment (1432 subjects to Skyla and 1452 to LCS16); the phase 2 trial randomized a total of 741 women to treatment (240 subjects to Skyla, 245 subjects to LCS16, and 256 to Mirena).

The pooled safety database consisted of a total of 3625 subjects who were exposed to an IUS in the clinical development program. Of these subjects:

- A total of 1672 subjects received Skyla
- A total of 1697 subjects received LCS16
- A total of 257 received Mirena (an approved IUS containing LNG)

Comments:

1. *The focus of the safety review for this application was primarily on those subjects in the phase 2 and 3 trials that received Skyla. However, safety information from all subjects who received an IUS also were reviewed, where pertinent to provide additional safety data.*
2. *The Division also requested all available data that utilized the to-be-marketed inserter. The Applicant submitted some data in the 4-month safety Update and then provided additional data from 3 ongoing phase 3 trials (Protocols 13362, 13363 and 14371) that utilized the new inserter. Safety data on the new inserter were analyzed and the findings are briefly summarized in the section entitled, "Data on the "* (b) (4) *inserter" below.*

Specifically, the duration of exposure to LCS12 from a safety perspective was as follows:

- In trial A52238, the mean treatment duration was 813 days or 2.23 women years (WY)
- In trial A46796, the mean treatment duration was 915 days or 2.51 WY
- In the pooled analysis of both trials, the mean treatment duration was 834 days or 2.29 WY

In his review dated December 27, 2012, the Medical Officer commented on the duration of exposure, and noted that, "The pooled (safety) data cover about 40,000 cycles of exposure."

Comment: I concur with the Medical Officer that the safety database contained sufficient cycle exposures for clinical evaluation.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events in the pooled analysis (Trials A52238 and A46796):

Deaths: There were no deaths among subjects treated with Skyla (LCS12).

There was one death in Study 52238 that was in a 20 year old woman who committed suicide. She had received the LCS16 IUS and was reported to have a history of depression and an eating disorder (Subject 210112).

Non-fatal Serious Adverse Events (SAE) in the pooled analysis (Trials A52238 and A46796

In the pooled analysis, SAEs were reported in 78 women (4.7%) in the Skyla (LCS12) cohort and 83 women (4.9%) in the LCS16 group. Selected potential serious adverse reactions (i.e. SAEs that might possibly related to study drug) are shown in the table below:

Table 6: Selected SAEs in the pooled database*:

Preferred Term	LCS12 N = 1,672		LCS16 N = 1,697		Mirena N = 256	
	n	%	n	%	n	%
Abdominal pain	5	0.3	4	0.2	1	0.4
Ovarian cyst, ovarian cysts ruptured, ovarian cyst torsion or hemorrhagic ovarian cyst	4	0.2	4	0.2	5	2.0
Ectopic pregnancy or ruptured ectopic pregnancy	4	0.2	9	0.5	0	
PID or tubo-ovarian abscess	3	0.2	5	0.3	1	0.4
Spontaneous abortion or incomplete spontaneous abortion or blighted ovum	3	0.2	3	0.2	0	
Completed suicide, suicide attempt or depression, suicidal	1	< 0.1	1	< 0.1	0	
Depression or affective disorder	1	< 0.1	2	0.1	0	
Anaphylactic reaction or drug hypersensitivity	1	< 0.1	1	< 0.1	0	
Adhesions, abdominal or pelvic	1	< 0.1	1	< 0.1	0	
Weight increased	1	< 0.1	0		0	
Deep vein thrombosis	1	< 0.1	0		0	
Hypertension	1	< 0.1	0		0	
Cervical dysplasia or cervix carcinoma stage 0	0		1	< 0.1	1	0.4
Vaginal perforation	0		1	< 0.1	0	
Device dislocation	0		1	< 0.1	0	
Vaginal hemorrhage	0		0		1	0.4

*Adapted from Table 11 of the CDTL's review dated January 9, 2013

The Medical Officer commented in his December 2012 review that, "Only a total of 10 of the SAEs were considered by the investigator to be related to use of LCS12. Although there were 4 ectopic pregnancies reported in the LCS12 group, one occurred in a patient with a bicornuate uterus and was not considered by the investigator to be drug-related."

