CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022247Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA #	NDA 022247
Applicant Name	Wyeth Pharmaceuticals Inc., a wholly-owned subsidiary of Pfizer Inc.
Date of Submission	October 3, 2012
PDUFA Goal Date	October 3, 2013
Proprietary Name / Established (USAN) Name	Duavee Conjugated estrogens/bazedoxifene acetate
Dosage Forms / Strength	0.45 mg/20 mg and 0.625 mg/20 mg
Proposed Indications	• Treatment of moderate to severe vasomotor symptoms associated with menopause • Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause • Prevention of postmenopausal osteoporosis
Action:	• Approval of the 0.45 mg/20 mg dose for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis • Complete response for the 0.625 mg/20 mg dose for all three indications

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Marcea Whitaker, M.D., Stephen Bienz, M.D., Gerald Willett, M.D. and Stephen Voss, M.D.
Statistical Reviews	Kate Dwyer, Ph.D., Sonia Castillo, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Leslie McKinney, Ph.D. and Alexander Jordan, Ph.D.
CMC Reviews	Donna Christner, Ph.D., Hamid Shafiei, Ph.D. and Moo Jhong Rhee, Ph.D. Sarah Pope Miksinski, Ph.D.
Division of Pharmaceutical Analysis	Michael Trehy and John Kauffman, Ph.D.
Office of Pharmaceutical Science	James Laurenson and Nakissa Sadrieh, Ph.D.
Clinical Pharmacology Review	Sayed Al Habet, R.Ph., Ph.D., LaiMing Lee, Ph.D., Fang Li, Ph.D., Yaning Wang, Ph.D., Myong Jin Kim, Pharm D. and E. Dennis Bashaw, Pharm D.
Biopharmaceutics Review	Kareen Riviere, Ph.D., John Duan, Ph.D. and Tapash Ghosh, Ph.D.
CDTL Review	Theresa Kehoe, M.D.
OSE/DMEPA	Manizheh Siahpoushan, Pharm.D., James Schlick, R.Ph., M.B.A. and Carol Holquist, R.Ph.
OMPI/DMPP	Robin Duer, M.B.A, B.S.N., R.N., Melissa Hulett, R.N., B.S.N., M.S.B.A. and LaShawn Griffiths, M.S.H.S-P.H., B.S.N, R.N.
OPDP	Lynn Panholzer, Pharm.D.
Office of Scientific Investigations	Roy Blay, Ph.D., Janice Pohlman, M.D., M.P.H. and Kassa Ayalew, M.D., M.P.H.
SEALD	Abimbola Adebowale, Ph.D. and Laurie Burke, R.Ph., M.P.H.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion
OMPI=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
PMHS=Pediatric and Maternal Health Staff
SEALD=Study Endpoints and Labeling Development

Summary Review for Regulatory Action

1. Introduction

Wyeth Pharmaceuticals Inc., a wholly-owned subsidiary of Pfizer Inc., has submitted this new drug application (NDA) for a fixed-dose combination tablet containing conjugated estrogens and bazedoxifene acetate (tradename Duavee). Conjugated estrogens are derived from the urine of pregnant mares and are marketed as Premarin in dosage strengths ranging from 0.3 mg to 1.25 mg. Bazedoxifene, a new molecular entity, is an estrogen receptor agonist at some tissues (e.g., bone) and an estrogen receptor antagonist at others (e.g., uterus).

The Applicant is seeking the following three indications, all of which are approved indications for Premarin:

1. Treatment of moderate to severe vasomotor symptoms associated with menopause
2. Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause
3. Prevention of postmenopausal osteoporosis

Unopposed estrogen increases the risk of endometrial cancer in women with a uterus. To date, only progestins are approved for use with estrogen to mitigate the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. If Duavee is approved, it will be the first product that uses a non-progestin (bazedoxifene) to mitigate the proliferative effects of estrogen on the uterus. Because of its anti-estrogenic effects at the breast, bazedoxifene could potentially provide protection to breast tissue as wel (b) (4)

The Applicant is proposing Duavee doses (shown as conjugated estrogens/bazedoxifene) of 0.45 mg/20 mg and 0.625 mg/20 mg for the vasomotor symptoms indication and the osteoporosis prevention indication. The Applicant is proposing only the 0.625 mg/20 mg dose for the vulvar and vaginal atrophy indication.

This NDA is in "The Program" under PDUFA V because one of the components in the drug product is a new molecular entity and the NDA was received after October 1, 2012.

This document serves as the Division's decisional memorandum for the application.

2. Background

(b) (4)

(b) (4)

This memorandum will focus on the efficacy of the combination of conjugated estrogens/bazedoxifene for the proposed indications, endometrial safety, and well-known adverse events of interest for estrogens as well as the adverse events identified during the reviews of the bazedoxifene monotherapy (b) (4).

3. CMC

The Chemistry/Manufacturing/Controls (CMC) reviewers recommend approval of the NDA. See the reviews by Donna Christner, Ph.D. and Sarah Pope Miksinski, Ph.D. for details.

(b) (4)

None of the impurities raise concerns and all Drug Master Files are acceptable.

The conjugated estrogens drug substance consists of a mixture of estrogenic substances, including estrone and equilin sulfates that are extracted from the urine of pregnant mares. (b) (4)

The Applicant has also provided sufficient information to support use of the bazedoxifene drug substance. (b) (4)

At CMC's request, the Applicant set appropriate specification and acceptance criteria (b) (4)

An important issue considered during the CMC review involved (b) (4)

(b) (4) The Applicant resolved this issue (b) (4) CMC agrees that the Applicant has adequately addressed this (b) (4) phenomenon.

The Office of Compliance has issued an acceptable recommendation for all manufacturing sites.

The CMC reviewers support expiration dating periods of 36 months for the Duavee 0.45 mg/20 mg dose (b) (4) The (b) (4) blister configuration must be used within 60 days after first opening.

