CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	March 28, 2013
From	Audrey Gassman, MD
NDA #	204061
Applicant name	Teva Branded Pharmaceutical Products R&D, Inc.
Date of submission receipt	May 31, 2012
PDUFA goal date	March 31, 2013
Proprietary name/established name	Quartette/levonorgestrel and ethinyl estradiol and ethinyl estradiol
Dosage form/strengths/regimen	Oral tablets: 42 tablets containing 0.15 mg levonorgestrel and 0.02 mg ethinyl estradiol; 21 tablets containing 0.15 mg of levonorgestrel and 0.025 mg ethinyl estradiol; 21 tablets containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol; and 7 tablets containing 0.01 mg of ethinyl estradiol tablets to be taken sequentially at the same time every day for 91 total days per package
Proposed indication	For use by women to prevent pregnancy
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Lisa Soule, MD
Medical Officer Review	Vaishali Popat, MD
Statistical Review	Jia Guo, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Krishan Raheja, DVM, PhD Alex Jordan, PhD
Clinical Pharmacology Review Pharmacometrics Review:	Sayed Al Habet, RPh, PhD Myong-Jin Kim, PharmD Jeff Florian, PhD Yaning Wang, PhD
ONDQA (CMC) Review	Rajiv Agarwal, PhD Donna Christner, PhD Moo Jhong Rhee, PhD
DMEPA	Manizheh Siahpoushan, PharmD Zachary Oleszczuk, PharmD Carol Holquist, RPh
OPDP	Melinda McLawhorn, PharmD, BCPS Carrie Newcomer, PharmD
OSI	Roy Blay, PhD Janice Pohlman, MD, MPH Susan Thompson, MD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
CMC = Chemistry, Manufacturing and Controls
ONDQA = Office of New Drug Quality Assessment
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

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1. Introduction

This NDA (204-061) submitted by Teva Branded Pharmaceutical Products R&D, Inc. seeks the marketing approval for a new extended-regimen of combination oral contraceptive (COC). Hereafter, this new regime will be referred to by the product's approved tradename, Quartette. Each Quartette package consists of 91 total tablets: 84 tablets that contain the combination of levonorgestrel and ethinyl estradiol (LNG/EE), with ascending doses of EE, and 7 tablets of ethinyl estradiol (EE) alone. The indication for this new COC regimen is for use in women to prevent pregnancy. The goal of this combined oral contraceptive regime (84 active tablets) was to provide a COC product that has a lower total hormonal dose exposure compared to other approved regimes and offers the convenience of 4 scheduled withdrawal periods per year. Quartette has not approved for marketing in any foreign country.

Products such as Quartette are considered "extended" regimes as they provide for more than one month of continuous active tablets to be taken consecutively on a daily basis. Three other approved combined oral contraceptives with extended regimes containing ethinyl estradiol and levonorgestrel include: Seasonique (NDA 21840), LoSeasonique (NDA 22-262), and Seasonale (NDA 21544). Quartette will be supplied as oral tablets that contain the following:

- Days 1 through 42: LNG 150 mcg/EE 20 mcg
- Days 43 through 63: LNG 150 mcg/EE 25 mcg
- Days 64 through 84: LNG 150 mcg/EE 30 mcg
- Days 85 through 91: EE 10 mcg

Because of the extended dosing cycle of Quartette, women can expect to have only 4 scheduled withdrawal periods, generally while taking the EE tablets (days 85 through 91). However, women who use this product are also likely to also have unscheduled spotting/bleeding days when taking the LNG/EE tablets (days 1 through 84). No safety issues were identified during the review of the Quartette application that would preclude approval.

This review focuses on the following major issues:

- The acceptability of efficacy and safety findings for Quartette for prevention of pregnancy in women
- The acceptability of the bleeding patterns (days of scheduled and unscheduled bleeding and spotting) that occur with use of Quartette
- The extent to which labeling can be used to describe the efficacy, safety and anticipated bleeding pattern with Quartette

2. Background

Combined oral contraceptives (COCs) containing ethinyl estradiol and levonorgestrel as active drug substances approved in the US have various dosing regimes, including extended regimes (active tablets taken continuously for greater than one month in duration). Quartette is a COC that contains a four-phasic regimen of tablets extending for 91 consecutive days. Tablets will be taken orally once daily and consist of ascending doses of ethinyl estradiol (EE) as follows:

First 42 days (days 1 – 42): 150 mcg levonorgestrel (LNG) and 20 mcg of EE
Following 21 days (days 43 – 63): 150 mcg LNG and 25 mcg EE
Following 21 days (days 64 – 84): 150 mcg LNG and 30 mcg EE
Following 7 days (days 85 – 91): 10 mcg EE

A Type B pIND teleconference was held with the original Sponsor on August 7, 2006 to discuss a proposed Phase 2 dose-ranging trial. IND (72,290) was opened with a submission containing a revised Phase 2 protocol on August 28, 2006.

