

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022247Orig1s000

ENVIRONMENTAL ASSESSMENT



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: August 26, 2013

From: James P. Laurenson
OPS/IO/SRS

To: Kerri-Ann Jennings
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: Review of Environmental Assessment for DUAVEE, NDA 022-247, Bazedoxifene Acetate/Conjugated Estrogens (BZA/CE) Film-coated Tablets

Sponsor: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc. (hereafter referred to as Wyeth), 235 East 42nd St., New York, NY 10017

A. Background

Wyeth has filed a new drug application (NDA) for DUAVEE, NDA 022-247, which is a combination of bazedoxifene acetate/conjugated estrogens (BZA/CE) in film-coated tablets with two dose strengths: BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg. The proposed indications include:

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

BZA is a new molecular entity (NME). CEs are used in Wyeth Premarin products. IMS 2012 drug use database estimates total use of CEs [REDACTED] (b) (4) with Pfizer/Wyeth CE products [REDACTED] (b) (4).

Wyeth claimed a categorical exclusion [REDACTED] (b) (4)

[REDACTED]

FDA denied the categorical exclusion (Information Request COR-NDAIR-01, March 18, 2013) and required the preparation of an environmental assessment (EA) based on FDA's "extraordinary circumstances" provision (21 CFR 25.21), including information indicating that at the expected level of exposure for these hormonally active compounds—BZA being an NME and a selective estrogen receptor modulator (SERM), and CE being composed of highly estrogenic substances and contributing to an increased use—there is the potential for serious harm to the environment (e.g., see GLELC and NRDC, 2010, Docket # FDA-2010-P-0377). Wyeth submitted a testing strategy to support the EA (March 29, 2013). Following subsequent discussions, including the June 26, 2013 Late Cycle Meeting (LCM), Wyeth submitted a proposal for conducting an EA for BZA/CE (July 3, 2013), which FDA reviewed (July 15, 2013). Wyeth submitted the EA (August 1, 2013) and anticipates submitting the additional analysis and study reports for BZA by 1Q 2014 and additional analysis and study reports for CE by 1Q 2015. FDA will review the additional information when it becomes available and will update this current review if needed.

Subsequent to the August 1 submission, FDA concluded that neither the second indication above (treatment of moderate to severe vulvar and vaginal atrophy associated with menopause) nor the second dose (BZA 20 mg/CE 0.625 mg) would be approved. This memo provides FDA's review of the EA with these changes incorporated.

B. Discussion

Wyeth has filed an NDA for DUAVEE, which is a combination of BZA/CE in film-coated tablets with two dose strengths and three indications. BZA is an NME, while CEs are used in Wyeth Premarin products. (b) (4)

Wyeth submitted the EA and anticipates submitting additional analysis and study reports for BZA and CE in the future. FDA will review the additional information when it becomes available and will update this current review if needed. Subsequent to submission of the EA, FDA concluded that one of the indications and one of the dosage forms would not be approved.

In the EA, the sponsor describes how following ingestion, excretion, wastewater treatment, and discharge of effluents into the aquatic environment, BZA and CE enter the environment. BZA and its residues are expected to reside in the water compartment and subsequently in the sediment compartment. BZA will likely undergo some hydrolysis and aerobic and anaerobic water-sediment degradation, but for this EA, the sponsor used the conservative assumption that no depletion of BZA occurs. The sponsor subsequently developed a screening level expected environmental concentration (EEC) (b) (4). The sponsor also developed a predicted no-effects concentration (PNEC) (b) (4). These values would result in a Risk Quotient (RQ) (b) (4). FDA developed an alternative PNEC for the purposes of this screening assessment, however, pending the results of the additional testing underway by Wyeth. This alternative used an additional assessment factor (AF) of 10, for an alternative PNEC (b) (4). With this EEC and alternative

PNEC, the RQ for BZA would be (b) (4). This RQ is less than 1, and given the conservative assumptions used for this EEC (e.g., no depletion), the environmental concentrations of BZA from this NDA are not expected to cause a significant impact on the environment.

CE is composed on numerous estrogenic substances. The sponsor selected three of these substances to represent CE in the EA: estrone (E1), 17 β -dihydroequilin (DHE), and 17 β -estradiol (E2). Wastewater treatment is expected to remove at least 50% of these substances, and further substantial degradation is expected in the surface water. The sponsor notes that the CE markers selected for this EA—E1, E2, and DHE—are expected to reside in the water compartment and subsequently in the sediment compartment following wastewater treatment and discharge of effluents. Given the depletion mechanisms noted above, however, these markers likely will not subsequently persist or accumulate in the aquatic environment. Nevertheless, for this EA, the sponsor used the conservative assumption that no depletion of these markers occurs. The sponsor thus developed a screening level EEC (b) (4). Based on a preliminary analysis by the sponsor of the available aquatic toxicity data, a PNEC (b) (4) was selected. Using this EEC and PNEC, an RQ (b) (4) was developed. This RQ is less than 1, and given the screening level assumptions used, the environmental concentrations of CE from this NDA and from currently approved uses of CE marketed by this sponsor are not expected to cause a significant impact on the environment.