The Office of Pharmaceutical Science required the Applicant to prepare an Environmental Assessment to evaluate the potential environmental impact from the use and disposal of Duavee. The review team found this Environmental Assessment to be acceptable and concluded that Duavee is not expected to have significant impact on the environment, obviating the need for an environmental impact statement. See the reviews by James Laurenson for details.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers have concluded that the available nonclinical data support approval of all three proposed indications and recommend approval of the NDA. See the review by Leslie McKinney, Ph.D. for details. Conjugated estrogens are already approved for the proposed indications and there are adequate nonclinical pharmacology/toxicology data for bazedoxifene monotherapy (b) (4) Nonclinical data to support Duavee also include pivotal repeat-dose toxicology studies with the combination of conjugated estrogens and bazedoxifene as well as additional mechanistic and efficacy pharmacology studies. Based on these studies, no new nonclinical safety concerns were identified.

Key nonclinical pharmacology/toxicology findings include:

- In general toxicology studies using bazedoxifene, a 16-fold safety margin (compared to the rat NOAEL) and a 39-fold safety margin (compared to the monkey NOAEL) based on area under the time-concentration curve (AUC) with the 20 mg/day clinical dose.

- Bazedoxifene alone is not genotoxic. In the rat and mice carcinogenicity studies, there is a dose-related increase in benign granulosa cell tumors of the ovary. This has been seen with other estrogen receptor agonists/antagonists (e.g., raloxifene) and may be a pharmacologic effect (central anti-estrogenic effects leading to hyperstimulation of the ovary by pituitary gonadotropins), although such data are lacking; therefore, a direct effect of bazedoxifene on the ovary cannot be excluded. This effect will be appropriately labeled.

- In reproductive toxicity studies, bazedoxifene interferes with estrous cyclicity, fertility and ability to maintain pregnancy in female rats, likely due to the anti-estrogenic effects. In both rats and rabbits, maternal toxicity was observed at all tested doses along with reduced implantation (rat) or increased abortion (rabbit). No major malformations were observed but there were vascular abnormalities, delayed ossification and enlarged thyroid glands. Duavee will be indicated for postmenopausal women only, but these findings will be described in labeling.

- Conjugated estrogens do not appear to overcome bazedoxifene-induced changes in the ovary, vagina and cervix. For example, bazedoxifene-induced vaginal and cervical atrophy was not prevented by the presence of conjugated estrogens. In addition, benign granulosa cell tumors are also seen in animals treated chronically with the combination of conjugated estrogens plus bazedoxifene. The clinical relevance of these findings is unclear, but these findings will also be included in labeling.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted an extensive clinical pharmacology program to support Duavee and also relies on data from the previously conducted bazedoxifene monotherapy program.

The Applicant used three different formulations (A, B and C) in the phase 3 program, none of which are the to-be-marketed formulation. The Clinical Pharmacology reviewers are satisfied that these formulations are adequately bridged via bioequivalence studies to the to-be-marketed product (formulation CF) and find the NDA acceptable for approval. The bridging is briefly discussed here. See the review and review addendum by Sayed Al Habet, R.Ph., Ph.D. for details.

Formulation A was used in Study 303, which supports the endometrial safety of Duavee and is one of two pivotal trials supporting the osteoporosis prevention indication. Formulation B was used in Study 305 (which is the pivotal trial supporting the vasomotor symptoms indication) and Study 306 (which is the pivotal trial supporting the vulvar and vaginal atrophy indication). (b) (4) Study 304, which was initially intended to also support the endometrial safety of Duavee and the osteoporosis indication, used Formulation B for the first several months and then switched patients to Formulation C. (b) (4)

(b) (4) Applicant's subsequent testing showed that Formulation C was not bioequivalent to Formulation A. Therefore, the Applicant chose to conduct a new phase 3 trial (Study 3307) to replace Study 304 and to support endometrial safety and the osteoporosis indication.

(b) (4) Table 1 below shows how Formulations A and B are bridged to Formulation CF with regard to the bazedoxifene exposures. Although not shown in this memorandum, Clinical Pharmacology determined that there is adequate bridging of the conjugated estrogens component as well.

Table 1. Pivotal bioequivalence studies comparing bazedoxifene pharmacokinetics (Cmax, AUC) with the to-be-marketed formulation (CF) to formulations A and B used in the phase 3 trials

Study	Conjugated Estrogens/ Bazedoxifene dose	Compared Formulations	Cmax Ratio[1] (90% CI)	AUC Ratio[1] (90% CI)
1122	0.625 mg/20 mg	CF vs. A	98 (86-112)	101 (92-110)
1137	0.45 mg/20 mg	CF vs. A	106 (96-117)	105 (98-112)
1139	0.625 mg/20 mg	CF vs. B	107 (95-121)	106 (96-116)
1142	0.45 mg/20 mg	CF vs. B	99 (87-113)	99 (90-109)

CI = confidence interval
CF = to-be-marketed formulation
A, B = formulations used in the phase 3 trials
[1]Geometric Least Squares Means Ratios

As mentioned above, Formulation C is not bioequivalent to Formulation A. Based on three bioavailability studies, the mean Cmax for bazedoxifene was 16-32% lower and the mean AUC for bazedoxifene was 18-36% lower when Formulation C was compared to Formulation A. Although the to-be-marketed formulation (which is bioequivalent to Formulation A) yields higher bazedoxifene exposures than Formulation C, the Clinical Pharmacology reviewers note that bazedoxifene exposures with the to-be-marketed formulation could be modestly reduced in some patients to the levels seen with Formulation C due to co-existing intrinsic or extrinsic factors. For example, Pharmacometrics estimates a 19% decrease in bazedoxifene exposures in patients with a body mass index >27 kg/m^2 compared to those ≤27 kg/m^2. (b) (4) This issue of reduced bazedoxifene exposures and corresponding loss of endometrial protection is discussed in more detail in the Safety Section of this memorandum.

There is no significant pharmacokinetic interaction between conjugated estrogens and bazedoxifene.

When a conjugated estrogens/bazedoxifene 0.625 mg/20 mg tablet (Formulation C) was given with a high-fat meal there was a 27% increase in bazedoxifene AUC compared to fasting conditions. There was no appreciable food-effect for the conjugated estrogens component. In the phase 3 trials, study drug was taken without regard to food.

