CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 24, 2008
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-262
Applicant	Duramed Research, Inc.
Date of Submission	December 26, 2007
PDUFA Goal Date	October 24, 2008
Proprietary Name / Established (USAN) names	LoSeasonique™ Levonorgestrel (LNG) + Ethinyl Estradiol (EE)
Dosage forms / Strength	Tablet; 100 µg LNG/20 µg EE x 84 days; 10 µg EE x 7 days
Proposed Indication(s)	Prevention of pregnancy
Recommended:	***Approval***

1. Introduction

This NDA seeks marketing approval for LoSeasonique (hereinafter referred to as Lo Seasonique), a lower dose variant of an approved combined oral contraceptive (OC), Seasonique®. Lo Seasonique contains 100 µg of levonorgestrel (LNG) and 20 µg of ethinyl estradiol (EE) in the "active" pills taken continuously for 84 days, and 10 µg of EE taken for seven days at the end of the 84 day active treatment period. In contrast, Seasonique contains 150 µg of LNG and 30 µg of EE in the active pills. Given the proportional decrease in dose of both steroid hormones as compared to the approved product, the Applicant submitted an acceptable safety and efficacy database comprising a full year clinical trial with over 20,000 28-day cycles and over 1,200 women who completed one year of exposure. The Pearl Index obtained in this trial is **2.74,** marginally higher than the Pearl Index previously associated with a contraceptive product approved by the Division of Reproductive and Urologic Products (DRUP). This is judged to be acceptable provided clear labeling is agreed upon by the Applicant. The product appears to work equally well in women of low/normal and higher weight. The safety profile is typical of that for a hormonal contraceptive and does not suggest any unexpected safety signals.

2. Background

2.1 DESCRIPTION OF PRODUCT

Lo Seasonique is a combined estrogen/progestin oral contraceptive (OC) administered over a 91-day cycle, comprising 84 active tablets of 100 µg of LNG/20 µg of EE, followed by seven tablets containing 10 µg of EE. Levonorgestrel is a gonane derivative of 19-nortestosterone, first approved in the U.S. in 1982, in Nordette (NDA 18-668). Currently, there are more than a dozen approved OCs containing LNG in the U.S. Lo Seasonique has not been approved for marketing in any foreign country.

The first extended cycle OC regimen was Seasonale®, approved in 2003 under NDA 21-544. Seasonale contains 150 µg of LNG and 30 µg of EE, which is given for 84 days, followed by seven days of placebo. Subsequently, Seasonique® was approved in 2006 (NDA 21-840), providing the same doses of estrogen and progestin, but replacing the seven placebo tablets with seven tablets of 10 µg of EE. A lower dose version of Seasonale (Seasonale Lo, containing 100 µg of LNG/20 µg of EE plus seven days of placebo) was the subject of an NDA (21-921) submitted in 2006. This NDA was withdrawn (b) (4)

(b) (4)

Lo Seasonique now presents the same low dose proposed in Seasonale Lo, with the additional seven days of EE-alone tablets used in the Seasonique regimen. The combination doses found in Lo Seasonique are also in the approved products Levlite® and its AB2-rated generic, Lessina®, approved on May 20, 2002 under ANDA 75-803. Lessina is owned by Duramed, the Applicant for the current NDA. Lo Seasonique is identical with regard to suppliers, formulation, manufacturing process, manufacturing sites and packaging components to Lessina.

2.2 REGULATORY HISTORY

The protocol for Study PSE-309 was submitted to DRUP on June 6, 2005. Comments on the Statistical Analysis Plan were conveyed to the Sponsor on October 16, 2007, including requests to:

- Calculate the Pearl Index using 28-day cycle intervals as well as 91-day cycle intervals
- Calculate the Pearl Index using all complete cycles in which no other birth control method, including condoms, was used
- Calculate the Pearl Index using "on drug" pregnancies defined as those occurring within 14 days of the last dose of study drug (this is clarified by the Division to refer to 14 days after the last dose of combination drug)

No pre-NDA meeting was requested. The Applicant responded on December 20, 2007 to the statistical comments by agreeing to all requests. The data analysis and final study report preparation had been concluded before the comments were received; therefore, the study report provided data based on exclusion of cycles in which another birth control method was used, exclusive of condoms. However, the Applicant provided the requested analysis in a separate analysis and dataset.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ronald Orleans, stated in his review, dated October 23, 2008:

> *Approval of Lo Seasonique™ for prevention of pregnancy is recommended based on Duramed Research, Inc. (the Applicant) having demonstrated an acceptable Pearl Index and an acceptable safety profile for this product.*

Team Leader Comment

I concur with Dr. Orleans' recommendation.

3. CMC/Device

The primary Chemistry Reviewer, Bogdan Kurtyka, Ph.D., made the following recommendations in his review dated September 15, 2008:

> *This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Facilities are in compliance with cGMP. Labels/labeling have required information. Therefore, from a CMC perspective, this NDA is recommended for "Approval."*

3.1 General product quality considerations

The CMC information relevant to LNG and EE drug substances was based on references to the appropriate Drug Master Files (DMFs) and was deemed adequate. The drug product consists of combined LNG/EE tablets, which is a low-strength version of the approved drug Seasonique, and of EE-alone tablets, which is identical to the single component tablet of Seasonique. The container/closure system is identical to that used in the approved products Seasonique (NDA 21-840) and Seasonale (NDA 21-544). The Applicant provided up to 24 months of stability data on both the LNG/EE and EE-alone tablets packaged using the to-be-marketed container/closure system. The Applicant requested 18 months expiry for the to-be-marketed product, which the CMC reviewer granted.

The Applicant follows the drug substance specifications of the (b) (4) for EE, and follows the specifications of the (b) (4) for LNG. The analytic procedures used for release and stability studies were found to be adequate.

3.2 Facilities review/inspection

The two (b) (4) manufacturing sites (b) (4) for LNG and the two (b) (4) drug substance manufacturing sites (b) (4) for EE were found to be acceptable as of April 14, 2008.

3.3 Other notable issues (resolved or outstanding)

A microbiology consult was requested, which identified a deficiency in that the Applicant did not test the drug product for microbial load at release. This was conveyed to the Applicant, who responded with an amendment on July 11, 2008, providing validated test methods and microbial limits specifications. This was acceptable to the microbiology reviewer (see Section 6) and was deemed adequate by the CMC reviewer.