The Applicant conducted a single, multicenter, open-label, non-comparative clinical trial (DR-103-301) that was the focus of the efficacy analysis, although no formal Special Protocol Assessment was requested for the protocol. On December 28, 2011, the Applicant requested a preNDA meeting to discuss the format and content of their NDA submission consisting of the single phase 2 and phase 3 studies submitted previous to the IND. In lieu of a meeting, written responses were sent in an Advice Letter on March 29, 2012. The Advice Letter outlined several key recommendations, including calculation of the primary efficacy analysis for Study DR-103-301.

NDA 204-061 was received by the Agency on May 31, 2012, for the purposes of marketing Quartette in the US. The single uncontrolled trial (DR-103-301) was the primary support for efficacy and safety of Quartette, and the phase 2 study (DR-ASC-201) provided supportive dose selection and safety data.

3. CMC

The proposed drug substances in Quartette are levonorgestrel (LNG) and ethinyl estradiol (EE). A total of 91 tablets are contained in 3 blister cards which are placed into a single (b) (4) compact. Information regarding the drug substances in the tablets (LNG and EE) were cross-referenced to two DMFs that were reviewed several times and found to be adequate. The tablets are presented as follows:

- The first 28 count blister card contains 28 light pink levonorgestrel and ethinyl estradiol tablets, 0.15 mg / 0.02 mg.
- The second 28 count blister card contains 14 light pink levonorgestrel and ethinyl estradiol tablets, 0.15 mg / 0.02 mg, followed by 14 pink levonorgestrel and ethinyl estradiol tablets, 0.15mg / 0.025 mg.
- The third blister card is a 35 count blister card containing 7 pink levonorgestrel and ethinyl estradiol Tablets, 0.15 mg / 0.025 mg followed by 21 purple levonorgestrel and ethinyl estradiol tablets,0.15 mg / 0.03 mg and then 7 yellow ethinyl estradiol tablets, 0.01 mg.

The CMC reviewer stated in her January 2013, review that compendial excipients are used in the manufacture of tablets. The reviewer noted that the tablets are coated with (b) (4) colorants, which are not compendial, but meet the regulatory requirements for their intended use. Finally, justification for the proposed specifications for excipients and release acceptance criteria for excipients were compliant with the appropriate USP/NF monograph and were therefore determined by the CMC reviewer to be adequate (See CMC review dated January 31, 2013).

The CMC review team concluded in their review, dated January 31, 2013, that, "This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application. However, the issues on the label/labeling of the drug product have not been resolved. Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR 314.125(b) (6) in its present form until label/labeling issues are satisfactorily resolved."

In an addendum dated March 21, 2013, the CMC review team stated that the CMC issues for this application were now satisfactorily resolved. The March 2013 CMC addendum concluded that, "This NDA is now recommended for approval from the ONDQA perspective with expiration dating period of 18 months."

The CMC review team did not recommend any postmarketing commitments or requirements.

Comment: There are no outstanding CMC issues. I concur with the approval recommendation of the CMC review teams.

1. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team stated that the Applicant submitted no nonclinical information and relied on published studies of levonorgestrel and ethinyl estradiol and studies conducted in submissions for approval of the Applicant's previously approved combined oral contractive products, Seasonale and LoSeasonique (NDAs 21-54 and 21-840, respectively). The pharmacology/toxicology team concluded in their review dated October 22, 2012, that "P/T recommends approved of NDA 204061 for prevention

of pregnancy." No postmarketing commitments or requirements were recommended by the Pharmacology/Toxicology review team.

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

2. Clinical Pharmacology

The Clinical Pharmacology review team evaluated data from three clinical studies that contained Clinical Pharmacology data and presented their findings in a review dated February 22, 2013. These studies included one pharmacokinetic study (DR-103-101) to evaluate the relative bioavailability of levonorgestrel (LNG) and ethinyl estradiol (EE) components of each of the three tablet strengths. In addition, a Phase 2 study to investigate the bleeding patterns of three ascending dose regimens (DR-ASC-201) was submitted as supportive of the single Phase III safety and efficacy study (DR-ASC-301).