Comment: Selected SAEs of specific concern, including pelvic inflammatory disease (PID) and ectopic pregnancies are discussed in later sections of this review.

Discontinuations for adverse events (AEs):

In the Skyla cohort, a total of 361 subjects who terminated prematurely from either the phase 2 or 3 trials (21.6%) did so due to an adverse event (AE) and 15 subjects (0.9%) discontinued due to an SAE, resulting in a total of 23% of discontinuations due to an AE. AEs that resulted in discontinuation are outlined in the table below:

Table 7: Adverse events (AEs) resulting in discontinuation (>2% in either group) in the pooled database*:

	Skyla N=1672 n(%)	**LCS16 N=1697 n(%)**
Any AE	361 (21.6)	337 (19.9)
Vaginal hemorrhage	55 (3.3)	50 (2.9)
Device expulsion, total	54 (3.2)**	51(3.0)**
Acne	45 (2.7)	33(1.9)
Pelvic pain	29(1.7)	39(2.3)

*Adapted from Table 31 of the Medical Officer's review dated December 27, 2012
** All device expulsions were counted, whether or not the expulsion was reported as an adverse event or not.

After review of the adverse events that led to IUS discontinuation, the Medical Officer concluded that, "Overall, the pattern of AEs that led to study drug discontinuation was comparable between the studies and between LCS treatment groups."

Comments:

1. *The Medical Officer and CDTL reviewed narratives of the reported death, non-fatal serious adverse events and discontinuations and concluded that there were no events that raised new safety concern or imbalances that indicated new safety trends or signals with Skyla. I concur with their assessments. In addition, it was reassuring that although adverse reactions of vaginal hemorrhage were identified, no serious adverse events of vaginal hemorrhage and no transfusions in subjects using Skyla were reported.*
2. *Only one partial perforation was reported in the pooled safety analysis, which was reported in a subject who received the LCS16 IUS. This subject had the IUS removed vaginally without complications. The reported expulsion rate and lack of identified perforation in this small database support that Skyla will have a similar profile to a current IUS product, Mirena, although this database is too small to determine what the incidence of these adverse events will be in the general population.*
3. *A more detailed discussion of other safety concerns, including IUS expulsion and ectopic pregnancy are addressed in a section below entitled, "Other Significant Safety Issues" in this review.*

Common Adverse Events

The Applicant pooled data from the phase 2 and phase 3 trials and provided rates of adverse events seen with Skyla (LCS12) and LCS16 using MedDRA version 14.0. The clinical review team discussed with the Applicant as to how the adverse events reported in the safety database would be presented in labeling. The Applicant and the Division agreed that the pooled safety data from the phase 2 and 3 trials would form the basis of labeling and that adverse reactions rather than adverse events would be labeled. Finally, the Division agreed that the Applicant could conduct a step-wise causality assessment to determine which of the AEs were drug-related for the purposes of labeling, rather than accepting the investigator's assessment. The final common adverse reactions from the pooled database will be included in labeling are outlined in the table below:

Table 8: (b) (4) adverse reactions (in at least 1% of Skyla users) in the pooled database*

System Organ Class	Adverse Reaction	Incidence (%) (N=1,672)
Psychiatric Disorders	Depression/ Depressed mood	3.8/0.5
Nervous System Disorders	Headache	12.4
	Migraine	2.3
Gastrointestinal Disorders	Abdominal pain/pelvic pain	12.7/6.2
	Nausea	5.5
Skin and Subcutaneous Tissue Disorders	Acne/Seborrhoea	13.6/1.4
	Alopecia	1.2
Reproductive System and Breast Disorders	(b) (4)	
	Vulvovaginitis	20.2
	Ovarian cyst[a]	13.2
	Dysmenorrhoea	8.6
	Breast pain/ discomfort	5.3/3.3
	Genital discharge	4.2
	Device expulsion (complete and partial)	3.2
	Upper genital tract infection	1.4