4. Nonclinical Pharmacology/Toxicology

The components of Lo Seasonique, LNG and EE, have been marketed in a number of products for many years. No nonclinical studies were submitted in the NDA; safety was supported by reference to approved products containing the same steroid hormones at equal or higher levels than those used in Lo Seasonique. The primary Toxicology Reviewer, Alex Jordan, Ph.D., made the following recommendations in his review dated January 28, 2008:

> *Recommendations on approvability: Pharmacology recommends approval of Lo Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol.*
>
> *Recommendations for nonclinical studies: None*
>
> *Recommendations on labeling: Labeling will be similar to Seasonique approved under NDA 21-840, which has the same formulation composition and dosing schedule and is used for a similar indication.*

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology Reviewer, Chongwoo Yu, Ph.D., stated the following in his review dated May 20, 2008:

> *The overall Clinical Pharmacology data submitted to support this NDA are acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language.*

No phase 4 commitments were recommended.

Dr. Yu has noted that the Lo Seasonique formulation for the combination tablets used in the clinical trial and to be marketed is that of Lessina®, the AB2-rated generic of Levlite®. The sole difference between Lo Seasonique and Lessina is a change in color of the nonfunctional film coating. This is classified as a Level 1 change, unlikely to affect drug performance. The EE tablet formulation is identical to the marketed Seasonique formulation. The manufacturing process for Lo Seasonique is also the same as that for Lessina. The NDA submission for Lo Seasonique included the bioequivalence (BE) study submitted in support of the ANDA approval for Lessina (ANDA 75-803), which was previously reviewed by the Office of Generic Drugs. This is Study 99027, which compared the 100 µg LNG/20 µg EE combination tablets of Levlite and Lessina. The Applicant is relying on the distribution, metabolism and excretion profiles of Lessina and Seasonique, and provided single dose pharmacokinetic (PK) data in the BE study, which characterized the absorption profile. Table 1 will be included in the labeling for Lo Seasonique.

Table 1 Mean (SD) Single Dose PK Parameters of Lo Seasonique

	$AUC_{0-\infty}$	C_{max}	T_{max}	$T_{½}$
Levonorgestrel	76.5 ± 24.9 ng*hr/mL	6.0 ± 1.6 ng/mL	1.6 ± 0.6 hours	28.5 ± 8.7 hours
Ethinyl estradiol	1335.8 ± 365.3 pg*hr/mL	122.8 ± 39.5 pg/mL	1.8 ± 0.7 hours	17.5 ± 7.4 hours

$AUC_{0-\infty}$ = area under the drug concentration curve from time 0 to infinity
C_{max} = maximum concentration
T_{max} = time to maximum concentration
Source: Lo Seasonique proposed label, table prepared by Dr. Yu

Drug interaction labeling for oral contraceptives generally relies on class labeling. No drug-drug interaction study was conducted with Lo Seasonique. The effect of food on Lo Seasonique bioavailability has not been evaluated and this is noted in labeling. The effects of renal or hepatic impairment were not assessed, but Dr. Yu recommends inclusion of a statement that steroid hormones may be poorly metabolized in patients with impaired liver function. This is consistent with class labeling for oral contraceptives. The effect of race on Lo Seasonique PK was not characterized and this fact will be labeled.

6. Clinical Microbiology

According to the primary CMC Reviewer, Dr. Kurtyka, the original Application did not contain a discussion of microbiological properties. The Applicant subsequently justified the absence of microbial testing of the drug product in an Amendment dated June 6, 2008. The Applicant stated in the Amendment that the microbiological safety of the drug product was

assured because water level was controlled at multiple stages of the drug production to prevent microbial growth. Dr. Kurtyka concluded in his review:

> *Two very similar formulations (Seasonale and Seasonique) were approved without microbial limit tests and marketed.....The justification presented above is ADEQUATE and warrants the absence of microbial testing.*

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

Clinical data submitted in this NDA include a single phase 3 safety and efficacy trial, Study DR-PSE-309, and the BE study (Study 99027) used to support bioequivalence of the generic product Lessina (identical to the Lo Seasonique formulation used in the clinical trial and to be marketed) to the approved product Levlite. The utility of the BE study in this NDA was primarily to provide PK data for labeling.

Study DR-PSE-309 was a 12-month, multicenter, open-label trial that enrolled 2,185 women aged 18-41 years, providing efficacy data based on 17,068 28-day cycles in which no other birth control method was used, and safety data based on 20,937 28-day cycles. Inclusion and exclusion criteria are detailed in Dr. Orleans' review, and were consistent with those generally employed in OC trials. Notably, the Applicant did not exclude subjects on the basis of weight or body mass index (BMI).

Team Leader Comment

The phase 3 trial met the Division's requirements regarding cycles of exposure for an efficacy trial evaluating a dose reduction for an approved OC.

7.2 DEMOGRAPHICS

Table 2 shows the demographics of the safety population.

Table 2 Demographic characteristics: All-Treated Subjects (Safety population)

	DP3-Lo 84/10 (N=2185)
Race	
African-American	256 (11.7%)
Asian	36 (1.6%)
Caucasian	1627 (74.5%)
Hispanic	218 (10.0%)
Other	48 (2.2%)
Age (yrs)	
Mean (Std)	27.7 (5.80)
Median	26.7
(Min, Max)	(18.0, 41.0)
Weight (lbs)	
Mean (Std)	158.7 (41.26)
Median	148.0
(Min, Max)	(87.0, 381.0)
Body Mass Index (kg/m^2) [1]	
Mean (Std)	26.7 (6.65)
Median	25.0
(Min, Max)	(15.7, 62.8)
Systolic Blood Pressure (mmHg)	
Mean (Std)	111.7 (10.48)
Median	110.0
(Min, Max)	(78.0, 143.0)
Diastolic Blood Pressure (mmHg)	
Mean (Std)	71.0 (7.88)
Median	70.0
(Min, Max)	(42.0, 98.0)
Heart Rate (beat/min)	
Mean (Std)	73.3 (9.32)
Median	72.0
(Min, Max)	(40.0, 128.0)
Smoking Status	
Current Smoker	398 (18.2%)
Past Smoker	388 (17.8%)
Non-Smoker	1399 (64.0%)
OC Use History	
Unknown[2]	5 (0.2%)
Continuous User	1297 (59.4%)
Prior User	644 (29.5%)
Fresh-Start	239 (10.9%)

[1]Two subjects (23/2372 and 25/2548) did not provide data for the BMI calculation.
[2]Subjects 19/1944, 30/3009, 30/3016, 30/3022 and 56/5665 had no OC history

Source: Applicant's Table 7, page 61 of final study report.