The majority of the clinical pharmacokinetic data was obtained through cross-reference to other approved extended regime combined oral contraceptive (COC) products (Seasonique and LoSeasonique). No drug-drug interaction studies were conducted to support approval of Quartette. The Clinical Pharmacology review team determined that this was acceptable and also concurred with the Applicant that the label for Quartette would contain the same information in reference to absorption, distribution, metabolism and excretion as other products in the extended regime COC class. Similarly, the information related to drug-drug interaction, food effect, and PK in specific population will be the same as that in other approved extended regime combined oral contraceptive products (Seasonique® and LoSeasonique®).

The Pharmacometrics Group in the Office of Clinical Pharmacology also reviewed the available data to determine whether the scheduled tiered dose escalation of EE/LNG was supported by the Applicant's Phase 2 data (DR-ASC-201). In their addendum to the February 2013 Clinical Pharmacology review, the Pharmacometrics reviewer concluded:

- **Bleeding:** Phase II dose-finding data showed no distinct differences in the incidence of bleeding/spotting between the three phasic dose regimens evaluated and the minimum cumulative dose arm was selected for Phase 3 evaluation.
- **Exposure:** The predicted EE exposure for Quartette falls between that of Seasonique and LoSeasonique.
- **Efficacy:** Body weight > 90 kg and African American race were associated with an increased Pearl Index compared to that in thinner or non-African American women. The increased Pearl Index in African American women did not appear to be attributable solely to higher body weight.

In their review dated February 22, 2013, the Clinical Pharmacology review team recommended that, "From the Clinical Pharmacology perspective, this NDA is acceptable." No postmarketing commitments or requirements were recommended by the Clinical Pharmacology or Pharmacometrics review teams.

In an addendum to the Clinical Pharmacology review (dated February 25, 2013), the Pharmacometrics group also agreed with the Clinical Pharmacology review team that the application was approvable from a clinical pharmacology perspective,

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

3. Clinical Microbiology

A Microbiology review was not conducted for this application because the product consists of oral tablets.

4. Efficacy/Statistics

Overview and Demographics:

The Applicant conducted a single, multicenter, open-label, non-comparative clinical trial (DR-103-301), hereafter referred to as Trial 301, that served as the primary support for the efficacy and safety of Quartette. Subjects were 18-40 years of age and were to be treated for up to 12 months. The inclusion and exclusion criteria were consistent with those of other clinical trials for oral contraceptives and there was no entry restriction based on Body Mass Index (BMI). The mean age was 27.1 and mean weight of the subjects in this clinical trial was 162.5 pounds. The racial distribution of subjects who received at least one dose of study drug was 64.6% Caucasian, 19.3% Black, 11.2% Hispanic, 2.2% Asian, 0.4% American Indian or Alaska native and 2.0% Other. Among treated subjects, 17.2% were "new" (first time) users of COCs, 43.6% were "continuous users" (had used COCs within the prior 6 months, and 39.1% were "prior users" (had used COCs more than 6 months prior to study participation).

Subject Demographics and Disposition:

A total of 4,692 subjects were screened and 3,701 were enrolled. Of those enrolled, 3,597 (97.2%) took at least one dose of Quartette (Safety cohort)
Other evaluated populations included:

- Intent to Treat Cohort (ITT) – A total of 3,352 (93.2%) subjects, regardless of age, who completed at least one 28-day cycle of Quartette
- Pregnancy ITT Cohort (PITT) – A total of 3,019 (90.1%) subjects ages 18-35 years who completed at least one 28-day cycle of therapy.

Comment: The PITT population was the cohort used for the primary efficacy analysis.

An overview of the demographics for Trial 301 is outlined in the table below:

Table 1: Demographics reported from subjects in Trial 301*

Parameter	Safety (N = 3597)		ITT (N = 3352)		PITT (N=3019)	
Mean Age (years)	27.1		27.1		25.9	
Body Mass Index (kg/m2)Mean	27.4		27.4		27.2	
Race	**N**	**%**	**N**	**%**	**N**	**%**
American Indian or Alaska native	14	0.4	14	0.4	12	0.4
Asian	78	2.2	75	2.2	70	2.3
Black	696	19.3	633	18.9	550	18.2
Native Hawaiian	10	0.3	10	0.3	10	0.3
White	2324	64.6	2181	65.1	1977	65.5
Hispanic	404	11.2	371	11.1	335	11.1
Other	71	2.0	68	2.0	65	2.2
Contraceptive History						
Continuous User	1570	43.6	1509	45.0	1337	44.3
New start	619	17.2	555	16.6	523	17.3
Prior user	1408	39.1	1288	38.4	1159	38.4
Smoking History						
Currently	602	16.7	550	16.4	549	18.2
Former	636	17.7	601	17.9	529	17.5
Never	2359	65.6	2201	65.7	1941	64.3

*Source: Obtained from Table of the DRUP Medical Officer's review dated March 1, 2013.