Bazedoxifene has a Tmax around 2 hours and a half-life of approximately 30 hours. Its pharmacokinetics are not affected by race/ethnicity and are dose-proportional from 2.5 mg to 120 mg. Bazedoxifene AUC and Cmax is about 2-fold higher after multiple dosing compared to single doses. Bazedoxifene is highly protein-bound (97%) but does not affect the protein binding of warfarin, digoxin or diazepam, and these drugs do not affect the protein binding of bazedoxifene.

Bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver. Concomitant use of products that induce UGT enzymes (e.g., rifampin, phenobarbital, carbamazepine and phenytoin) may increase bazedoxifene metabolism, reducing bazedoxifene exposures. Clinical Pharmacology is recommending that this information be included in labeling under Section 7 (Drug Interactions).

Approved labels for conjugated estrogens state that estrogens are partially metabolized by CYP3A4 and that CYP3A4 inhibitors may increase plasma concentrations of estrogen. However, the extent to which this interaction may occur with Duavee is uncertain because a CYP3A4 inhibitor drug-drug interaction study has not been conducted with Duavee or any of the approved conjugated estrogens products. Therefore, Clinical Pharmacology is recommending that we require a drug-drug interaction study post-approval to better define the potential effect of CYP3A4 inhibitors on exposures to conjugated estrogens. I agree with this request because, as discussed under the Safety section of this memorandum, there is the potential for loss of uterine protection when exposures to conjugated estrogens increase relative to exposures with bazedoxifene. Information from this study would inform on the extent of the concern with co-administered CYP3A4 inhibitors. The Applicant has agreed to conduct this drug-drug interaction study and both FDA and the Applicant have reached agreement on the study timelines, which will be included in the approval letter. Labeling under Drug Interactions will mention the potential increase in risk of endometrial hyperplasia when CYP3A4 inhibitors are chronically administered with Duavee and will remind the healthcare provider to evaluate abnormal vaginal bleeding in such patients. Additional revisions to this labeling may be needed once results of the postmarketing required study are available.

In a Thorough QT Study, bazedoxifene doses up to 120 mg did not prolong the QTc interval.

There is no significant pharmacokinetic interaction between bazedoxifene and ibuprofen, atorvastatin or azithromycin.

The clinical pharmacology reviewers are recommending against the following:

- (b) (4)

(b) (4)

- Use of Duavee in those with hepatic impairment, due to an increase in bazedoxifene exposure (AUC) in those with mild (2.4-fold increase), moderate (2.1-fold increase) and severe (3.7-fold increase) disease. As discussed in the Efficacy section, there is evidence of attenuated efficacy with increasing bazedoxifene doses.
- Use of Duavee in those with renal impairment, due to inadequate data in this population. The Applicant excluded patients with renal impairment from the phase 3 studies and did not conduct an appropriately designed renal impairment pharmacokinetic study. Based on the available data, the clinical pharmacology reviewers have concluded that the impact of renal impairment on bazedoxifene pharmacokinetics is unknown.
- Use of Duavee in the elderly (>75 years old), due to an age-related increase in bazedoxifene exposures (2.6-fold increase) compared to those 51-64 years old. None of the phase 3 clinical trials submitted in support of conjugated estrogens/bazedoxifene enrolled women over 75 years of age.

The NDA includes an *in vitro in vivo* correlation (IVIVC) for the conjugated estrogens portion of Duavee. The Biopharmaceutics reviewers identified several deficiencies with the model and communicated those deficiencies during the Late Cycle Meeting. In a follow-up submission, the Applicant stated that they do not intend to use the proposed IVIVC model and that they will submit a post-approval supplement to address these comments if they decide to pursue the IVIVC model at a later date. See the review by Dr. Duan for details.

6. Clinical Microbiology

Not applicable because Duavee is a tablet.

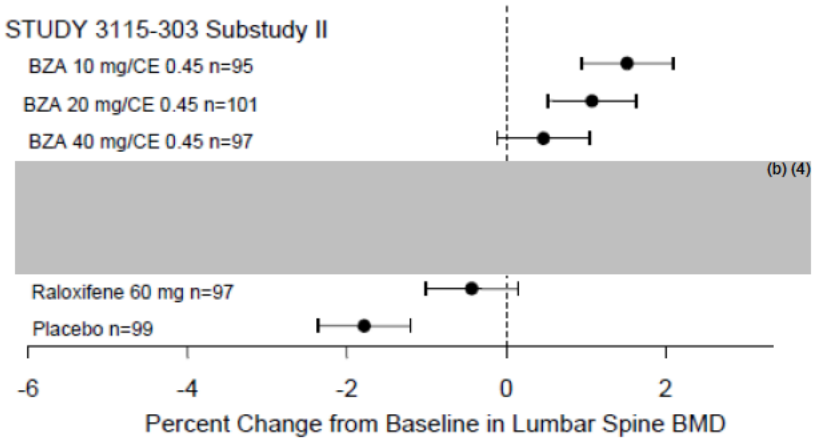
7. Clinical/Statistical-Efficacy

This section focuses on the key efficacy findings from the four Phase 3 trials that the Applicant has submitted in support of the proposed indications. These trials enrolled postmenopausal women with intact uteri to provide evaluation of uterine safety. For further details see the statistical reviews by Drs. Kate Dwyer and Sonia Castillo and the clinical review co-authored by Drs. Marcea Whitaker, Stephen Bienz, Gerald Willett and Stephen Voss.

Although Duavee is a fixed-dose combination product, it is acceptable that the Applicant did not conduct factorial trials to compare the efficacy of the combination product to that of both components given individually. The principle reason for including the bazedoxifene component in Duavee is to mitigate the well-known proliferative effects of estrogen on the uterus and not to provide additive efficacy to that of conjugated estrogens. In fact, there is evidence that bazedoxifene alone exacerbates vasomotor symptoms based on adverse event

reporting in the bazedoxifene monotherapy trials (see pages 69-70 of the primary clinical review) and that increasing bazedoxifene doses mitigate the effects of conjugated estrogens on bone (Figure 1).