The results of the risk characterizations in the EA and this review suggest that the specific use of DUAVEE tablets will not significantly impact the environment. The reviewers are cognizant, however, of the potential for cumulative exposure and effects due to multiple applications of estrogenic substances, including SERMs. Therefore, the EA review staff believe that monitoring of the scientific literature on the potential environmental impacts of BZA/CE is warranted. The updated EA being developed by the sponsor also is expected to include new data and analysis that will be reviewed.

Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

C. Environmental Assessment Review

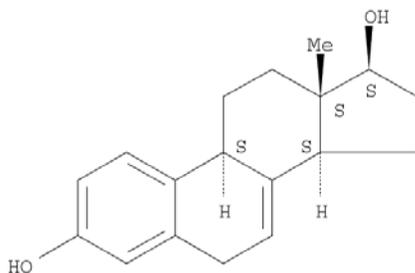
A summary of the EA provided by the sponsor is provided below. Comments based on the FDA review of the EA are provided in italics.

- 1. EA Date:** July 26, 2013
- 2. Sponsor:** Wyeth Pharmaceuticals, Inc. Inc., a wholly owned subsidiary of Pfizer, Inc. (Wyeth)
- 3. Address:** 235 East 42nd Street, New York, NY 10017
- 4. Proposed Action:** Wyeth has submitted an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) for DUAVEE, a medicinal combination drug containing BZA/CE in dose strengths of BZA 20 mg/CE 0.45 mg and BZA 20

mg/CE 0.625 mg in film-coated tablets, for treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of moderate to severe vulvar and vaginal atrophy associated with menopause, and prevention of postmenopausal osteoporosis

5. Identification of Chemicals

- (i) Established Name: Bazedoxifene Acetate
- Brand/Proprietary Name/Tradename: DUAVEE
 - Chemical Abstracts Names: Bazedoxifene Acetate (USAN)
Systematic Chemical Name: 1-(p-(2-(Hexahydro-1H-azepin-1-yl)ethoxy)benzyl)-2-(p-hydroxyphenyl)-3-methylindol-5-ol monoacetate (salt)
Other Name(s): 1H-Indol-5-ol, 1-((4-(2-(hexahydro-1H-azepin-1-yl)ethoxy)phenyl)methyl)-2-(4-hydroxyphenyl)-3-methyl-, monoacetate (salt)
 - Chemical Abstract Services Number (CASN): 198481-33-3
 - Molecular Formula: $C_{30}H_{34}N_2O_3 \cdot C_2H_4O_2$
 - Molecular Weight: 530.65 g/mol
 - Chemical Structure:



- (ii) Established Name: Conjugated Estrogens (CE)
- Brand/Proprietary Name/Tradename: DUAVEE
 - Chemical Abstracts Names: Estrogens, conjugated
Systematic Chemical Name: Conjugated estrogenic hormones; see table below (modified from Appendix 1 of the sponsor's EA) for principal CE components
Other Name(s):
Estrogens, conjugates
Premarin
 - CASN: 12126-59-9; see table below (modified from Appendix 1 of the sponsor's EA) for principal CE components
 - Molecular Formula: see table below (modified from Appendix 1 of the sponsor's EA) for principal CE components
 - Molecular Weight: see table below (modified from Appendix 1 of the sponsor's EA) for principal CE components
 - Chemical Structure: see table below (modified from Appendix 1 of the sponsor's EA) for principal CE components

Principal Components of CE

Name	Systematic Chemical Name	CASN	Molecular Formula	Molecular Weight	Chemical Structure
Sodium Estrone Sulphate ^a	estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-, sodium salt	438-67-5	C ₁₈ H ₂₁ NaO ₅ S	372.4	
Sodium Equilin Sulphate	estra-1,3,5(10),7-tetraen-17-one, 3-(sulfooxy)-, sodium salt	16680-47-0	C ₁₈ H ₁₉ NaO ₅ S	370.4	
Sodium 17α-Dihydroequilin Sulphate	estra-1,3,5(10),7-tetraene-3,17-diol, 3-(hydrogen sulfate), monosodium salt, (17α)-	56050-05-6	C ₁₈ H ₂₁ NaO ₅ S	372.4	
Sodium 17β-Dihydroequilin Sulphate ^a	estra-1,3,5(10),7-tetraene-3,17-diol, 3-(hydrogen sulfate), monosodium salt, (17β)-	16680-49-2	C ₁₈ H ₂₁ NaO ₅ S	372.4	
Sodium 17α-Estradiol Sulphate	estra-1,3,5(10)-triene-3,17-diol, 3-(hydrogen sulfate), monosodium salt, (17α)-	56050-04-5	C ₁₈ H ₂₃ NaO ₅ S	374.4	
Sodium 17β-Estradiol Sulphate ^a	estra-1,3,5(10)-triene-3,17-diol, 3-(hydrogen sulfate), monosodium salt, (17β)-	4999-79-5	C ₁₈ H ₂₃ NaO ₅ S	374.4	
Sodium 8,9-Dehydroestrone Sulphate	estra-1,3,5(10),8-tetraen-17-one, 3-hydroxy, monosodium salt	61612-83-7	C ₁₈ H ₁₉ NaO ₅ S	370.4	

^aComponent selected to represent CE in the EA. See next section for details.