*Adapted from agreed to labeling finalized on January 9, 2013

The Medical Officer reviewed common AEs and drug-related AEs (as determined by the investigators). He stated that drug-related adverse reactions (as determined by either classification by the investigator in phase 2 or through voluntary reporting in phase 3)

occurred in 872 (52.2%) subjects in the Skyla group. The most common adverse reactions reported for Skyla included acne (12.3%), ovarian cyst (7.4%), dysmenorrhea (6.6%), headache (4.5%), vaginal hemorrhage (4.5%), pelvic pain (4.2%), abdominal pain (3.6%) and weight gain (3.6%). The CDTL also noted that women who reported an AE decreased over time during Skyla use. In the first year of treatment with Skyla, 74% had an AE, in the year 2 of treatment 52% had an adverse event and 49% had an AE in year 3 of treatment with Skyla.

In her CDTL review dated January 9, 2013, she commented that overall, AEs occurred more frequently in nulliparous women. AEs likely to have been drug-related that were more common in nulliparous women were acne (18% vs. 11%), dysmenorrhea (16% vs. 5%), ovarian cysts (14% vs. 11%), and abdominal pain (10% vs. 6%). Cervical dysplasia was also slightly more common (8% vs. 7%).

Comments:

1. *The Medical Officer also stated that drug related (i.e. progestin related) side effects were assessed at each visit in the phase 2 trial, but were voluntarily reported in the phase 3 trial. The difference in collection of AEs in the two trials led to some discrepancies in rates of some progestin adverse events between the two trials (such as acne and headache) and it was unclear whether these progestin adverse effects were over-reported in the phase 2 trial or underreported in the phase 3 trial. In the absence of a placebo-control in either trial, it is difficult to attribute adverse events to the progestin component (LNG). However, I do not believe that the voluntary collection of these progestin-associated AEs in the phase 3 trial resulted in significant under-reporting of these AEs.*
2. *Regarding the differences noted between parous and nulliparous adverse events in women, it appears that there are point estimate differences in reporting rates. Furthermore, although the point estimates differ, risks of serious adverse events and discontinuations appear to be similar and therefore the reported differences between these groups are of interest, but do not suggest that these represent unique safety signals or trends that would make Skyla unacceptable to nulliparous women.*
3. *In summary, from my perspective, the overall adverse reaction data in the table above does not demonstrate that there is a unique signal or trend for Skyla that precludes approval.*

Data on the new (b) (4) inserter

The phase 2 and 3 trials were conducted with an inserter identical to that used for an approved IUS, Mirena. During the review, the Division confirmed that the Applicant was planning on marketing Skyla with a different inserter (b) (4) from that used in the phase 2 and phase 3 trials. The Applicant stated that the (b) (4) inserter would (b) (4) . Although the Applicant asserted that the new inserter would not pose new safety concerns, Division requested the submission of safety data from three ongoing protocols that utilize the new (b) (4) inserter with the LCS12 IUS.

The Applicant provided data on expulsions, perforations, genital tract infections (including pelvic inflammatory disease) and other events of interest, including number of subjects with post-insertion ultrasound, in an amendment to the NDA dated August 10, 2012. The Division considered the amendment to be a major amendment, which extended the review clock by 3 months with a revised PDUFA date of January 9, 2013. A brief overview of selected safety data on the new inserter solely for the LCS12 device is outlined in the table below:

Table 9: Skyla (LCS12) insertions using the (b) (4) inserter*:

Protocol	Skyla subjects n	Nulliparous subjects n(%)	First insertion successful N(%)	Reasons for malfunction	Second insertion successful/failed
13362 (Phase 3 study comparing LCS12 to Yasmin – a combined oral contraceptive containing drosperinone)	279	216(77)	276(99)	-IUS did not release from tube -slider problem -strings stuck to scissors	3/0
13363 (Phase 3 study comparing LCS12 to Nexplanon (an implant containing etonorgestrel)	381	288(76)	375(98)	-uterine position -pain -expelled after insertion -device problem, stenotic os	3/1 (stenotic os)
14371 (Single arm phase 3 adolescent study)	303	296(98)	297(98)	-stenotic os -pain -expelled after insertion, strings -stuck to scissors	6/0

*Adapted from Table 44 of the Medical Officer's review dated December 27, 2012

After reviewing the safety data in the August amendment and comparing the insertion data from the pooled phase 2 and 3 trials, the Medical Officer reported that the rate of successful insertions is equivalent to that with the inserter used in the phase 3 trial and the rate of expulsion appeared to be lower. He concluded that, "The data submitted by Bayer from the ongoing trials are reassuring regarding the safety and efficacy of the (b) (4) inserter. The data do not provide any evidence that this inserter is less effective or less safe than the inserter used in the phase 2 and phase 3 clinical trials."