The overall disposition of study subjects in Trial 301 are summarized in the table below:

Table 2: Disposition in Trial 301*

Screened	4,962
Enrolled	3,701
Safety cohort (took at least one dose)	3,597 (100%)
Intent to treat (ITT) cohort	3,352 (93.2%)
Pregnancy Intent to Treat (PITT) cohort	3,019 (90.1%)
Completed Trial*	2,144 (59.6%)
Discontinued Prematurely	1,453 (40.4%)
Discontinued for an Adverse Event -Bleeding and Spotting Related	466 (13.0%) 168 (4.6%)
Lost to Follow-Up	480 (13.3%)
Noncompliance with protocol	137 (3.8%)
Investigator discretion	5 (0.1%)
Pregnancy	68 (1.9%)
Protocol Violation	16(0.4%)
Applicant's Requested Subject Withdrawal	35 (0.1%)
Subject Requested Withdrawal	217 (6.0%)
Other	28 (0.8%)

*Completed Trial = completed one year of treatment
Source: Obtained from Table 14 of the DRUP Medical Officer's review dated March 1, 2013.

Comment: In terms of patient exposure, 2,144 subjects completed one year of treatment, which exceeds the Division's recommendation on subject exposure over 1 year (200 women for at least 12 months). In addition, the overall discontinuation rate in Trial 301

of 40.1% was similar to those of other COC trials and was acceptable to the clinical review team.

Primary Efficacy Findings:

The primary outcome for Trial 301 was the Pearl Index (PI) using on-drug pregnancies. On-drug pregnancies were defined as those pregnancies for which conception occurred on or after the date of first intake of study drug and extending through 7 days following the last tablet. The Applicant identified 65 pregnancies for which the conception date was considered to be on-treatment (i.e., conception was assessed as having occurred after use of the last combination tablet of LNG/EE). The Division clarified that all pregnancies conceived within 7 days of taking the last tablet, whether LNG/EE or EE alone should be included. The Applicant agreed to this definition and revised the number of on-treatment pregnancies to 67. The DRUP Medical Reviewer identified 3 additional pregnancies (Subjects FL-001-10001115, MD-005-10005055 and NC-0042-10042029) that she considered to have occurred while the subjects were on-treatment, for a total of 70 on-drug pregnancies.

Primary Efficacy Analysis:

The Pearl Index (PI) was derived from the PITT, which consisted of all women ages 18-35 who completed at least one 28-day cycle of therapy. All 28-day cycles where additional back-up methods of birth control (including condoms) were used and all incomplete 28-day cycles (except those in which conception occurred) were excluded from this calculation.

Statistical Review and Conclusions:

The primary Statistical Reviewer calculated the Pearl Index (PI) value based on the data obtained in Trial 301 in her review dated February 22, 2013. Her PI calculations were based on the following formula: (100) x (total number of on-treatment pregnancies) x (4)/(total number of 28 day cycles). Calculations were based both on the 67 pregnancies considered as "on-treatment" as agreed to with the Applicant and the 70 pregnancies determined by DRUP (67 pregnancies identified with the Applicant plus three additional pregnancies considered by the DRUP Medical Officer to be "on-treatment"). The Statistical Reviewer's findings are presented below in Table 3.

Table 3: PI analyses for complete 28-day cycle equivalents – PITT population*

	N	Number of On-Drug Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
Applicant	2,992	67	30,363	1,848	28,515	3.05	(2.37, 3.88)
Reviewer	2,992	70	30,363	1,848	28,515	3.19	(2.49, 4.03)

*Source: Obtained from Table 16 of the DRUP Medical Officer's Review dated March 1, 2013.

Based on DRUP's on-treatment pregnancies and a total of 28,515 completed 28-day cycle equivalents of treatment for subjects ≤ 35 years of age during which no backup contraception was used, the Pearl Index was calculated by the FDA statistician to be 3.19 (95% Confidence Interval: 2.49, 4.03) per 100 women-years of use.