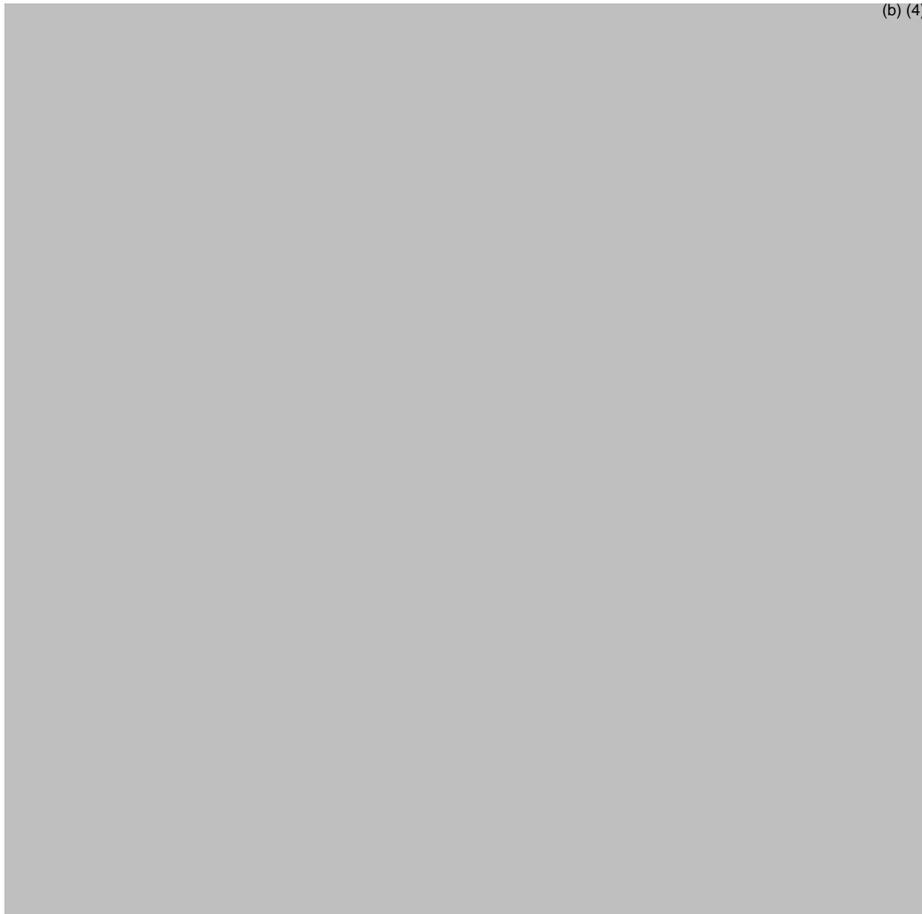
6. Environmental Characterization

A summary of the physical/chemical values, environmental depletion mechanisms, and environmental fate and effects for this product is provided in the subsections, below.