Figure 1. Percent change (with 95% confidence intervals) in lumbar spine bone mineral density (BMD) from baseline to month 12 in one of the osteoporosis substudies (CE = conjugated estrogens; BZA = bazedoxifene) – from the Applicant's Integrated Summary of Safety



Vasomotor Symptoms: Study 305 is the pivotal trial supporting the efficacy of Duavee for the treatment of moderate to severe vasomotor symptoms. Dr. Dwyer considers the analyses involving a small number of patients from Study 303 (n=28-33/group) as supportive. Due to the limitations involving Study 303, this memorandum focuses only on Study 305 for the vasomotor symptoms indication.

Study 305 was a 12-week, multicenter, double-blind trial that randomized 332 postmenopausal women with ≥7 moderate to severe vasomotor symptoms per day (or ≥50 per week) to conjugated estrogens/bazedoxifene 0.45 mg/20 mg (n=133), (b) (4) or placebo (n=66). This trial used the four standard co-primary efficacy endpoints for vasomotor symptoms, as recommended in the draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." These co-primary endpoints evaluated the change in frequency and severity of moderate to severe hot flushes from baseline to Week 4 and from baseline to Week 12. Severity of hot flushes was defined as outlined in the 2003 draft guidance – mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity) or severe (sensation of heat with sweating causing cessation of activity). Dr. Dwyer discusses how the severity scores were calculated. This approach has been used with virtually all other approved estrogen and estrogen/progestin products for this indication.

The primary statistical population used the modified intent-to-treat population (all randomized patients who had taken at least one dose of study medication and had recorded at least 5 days

of data at baseline and at least 5 days of data for at least one on-therapy week) with last-observation-carried-forward for missing data. The primary analysis was conducted using an ANCOVA model with treatment and study site as factors and baseline value as a covariate with a term for treatment-by-study-site interaction. The Applicant controlled the type 1 error rate using a stepwise testing procedure so that the conjugated estrogens/bazedoxifene 0.45 mg/20 mg dose was tested only if there was a win on all four co-primary endpoints with the higher 0.625 mg/20 mg dose.

As shown in Table 2, conjugated estrogens/bazedoxifene results in a statistically significant reduction in both the frequency and severity of moderate to severe hot flushes from baseline to Week 4 and from baseline to Week 12 (all p-values <0.001).

Dr. Dwyer conducted sensitivity analyses using other statistical populations (e.g., observed data, the per-protocol population), excluding the 5 patients with missing source documentation (<2% of the modified intent-to-treat population) and excluding all 22 patients (~7% of the modified intent-to-treat population) enrolled at the Christopher Hutchison study site (the Office of Scientific Investigations raised concerns with data integrity at this site - see Section 11). All of these analyses yielded results that were consistent with the primary efficacy analysis.

This phase 3 trial provides sufficient evidence to support the efficacy of Duavee for the vasomotor symptoms indication. The efficacy results are adequately supported by low p-values and an acceptable magnitude of the treatment effect. For example, the mean treatment difference between drug and placebo in hot flush frequency at Weeks 4 and 12 is greater than 2/day, which is the threshold that has historically been considered acceptable without the need to further evaluate clinical meaningfulness using an anchoring question. In addition, these results are considered in the backdrop of extensive clinical trial experience establishing the efficacy of various hormonal preparations (estrogen and estrogen plus progestin), including conjugated estrogens (i.e., Premarin) itself, for the treatment of vasomotor symptoms.

Table 2. Primary efficacy analyses (Study 305, modified intent-to-treat population) (Adapted from Table 5 in Dr. Dwyer's review)

	Frequency			**Severity**		
	CE/bazedoxifene		**Placebo**	**CE/bazedoxifene**		**Placebo**
	0.45 mg/20 mg	**0.625 mg/20 mg**		**0.45 mg/20 mg**	**0.625 mg/20 mg**	
		(b) (4)			(b) (4)	
Baseline	10.3		10.5	2.3		2.3
Week 4						
Change	-5.9		-2.8	-0.5		-0.1
Treatment effect	-3.1 (-4.4, -1.7)*			-0.5 (-0.7, -0.3)*		
Week 12						
Change	-7.6		-4.9	-0.9		-0.3
Treatment effect	-2.7 (-3.8, -1.6)*			-0.6 (-0.9, -0.4)*		

Change = change from baseline; Treatment effect = placebo-subtracted treatment difference
*p<0.001

Osteoporosis: The Applicant submitted data from two trials (Study 303 and Study 3307) to support the prevention of osteoporosis indication.

Study 303: This 2-year, multicenter, double-blind trial randomized postmenopausal women to one of six daily doses of conjugated estrogens/bazedoxifene (0.45 mg/10 mg, 0.45 mg/20 mg, 0.45 mg/40 mg, 0.625 mg/10 mg, 0.625 mg/20 mg, 0.625 mg/40 mg), raloxifene 60 mg and placebo. Patients were to have adequate intake of calcium and vitamin D throughout the study. The primary endpoint for the overall trial was the incidence of endometrial hyperplasia at Year 1. Results for this endpoint are discussed in the Safety section. The efficacy for osteoporosis prevention was assessed in two substudies. Women in Substudy I (n=1454) had to be >5 years postmenopausal, have a lumbar spine or total hip T-score of -1 to -2.5, and have at least one additional risk factor for osteoporosis. Those in Substudy II (n=861) had to be 1-5 years postmenopausal with at least one additional risk factor for osteoporosis. Dual-energy x-ray absorptiometry (DXA) scans were obtained at screening and Months 6, 12, 18 and 24, and were evaluated centrally. The primary efficacy endpoint for the two substudies was the mean percent change from baseline at Year 2 in lumbar spine bone mineral density. A key secondary endpoint was the mean change from baseline at Year 2 in total hip bone mineral density. These analyses used the modified intent-to-treat population (randomized patients who took at least one dose of study medication and had a baseline and at least one post-baseline bone mineral density value) with last observation-carried-forward for missing data. The ANCOVA model had treatment and region as factors and baseline bone mineral density and years since menopause as covariates.

The Applicant used an alpha of 0.048 for the primary efficacy analyses of bone mineral density because some alpha was spent on an interim analysis. The Applicant used hierarchical testing to control the overall type 1 error rate across the different conjugated estrogens and bazedoxifene doses.