PI results for 91-day cycles in the PITT calculations were also calculated. The Applicant reported Pearl Index was 3.37 (95% CI: 2.61-4.27) and the reviewer-reported Pearl Index was 3.52 (95% CI: 2.75-4.44). Finally, life-table analyses were calculated with the statistical reviewer's life table pregnancy rate in all subjects 18-35 years of age using 70 pregnancies and all 91-day cycles was 2.85% (95% CI 2.25 to 3.61%) and 2.82 (95% CI from 2.22% to 3.57%) using all 28-day equivalent cycles.

In her statistical review dated February 22, 2013, the Statistical Reviewer concluded that, "From a statistical perspective, the study results support the efficacy of Quartette, an oral regimen of levonorgestrel (LNG)/ethinyl estradiol (EE) 0.15 mg/0.020 mg, 0.15 mg/ 0.030 mg and 0.01 mg EE), in the prevention of pregnancy."

Efficacy Summary:

One multicenter, open-label, non-comparative clinical trial provided adequate evidence of efficacy for Quartette. The Pearl Index was 3.19 (CI of 2.49, 4.03). Although this 3.9 point estimate is marginally higher than those of PI usually seen with other currently marketed low-dose COCs, the upper bound of the 95% confidence interval (4.03) is well within the range that is acceptable to the review teams. Quartette provides a lower dose alternative for women presently using a COC who wish to extend their dosing cycles.

The DRUP Medical Officer stated the following conclusion regarding the Pearl Index in her March 1, 2013 review, "The contraceptive benefit of this product is comparable to that of other approved COCs."

In her review dated, March 27, 2013, the Cross-Discipline Team Leader similarly concluded that, "The data in the phase 3 study provides acceptable evidence of efficacy to warrant approval of this NDA for prevention of pregnancy."

Based on the Pearl Index and supportive life table analysis from Trial 301 for Quartette, I conclude that Quartette provides acceptable efficacy for prevention of pregnancy. Therefore, I concur with the recommendations of the DRUP Medical Officer, Statistical Review team and CDTL that there are no outstanding efficacy concerns for this new extended regime COC product.

5. Safety

The DRUP Medical Officer has provided a thorough discussion and review of the safety findings for Quartette. The CDTL has also thoroughly reviewed the safety data. Neither the DRUP Medical Officer nor CDTL identified any safety issues that suggest that the overall safety profile for Quartette would be different or less acceptable than for other approved COCs. Therefore, the following safety review focuses only on key safety issues that were identified during this review.

The integrated safety database consisted of study subjects who received at least one dose of Quartette in both the phase 2 (Trial 201) and phase 3 (Trial 301) trials. A total of 3,737 subjects were included in this integrated safety cohort. The mean age of the safety population was 27 years and approximately two-thirds of the population did not have a smoking history. The mean and median exposure to Quartette was 260 and 364 days, respectively. The discussion in this section will focus on findings from the integrated safety cohort.

Deaths and Non-fatal Serious Adverse Events:

No deaths occurred in the 2 trials conducted for this NDA. In the integrated safety cohort, a total of 59 of the 3,737 subjects (2%) had a total of 78 serious adverse events (SAEs). An overview of the SAEs is provided in the table below:

Table 4: Summary of Serious Adverse Events (SAEs) in Integrated Safety Cohort*

Adverse Events	**N**
Appendicitis, Pneumonia, Pyelonephritis, Viral Infection	2 events each, total 8
Helicobacter gastritis, Hepatitis C, Pelvic Inflammatory Disease, Pharyngitis, Rectal Abscess, Salpingitis, Staph infection, UTI	1 event each, total 8
Abortion, spontaneous	5
Abortion, missed, Ectopic pregnancy	2 each, total 4
Blighted ovum, Premature separation of placebo	1 each, total 2
Overdose	2
Injury, Joint injury, Lower limb fracture, multiple drug overdose, spinal fracture	1 each, total 5
Suicide attempt	5
Anxiety, Depression, Depression Suicidal, Drug dependence, Mental status changes	1 each, total 5
Abdominal pain	3
Gastrointestinal hemorrhage	2
Colitis, ileitis	1 each, total 2
Cholelithiasis, cholecystitis	3 each, total 6

Convulsion	3
Hemiparesis, hypoanesthesia	1 each, total 2
Headache, syncope	1 each, total 2
Bursitis, intervertebral disc protrusion, pain in extremity	1 each, total 3
Angina pectoris, supraventricular tachycardia, atrial fibrillation	1 each, total 3
Deep vein thrombosis	3
Pleural effusion, pulmonary embolism	1 each, total 2
Other events: Anemia, Hip dysplasia, uterine inflammation	1 each, total 3