Team Leader Comments

- **The racial distribution of the population appears fairly representative of the general population.**
- **The mean BMI (26.7 kg/m^2) is similar to that in recent (1999-2002) NHANES data for women aged 20-29 (26.5) and aged 30-39 (27.5), suggesting that this population is**

also representative of the general population with respect to BMI.[1]

- **Among "all-treated subjects," 11% were new users of OCs, while 59% were continuous users and 30% had used OCs at some previous time. These proportions were similar when considering the primary efficacy population.**

7.3 DISPOSITION OF SUBJECTS

A total of 2,968 women were screened for the study, with 2,235 enrolled. The vast majority of these, 2,185 women, took at least one dose of study drug (safety population), and 1,950 completed one 91-day cycle of drug use (defined as completing all 84 days of combination tablets), comprising the intent-to-treat (ITT) population. Review of the Applicant's Table 16.2.1 in Appendix 16.2 provides data that are slightly inconsistent with the Applicant's statements about rate and reasons for discontinuation. Per my calculations based on Table 16.2.1, about 56% completed the study. A total of 952 women from the safety population discontinued prematurely for the reasons described in Table 3.

Team Leader Comments

- **The reason for the numerical discrepancy in withdrawals is not entirely clear. There are seven more subjects who were lost to follow-up; six more who discontinued for "other" reasons, and one more each discontinuing due to patient request, noncompliance and pregnancy, for a total of 16 additional subjects who discontinued according to Table 16.2.1, as compared to the Applicant's Table 3.**

Table 3 Reasons for Discontinuation (Safety Cohort)

	Applicant's N (%of safety population)	Reviewer's N (%of safety population)
Safety Population	2,185 (100)	2,185 (100)
Completed study	1,249 (57.2)	1,233 (56.4)
Did not complete	936 (42.8)	952 (43.6)
Reason for Discontinuation		
Lost to follow-up	304 (13.9)	311 (14.2)
Adverse event	253 (11.6)	253 (11.6)
Patient request for withdrawal	225 (10.3)	226 (10.3)
Noncompliance with protocol	81 (3.7)	82 (3.8)
Pregnant	34 (1.6)	35 (1.6)
Other	22 (1.0)	28 (1.3)
Did not meet protocol requirements	14 (0.6)	14 (0.6)
Investigator discretion	3 (0.1)	3 (0.1)

Based on Applicant's Table 4, page 55 and Table 16.2.1, pp 1-95, Appendix 16.2, of final study report

[1] Ogden, CL et al; Mean Body Weight, Height, and Body Mass Index, United States 1960-2002 http://usgovinfo.about.com/gi/dynamic/offsite.htm?zi=1/XJ&sdn=usgovinfo&cdn=newsissues&tm=812&gps=125_177_816_643&f=00&tt=2&bt=1&bts=1&zu=http%3A//www.cdc.gov/nchs/data/ad/ad347.pdf

Team Leader Comments

- **The three subjects withdrawn due to "investigator discretion" were discontinued based on lack of completing study visits, change in mental status (see Subject 1/115 in Table 13), and findings of condyloma accuminata at an unscheduled visit.**
- **The 226 subjects withdrawn due to "patient request" included:**
  - **97 due to bleeding**
  - **46 due to personal reasons (e.g., not sexually active, noncompliance, disliked not having monthly period, not otherwise specified)**
  - **45 due to inconvenience (e.g., moving, insufficient time)**
  - **23 due to desire for pregnancy**
  - **15 due to adverse events or non-bleeding health complaint**
- **The 28 subjects withdrawn due to "other" include 11 who relocated, five due to drug noncompliance, four due to bleeding, two unable to return for visit, two due to taking exclusionary medication, one who was unable to return to the country, one who desired pregnancy, one due to no longer being sexually active, and one per primary MD request.**
- **Withdrawals due to AEs are discussed further in Section 8.1.1.**
- **Loss to follow-up of almost 14% of the population appears somewhat higher than that seen in recent trials of other OCs.**

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary endpoint in contraceptive trials is the Pearl Index, which is computed as

- Pearl Index = $\frac{(100) \times (\text{number of pregnancies}) \times (13 \text{ cycles/year})}{(\text{total number of 28-day cycles completed})}$

The analysis population was the pregnancy intent-to-treat (PITT) population, defined as all subjects who completed at least one 91-day cycle of drug use and were between the ages of 18-35 years, with exclusion of any cycles in which an alternate method of birth control was used; this is known as the PITT, non-BCM population. The Applicant also calculated Pearl Indices for the PITT population, including cycles in which another method of birth control was used, as well as the Compliant Use population (PITT subjects, excluding cycles in which a subject missed two or more consecutive pills or had a pattern of substantial noncompliance). Women were excluded from participation in the trial if they routinely used condoms for protection from sexually transmitted disease; however, condom use was required for the first seven days of OC use (following a Sunday start), and if a subject missed two or more consecutive pills.

Team Leader Comments

- **The PITT, non-BCM analysis population is the appropriate one for evaluation of the primary endpoint (Pearl Index).**
- **For extended cycle OCs, a comparable analysis is provided by changing the numerator to four cycles/year and the denominator to the total number of 91-day cycles completed. However, this involves loss of too much data when a subject uses an alternate birth control method once in a 91-day cycle (the entire cycle is excluded); therefore, I have relied upon the analysis using 28-day cycles, in which only a single 28-day cycle is excluded if a subject uses an alternate birth control method once in a 91-day cycle.**

The Applicant included only complete cycles (84 days on combination OC) in the denominator of "at risk" cycles; however, any cycle in which a pregnancy occurred was counted.

Pregnancies were counted by the Applicant based on an algorithm specified in the protocol, which defined pregnancy as a positive pregnancy test verified by study staff. Conception date was determined by ultrasound information, if available. Pregnancies with a date of conception prior to starting the first dose, or more than 14 days after the last combination tablet, were considered "off-drug" pregnancies. Any pregnancy not verified by the methods described in the protocol was defined as "unverified" and not counted. The example given is a third-party report that a subject was pregnant, with no confirmatory information from the subject herself or an involved healthcare provider.

Team Leader Comment

There were three additional pregnancies identified by the primary reviewer, all of which the Applicant considered unverified. The protocol algorithm does not completely address these cases, which are discussed further in Section 7.4.1.1.