Comment: I concur with the conclusions of the Medical Officer that there are no outstanding issues with use of the new (b) (4) inserter.

Bone Mineral Density safety data

Bone mineral density (BMD) was measured at the lumbar spine using DEXA in a subgroup of 102 women who received the LCS12 device in the phase 3 trial. Baseline measurements were compared with measurements at Months 12, 24 and end of study or premature discontinuation. The Medical Officer stated in his review dated December 27, 2012, that in the Skyla treatment group, the mean BMD increase from baseline in lumbar spine was 0.02% and in the total hip, the mean BMD increase from baseline was 0.01%. The CDTL reviewer also evaluated the BMD data, and concluded in her review dated January 9, 2013, that, "Thus, it does not appear that LCS12 (Skyla) has any significant impact on BMD.

Comment: I concur with the clinical review team that Skyla does not appear to have any clinical impact on BMD.

Several safety issues, from a historical perspective, were identified during use of other IUS and IUD devices. These issues, among others, were evaluated during this review cycle by the clinical review team. These safety issues included the following:

1. Infections:

IUS insertion and use is known to be associated with risks of pelvic inflammatory disease (PID) and endometritis.

PID: The diagnosis of PID was based on the investigator's assessment. In the pooled database of phase 2 and phase 3 trial data, a total of 14 cases of PID were reported. In the phase 3 trial (A52238), a total of 12 adverse events of PID were reported and 2 adverse events of PID were reported in the phase 2 trial (A46976).

For Skyla, a total of 6 cases of PID were reported (0.4%), all occurring in the phase 3 trial (A52238). In trial A52238, cases of PID with Skyla use occurred during the following timeframe: 3 adverse events in Year 1, 1 in Year 2 and 2 in Year 3. A table of the pooled data of the adverse events of PID reported in the two trials is outlined below:

Table 10: Pelvic Inflammatory Disease (PID), pooled database*:

Trial	Skyla n=1672	LCS16 n=1697	Mirena n=256
A52238	6	6	0
A46796	0	1	1
Pooled safety data	6(0.4%)	7(0.4%)	1(0.4%)

*Adapted from Table 37 in the Medical Officer's review dated December 27, 2012

None of the 6 PID cases with LCS12 were serious, although one woman had a case of salpingo-oophoritis and all 6 women were reported to have recovered from their PID. The Medical Officer concluded in his December 2012 review that, "The incidence of PID with LCS12 (Skyla) is similar to the incidence reported with Mirena (see table above)."

Endometritis: The diagnosis of endometritis relied on the investigator's assessment. In the pooled database, 28 cases were reported over the three year treatment period. A total of 12 women developed endometritis in the LCS12 treatment arm (0.8%) compared to 1 case (0.4%) in the Mirena arm. These cases of endometritis with LCS12 occurred as follows: 11 in Year 1, 2 in Year 2 and 2 in Year 3.

None of these cases of endometritis were serious and none were suspected to have been pelvic inflammatory disease by the investigator. The Medical Officer noted that development of endometritis was more frequent in parous women and during the first year post- insertion.

C*omment: Intrauterine systems as a class may increase the risk of pelvic inflammatory disease and endometritis compared to non-IUS use. I concur with the Medical Officer that the rates of PID and endometritis were roughly similar among IUS treatment groups. The risks of PID and endometritis, as with all IUS products, will be conveyed in labeling so that practitioners can carefully evaluate any symptomatic patients for these infections.*

2. Uterine perforation or expulsion:

Expulsion: Total expulsion was confirmed if the IUS was observed in the vagina or was not visualized in the uterine cavity after the woman confirmed that her IUS has expelled. Partial expulsion was confirmed if the IUS could be identified in the cervical canal. Once total or partial expulsion was confirmed, the woman was discontinued from study treatment. A brief overview of the number of women who experienced expulsion with LCS12 or LCS16 is outlined in the table below