*Source: Adapted from Table 21 of the DRUP Medical Officer's review dated March 1, 2013

The DRUP Medical Officer also performed an in-depth review of two serious safety concerns - thrombosis and suicidality (suicide attempt and suicidal ideation) that were reported in the integrated safety cohort. Both of these potentially serious adverse events have been reported with other COCs:

- **Thromboembolism:** A total of 4 thromboembolic events in 4 subjects (1 pulmonary embolism and 3 deep venous thrombosis (DVTs) were reported with Quartette use. The incidence of DVTs was 3/3,700, which was similar to that reported with other contraceptives (3-9/10,000 women-years).
- **Suicidality**: A total of 6 reports of suicide attempts/ideation, associated with drug overdoses, were associated with Quartette use. Although noting that it is difficult to perform an assessment of suicidality in a one-arm trial, the DRUP Medical Officer concluded that "Overall, there does not appear to be a higher risk of suicidality compared to the background rate."

After review of the SAEs reported with Quartette use, the DRUP Medical Officer concluded that, "These serious adverse events have been previously reported in association with COCs. There are no new safety signals." (See DRUP Medical Officer's review dated March 1, 2013)

The CDTL also commented in her March 27, 2013 review regarding the SAEs that, "The overall rate of SAEs is consistent with that in other US contraceptive trials."

Comments:

1. *The DRUP Medical Officer and CDTL evaluated the SAEs and concluded that the serious adverse events reported did not demonstrate a new safety signal or trend. I concur with their assessments.*
2. *I also concur that the reported thrombosis events do not represent a trend that appears higher than the background rates anticipated with COC use.*
3. *Suicidal ideation and suicidal attempts were reported at a somewhat higher rate than that reported in other trials. The DRUP Medical Officer evaluated the reports and concluded that there was no evidence that Quartette use would result in increased risk of these events above the background rate in the general population. I agree with that assessment.*

Discontinuations for Adverse Events:

A total of 476 of 3,737 subjects (13%) discontinued prematurely because of an adverse event (AE). Adverse events leading to drug discontinuation were evaluated by system organ class (SOC) and preferred term (PT). Adverse events leading to drug discontinuation reported by at least 0.5% of subjects are listed in the table below:

Table 5: Adverse events leading to discontinuation (≥ 0.5%) by PT*

Adverse events leading to drug discontinuation	**Quartette (n=3.737)**		
PT	**Events**	**Number of subjects**	**%**
Metrorrhagia	107	107	2.9
Vaginal hemorrhage	59	55	1.5
Weight increased	47	47	1.3
Acne	37	34	0.9
Headache	33	31	0.8
Mood swings	29	28	0.8
Nausea	29	28	0.8
Mood altered	19	17	0.5

*Source: Adapted from Table 22 of the DRUP Medical Officer's review dated March 1, 2013

Common adverse events leading to discontinuation occurred most frequently in the reproductive system organ class, which is expected with COC use. Adverse events related to bleeding and spotting were the most common reason for discontinuation. The DRUP Medical Officer reported that the combined incidence of bleeding and spotting events that led to discontinuation was 4.54%.

Comment: I agree with the DRUP Medical Officer that the rates of common adverse events and discontinuation reported in this integrated safety cohort are similar to those seen with other COC products.

Common Adverse Events (>5% of Subjects)

A total of 1,122 of 3,737 subjects (30%) reported at least 1 adverse event. These events were evaluated and those occurring in ≥ 5% of subjects are presented below:

Table 6: Common Adverse Events (≥ 5%) in the Integrated Safety Cohort by PT*

Adverse events	Quartette (n=3.737)		
PT	**Events**	**Number of subjects**	**Subject %**
Headache	863	457	12.2
Nasopharyngitis	498	395	10.6
Upper respiratory infection	459	368	9.9
Sinusitis	332	270	7.2
Nausea	304	250	6.7
Urinary tract infection	290	247	6.6
Metrorrhagia	331	219	5.9
Dysmenorrhea	283	212	5.7
Acne	218	195	5.2

*Source: Obtained from Table 22 of the DRUP Medical Officer's review dated March 1, 2013

The two most common adverse reactions for Quartette identified by the DRUP Medical Officer with a rate greater than 10% was headache (12.2%) and vaginal bleeding or metrorrhagia was reported at a rate of 9%.

Comment: The DRUP Medical Officer evaluated the common adverse events, including analysis of potential anaphylactic reactions. She did not identify any new safety signals or trends and agreed with the Applicant's assessment that the adverse events identified were not related to anaphylactic reactions. (See DRUP Medical Officer's review dated March 1, 2013). I concur with her conclusion.