The Applicant provided Pearl Indices based on the number of pregnancies occurring in two "windows" following intake of the last combination tablet: 7 days and 14 days.

Team Leader Comment

The 14 day window is the current standard used by DRUP for counting "on treatment" pregnancies, and was agreed to by the Applicant prior to submission on the NDA.

Life table methods are also commonly used to assess contraceptive efficacy; these provide cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. Life tables do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, so they are not directly comparable to the Pearl Index based on the PITT, non-BCM population. The Applicant computed life tables for the PITT and Compliant Use populations; for the latter analysis, subjects were completely excluded if they had any noncompliant cycles.

7.4.1.1 Primary Efficacy Analysis

Pregnancies

The PITT population comprised 1,729 women aged 18-35 years, who contributed a total of 17,069 non-BCM 28-day cycles that also excluded condom use (the Applicant counted one more cycle than did the DRUP statistician). The Applicant determined that a total of 58 pregnancies occurred in subjects enrolled in the trial. Of these, nine women never started the drug, and their pregnancies were deemed "off-treatment." Within this group, six subjects returned unopened pill packs to the study site, in other cases; either the drug accountability log or the subject herself confirmed that no pills had been taken. An additional three women did take some study drug, but their conceptions were dated prior to the onset of treatment; they are also considered "off-treatment" pregnancies. The Applicant considered that 33 pregnancies occurred on treatment, three were unverified and ten occurred more than 14 days after treatment (see Table 4).

According to the FDA reviewers, thirty-one women became pregnant on treatment, and five additional women became pregnant within 14 days after discontinuing treatment (i.e., 14 days after the last combination "E+P" tablet taken), for a total of 36 on-treatment pregnancies.

Table 4 Timing of Conception per FDA and Applicant

Timing of conception	N per Reviewer	N per Applicant	Comment
Never took OCs	9	9	
Prior to starting treatment	3	3	
Unverified pregnancy	0	3	
On treatment	**31***	**30**	*This includes Subject 10/1096 (see below), whose pregnancy may be either on treatment or within 14 days after discontinuing E+P
≤ 14 days after last E+P pill	**5**	**3**	
> 14 days after last E+P pill	10	10	

Bold = Pregnancies counted in computing the Pearl Index

Team Leader Comments

- **The Applicant counted two pregnancies as "on-treatment" that I consider to have occurred within 14 days after her final combination pill: Subject 13/1345, whose estimated date of conception (EDC) was two days after her last combination tablet; and Subject 47/4714 whose EDC was 10 days after her last combination tablet.**
- **Of the 10 subjects with conception > 14 days after the last combination pill, four conceptions occurred within 21 days of the last combination pill: on each at 16, 17, 19 and 21 days.**

There were three pregnancies on which the Applicant and the FDA reviewers disagreed:

- Subject 8/801 began treatment on September 11, 2005, and reported taking her last pill on April 11, 2006, at which time she reported having a positive pregnancy test. She reported that a sonogram on April 13, 2006 revealed an ectopic pregnancy, which was surgically treated on (b) (6), with hospital discharge on (b) (6). Her imputed date of conception was April 7, 2006. However, she did not return her pill packs and diaries, and refused to sign a release to obtain medical records regarding the pregnancy. She stated she was compliant with drug use. She withdrew from the study on May 3, 2006. The Applicant considered this an unverified pregnancy. I consider this to have occurred on-treatment, as she would have been taking combination pills on April 11, 2006.
- Subject 10/1096 began treatment on November 14, 2005. She reported having had a positive pregnancy test at home "three to four weeks ago" during a follow-up phone call on March 27, 2006. She did not recall the exact date of the pregnancy test. Her imputed date of conception was March 3, 2006. The patient reported missing four to five combination pills in February. She did not come in for the study termination visit and did not return pill packs or diaries. She was considered lost to follow-up. The Applicant considered that, in the absence of documentation of the pregnancy, it was an unverified pregnancy. I consider this an on-treatment pregnancy.
- Subject 37/37104 began treatment on March 19, 2006. She reported a positive pregnancy test and discontinued study drug on May 15, 2006. She did not return for the study termination visit but informed the site that she had had a medical abortion "on or before" (b) (6). She reported having been compliant with her medical,

but did not respond to any further requests for information. The Applicant considered this an unverified pregnancy. I consider this an on-treatment pregnancy.

Team Leader Comments

- **I concur with Dr. Orleans that subjects 8/801, 10/1096 and 37/37104 should be considered on-treatment pregnancies.**
- **For Subject 8/801, the Applicant's algorithm regarding verification of pregnancy does not directly address this situation, where the subject provides internally consistent information, but no records are available to confirm her reports. In the absence of data to the contrary, I accept the subject's report.**
- **For Subject 10/1096, the data are minimal, but it appears that the subject would have been taking the EE-alone tablets during February 6-12, 2006, and would have been scheduled to resume the combination pills on February 13, 2006. Per her report of missing four or five combination pills during February, it appears that she did, in fact, continue taking active pills following the EE-alone interval. This would suggest that her conception occurred on treatment, or within 14 days of last combination pill if she stopped taking study drug as early as February 17, 2006. In the absence of clear data, I prefer to err on the conservative side; therefore, I count this pregnancy. Particularly in a study with such a high a lost-to-follow-up rate (14%), the verified pregnancies may be only a subgroup of all pregnancies that occurred on treatment.**
- **For Subject 37/37104, in the absence of data to the contrary, I accept the subject's report. Per her reported timing of her medical abortion, it is likely that her date of conception was between May 1-14, 2006, dates when she would have been on active drug.**

Pearl Index

The Applicant provided revised PITT, non-BCM data, which also excluded all 28-day cycles in which condoms were used and that counted the 36 pregnancies identified by DRUP, upon the Division's request (see Table 5). The statistical reviewer, Sonia Castillo, Ph.D., computed the Pearl Index for the same population and cycles and confirmed the Applicant's analysis. The "gold standard analysis" relied upon by the Division is the PITT analysis in the top row of the table, which gives a Pearl Index of 2.74 (95% confidence interval [CI] 1.92 – 3.79).