Table 11: IUS expulsion rates, pooled database*:

	Skyla N=1672 n(%)	**LCS16 N=1697 n(%)**
IUS partially expelled	25(1.5%)	32(1.9%)
IUS totally expelled	29(1.7%)	19(1.1%)
Total IUS expelled	54(3.2%)	51(3.0%)

*Adapted from Table 42 of the Medical Officer's review dated December 27, 2012

The Medical Officer commented in his December 2012 review regarding expulsions, "The 3.2% expulsion rate is similar to the rate of 4.9% reported in the Mirena label."

Perforation: Only one partial uterine perforation was reported in the phase 3 trial. The partial perforation was diagnosed by ultrasound during a Year 2 visit in a woman with the LCS16 device. The Medical Officer stated that the device was removed vaginally without complications.

Comment: Expulsion of an IUS is an expected complication and the reported rate with Skyla is acceptable compared to Mirena. Uterine perforation is also an expected,

although unusual complication of IUS. Based on the submitted data, the reported rate of perforation for Skyla would be expected to be similar to other approved IUS.

3. Risk of ectopic pregnancy/Return to fertility:

There were a total of 4 ectopic pregnancies with Skyla use in the pooled safety database of the phase 2 and 3 trials (0.2%). The Medical Officer summarized the ectopic pregnancy rates for Skyla in the table below:

Table 12: Ectopic pregnancy analysis, pooled database*:

	Skyla N=1672 n(%)	
	Number of ectopic pregnancies	**Pearl Index**
Phase 3 trial	3	0.10
Phase 2 trial	1	0.17
Pooled phase 2 and 3 trials	4	0.11

*Adapted from Table 42 of the Medical Officer's review dated December 27, 2012

A supportive analysis from the Statistical Reviewer of the ectopic pregnancy rate with Skyla by timeframe showed that the PI at Year 1 was 0.14 (95% CI upper bound of 0.50 and over three years was 0.11 (upper bound 0.28). The outcomes of the ectopic pregnancies in the Skyla arm included one spontaneous abortion, two salpingectomies and one laparoscopic removal of the ectopic pregnancy. No ruptured ectopics were identified. In her review dated January 9, 2013, the CDTL commented on the risk of ectopic pregnancy that, "The risk of ectopic pregnancy with IUDs has been well-characterized; while IUDs prevent both intrauterine and ectopic pregnancy the proportion of pregnancies that are ectopic is likely to be higher among women using an IUD. However, as shown by the Pearl Indices, the absolute risk of ectopic pregnancy is quite low."

Specific EMA concerns regarding use of Skyla in nulliparous women: The Applicant received a preliminary report from the Swedish health authority on March 2, 2012, which noted that the product was considered nonapprovable due to concerns about risk of ectopic pregnancy in nulliparous women. A concern was raised that the potential adverse impact of an ectopic pregnancy on future fertility might be particularly devastating to nulliparous women, and that nulliparous women might have more difficulty identifying early signs of pregnancy due to the Skyla's effect to decrease menstrual bleeding. The Applicant countered that the actual risk of ectopic pregnancy overall in Skyla users was very low, and that any cross-study comparisons to Mirena data were not warranted. In addition, the Applicant noted that with today's earlier diagnosis of ectopic pregnancy, medical management and avoidance of complications that may impair fertility are more likely outcomes.

As a result of the concern of ectopic pregnancy in nulliparous women, the clinical and statistical review teams evaluated the ectopic pregnancy rates by parity. These rates are outlined in the table below:

Table 13: Ectopic pregnancy rates by parity for Skyla, pooled database*

Time	Parity	# of Pregnancies	Pearl Index (95% CI)	# of Pregnancies	Pearl Index (95% CI)
		Study A52238		Pooled Data	
Year 1	Nulliparous	1	0.23 (0.01, 1.25)	1	0.20 (0.005, 1.14)
	Parous	1	0.13 (0.003, 0.73)	1	0.11 (0.003, 0.59)
		# of Pregnancies	Kaplan-Meier estimate per 100 women (95% CI)	# of Pregnacies	Kaplan-Meier estimate per 100 women (95% CI)
Cumulative 3-year	Nulliparous	2	0.43 (0.11, 1.74)	2	0.40 (0.10, 1.60)
	Parous	1	0.13 (0.02, 0.93)	2	0.23 (0.06, 0.92)