Study 3307: This 1-year, multicenter, double-blind trial randomized postmenopausal women to one of two daily doses of conjugated estrogens/bazedoxifene (0.45 mg/20 mg or 0.625 mg/20 mg), bazedoxifene 20 mg alone, conjugated estrogens/medroxyprogesterone 0.45 mg/1.5 mg or placebo. Patients were to have adequate intake of calcium and vitamin D throughout the study. The primary endpoint of the overall trial was the incidence of endometrial hyperplasia at Year 1. Results for this endpoint are discussed in the Safety section. The efficacy for osteoporosis prevention was assessed in a substudy, which included 590 patients ≤5 years postmenopausal. The primary efficacy endpoint for the substudy was the mean percent change from baseline at Year 1 in lumbar spine bone mineral density. A key secondary endpoint of the substudy was the mean change from baseline at Year 1 in total hip bone mineral density. DXA scans were obtained at screening and Months 6 and 12, and were evaluated centrally. The statistical population and the statistical model for the osteoporosis analyses were the same as those described for Study 303. The Applicant again used a hierarchical testing strategy to control type I error for the two conjugated estrogens/ bazedoxifene doses.

Results from Studies 303 and 3307: Table 3 summarizes the lumbar spine and total hip bone mineral density changes at 2 years (Study 303) and at 1 year (Study 3307). All comparisons of conjugated estrogens/bazedoxifene 0.45 mg/20 mg and 0.625 mg/20 mg to placebo were highly statistically significant ($p<0.001$). In Study 303, both the 0.625 mg/20 mg and 0.45 mg/20 mg doses of conjugated estrogens/bazedoxifene also compare favorably to raloxifene at both the lumbar spine and total hip. However, in Study 3307, the treatment effect for both the 0.625 mg/20 mg and 0.45 mg/20 mg doses of conjugated estrogens/bazedoxifene were numerically less than that seen with conjugated estrogens/medroxyprogesterone acetate 0.45 mg/1.5 mg, particularly at the lumbar spine.

As a sensitivity analysis, Dr. Castillo excluded those patients in the Study 303 substudies with missing source documentation (<10% of patients across the placebo and conjugated estrogens/bazedoxifene 0.45 mg/20 mg and 0.625 mg/20 mg groups). These results were still highly statistically significant and not meaningfully different from the results including all patients (see Tables 3.4, 3.6 and 3.8 in Dr. Castillo's review).

As discussed by Dr. Kehoe, few fractures were reported in the Duavee clinical program. The Applicant did not power the trials to show a reduction in fracture outcomes. Nonetheless, it is still reasonable to grant an osteoporosis prevention indication for Duavee based only on the bone mineral density data because:

- Duavee contains the same conjugated estrogens as that contained in Premarin, and Premarin is indicated for the prevention of postmenopausal osteoporosis.
- (b) (4) bazedoxifene 20 mg/day has been shown to provide fracture risk reduction (b) (4) In Study 3307, both the 0.625 mg/20 mg and 0.45 mg/20 mg doses of conjugated estrogens/bazedoxifene result in comparable or numerically greater improvements in bone mineral density than bazedoxifene 20 mg alone.
- The bone mineral density changes with conjugated estrogens/bazedoxifene compare favorably to that of raloxifene, which also has an osteoporosis prevention indication.

However, labeling should include a Limitation of Use consistent with how other estrogens are labeled, noting that use of Duavee only for the prevention of postmenopausal osteoporosis should be limited to women at significant risk of osteoporosis after non-estrogen alternatives have been carefully considered.

Table 3. Primary and key secondary efficacy analyses to support the osteoporosis prevention indication (modified intent-to-treat population with last-observation-carried-forward) (Adapted from Tables 3.3, 3.5, 3.8 and 3.9 in Dr. Castillo's review)

	Lumbar Spine Bone Mineral Density			Total Hip Bone Mineral Density		
	n	LS Mean % Change from Baseline	LS Mean Difference from Placebo (95% CI)	n	LS Mean % Change from Baseline	LS Mean Difference from Placebo (95% CI)
Study 303 – Substudy I (>5 years postmenopausal); Endpoint at 2 years						
CE/BZA 0.625 mg/20 mg	[redacted] (b) (4)					
CE/BZA 0.45 mg/20 mg	160	1.6%	3.1% (2.3%, 3.9%)	160	1.1%	1.7% (1.2%, 2.3%)
Raloxifene	164	0.7%	2.2% (1.4%, 3.0%)	164	0.9%	1.5% (1.0%, 2.1%)
Placebo	159	-1.5%		158	-0.7%	
Study 303 – Substudy II (1-5 years postmenopausal); Endpoint at 2 years						
CE/BZA 0.625 mg/20 mg	[redacted] (b) (4)					
CE/BZA 0.45 mg/20 mg	101	1.7%	3.6% (2.6%, 4.6%)	102	0.5%	1.9% (1.2%, 2.5%)
Raloxifene	97	0.2%	2.1% (1.1%, 3.1%)	96	-0.3%	1.1% (0.5%, 1.8%)
Placebo	99	-1.9%		99	-1.4%	
Study 3307 (<5 years postmenopausal); Endpoint at 1 year						
CE/BZA 0.625 mg/20 mg	[redacted] (b) (4)					
CE/BZA 0.45 mg/20 mg	119	0.2%	1.5% (0.8%, 2.2%)	119	0.5%	1.2% (0.8%, 1.7%)
BZA 20 mg	56	0.1%	1.3% (0.5%, 2.2%)	56	0.5%	1.2% (0.6%, 1.8%)
CE/MPA 0.45 mg/1.5 mg	59	1.3%	2.6% (1.7%, 3.4%)	59	0.7%	1.4% (0.9%, 2.0%)
Placebo	139	-1.3%		139	-0.7%	

CI = confidence interval
CE = conjugated estrogens; BZA = bazedoxifene; MPA = medroxyprogesterone acetate
All p-values <0.001 except for the p-value <0.01 comparing bazedoxifene 20 mg vs. placebo in Study 3307

Vulvar and Vaginal Atrophy: [redacted] (b) (4)

[redacted] (b) (4)

[redacted]

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8. Safety

Approximately 1,000 patients were treated for at least one year with each of the two Duavee doses the Applicant is proposing to market. Stephen Bienz, M.D. conducted the integrated review of safety. As discussed by Drs. Bienz and Kehoe, the safety profile is generally consistent with that of other approved estrogen products and there are no findings that represent a new safety signal or trend based on the standard analyses involving deaths, serious adverse events, discontinuations due to adverse events, overall adverse events, vital signs and laboratory data. This memorandum will focus on key adverse events of interest based on findings in the bazedoxifene monotherapy (b) (4) and known safety concerns with estrogens.