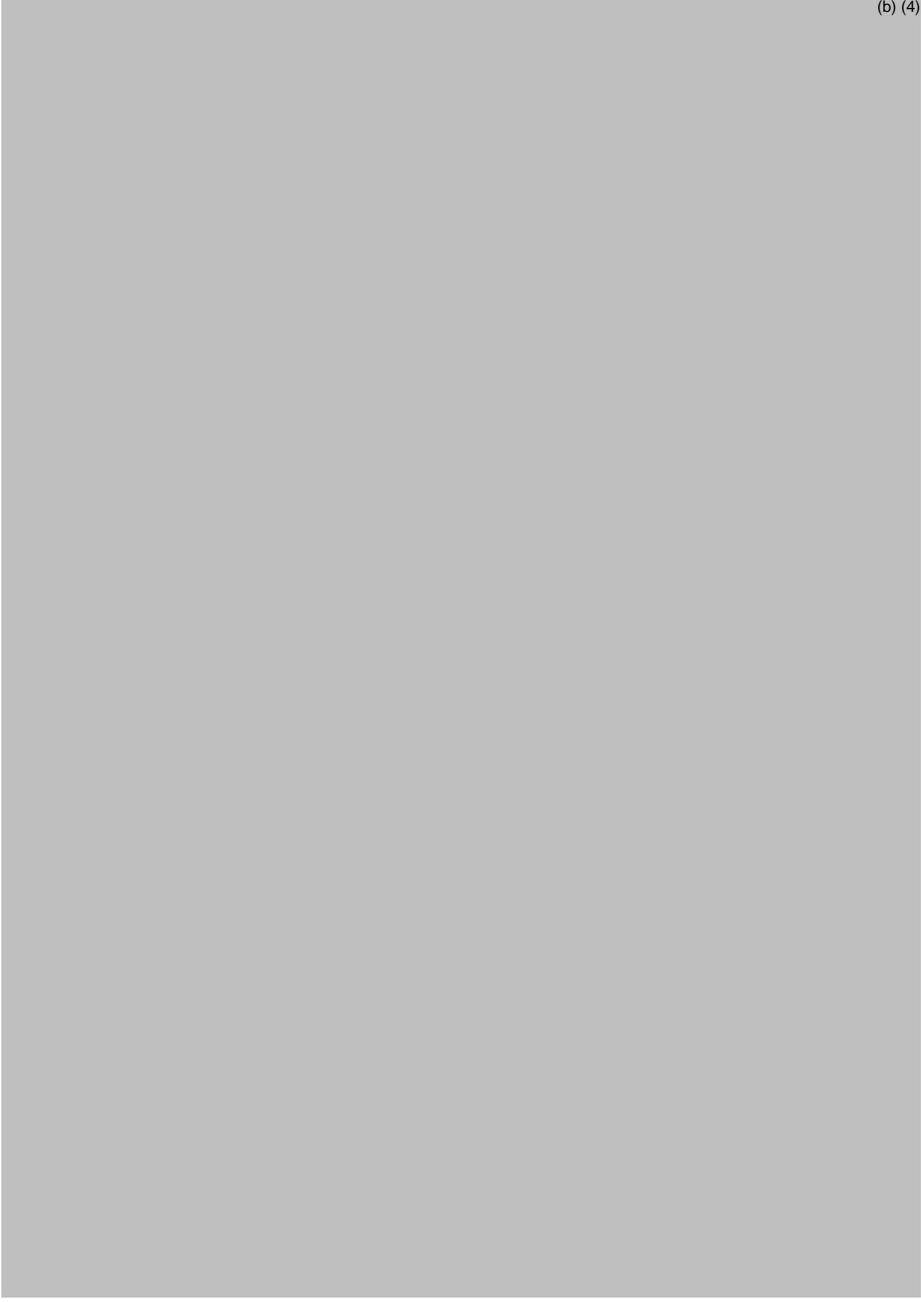
Because of the large number of conjugated estrogen (CE) components, three components were selected by the sponsor to represent CE in the EA: E1, DHE, and E2. The sponsor selected these components taking into consideration the following: (1) composition of drug substances found in the CE product, (2) the relative potency of each of those substances, and (3) the profile of the relevant excretion products entering the environment. Specifically, E1 is noted as the most abundant estrogen in CE, present ^{(b) (4)} E2 and DHE are the first and second most potent, respectively, based on human estrogen receptor binding studies (Dey et al. 2000, Bhavnani et al. 2008).

Review Comments: Given the worst-case assumptions used in the EA regarding the relative concentrations of these components, the selection of these three components are reasonable for representing CE.

Physical/Chemical Values (modified from Appendices 2, 4, 5, and 6 of the sponsor's EA)



(b) (4)



Environmental Depletion Mechanisms

BZA

The sponsor reports that greater than 85 percent of BZA is excreted in the feces unchanged. Thus, BZA is considered the primary entity released into the environment following patient use. BZA was shown by the sponsor to hydrolyze by 15% at pH 4, 47% at pH 7, and close to 100% (less than detection) at pH 9. BZA also was shown to have some inherent biodegradability in activated sludge, although it is not considered readily biodegradable. Under aerobic and anaerobic water-sediment test conditions, BZA underwent some primary degradation converting to

multiple degradation products, with a half-life in aerobic water-sediment systems of 23.9-26.3 days and a half-life in anaerobic water-sediment systems of 72.9-79.7 days. BZA is not volatile and therefore will not enter the air compartment.

Review Comments: The 85 percent excreted was confirmed in the published literature (Chandrasekaran et al. 2009). The sponsor did not address metabolites, and therefore a literature search was conducted. The predominant plasma metabolite was bazedoxifene-5-glucuronide in all species examined (EMEA 2009). This metabolite was not detected in feces, however, possibly due to rapid hydrolysis by intestinal bacterial enzymes (Chandrasekaran et al. 2009). Therefore, BZA is considered valid as a model for assessing environmental fate and effects resulting from BZA use.