*Adapted from Table 18 of the statistical review dated December 4, 2012

After review of the above safety data on ectopic pregnancies, the Medical Officer stated that, "The confidence intervals of the calculated PIs overlap, so no conclusions can be made regarding relative risks relating to parity." The CDTL also evaluated the risk in parous and nulliparous women based on the above calculations and additional calculations using Kaplan Meier estimates and agreed with the Medical Officer that it is not possible from these data to determine if there is a true difference in risk between the two treated groups.

From a regulatory perspective, on December 6, 2012, the Applicant notified the Division that issues had been resolved with the EMA member state and approval granted (Skyla is known as Jaydess in Europe) on December 4, 2012. The Summary of Product Characteristics was provided and was similar to US proposed labeling, with the exception of a statement under "Special Warnings and Precautions for Use" that "Because an ectopic pregnancy may impact future fertility the benefits and risks of using Jaydess should be carefully evaluated, in particular for nulliparous women. Jaydess is not first choice for contraception in nulliparous women as clinical experience is limited."

Another concern with use of this product in women is return to fertility, which would be especially important in nulliparous women. The Applicant provided limited data from the phase 2 trial A46796 on return-to-fertility in treated subjects. Subjects were contacted if they became pregnant within 3 months or 12 months of discontinuing the study. Of the 7 subjects who discontinued Skyla to become pregnant, 6 conceived within 12 months of discontinuing therapy.

Comments:

1. *I concur with the clinical review team that the risk of an ectopic pregnancy for the overall population is increased with use of any IUS and that the risk of an ectopic pregnancy for a woman using Skyla is low (<0.5%). In my opinion, the risk of an*

ectopic pregnancy with Skyla is similar to the risks reported for the approved Mirena IUS.

2. *I also agree with the Medical Officer and CDTL that although the risk in nulliparous women appears to be higher than parous women, the event rates are very low (n=1 or 2 in the various comparison groups) and the CI around the point estimates overlap and it is not possible to determine if there is a true difference. As the overall risk of ectopic pregnancies in either nulliparous or parous women is very low (< 0.5%) and the absolute risk of ectopic pregnancies in nulliparous women is also relatively small, I agree with the clinical review team that there is no reason to limit use of Skyla solely to parous women and that this risk of ectopic pregnancy can be adequately communicated in labeling.*
3. *I also concur with the Medical Officer that the return-to-fertility data are very limited. However, it does not appear that women who wished to become pregnant have a significant delay in return to fertility once Skyla is removed.*

4. 120-Day Safety Update/Postmarketing data summary:

A 120-day Safety Update Report was submitted on April 5, 2012, covering the period from September 1, 2011 through January 31, 2012. The safety update included information about five ongoing LCS clinical trials, preliminary feedback related to the European submission (see Section 8.8.1) and information from the Mirena PSUR and 2011 Annual Report. In the Safety Update and the amendment to the Safety Update, the Applicant did not identify any new safety concerns for Skyla.

There are no postmarketing data for Skyla as this product is not marketed in any country to date. The Applicant did submit a Periodic Safety Report Update (PSUR) covering a period from September 1, 2011, to January 31, 2012, with additional data on 5 ongoing studies with LCS12, 3 of which utilize the new (b) (4) inserter. This PSUR also described that a marketing application had been submitted to Europe in parallel with this NDA submission.

On March 2, 2012, the Applicant was notified by the Swedish health authority (the reference member state for the EU) that Skyla (referred to under the tradename Jaydess in the EMA application) was not approvable due to the risk of ectopic pregnancy especially in nulliparous women. Skyla (under the tradename Jaydess) has subsequently been approved in Sweden with a "Special Warnings and Precautions for Use" statement. The Applicant is planning to (b) (4) The Applicant also agreed to not specifically target nulliparous patients for LCS12 and added that this product would not be first line contraception for nulliparous women in the WARNINGS section of labeling.