Endometrial safety: Gerald Willett, M.D. conducted an extensive review of the endometrial safety of Duavee. As discussed by Dr. Willett, endometrial hyperplasia on tissue obtained by endometrial biopsy is typically used as a surrogate endpoint for endometrial cancer. The 2003 draft guidance "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that the endometrial hyperplasia rate not exceed 1% with the upper bound of the corresponding one-sided 95% confidence interval not exceeding 4%. The Applicant assessed endometrial hyperplasia in three of the five phase 3 Duavee clinical trials (Studies 303, 304 and 3307). The incidence of endometrial hyperplasia at Year 1 was the primary endpoint for Studies 303 and 304 and a co-primary endpoint for Study 3307. Dr. Willett also reviewed the available 2-year endometrial hyperplasia data (Studies 303 and 304) because these longer term safety data are relevant for the proposed chronic indications.

Endometrial hyperplasia results are summarized in Table 5. Based on the recommended thresholds of 1% and 4% described above, the 10 mg dose of bazedoxifene does not provide adequate endometrial protection when combined with 0.45 mg or 0.625 mg of conjugated estrogens. In all three trials, the 20 mg dose of bazedoxifene provides adequate endometrial protection when combined with 0.45 mg of conjugated estrogens. However, the 20 mg bazedoxifene dose does not provide adequate endometrial protection in Study 304 when combined with 0.625 mg of conjugated estrogens, particularly through Year 2. As discussed by Drs. Willett and Kehoe, Study 304 was originally designed to serve as one of two trials to support the endometrial safety of Duavee. (b) (4)

This unexpected finding has been attributed to a change in formulation partway through the trial from Formulation B to Formulation C. As discussed in the CMC section of this memorandum, the formulation was changed to address the (b) (4) phenomenon with Formulation B that affected dissolution testing. In one single-dose study, bazedoxifene exposure (AUC) was about 18% lower with Formulation C than Formulation A. In another single-dose study, bazedoxifene exposure (AUC) was about 26% lower with Formulation C than Formulation A. In a multiple-dose study, bazedoxifene exposure (AUC) was about 36% lower with Formulation C than Formulation A (Formulation B is bioequivalent to Formulation A, and both Formulation A and B are bioequivalent to the to-be-marketed product). As discussed by Dr. Kehoe, all cases of endometrial hyperplasia in Study 304 occurred while patients were taking Formulation C. The number of months on Formulation C until a concerning endometrial biopsy result was identified ranged from 5 to 18.

Table 5. Endometrial hyperplasia findings in the phase 3 program
Data in red exceed the recommended threshold
(Adapted from Tables 82, 83, 93, 94 and 100 in the primary clinical review)

Treatment Group	Through Year 1 (primary endpoint)			Through Year 2		
	n/N	Hyperplasia Incidence (%)	Upper Bound (%)[1]	n/N	Hyperplasia Incidence (%)	Upper Bound (%)[1]
Study 303						
CE 0.45 mg/BZA 40 mg	0/309	0.0	1.2[2]	0/268	0.0	1.4
CE 0.45 mg/BZA 20 mg	0/335	0.0	1.1[2]	2/293	0.7	<4
CE 0.45 mg/BZA 10 mg	3/320	0.9	2.7	7/277	**2.5**	**5.1**
CE 0.625 mg/BZA 40 mg	(b) (4)					
CE 0.625 mg/BZA 20 mg						
CE 0.625 mg/BZA 10 mg						
Raloxifene 60 mg	0/298	0.0	1.2	0/261	0.0	1.4
Placebo	0/312	0.0	1.2	0/259	0.0	1.4
Study 304						
CE 0.45 mg/BZA 20 mg	0/261	0.0	1.1	0/131	0.0	2.3
CE 0.625 mg/BZA 20 mg[3]	(b) (4)					
CE 0.45 mg/1.5 mg MPA	0/119	0.0	2.5	0/66	0.0	**4.4**
Placebo	0/135	0.0	2.2	0/79	0.0	3.7
Study 3307						
CE 0.45 mg/BZA 20 mg	1/335	0.3	1.4	-	-	-
CE 0.625 mg/BZA 20 mg	(b) (4)					
Bazedoxifene 20 mg	0/169	0.0	1.8	-	-	-
CE 0.45 mg/1.5 mg MPA	0/149	0.0	2.0	-	-	-
Placebo	1/354	0.3	1.3	-	-	-

CE = conjugated estrogens; BZA = bazedoxifene; MPA = medroxyprogesterone acetate
[1]Upper bound of the one-sided confidence interval for the incidence of endometrial hyperplasia; all analyses used a 95% one-sided confidence interval unless specified otherwise
[2] 97.5% one-sided confidence interval was used to address multiplicity for these primary analyses

(b) (4)

Based on dense pharmacokinetic sampling, the clinical pharmacology team has identified an association between increased body mass index and increased clearance of bazedoxifene. On average, there is a 16% decrease in bazedoxifene exposure in patients with body mass index >27 kg/m^2 (n=144) compared to those with body mass index ≤27 kg/m^2 (n=93). This cutpoint of 27 kg/m^2 reflects the average body mass index of patients in the dense pharmacokinetic dataset. Table 6 shows the incidence of endometrial hyperplasia through Year 2 in Study 303 according to body mass index, using the 27 kg/m^2 cutpoint. These data show a clear concern for loss of endometrial protection among those with body mass index >27 kg/m^2 when the 10

mg bazedoxifene dose is used in combination with either the 0.45 mg or 0.625 mg dose of conjugated estrogens. There is less of a concern with the 20 mg bazedoxifene dose, particularly when combined with the 0.45 mg dose of conjugated estrogens.