Table 5 Applicant's Calculated Pearl Index Based on Pregnancies Counted by DRUP (PITT, non-BCM Analysis)

PSE-309: Pearl Index Calculations for the PITT Cohort, Excluding 28-Day Cycle Portions Where Other BCMs, Including Condoms, Were Used

	N	Number of 28-Day Cycles	Number of On-Drug Pregnancies	Pearl Index	95% CI
PITT	1729	17069	36	2.74	(1.92, 3.79)
PITT (Body Weight < 90 kg at Enrollment)	1460	14383	30	2.71	(1.83, 3.87)
PITT (Compliant-Use)	1724	16537	22	1.73	(1.08, 2.62)

Source: Applicant submission of October 8, 2008

Team Leader Comment

Based on clinical trial data submitted in support of NDAs for OCs, this Pearl Index slightly exceeds that of any recently approved combination OC in the U.S. However,

with labeling that clearly communicates the likelihood of pregnancy when using Lo Seasonique, I believe that this Pearl Index is acceptable.

Life Table Analysis

The Applicant provided a twelve-month life table estimate of the pregnancy rate based upon the 33 pregnancies it considered to be on-treatment on the PITT cohort (Table 6). As life table analysis typically does not exclude cycles mid-treatment, this analysis includes cycles in which some form of back-up contraception was used.

Table 6 Life Table Estimates of Treatment Failure Rates - Patients 18-35 Years of Age with at Least One Complete Cycle of Treatment (PITT), 33 Pregnancies

Cycle	Pregnancy Rate	95% C.I.
1	0.0041	0.0020-0.0087
2	0.0108	0.0067-0.0173
3	0.0155	0.0103-0.0234
4	0.0219	0.0153-0.0314

Based on Applicant's Table 27, page 74 of final study report

Team Leader Comments

- **The life table estimate of the annual pregnancy rate is the same when the life table is calculated based upon 13 28-day cycles, although intermediate cycles vary slightly.**
- **Dr. Castillo's life table calculation, which includes all 36 pregnancies identified by DRUP as on-treatment, is 3.2% (95% CI 1.2 – 5.2%).**

Effect of Weight on Efficacy

Many trials have set exclusionary rules to limit enrollment to women having BMIs < 30 or 35 kg/m^2. DRUP has been encouraging Sponsors to enroll women of all weights and BMIs, and some recent, unrestricted, trials of low-dose OCs have suggested that efficacy may be lower in heavier subjects. For this reason, the effect of weight and BMI was assessed in the current study. Table 7 displays pregnant subjects sorted by BMI.

Table 7 Screening Weight and BMI of Subjects with "On Treatment" Pregnancies

Patient #	Weight (pounds)	Height (inches)	BMI	OC cycle (91 days) at Conception
6/628	119	67	18.6	Cycle 2
10/1096	108	61	20.4	Cycle 2
13/1359	117	63	20.7	Cycle 2
45/4501	108	60	21.1	Cycle 4
56/5639	142	67	22.2	Cycle 4
10/1014	122	62	22.3	11 days post E+P in Cycle 4
13/1345	126	63	22.3	2 days post E+P in Cycle 4
17/1703	130	64	22.3	4 days post E+P in Cycle 2
44/4489	147	68	22.3	Cycle 3
50/5004	127	63	22.5	3 days post E+P in Cycle 3
56/5660	140	66	22.6	Cycle 3
25/2571	140	65	23.3	Cycle 1
15/1515	130	62	23.8	Cycle 2
37/37111	142	64	24.4	Cycle 2
29/2905	144	64	24.7	Cycle 1
50/5006	175	70	25.1	Cycle 1
35/3562	143	63	25.3	11 days post E+P in Cycle 4
56/5618	131	60	25.6	9 days post E+P in Cycle 4
37/37104	150	64	25.7	Cycle 1
59/5947	154	64	26.4	Cycle 3
54/5433	169	66	27.3	Cycle 4
59/5918	145	61	27.4	Cycle 2
5/596	198	70	28.4	Cycle 2
59/5925	161	63	28.5	Cycle 2
6/680	188	68	28.6	Cycle 1
53/5341	172	63	30.5	Cycle 3
8/812	184	65	30.6	Cycle 4
8/801	208	68	31.6	Cycle 3
53/5307	168	61	31.7	Cycle 4
10/10168	179	62	32.7	Cycle 2
18/1869	221	66	35.7	Cycle 1
46/4604	187	60	36.5	Cycle 3
13/1362	233	67	36.5	Cycle 4
37/37110	247	67	38.7	Cycle 1
47/4714	270	69	39.9	10 days post E+P in Cycle 4
29/2909	283	67	44.3	Cycle 3

The Applicant was asked to compute weight deciles, based upon baseline weight. The number of pregnancies occurring in each decile is shown in Table 8.

Table 8 Baseline Weight Deciles and Pregnancies per Decile (PITT Population)

Weight Decile	N	Weight (lbs.)	On-Drug Pregnancies (N=36)
1	220	87 - 116	2
2	206	117 - 125	3
3	222	126 - 133	5
4	231	134 - 140	2
5	219	141 - 148	6
6	211	149 - 157	2
7	223	158 - 170	3
8	215	171 - 187	5
9	220	188 - 217	3
10	218	218 - 391	5

Source: Based on calculations made by Sonia Castillo, Ph.D., from data provided by the Applicant on June 3, 2008

Team Leader Comment

Of 36 on-treatment pregnancies, 18 occurred in the lower five deciles of weight, and 18 in the upper five deciles. Thirteen of 36 pregnancies (36%) occurred in the top three deciles. Thus, there does not appear to be a disproportionate number of pregnancies in heavier women.

Statistician's Conclusion

The statistical reviewer, Sonia Castillo, Ph.D., analyzed the data including the three additional pregnancies identified by the primary reviewer. She also computed the Pearl Index for the PITT, non-BCM cohort where only 28-day cycles are excluded if another method of birth control was used during that cycle. This resulted in a rate of 36 pregnancies occurring in 1,729 subjects, with 17,068 28-day cycles, providing a **Pearl Index of 2.74 (95% CI 1.92 – 3.78)**. Dr. Castillo also calculated the life table pregnancy rate in all treated subjects aged 18-35 years, using all completed 91-day cycles and counting the 36 pregnancies identified by DRUP. This pregnancy rate was **3.2% (95% CI 1.2 – 5.2%)**. She made the following recommendation in her review dated June 5, 2008:

> *From a statistical standpoint, the Sponsor has provided one adequate study that provides evidence of the effectiveness of Lo Seasonique 91-day extended regimen oral contraceptive in the prevention of pregnancy.*

Team Leader Comment

Dr. Castillo's calculation of the Pearl Index is virtually identical to that submitted by the Applicant upon the Division's request, which included all 36 pregnancies, and excluded only 28-day cycles in which another birth control method was used.