Comments:

1. *The Medical Officer concluded in his December 27, 2012 review that, The submitted PSUR covering the period from September 1, 2011 to January 31, 2012 does not document any unexpected safety findings for LCS12 (Skyla)." The CDTL and I concur with this assessment.*
2. *I do not observe a concerning trend or signal from the clinical trial database that indicates that Skyla use increases the risk of ectopic pregnancy in the overall reproductive age population. Although there is a theoretical risk that a lower LNG dose in an IUS could increase an individual risk of pregnancy, and therefore, possibly ectopic pregnancy, the actual risk of an ectopic pregnancy in the pooled analysis was very low (0.2%) and the PIs for ectopic pregnancies from the pooled data were small with overlapping CIs for parous and nulliparous women. Therefore, I, as well as the CDTL, do not share the EU's concerns regarding risks of ectopic pregnancy with this IUS product.*

Based on the data from the 2 clinical trials, I concur with the clinical review team's decision to approve Skyla for use in both parous and nulliparous women.

Safety summary:

The safety database for Skyla provided adequate patient exposure and supports approval for women who need prevention of pregnancy for up to 3 years. The majority of the safety issues identified in the pooled safety data for Skyla are sufficiently addressed in labeling, including ectopic pregnancies, perforations, expulsions, and infections (i.e. endometritis, pelvic inflammatory disease). In addition, additional safety data submitted by the Applicant to support use of the new (b) (4) inserter was determined by the clinical review team to be acceptable for Approval.

No concerning laboratory findings, vital sign changes or device concerns were identified by the Medical Officer. In summary, the Medical Officer concluded the following on the safety database for Skyla in his review dated December 27, 2012: "The safety profile of LCS12 (Skyla) did not raise any specific safety concerns."

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's recommendation that the safety profile of Skyla was acceptable in her CDTL review (dated January 9, 2013) and stated, "The safety data on the large proportion of nulliparous women (about one-third of safety cycles) enrolled in the phase 2 and 3 studies do not suggest a unique or unacceptable safety signal when Skyla is used in women without regard to parity. Safety data obtained from ongoing studies using the new (b) (4) inserter do not suggest reason for concern associated with use of this inserter in the to-be-marketed product."

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA.

9. Advisory Committee Meeting

An Advisory Committee was not recommended by any of the review teams because this was not an NME and there were no outstanding efficacy or safety issues that were identified during development or the review cycle that required input from the committee.

Comment: I concur with the recommendations of the review teams that there were no outstanding efficacy or safety concerns that required an Advisory Committee meeting.

10. Pediatrics

The Applicant requested a partial waiver from PREA for pediatric studies in premenarchal patients. The Applicant also requested use of extrapolated data from adults for use in [redacted] (b) (4) females [redacted] (b) (4) to fulfill PREA requirements in post-menarchal pediatric patients.

The Pediatric Review Committee (PeRC) agreed with the Applicant's requests and granted a partial waiver in premenarchal girls and data extrapolation for post-pubertal adolescents. Therefore, no PREA postmarketing studies will be required for Skyla.

11. Other Relevant Regulatory Issues

Center for Devices and Radiologic Health (CDRH):

CDRH was consulted to evaluate the functionality of the to-be-marketed inserter and other aspects of the device. Several consults were sent to CDRH on the following topics:

- Functionality of the inserter
- Information pertaining to MRI labeling, because of the silver included in the IUS
- Evaluation of adequacy of the device manufacturing process

The CDRH review teams provided:

1) An addendum to their review on the functionality of the inserter on October 18, 2012 and stated that the information provided was sufficient to demonstrate adequate performance and stability data for the inserter.
2) Evaluation of MRI induced force, torque and artifact testing and labeling with Skyla use. After review, the CDRH reviewer concluded that the testing for force, torque and artifact was acceptable and also provided labeling comments on MRI safety for women who use Skyla (See CDRH memos entered on November 7, 2012 and December 21, 2012.
3) A determination was made in a review from the CDRH Office of Compliance dated June 13, 2012 that a preapproval inspection of the device manufacturing process in Finland was necessary. This inspection was completed on October 2, 2012 and a final report of this site was classified as NAI by the CDRH Compliance branch (See PMA EIR Review Memorandum dated December 5, 2012 and entered on December 19, 2012).