Table 6. Incidence of endometrial hyperplasia through Year 2 in Study 303 according to body mass index (adapted from Table 14 in the clinical pharmacology addendum)

Dose	Body Mass Index ≤27 kg/m^2		Body Mass Index >27 kg/m^2	
	n/N	Incidence	n/N	Incidence
0.45 mg/10 mg	3/242	1.2%	5/124	4.0%
0.45 mg/20 mg	2/228	0.9%	0/145	0%
0.45 mg/40 mg	0/241	0%	0/116	0%
0.625 mg/10 mg	[redacted]			
0.625 mg/20 mg				
0.625 mg/40 mg				

(b) (4)

[redacted]

(b) (4)

Of note, Dr. Willett identified one case of endometrial cancer in the Duavee program (Subject 307474 in Study 303 who received conjugated estrogens/bazedoxifene 0.45 mg/20 mg for 723 days). Based on the Day 723 endometrial biopsy, two pathologists diagnosed endometrial cancer and a third diagnosed complex hyperplasia with atypia. The post-study dilatation and curettage showed small fragments of atypical endometrium suspicious for carcinoma. No residual atypical endometrium was identified at the time of hysterectomy. Conclusions regarding causality are not possible based on this isolated case.

Venous thromboembolism: Bazedoxifene and other estrogen antagonists/agonists such as tamoxifene as well as conjugated estrogens share safety concerns that include a potential increased risk of venous thromboembolism with chronic use. As discussed by Dr. Kehoe, venous thromboembolic events from the five phase 3 trials were adjudicated by an independent venous thromboembolic event committee. There were no reported events of pulmonary embolism or retinal vein thrombosis. The incidence of deep vein thrombosis was low (3 patients in the conjugated estrogens/ bazedoxifene 0.45 mg/20 mg group, no patients in the conjugated estrogens/bazedoxifene 0.625 mg/20 mg group and 1 patient in the placebo group). These data are inconclusive due to the small number of events; therefore, the Duavee label should include the standard class warning for estrogens regarding venous thromboembolism. There is some discussion in the clinical reviews about the low incidence of

venous thromboembolism in the Duavee trials compared to that seen in the Women's Health Initiative. One explanation is the younger population in the Duavee trials (mean age around the mid-50s) compared to the older population enrolled in the Women's Health Initiative (mid-60s).

Cerebrovascular events: Conjugated estrogens and bazedoxifene also have the potential to increase the risk of cerebrovascular events. As discussed by Dr. Kehoe, cerebrovascular events from the five phase 3 trials were adjudicated by an independent cerebrovascular event committee. The incidence of stroke was low (1 patient in each conjugated estrogens/ bazedoxifene group and 0 patients in the placebo group) as was the incidence of transient ischemic attack (2 patients in the conjugated estrogens/bazedoxifene 0.45 mg/20 mg group and no patients in the conjugated estrogens/bazedoxifene 0.625 mg/20 mg and placebo groups). These data are inconclusive due to the small number of events; therefore, the Duavee label should include the standard class warning for estrogens regarding stroke. The low event rate of stroke compared to that seen in the Women's Health Initiative is also possibly explained by the younger patient population enrolled into the Duavee trials.

Cardiovascular events: As discussed by Dr. Kehoe, cardiovascular events from the five phase 3 trials were adjudicated by an independent cardiovascular event committee. The incidence of myocardial infarction was low (2 patients in the conjugated estrogens/ bazedoxifene 0.45 mg/20 mg group, 1 patient in the conjugated estrogens/bazedoxifene 0.625 mg/20 mg group and 2 patients in the placebo group). These data are inconclusive due to the small number of events; therefore, the Duavee label should include the standard estrogen text regarding cardiovascular events.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee. We did not identify efficacy or safety issues that needed input from an advisory panel.

10. Pediatrics

This NDA triggers the Pediatric Research Equity Act (PREA) because of the new active ingredient. The Division and the Pediatric Review Committee (PeRC) concur with the Applicant's request for a full waiver of the pediatric requirements. Such studies would be impossible/impractical because the intended indications all occur in postmenopausal women.

11. Other Relevant Regulatory Issues

Tradename Review: The Division of Medication Error Prevention and Analysis reviewed the tradename Duavee and found it acceptable within 90 days of the action goal date. See the reviews by Manizheh Siahpoushan, Pharm.D. and James Schlick, R.Ph., M.B.A. for details.

Financial Disclosures: As discussed by Dr. Kehoe, about 50% of investigators disclosed financial interests ranging from $26,000 to $626,000, mainly for speaking engagements, honoraria and consulting fees. However, these investigators individually enrolled a small number of patients into the trials (b) (6) In addition, some features of the studies (e.g., double-blinded design, centrally analyzed bone mineral density measures, central pathology review of the endometrial biopsy specimens) protect against bias. Based on these considerations, I agree that the financial interests would not be expected to impact study results.

Site Inspections: The Office of Scientific Investigations (OSI) inspected six clinical sites (one of these sites – David Portman, M.D. – was inspected for both Study 306 and Study 3307), the bone mineral density central site, and the Applicant. The final classification was NAI (No deviation from regulations) for the bone mineral density central site and for three of the clinical sites. The Applicant and two clinical sites received a VAI (Deviations from regulations). A third clinical site received a classification of OAI (Significant deviations from regulations; data unreliable) from the field investigator; however, OSI subsequently downgraded the final classification to VIA. Additional information regarding these sites is summarized below. For further details, see the review by Roy Blay, Ph.D.

VAI: The Edmund Baracat, M.D., Ph.D. enrolled 889 patients (25%) into Study 303. No major discrepancies were found when data line listings were compared with source documents and case report forms. There were some minor observations, but the most troubling finding was that 80 patients (9%) were missing all of their source documents. There were some data to suggest that these patients existed (e.g., screening log and data clarification forms) but OSI could not verify data integrity for these 80 patients. OSI recommends that we consider the potential implications of these missing records (e.g., under-reporting of adverse events or overstatement of efficacy) in deciding whether to rely upon data from this site. During the Late Cycle Meeting, the Applicant clarified that the missing source documents were related to closure of the study site and movement of the patient files to storage facilities. The Applicant stated that they conducted both internal and third-party quality assurance inspections and determined that the pattern of missing source documentation was random. They were unable to identify the reasons for the missing files. As discussed by Dr. Kehoe, exclusion of the 80 patients with missing source documentation did not impact overall conclusions regarding the efficacy of conjugated estrogens/bazedoxifene on bone mineral density. Dr. Castillo also conducted a sensitivity analysis excluding all patients from this site and results were still statistically significant.