Analysis of Bleeding and Spotting Patterns:

Unscheduled bleeding may not be acceptable to some women, and these women may discontinue use of the product. The Applicant collected the number of days of bleeding and/or spotting reported by subjects in a daily diary in Trial 301. Results from these diaries were summarized using descriptive statistics for both 28-day and 91-day cycles for scheduled and unscheduled bleeding. A summary of the proportion of subjects with no unscheduled bleeding and/or spotting days is presented in the table below.

Table 7: Subjects Reporting No Unscheduled Days of Bleeding and/or Spotting

Cycle (91 Day)	Subjects	Subjects w/o Bleeding and/or Spotting	%
1	3,064	242	7.9
2	2,615	520	19.9
3	2,361	713	30.2
4	2,170	696	32.1

*Source: Obtained from Table 30 from the DRUP Medical Officer's review dated March 1, 2013

The DRUP Medical Officer also evaluated other parameters of bleeding and spotting, including total number of bleeding and/or spotting days, scheduled total number of

bleeding and or spotting days, and a post hoc comparison of mean unscheduled bleeding and/or spotting days to other extended cycle combination oral contraceptives (COCs). She concluded in her March 2013 review that, "Overall, the bleeding profile of Quartette is similar to other extended cycle oral contraceptives." In addition, the DRUP Medical Officer observed that the pattern of scheduled bleeding and or spotting days was stable across all 4 extended cycles of Quartette, although approximately 70% of subjects had unscheduled bleeding or spotting by Cycle 4.

After review of the bleeding and spotting data, the DRUP Medical Officer concluded in her review that, "The choice of extended cycle must be balanced against the inconvenience of unscheduled bleeding or spotting."

The CDTL also commented in her March 27, 2013 review that, "The demonstrated bleeding profile was acceptable."

Comment: From my perspective, it appears that women who have unscheduled bleeding or spotting do drop out, which decreases compliance. However, for women who stay on Quartette, bleeding and spotting improves with continued use. Labeling will address findings related to the bleeding profile for Quartette.

Evaluation of Other Pertinent Safety Assessments:

The DRUP Medical Officer performed evaluations of the vital signs and trends in laboratory values, including assessment of changes in liver function testing. She also reviewed the 120-day Safety Update (submitted on September 27, 2012) that contained five updated pregnancy narratives. Although there is no postmarketing experience with this product, she did not identify any new safety information from these safety assessments or from other EE/LNG products that would impact approval of Quartette.

Overall Assessment of Safety:

The overall safety profile for Quartette, based on data obtained from the phase 2 and phase 3 trials (DR-ASC-201 and DR-103-301) appears to be comparable to other COCs approved for marketing in the US. Among the safety issues of greatest concern identified were those related to serious thromboembolic events such as a deep venous thrombosis (DVT) or a pulmonary embolism (PE). Although the total exposure to Quartette in trial 301 was greater than 34,000 28-day equivalent treatment cycles, it was not adequate to estimate accurately the risk of a serious VTE in Quartette users, there is no signal or trend in the integrated safety data that indicate that Quartette users will have a different thromboembolic risk than those using other COC products.

Data on unscheduled bleeding/spotting did not indicate that this product was significantly different from other extended COC regimes currently marketed in the US. Therefore, labeling will include unscheduled spotting/bleeding data from the Quartette safety database to inform risk/benefit for the individual woman seeking hormonal oral contraception.

The DRUP Medical Officer stated the following in her March 2013 review regarding the safety profile of Quartette that, "There are no new and unexpected safety issues identified upon review of the safety database submitted in this NDA or any suggestion that use of this product will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs."

The CDTL concurred with the DRUP Medical Officer in her review dated March 27, 2013 and commented that, "Overall, I believe that the safety profile of Quartette is consistent with that generally observed for other hormonal contraceptives."

No postmarketing requirements or postmarketing commitments were recommended by either the DRUP Medical Officer or CDTL.

Comment: I concur with the conclusions of the DRUP Medical Officer and CDTL that no new safety signals or trends, such as an increased reporting of venous thrombosis, were identified in the safety database of Quartette.

6. Advisory Committee Meeting

Combined oral contraceptives (COCs) have been approved for use in the US market since the 1960's. These COCs include a variety of progestins, dosage strengths and regimes, some of whom contain levonorgestrel and ethinyl estradiol as active drug substances, and have been approved using extended regimes. The safety issues associated with COCs containing levonorgestrel and ethinyl estradiol as extended regimes are well known and can be adequately labeled. Therefore, no Advisory Committee advice was necessary to make a regulatory determination on this application.