CE

The sponsor notes that based on the human metabolism and excretion profile for E1, a major component of CE, the primary urinary metabolites were identified as glucuronide and sulfate forms of E1, and glucuronide, sulfate and sulfoglucuronide forms of estriol and 16 α -hydroxyestrone. The glucuronides are expected to convert back to their unconjugated forms during the wastewater treatment process. E1 also is a major metabolite of E2, the most estrogenic component of CE. The sponsor also describes the metabolism of equilin and 17 α -dihydroequilin, the other major components of CE besides E1. One of the active metabolites of these two components is DHE, which is noted as demonstrating the highest estrogen receptor binding affinity and functional activity of all of the CE components examined. Therefore, DHE is considered a conservative representation of the excretion products, along with E1 and E2.

Hydrolysis of the unconjugated forms of E1, E2, and DHE are expected by the sponsor to be minimal at environmentally relevant pHs of 4 through 9. However, based on a substantial body of literature for E1 and E2, and a somewhat less though still reasonable amount of information on DHE, the monitoring of wastewater treatment facilities for these substances demonstrate average removal efficiencies of approximately 53%, 78%, and 67% for E1, E2, and DHE, respectively, indicating these substances undergo substantial sludge biodegradation. The half-lives of E1 and E2 are noted to be 2.5 and 2.2 hours in water, respectively, and 0.42 and 0.11 days in sediment, respectively. The sponsor found no data in the literature on DHE, but it may be reasonable to assume similar results as those found in E1 and E2 would apply to DHE. These substances are not volatile and therefore will not enter the air compartment.

Review Comments: This analysis of CE constituents and selected markers for the assessment are reasonable.

Environmental Fate and Effects

BZA

Following wastewater treatment and discharge of effluents, BZA and its residues are expected to reside in the water compartment and subsequently in the sediment compartment. As noted above, BZA will likely undergo some hydrolysis and aerobic and anaerobic water-sediment degradation. Nevertheless, for this EA, the sponsor used the conservative assumption that no depletion of BZA occurs. The sponsor thus developed an expected introductory concentration (EIC) [REDACTED] (b) (4) for BZA in the aquatic environment, using the mass balance method described in FDA guidance (USFDA 1998). The sponsor also calculated an EEC [REDACTED] (b) (4) using a dilution factor of 10.

Review Comments: Neither of the concentration calculations incorporated FDA's conclusion that one of the indications (treatment of moderate to severe vulvar and vaginal atrophy associated with menopause) and one of the dosage forms (BZA 20 mg/CE 0.625 mg) would not be approved. This conclusion could reduce these concentrations if total use of the drug is reduced as a consequence, although determining the amount of any change is difficult to predict.

The table below summarizes the aquatic toxicity data for BZA provided by the sponsor. Based on these data, green algae is the most sensitive species tested, with a NOEC (EC₂₀) [REDACTED] (b) (4) using OECD 201. Using an AF of 10 for chronic data, a PNEC [REDACTED] (b) (4) is obtained.

Review Comments: Two caveats with this PNEC are that (1) the NOEC is technically an EC₂₀ and thus not a true NOEC, and (2) BZA is a SERM and thus hormonally active. An independent FDA literature search on the environmental effects of BZA and SERMs found no additional data on BZA, but did find relevant data on SERMs. For example, studies show that at environmentally relevant (ng/L) levels, tamoxifen (a SERM) causes developmental abnormalities in the sea urchin (*Stroglyocentrotus purpuratus*) and increased plasma vitellogenin in male Japanese medaka (*Oryzias latipes*) (Chikae et al. 2004, Roepke 2005). Another study found that male Japanese medaka exposed to ethinyl estradiol (EE2) and tamoxifen showed a significant increase in the transcription of hepatic vitellogenin mRNA compared to EE2 alone, but that higher tamoxifen concentrations reduced this response significantly (Sun et al. 2011). Therefore, this EA on BZA perhaps could be improved with the inclusion of the same fish reproduction and developmental studies being conducted for CE (OECD 229 and 234). The sponsor has indicated that additional testing for BZA is under way. Pending the results of the additional BZA tests, an alternative PNEC for BZA could be obtained by using an additional AF of 10 for this screening assessment, [REDACTED] (b) (4)

Species	Exposure	L(E)C ₅₀ mg a i./L	NOEC mg a i./L
Acute			
Daphnids (<i>Daphnia magna</i>)	48 hour OECD 202	5.85	4.58
Fathead minnow (<i>Pimephales</i>)	96 hour OECD 203	1.77	0.831
Chronic			
Green Alga (<i>Pseudokirchn eriella subcapitata</i>)	72 hour OECD 201	0.028 (biomass)	0.0069 ^a (biomass)
		0.095 (growth rate)	0.017 ^a (growth rate)
		LOEC mg a.i./L	NOEC mg a.i./L
Daphnids (<i>Daphnia magna</i>)	21 day OECD 211	-	1.1
Fathead Minnow (<i>Pimephales</i>)	Early lifecycle OECD 210	> 0.86	0.86
Fish Full Life Cycle (<i>Pimephales promelas</i>)	Full life cycle OPPTS 850.1500	0.021	0.014