7.4.1.2 Secondary Efficacy Analysis

Subjects completed a paper diary that recorded occurrence of bleeding or spotting, in addition to use of study drug and any other medications or use of contraception. Approximately half the subjects completed the diary on a weekly basis, answering based on recall over the preceding seven days; the subsequent subjects were provided with a daily diary. The Applicant provided the bleeding data separately for each cohort. The following definitions were used:

- Spotting: Not requiring use of either pads or tampons
- Bleeding: Requiring use of pads and/or tampons

Bleeding/spotting was characterized as "scheduled" if it occurred during the seven day interval when the subject was taking the EE-alone pills, and as "unscheduled" if it occurred during the 84 days of LNG/EE use. Unscheduled bleeding/spotting is likely to be more troublesome to subjects because it is unpredictable.

The Applicant initially submitted an analysis of bleeding in which only complete cycles (84 days of combination pills taken) were assessed. This would result in exclusion of bleeding data from subjects who discontinued due to intolerable intracyclic (unscheduled) bleeding. Following an information request by DRUP, the Applicant provided the following bleeding data, based on all cycles with bleeding data, regardless of the duration of pill-taking within the cycle (see Table 9 and Table 10). Data are provided over 91-day cycles, but median days of bleeding and/or spotting per month are also shown.

Table 9 Days with Unscheduled Bleeding and/or Spotting per 91-Day Cycle – Weekly Diary

Cycle	N	Mean (SD)	Minimum	Q1	Median	Q3	Maximum	Median per Subject-Month
1	1,129	15.9 (16.56)	0	2	11	24	84	2.8
2	953	10.0 (12.58)	0	0	6	14	84	1.5
3	817	8.5 (11.67)	0	0	4	12	83	1.0
4	693	6.7 (9.97)	0	0	3	10	60	0.8

Source: Based on Applicant submission dated September 5, 2008

Table 10 Days with Unscheduled Bleeding and/or Spotting per 91-Day Cycle – Daily Diary

Cycle	N	Mean (SD)	Minimum	Q1	Median	Q3	Maximum	Median per Subject-Month
1	942	21.0 (17.93)	0	7	16	30	84	4.0
2	786	14.3 (14.54)	0	3	10	22	76	2.5
3	685	11.7 (13.66)	0	1	7	18	71	1.8
4	605	9.8 (11.44)	0	0	6	15	65	1.5

Source: Based on Applicant submission dated September 5, 2008

Team Leader Comments

- **It is clear that more frequent bleeding/spotting is reported with use of a daily diary than with a weekly diary. As there is no reason to believe that a daily diary would be less accurate, and a real possibility that seven-day recall would result in under-reporting of**

actual bleeding/spotting, labeling with regard to bleeding should be based on the daily data.

- **With either method of recording, it can be seen that unscheduled bleeding/spotting decreases with duration of exposure, although it is possible that subjects with more frequent bleeding preferentially withdrew early from the study.**

Daily bleeding data was presented for subjects with at least one complete cycle, as this is the most accurate way to enumerate scheduled bleeding/spotting days.

Table 11 Days with Scheduled Bleeding/Spotting per 91-Day Cycle – Weekly Diary

Cycle	N	Mean (SD)	Minimum	Q1	Median	Q3	Maximum
1	996	1.9 (2.22)	0	0	1	4	7
2	852	1.9 (2.15)	0	0	1	4	7
3	726	1.8 (2.10)	0	0	1	3	7
4	644	2.1 (2.32)	0	0	2	4	7

Source: Based on Applicant's Table 172, p 642, final study report

Table 12 Days with Scheduled Bleeding/Spotting per 91-Day Cycle – Daily Diary

Cycle	N	Mean (SD)	Minimum	Q1	Median	Q3	Maximum
1	848	3.1 (2.51)	0	0	3	5	7
2	728	2.8 (2.47)	0	0	3	5	7
3	656	2.5 (2.48)	0	0	2	5	7
4	574	2.7 (2.62)	0	0	3	5	7

Source: Based on Applicant's Table 171, p 642, final study report

Team Leader Comments

- **Again, the daily diary data is believed to be a more accurate representation of the bleeding profile, and should be used in labeling.**
- **75% of subjects had ≤ 5 days of scheduled bleeding/spotting; this was consistent over all four cycles.**
- **The mean number of days of scheduled bleeding or spotting was also fairly stable across cycles, at about 3.**

The frequency of adverse events and discontinuations due to bleeding was also evaluated. Two hundred eighty-nine subjects (13.2%) reported bleeding-related AEs (metrorrhagia 8.2%, vaginal hemorrhage 3.4%, menorrhagia 1.3%, and irregular menstruation, uterine hemorrhage and menometrorrhagia at 0.05% each). As discussed in Section 8.1.1, 108 subjects discontinued due to bleeding-related adverse events (e.g., metrorrhagia, menorrhagia, vaginal or uterine hemorrhage). Another 97 subjects discontinued due to "patient-request," and four for "other" reasons, but bleeding-related reasons were noted. Thus, a total of 209 (9.6%) of subjects in the trial discontinued due to bleeding concerns.

Team Leader Comment

The bleeding profile of Lo Seasonique is acceptable; however, it should be clearly described in labeling. Patients should be informed that, along with fewer scheduled bleeds, they are likely to have increased rates of unscheduled bleeding/spotting on extended-regimen OCs.

7.4.2 Overall Assessment of Efficacy

The Applicant has submitted an acceptable clinical trial database supporting efficacy for this low-dose extended regimen OC. While the Pearl Index of 2.74 is marginally higher than that for other low-dose OCs, this product does not appear to have diminished efficacy in heavier women, and therefore, with clear labeling, I believe it provides acceptable contraceptive efficacy for the general population.

8. Safety

8.1 SAFETY FINDINGS

This review of the safety of Lo Seasonique is based on data from the 12-cycle safety and efficacy trial. The BE study conducted with Lessina was not examined for safety, as subjects in this trial received only a single dose.

The safety population in Study DR-PSE-309 included 2,185 women who took at least one dose of study medication, or 97.8% of all enrolled subjects.

8.1.1 Deaths and Serious Adverse Events

There were no deaths in the clinical trial. There were 39 SAEs reported by 35 subjects in the phase 3 trial, as displayed in Table 13. The Applicant reported that two of these resulted in discontinuation of the subject from the trial (illicit drug use and headache with a syncopal episode). However, in an additional three cases (excluding those related to pregnancy), the subject was terminated from study participation for reasons related to the SAE. Therefore, a total of 1.6% of subjects experienced SAEs, and 0.14% discontinued for reasons related to their SAEs.