7. Pediatrics

The Applicant requested a waiver of pediatric studies in premenarcheal females (b) (4) because the indication is not relevant to this population. The Applicant also requested a waiver of studies in postmenarcheal females (b) (4) with the justification that safety and efficacy data for this population can be extrapolated from the adult data. The Division concurred that a partial waiver and extrapolation was appropriate. On January 9, 2013, the Pediatric Review Committee (PeRC) agreed to a partial waiver for patients from birth to 11 years of age, and to extrapolate efficacy for patients from 12 to 16 years of age.

8. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information and the Patient Package Insert. OPDP completed their review of Prescribing Information on March 6, 2013 and review of the Patient Package Insert on March 8, 2013. Their recommendations were discussed with the Division and have been implemented.

Office of Scientific Investigations (OSI):

OSI conducted inspections of three clinical sites that participated in Study DR-103-301 (Drs. Seger, Gersten and Portman) in support of this NDA. The Clinical Inspection Summary stated that, "Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication." (See OSI Clinical Inspection Summary dated February 23, 2012).

Division of Medication Error Prevention and Analysis (DMEPA):
204061

The DMEPA review team assessed the proposed tradename "Quartette" on September 10, 2012, and found it acceptable. DMEPA reassessed the tradename on January 7, 2013, and did not identify any new concerns. Therefore, DMEPA had no objections to the proprietary name.

In addition, the DMEPA review team provided a final review with recommendations on February 3, 2013, regarding the blister pack (trade and professional) labels, carton (trade and professional), foil pouch (trade and professional) and insert labeling for areas of vulnerability that could lead to medication errors. DMEPA's recommendations have been implemented.

Financial Disclosure**:**

The clinical review team did not identify any issues related to financial disclosures for the phase 3 study that impacted the study outcome (See DRUP Medical Officer review dated March 1, 2013).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team reviewed the label in a review dated March 26, 2013 and provided recommendations. These recommendations have been implemented.

9. Labeling

Labeling discussions are complete and labeling is acceptable to the review teams and the Applicant. Labeling was also evaluated by the following groups:

1. Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.
2. Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was reviewed by the Study Endpoints and Label Development (SEALD) Team. An edited version of the label was sent to the Applicant. The Applicant accepted the requested edits from SEALD. No additional labeling review by SEALD was required.

10. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the CDTL, DRUP Medical Officer, and the Clinical Pharmacology, ONDQA, and Statistical review teams that this combined oral contraceptive tablet product should receive an Approval action.

Risk Benefit Assessment:

Data from the phase 3 trial (DR-103-301) provide substantial evidence of efficacy, based on the Pearl Index of 3.19 (CI of 2.49, 4.03). In addition, based on the conclusions of the OSI inspection, the DRUP Medical Officer, the CDTL, and the Clinical Pharmacology and Statistical Reviewers believe that the submitted data were sufficient to support efficacy in women who will use this product for prevention of pregnancy and I agree.

The overall safety profile for Quartette was acceptable and is similar to other oral COC products. As with other COCs, cases of serious adverse events of thrombembolism (2 deep vein thromboses and one pulmonary embolism) were reported with Quartette and this risk will be include as class labeling for serious thrombotic events in the **WARNINGS AND PRECAUTIONS** section of labeling. Although six reports of suicidal ideation and/or attempts were reported in this trial, it is difficult to assess this risk given that this was a single arm trial. Given the background rate in the general population, although worsening of depression related to Quartette cannot be ruled out from this data, these events will be labeled. The most common adverse events (seen in >2% of subjects) were heavy/irregular vaginal bleeding, headache, acne, nausea, dysmenorrhea, and weight increased, which are similar to those seen with other combined oral contraceptive products. Tolerability related to unscheduled bleeding/spotting with Quartette use appears to also be similar to other extended regimen COC's and will be included labeling to inform risks/benefits for the individual woman seeking oral contraception.

I believe that the overall risk/benefit assessment favors approval of Quartette for use by women for prevention of pregnancy. Quartette will offer a lower total dose COC over the extended duration of use (91 days) than currently available products for women who wish to use a COC with an extended dosing cycle (91 day cycle) for prevention of pregnancy.

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

- No postmarketing requirements or commitments were recommended by any of the review teams during this review cycle.
- No risk evaluation and management strategy (REMS) program was recommended by any of the review teams during this review cycle.

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
03/28/2013