^aEC₂₀CE

The sponsor notes that the CE markers selected for this EA—E1, E2, and DHE—are expected to reside in the water compartment and subsequently in the sediment compartment following wastewater treatment and discharge of effluents. Given the depletion mechanisms noted above, however, these markers likely will not subsequently persist or accumulate in the aquatic environment. Nevertheless, for this EA, the sponsor used the conservative assumption that no depletion of these markers occurs. The sponsor thus developed an EIC [REDACTED] (b)(4) for CE in the aquatic environment, using the mass balance method described in FDA guidance (USFDA 1998) for all of the CE produced by the sponsor (i.e., including CE in their currently approved products). The sponsor also calculated an EEC [REDACTED] (b)(4) using a dilution factor of 10.

Review Comments: The same caveat noted above for the concentration estimates still applies, i.e., that these calculations do not incorporate FDA's conclusion that one of the indications and one of the dosage forms would not be approved. One issue with the EIC and EEC is that part of the basis for these concentrations is the sponsor's estimate of use in 2018 of [REDACTED] (b)(4) for currently approved products, yet Wyeth/Pfizer CE data for 2012 as determined by IMS is [REDACTED] (b)(4). (The estimated incremental addition due to this NDA is [REDACTED] (b)(4) for a total of [REDACTED] (b)(4).) Therefore, FDA examined CE use over several years to assess the trend, and thus determine whether

the sponsor's projection was reasonable. As seen in the following graph developed for this review using IMS data, there indeed has been a (b) (4) trend of CE use over the past five years, and thus the projection of (b) (4) is considered reasonable.



The aquatic toxicity of the three CE markers has been well studied, as described in detail in the sponsor's EA. Furthermore, the sponsor is conducting a multigenerational fish life-cycle test using OECD 234 and the Japanese medaka to evaluate the effects of the predominant mixture of E1 and DHE. Only interim results currently are available following completion of the in-life phase of the study in July 2013 for the parental generation (F0) and first generation (F1). Fecundity of the F1 generation as well as hatching success of the F2 generation were evaluated to establish NOEC values for multiple generations. Based on a preliminary analysis of the available data, a PNEC for E1 and DHE (b) (4) was selected based on the F1 sex ratio NOEC (b) (4) and an AF of 10. For E2, the sponsor selected a PNEC (b) (4)

Review Comments: This assessment of CE aquatic toxicity highlights the unexpectedly higher toxicity of DHE, or possibly the DHE/E1 combination in a potentially interactive (e.g., synergistic) way, compared to E2. Assuming the combination of DHE/E1 is comparable to the combination in CE, the PNEC developed for DHE/E1 should be adequate for representing CE.

Risk Characterization

BZA

Using the EEC (b) (4) noted above and the sponsor's PNEC (b) (4) results in an RQ of (b) (4). Using the alternative PNEC (b) (4) results in an RQ of (b) (4). These RQs are less than 1, and given the conservative assumptions used for this EEC—including no depletion following human ingestion, wastewater treatment, or degradation in surface waters, as well as the reduced expected use of

BZA following FDA's decision to not approve DUAVEE for one of the indications and one of the tablet dosage amounts—the environmental concentrations of BZA from this NDA are not expected to cause a significant impact on the environment.

Review Comments: This assessment of BZA impact is reasonable.

CE

Using the EEC (b)(4) noted above for CE and the (b)(4) PNECs noted above, (b)(4) results in an RQ of (b)(4). This RQ is based on several screening level assumptions, including (1) the entire estimated amount of CE will be used (b)(4) (2) CE is composed entirely of the apparently more toxic E1/DHE combination rather than E2, and (3) there are no depletion mechanisms (other than some dilution) such as metabolism, treatment, or environmental degradation. This RQ is less than 1, and given the screening level assumptions, the environmental concentrations of CE from this NDA and from currently approved uses of CE marketed by this sponsor are not expected to cause a significant impact on the environment.

Review Comments: This assessment of CE impact is reasonable, based on the assumption that E1/DHE is representative of CE and that other more potent estrogenic constituents or combination effects would not have provided a lower PNEC.

7. Mitigation Measures and Alternatives

No significant adverse environmental impact is expected from this NDA based on the information available to date, and therefore no mitigation measures or alternatives are addressed other than the monitoring of scientific literature for potential environmental impacts due to cumulative effects and break-down products.

8. Submitted Study Reports

The following study reports were submitted with the EA. The studies were conducted in accordance with OECD guidelines and Good Laboratory Practice regulations.

13554.6171; “Bazedoxifene Acetate (BZA) - Determination of the n-Octanol/Water Partition Coefficient”, following OECD Guideline 107.