Table 13 Serious Adverse Events in Study DR-PSE-309

Subject #	SAE Verbatim	Discontinued from study	Applicant assessment of causality	Reviewer assessment of causality
1/115	Tylenol overdose	Terminated due to "change in mental status"	None	Possible – subject reported depression and a deliberate overdose
2/231	Cholelithiasis with biliary colic	No	Remote	Unlikely – subject's sx & dx preceded first dose
5/5109	Severe depression with suicidal ideation	No	Remote	Possible – subject had prior hx & d/c'd antidepressants
5/514	Premature labor	N/A*	None	None
5/519	Exacerbated asthma; Urticaria	No	Remote Remote	Unlikely for both – sx presented at next to last dose, Cycle 4
5/520	Symptomatic cholelithiasis	No	Possible	Possible
5/566	Biliary dyskinesia	No	None	Possible
6/650	Dilated biliary common duct Right upper quadrant pain	No	Possible Remote	Possible for both

Subject #	SAE Verbatim	Discontinued from study	Applicant assessment of causality	Reviewer assessment of causality
8/801	Ectopic pregnancy	N/A	None	None
10/10168	Miscarriage	N/A	None	None
10/1041	Asthma exacerbation	Terminated due to non-resolution of pneumomediastinum	None	None; subject also had pneumomediastinum
20/2010	Cholecystitis	Subject withdrew due to AEs 5 weeks after SAE	Possible	Possible
24/2423	Illicit drug use	Yes – due to entry into rehab	None	None
25/2599	Miscarriage	N/A	None	None
26/2613	Leukocytosis	No	None	None – post outpatient hernia repair
31/3118	R tibial fx	No	None	None
33/3306	Cleft palate repair Surgical wound breakdown	No	None	None
33/3331	Gastroenteritis	No	Possible	Unlikely
33/3346	Viral meningitis	No	None	None
35/3559	Appendicitis	No	None	None
37/3724	Depression	No	Remote	Possible – had prior hx; experienced suicidal ideation w/this SAE
43/4312	Cervical radiculopathy	No	None	None
44/44104	Headache Syncope	Yes	Possible Possible	Possible for both – CT and echo were nl
44/4486	Ectopic pregnancy	N/A	N/A	None
44/4489	Missed abortion	N/A	Remote	None
46/4619	Appendicitis	No	None	None
46/4628	R orbital floor fx	No	None	None
47/4706	Strep throat	No	None	None
47/4709	Broken collar bone	No	None	None
54/5438	Back pain related to herniated disc & spinal stenosis	No	None	None
56/5618	Hypospadius of infant	N/A	Remote	None – subject conceived 9 days after last E+P in Cycle 4
56/5623	Pyelonephritis	No	None	None
56/5660	Miscarriage	N/A	None	None
59/5925	Spontaneous abortion	N/A	None	None
59/5932	Worsening paroxysmal SVT	No	None	None

*** Subjects with pregnancy-related SAEs were discontinued on the basis of pregnancy alone.**
Source: Based on Applicant's Table 38, pp 84-5, and SAE narratives, pp 90-137, of final study report.

Team Leader Comments

- **There were no deep vein thromboses or pulmonary emboli in this trial.**
- **Two other relatively common SAEs are labeled events for hormonal contraceptives and could be drug-related (biliary dyskinesia/cholecystitis, reported by five subjects and depression, reported by two subjects).**

A total of 253 subjects (11.6%) discontinued the trial due to adverse events (AEs). Adverse events leading to study discontinuation by ≥ 1% of subjects are listed in Table 14; some events that were listed individually by the Applicant have been grouped better to demonstrate the frequency of related events.

Table 14 AEs Leading to Study Discontinuation in ≥ 1% of Safety Population

MedDRA SOC and Preferred Term	N	% of n = 2,185 (N/n)
Reproductive System and Breast Disorders	117	5.35
Metrorrhagia, menorrhagia, vaginal & uterine hemorrhage	106	4.85
Psychiatric Disorders	39	1.78
Nervous System Disorders	26	1.19
Headache & migraine	23	1.05
Skin & Subcutaneous Tissue Disorders	23	1.05

Source: Based on Applicant's Table 39, pp 86-8 of final study report.

Team Leader Comment

In some cases, related terms that did not reach the 1% cut-off individually exceeded 1% collectively. These include:

- **Psychiatric and general disorders comprising depression, anxiety, irritability and mood alterations/lability, at 2.1%**

A total of 89 subjects were reported by the Applicant to have discontinued due to bleeding-related AEs. However, Table 14 shows that 106 discontinued due to excessive bleeding complaints, while one each discontinued for irregular bleeding and for oligomenorrhea. Other AEs leading to discontinuation included those commonly associated with OCs, such as nausea (12), acne (12), increased weight (11), increased blood pressure/hypertension (8) and breast tenderness (4).

Team Leader Comments

- **Including the 97 subjects who discontinued for reasons related to bleeding, but were listed as "patient request," and the four who were listed as "other," a total of 209 subjects (9.6%) discontinued for bleeding.**
- **The rate of discontinuation due to adverse events is reasonably similar to that observed in other one year OC trials.**
- **The adverse event profile associated with study discontinuation appears typical for an OC.**

8.1.2 Other Adverse Events

The Applicant provided a table of treatment-emergent adverse events; the more common, defined as those occurring in at least 2% of the safety population and likely to be drug-related are listed in Table 15.