The ONDQA review team noted in their January 7, 2013, addendum that the Office of Compliance had issued a final "Acceptable" recommendation for all facilities involved in the Skyla NDA, including those involved with manufacturing the device and inserter.

Comment: I concur that there are no outstanding issues related to the device or the new inserter.

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) on December 6, 2012, and found it to be acceptable with several recommended changes. The Division discussed several of the recommendations with DMPP, and after minor editing, the agreed to recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information (PI) and the Patient Package Insert (PPI). OPDP completed their review of PI and carton/container on December 13, 2012, and review of the PPI on December 12, 2012. The Division discussed several of the recommendations with OPDP, and after editing, the agreed to recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI conducted inspections of four clinical sites (Drs. Seid, Aqua, Rinne and Jarvi) who each contributed a significant number of patients in the pivotal phase 3 trial. Dr. Seid's site, Dr. Rinne's site and Dr. Jarvi's site all received NAI evaluations (See OSI reviews dated November 16, 2012, November 1, 2012, November 16, 2012, respectively), Dr. Aqua's site received a VAI classification, however, the inspector stated in her note to the review division that, "Not withstanding the above observations, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication."(See DSI letter dated December 7, 2012)

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team provided a final review on November 18, 2012, of carton and container labels for areas of vulnerability that could lead to medication errors. DMEPA's recommendations were implemented.

DMEPA also assessed the proposed tradename "Skyla" on June 12, 2012, and reassessed the name on October 23, 2012, and found it acceptable.

Financial Disclosures:

The clinical review team reported that all investigators that had participated in the conduct of the study filed a Financial Disclosure form. The clinical reviewer identified two investigators that had financial arrangements that could potentially have biased the study (b) (6) After review, the clinical reviewer concluded that, "The potential for (b) (6) financial arrangements to bias the study finding is minimal as their sites recruited (b) (6)

Comment: I concur with the clinical reviewer that any potential bias in the pivotal phase 3 study based on the contributions of these investigators who had significant financial arrangements with the Applicant is highly unlikely given the minimal contribution of these sites to the total study population.

Study Endpoints and Labeling Development Team (SEALD):

The SEALD review team reviewed the label in a review dated January 7, 2013, and provided recommendations. These recommendations were implemented.

12. Labeling

Labeling discussions are complete. Labeling for Skyla (levonorgestrel releasing intrauterine system) was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Patient Package Insert and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Patient Package Insert and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was reviewed by the Study Endpoints and Label Development (SEALD) Team. A revised version of the label containing SEALD's requests was sent to the Applicant. The Applicant accepted the requested edits from SEALD.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that the Skyla (LCS12/levonorgestrel releasing intrauterine system) application should receive an Approval action.

Risk Benefit Assessment:

Data from the single pivotal phase 3 trial (A52238) provided adequate evidence of efficacy of Skyla (LCS12) and contained sufficient patient exposure to support approval for prevention of pregnancy in women 18 to 35 for up to 3 years. This efficacy determination was based on an acceptable Pearl Index for 1 year and supportive evidence from a Kaplan Meier analysis for up to three years.

The safety database from the supportive phase 2 (A46796) and phase 3 (A52238) trials did not identify any new safety issues or trends with Skyla use over the three year treatment period that precluded approval. The database from these two trials contained an adequate number of cycles of exposure to Skyla and demonstrated an acceptable safety profile for this IUS product that could be adequately labeled for safe use. In addition, data from ongoing studies using the new (b) (4) inserter did not suggest any concerns associated with use of this inserter with the to-be-marketed product. Finally, safety data do not convincingly indicate that the risk of ectopic pregnancy in nulliparous women is higher than parous women. However, the overall risk in both populations, regardless of parity is low (<0.5%), and therefore acceptable from my clinical perspective.

Therefore, in my opinion, the risk/benefit assessment favors approval of Skyla for prevention of pregnancy.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for this product.
- The review teams also determined that no new postmarketing requirements or commitments are necessary for this product.

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
01/09/2013