2438.6634; “[14C] Bazedoxifene Acetate (BZA) – Determining the Adsorption Coefficient (Koc)”, following OECD Guideline 106.

2676-WY; “Bazedoxifene: Determination of the Inherent Biodegradability (Biotic Degradation) Using Zahn-Wellens/EMPA Test”, following OECD Guideline 302B.

2438.6635; “[14C] Bazedoxifene Acetate (BZA) – Determination of the Biodegradability of a Test Substance in Activated Sludge”, following OECD Guideline 314B.

13554.6178; “[14C] Bazedoxifene Acetate (BZA) - Aerobic and Anaerobic Transformation in Aquatic Sediment Systems”, following OECD Guideline 308.

2636-WY; “Bazedoxifene: Hydrolysis as a Function of pH (Preliminary Test)”, following OECD Guideline 111.

13554.6200; “Bazedoxifene Acetate (BZA) – Activated Sludge Respiration Inhibition”, following OECD Guideline 209.

2631-WY; “Bazedoxifene: Static Acute Toxicity Test with the Daphnid, *Daphnia magna*”, following OECD Guideline 202.

2632-WY; “Bazedoxifene: Acute Toxicity Test with the Fathead Minnow, *Pimephales promelas*”, following OECD Guideline 203.

13554.6202; “Bazedoxifene Acetate (BZA) – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*”, following OECD Guideline 201.

13554.6201; “Bazedoxifene Acetate (BZA) – Full Life-Cycle Toxicity Test with Water Fleas, *Daphnid magna*, Under Flow-Through Conditions”, following OECD Guideline 211.

13554.6151; “Bazedoxifene Acetate (BZA) – Early Life-Stage Toxicity Test with Fathead Minnow (*Pimephales promelas*)”, following OECD Guideline 210.

13554.6199 “Bazedoxifene Acetate (BZA) – Full Life-Cycle Toxicity Test with Fathead Minnow (*Pimephales promelas*)”, following FIFRA Guideline 72-5 and OPPTS Draft Guideline 850-1500.

13554.6205; “Bazedoxifene Acetate (BZA) – Flow-Through Bioconcentration and Metabolism Study with Bluegill Sunfish (*Lepomis macrochirus*)”, following OECD Guideline 305.

13554.6170; “Bazedoxifene Acetate (BZA) – Full Life-cycle Toxicity Test with Sediment Dwelling Midges (*Chironomus riparius*) Under Static Conditions”, following OECD 218.

260E-256; “[14C] Estrone and 17 β -Dihydroequilin: Biodegradation in Activated sludge Screening Test”, following OECD Guideline 314B.

260A-226; “Estrone and 17 β -Dihydroequilin: Fish Multigeneration Test with Japanese Medaka (*Oryzias latipes*)”, following OECD Guideline 229 and OECD 234.

D. Additional Literature Considered by Reviewer

Anderson, P. D., A. C. Johnson, D. Pfeiffer, D. J. Caldwell, R. Hannah, F. Mastrocco, J. P. Sumpter, and R. J. Williams. 2012. Endocrine disruption due to estrogens derived from humans predicted to be low in the majority of U.S. surface waters. *Environmental Toxicology and Chemistry* **31**:1407-1415.

Bhavnani, B. R., S.-P. Tam, and X. Lu. 2008. Structure activity relationships and differential interactions and functional activity of various equine estrogens mediated via estrogen receptors (ERs) ER α and ER β . *Endocrinology* **149**:4857-4870.

Caldwell, D. J., F. Mastrocco, P. D. Anderson, R. Länge, and J. P. Sumpter. 2012. Predicted-no-effect concentrations for the steroid estrogens estrone, 17 β -estradiol, estriol, and 17 α -ethynylestradiol. *Environmental Toxicology and Chemistry* **31**:1396-1406.

Chandrasekaran, A., W. E. McKeand, P. Sullivan, W. DeMaio, R. Stoltz, and J. Scatina. 2009. Metabolic disposition of [14C] bazedoxifene in healthy postmenopausal women. *Drug Metabolism and Disposition* **37**:1219-1225.

Chikae, M., R. Ikeda, Q. Hasan, Y. Morita, and E. Tamiya. 2004. Effects of tamoxifen, 17 α -ethynylestradiol, flutamide, and methyltestosterone on plasma vitellogenin levels of male and female Japanese medaka (< i> Oryzias latipes</i>). *Environmental Toxicology and Pharmacology* **17**:29-33.

Dey, M., C. R. Lyttle, and J. H. Pickar. 2000. Recent insights into the varying activity of estrogens. *Maturitas* **34**:S25-S33.

EMA. 2009. Assessment Report for Conbriza; International Non-proprietary Name: Bazedoxifene. European Medicines Agency, London.

Fent, K., A. A. Weston, and D. Caminada. 2006. Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology* **76**:122-159.