VAI: The Sam Miller, M.D. site enrolled 120 patients (3%) into Study 303. Some minor observations were identified (e.g., some patients having study visits outside of specified time windows, serious adverse events not reported in a timely manner on five occasions). OSI determined that these observations are not likely to have had a significant effect on efficacy or safety. However, there were 13 patients (11%) whose records were not available for review at the time of inspection. OSI recommends that we consider the potential implications of these missing records in deciding whether to rely upon these data. As discussed by Dr. Kehoe, exclusion of the patients with missing source documentation did not impact overall

conclusions regarding the efficacy of conjugated estrogens/bazedoxifene on bone mineral density.

VAI: The Christopher Hutchison, M.D. site enrolled 22 patients into Study 305 (7%). The field investigator preliminarily classified this site as OAI due to the number and nature of identified deficiencies (e.g., 5 of the inspected 19 patients completed the study while taking excluded medications, there was lack of investigator conduct or supervision of the study, lack of documentation of adequate training of staff personnel, and lack of adequate records). However, OSI subsequently downgraded this site to VAI. As discussed by Dr. Kehoe, exclusion of the patients from this site did not impact overall conclusions regarding the efficacy of conjugated estrogens/bazedoxifene on moderate to severe vasomotor symptoms.

VAI: Pfizer, Inc. OSI inspected the Applicant with regard to its interactions (e.g., inspecting study records, monitoring activities) involving the Dr. Miller, Dr. Gallagher and Dr. Baracat sites. OSI issued a Form 483 to the Applicant because there was a delay in bringing the Dr. Baracat and Dr. Miller sites into compliance (e.g., some source documents were not available for review by the monitors). Also, Pfizer did not complete the reviews of site monitoring visit reports from all three sites in a timely manner. OSI did not raise new concerns with using data from any of these sites, other than the issues related to missing source documents.

12. Labeling

Key labeling points include the following:

- Duavee should only be indicated for women with a uterus. The label should explain that the bazedoxifene component is acting in place of a progestin for uterine protection. Those without a uterus can use estrogen alone.
- Factors that reduce exposures to bazedoxifene or increase exposures to conjugated estrogens (i.e., factors potentially leading to loss of endometrial protection) should be adequately labeled (e.g. increased body mass index, co-administered inducers of UGT enzymes, co-administered CYP3A4 inhibitors).
- Duavee should receive the class labeling used for estrogen-alone products, including the Boxed Warning.
- (b) (4)
- Although there are non-clinical data supporting a beneficial effect on the breast, the Applicant has not conducted adequately designed clinical trials to show a reduction in breast cancer risk. Therefore, there should be no language in the Duavee label that may suggest such a benefit.
- Efficacy data presented in the Clinical Studies section should be limited to those patients who had source documentation as we are unable to verify data integrity for those patients with missing source documents.

The package insert has been finalized, incorporating input from the various review disciplines as well as input from the Office of Prescription Drug Promotion (OPDP) and the Study

Endpoints and Labeling Development (SEALD) group. See the reviews by Lynn Panholzer, Pharm.D. (OPDP) and Abimbola Adebowale, Ph.D. (SEALD) for details.

Duavee's patient package insert has been optimized for the layperson with input from the Division of Medical Policy Programs (DMPP). See the review by Robin Duer, M.B.A, B.S.N. for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval of Duavee 0.45 mg/20 mg for (a) the treatment of moderate to severe vasomotor symptoms associated with menopause and (b) prevention of postmenopausal osteoporosis

Complete Response for Duavee 0.625 mg/20 mg for (a) the treatment of moderate to severe vasomotor symptoms associated with menopause, (b) prevention of postmenopausal osteoporosis, and (c) treatment of moderate to severe vulvar and vaginal atrophy associated with menopause.

- Risk Benefit Assessment

Based on the rationale provided in the Clinical/Statistical Efficacy section of this memorandum:

1. The Applicant has provided adequate evidence of efficacy for (b) (4) (b) (4) 0.45 mg/20 mg doses of Duavee for the vasomotor symptoms indication and the prevention of postmenopausal osteoporosis indication. (b) (4)

2. (b) (4)

Bazedoxifene is included as a component of Duavee to protect the endometrium from the proliferative effects of estrogen. This is a new treatment paradigm that provides an alternative to the long-standing approach of using a progestin for endometrial protection. A main safety concern with Duavee is the potential for loss of endometrial protection when intrinsic or extrinsic factors reduce bazedoxifene exposures or increase exposures of conjugated estrogens. (b) (4) In contrast, the 0.45 mg/20 mg dose has a larger safety margin for endometrial safety with reassuring results in the clinical program

(even Formulation C for the 0.45 mg/20 mg dose in Study 304 provides sufficient endometrial protection) and acceptable efficacy. Therefore, I agree with the clinical team that the available data support approval for only the 0.45 mg/20 mg dose.

Based on all of the considerations above, I recommend approval of Duavee 0.45 mg/20 mg for the vasomotor symptoms indication and prevention of postmenopausal osteoporosis indication. I recommend a Complete Response for the 0.625 mg/20 mg dose for all three proposed indications.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

As discussed under the Clinical Pharmacology section, CYP3A4 inhibitors may increase plasma concentrations of estrogen. Because of the potential for loss of uterine protection when

estrogen exposures increase relative to bazedoxifene exposures, I agree with the request by Clinical Pharmacology for a drug-drug interaction study post-approval to better define the potential effect of CYP3A4 inhibitors on exposures to conjugated estrogens. The Applicant has agreed to conduct this drug-drug interaction study and both FDA and the Applicant have reached agreement on the study timelines, which will be included in the approval letter.

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/s/

HYLTON V JOFFE
10/02/2013