Table 15 Common Adverse Events (≥ 2% of Safety Population) Likely to Be Drug-Related*

MedDRA SOC and Preferred Term	**N**	**%**
Nervous System Disorders	865	39.6
Headache + Migraine + Tension Headache + Migraine w/o Aura	854	39.1
Reproductive System & Breast Disorders	592	27.1
Dysmenorrhea	248	11.4
Metrorrhagia	180	8.2
Breast Tenderness + Breast Pain + Breast Swelling + Breast Engorgement	103	4.7
Vaginal hemorrhage	75	3.4
Menorrhagia	29	1.3
Menstruation Irregular	2	0.1
Uterine Hemorrhage	2	0.1
Menometrorrhagia	1	0.1
Gastrointestinal Disorders	571	26.1
Nausea + Vomiting	244	11.2
Abdominal Pain Upper + Abdominal Pain + Abdominal Pain Lower + Abdominal Discomfort	206	9.4
Psychiatric Disorders	248	11.4
Insomnia + Sleep Disorder	76	3.5
Depression + Crying + Major Depression + Affective Disorder + Depressed Mood + Depression Suicidal + Dysphoria	72	3.3
Mood Swings + Mood Altered + Affect Lability	81	3.7
Skin & Subcutaneous Tissue Disorders	206	9.4
Acne	88	4.0
Investigations	101	4.6
Weight increased	59	2.7

***In the absence of a comparator or placebo arm, it is not possible to determine which AEs occur more frequently in the active treatment group. I consider these listed AEs as "likely to be drug-related" based upon known OC-associated AEs.**
Source: Based on Applicant's Table 141, pp 543-58 of final study report

Team Leader Comments

- **Related terms are grouped together to provide a better estimate of the incidence of these events; however, uterine bleeding disorders are listed individually to show the relative contributions of each (individual listings may not reach 2% incidence).**
- **The rate of irregular and heavy uterine bleeding was calculated by summing the terms Metrorrhagia, Vaginal Hemorrhage, Menorrhagia, Menstruation Irregular, Uterine Hemorrhage and Menometrorrhagia. This provides an incidence rate of 289/2,185 or 13.2%.**
- **Hepatobiliary disorders did not reach 2%, with only nine cases occurring (0.4%).**
- **The common adverse event profile is typical for a hormonal contraceptive.**

Laboratory and vital signs data are discussed in Dr. Orleans' review, and did not provide any signal of concern.

The Applicant referenced data from an earlier trial using Seasonique to support the endometrial safety of Lo Seasonique. In this trial, baseline and end of treatment endometrial biopsies were obtained on 63 subjects randomized to Lo Seasonique; no endometrial hyperplasia (or worse) was seen. Almost half the subjects demonstrated inactive endometrium at the end of study biopsy.

8.1.3 Safety Update

The 120-day Safety Update Report was received on April 25, 2008, and contained follow-up on a number of pregnancies and several ongoing SAEs. There were no new safety signals noted in these updates, and there are no ongoing studies for Lo Seasonique.

8.1.4 Postmarketing Safety Findings

Lo Seasonique is not marketed in any country, so there are no postmarketing data on its safety. Years of marketing experience for the related, but higher-dose, products Seasonale and Seasonique have not raised any safety signals of concern. The Applicant submitted the Periodic Adverse Drug Experience Reports for Seasonale and Seasonique since each product's introduction; these were reviewed and no new safety signals were identified.

8.1.5 Overall Assessment of Safety Findings

Lo Seasonique does not appear to present an unusual or concerning safety profile. The common AEs and SAEs include irregular and heavy uterine bleeding, cholecystitis/biliary dyskinesia and depressive symptoms, all of which are labeled events for OCs. The impact of bleeding is greater than expressed by the Applicant, with almost 9% of subjects withdrawing due to bleeding-related complaints, and this should be addressed in labeling.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this application, as it was not a new molecular entity and raised no new safety concerns.

10. Pediatrics

The Applicant requested a waiver of pediatric studies. The Pediatric Review Committee (PeRC) granted a partial waiver for pre-menarchal patients, since such children are not at risk of pregnancy. The remainder of the PREA requirement has been fulfilled by extrapolation.

DRUP's long experience with a variety of hormonal contraceptives has supported the expectation that efficacy and safety results in postmenarchal adolescents do not differ from those in adult women.

11. Other Relevant Regulatory Issues

The Applicant submitted financial disclosure information for all investigators; only three had disclosable information and two enrolled fewer than (b) (6) subjects. (b) (6) enrolled (b) (6) subjects and reported receiving an honoraria of ≤ $15,000. His site reported (b) (6) (b) (6), so it does not appear to be an outlier with respect to frequency of these undesired outcomes.

Site inspections by the Division of Scientific Investigation were not requested; no sites appeared unusual in terms of adverse event reporting, pregnancies or dropouts.

12. Labeling

The Applicant proposed the trade name Lo Seasonique. The Division of Medication Error Prevention and Analysis (DMEPA) found this trade name acceptable, with a recommendation that the space between "Lo" and "Seasonique" be eliminated to minimize the chance that "Lo" will be omitted, thus causing confusion with the approved product Seasonique. The Applicant accepted this recommendation.

Carton and container labeling was reviewed and was revised by the Applicant in accordance with recommendations made by DMEPA and by the CMC reviewer.

The Lo Seasonique label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and, upon approval, will represent the first PLR label for an OC. DRUP has been developing an updated draft Guidance for OC labeling, and the discussions by members of a variety of disciplines involved in that project were useful in informing the revisions proposed to the Lo Seasonique label. Consults on the proposed label were obtained from the Study Endpoints and Labeling Development Team, the Division of Risk Management and the Division of Drug Marketing, Advertising and Communication. Their comments were incorporated into the label as appropriate.

The major changes from previous OC labels include:

- (b) (4)
- Revision of patient labeling to provide a more focused discussion of what a user needs to know.

Additional issues relative to the Lo Seasonique trial data that are addressed in labeling:

- Description of the bleeding profile demonstrated with Lo Seasonique, particularly the frequency and duration of unscheduled bleeding
- Addition of specific adverse reaction data from the clinical trial, including adverse reactions leading to discontinuation from the trial, and common adverse reactions

- Discussion of only a "Sunday start," as this was the method used exclusively in the clinical trial.

Agreement was reached with the Applicant on labeling.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Lo Seasonique be approved for the indication "for use by women to prevent pregnancy."

13.2 Risk Benefit Assessment

The one-year clinical trial demonstrated a Pearl Index that is marginally higher than that of previously approved OCs, but which I believe to be acceptable. The product does not show any signal of decreased efficacy in heavier women, who were adequately represented in the trial. The safety profile does not differ from that expected for a low-dose OC. With clear labeling that describes accurately the efficacy demonstrated for this product, I believe it has demonstrated safety and efficacy acceptable to allow approval for marketing in the general population of women.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for other Postmarketing Study Commitments

No postmarketing studies are recommended.

13.5 Recommended Comments to Applicant

None.

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

/s/

Lisa Soule
10/24/2008 03:20:55 PM
MEDICAL OFFICER

Scott Monroe
10/24/2008 04:30:02 PM
MEDICAL OFFICER
I concur with the recommendation of Dr. Soule that LoSeasonique be approved for the indication of "for use by women to prevent pregnancy."