Roepke, T. A. 2005. Estradiol and endocrine disrupting compounds effects on echinoderm reproduction and development: Development sensitivities and defense mechanisms. Doctoral. University of California Davis, Davis, CA.

Shanle, E. K. and W. Xu. 2011. Endocrine Disrupting Chemicals Targeting Estrogen Receptor Signaling: Identification and Mechanisms of Action. *Chemical Research in Toxicology* **24**:6-19.

Sun, L., X. Shao, X. Hu, J. Chi, Y. Jin, W. Ye, and Z. Fu. 2011. Transcriptional responses in Japanese medaka (*Oryzias latipes*) exposed to binary mixtures of an estrogen and anti-estrogens. *Aquatic Toxicology* **105**:629-639.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Page 39 in Center for Biologics Evaluation and Research, editor. US Food and Drug Administration, Rockville, MD.

Findings from Literature Review:

BZA is a SERM and thus hormonally active with potential mixture effects with CE. Therefore, FDA concluded that an independent literature review was needed on the environmental effects of BZA, SERMs, and estrogens. No additional studies were found on BZA, but relevant studies were found on SERMs and estrogens. These studies showed that at environmentally relevant (ng/L) levels, tamoxifen (a SERM) causes developmental abnormalities and other potentially adverse effects in aquatic organisms. Studies also found common modes of action among SERMs and between CE and other estrogenic substances, and that complex interactions occur between SERMs and other hormonally active compounds. Numerous other studies exist on the endocrine disruptor effects of estrogens, such as those in CE, in the environment. These findings raise concerns about the potential mixture and cumulative effects of CE/BZA and thus the need to monitor the environmental literature on these substances, but they do not preclude a FONSI for this specific application.

E. Cumulative Impacts

Cumulative impacts, such as the effects of multiple environmental stressors with similar mechanisms of toxicity, generally are not addressed in these EAs due to the typically low individual drug risks. Because many substances in the environment are believed to have similar physiological modes of action and/or mechanisms of toxicity, however, including possibly the pharmaceuticals addressed in this EA, cumulative impacts are being examined here.

BZA is a SERM with a calculated EEC (b)(4). While the modes of action of SERMs are complex and not well understood, they share a common, though broad, mode of action involving binding affinity for estrogen receptor- α (ER α) and ER β . Thus, it is conceivable that in the aquatic environment SERMs and SERM-like substances may have sufficiently similar mechanisms of toxicity such that their individual RQs should be summed to assess whether their cumulative impact is significant. One commonly used SERM, tamoxifen, has been found in the aquatic environment (in Europe) at a median concentration of 53 ng/L (Fent et al. 2006). In the US, however, while concentration data could not be found in the literature, the (b)(4) tamoxifen used in 2012 (from IMS data) would translate to an EEC of approximately (b)(4) using the FDA mass-balance approach and a dilution factor of 10. Similarly, other SERMs, including clomiphene and raloxifene, would be approximately (b)(4) respectively. Cumulatively, therefore, assuming a common mode of action and equivalent potencies, these SERMs would total to approximately (b)(4). This concentration when compared to the alternative PNEC (b)(4) described above results in a cumulative RQ of (b)(4). Because this RQ is less than 1, and several screening level assumptions are used (e.g., common mode of action, no depletion mechanisms), cumulative risks or impacts from SERMs do not appear to be significant. Nevertheless, other substances in the environment, both anthropogenic and natural, are known to have SERM-like properties, and thus the scientific literature on the overall cumulative impacts of SERM-like substances in the environment should be monitored and reanalyzed as needed.

For CE, a mixture of several estrogenic substances, three of which have been selected to represent CE, the calculated EEC is (b) (4) and the RQ, assuming a PNEC (b) (4) and based on several screening level assumptions, is (b) (4) (less than 1). Other pharmaceutical estrogens and other substances in the aquatic environment have similar MOAs, such that their individual RQs should be combined with the CE RQ to assess whether their cumulative impact is significant. Thus, a literature search was conducted, and data were found that showed how total estrogenicity from human derived estrogens (endogenous and pharmaceutical) compares to an overall PNEC for E2 equivalence (E2-eq) (Anderson et al. 2012). Specifically, E1, E2, E3, and EE2 concentrations were modeled using *PhATE* and by converting the estrogenicity of these compounds to E2-eq using potency factors of 0.3, 0.03, and 20 for E1, E3, and EE2, respectively, based on fish chronic reproductive toxicity and other data. These authors derived a long-term E2-eq PNEC of 2.0 ng/L and estimated that approximately 99% of stream segments have an RQ of less than 1 based on mean flow E2-eq concentration from human endogenous and pharmaceutical estrogens, and that the median EEC is more than two orders of magnitude less than this PNEC. Therefore, the CE RQ (b) (4) likely would not significantly add to this cumulative risk to the aquatic environment, especially given the several screening level assumptions incorporated into the CE RQ. Nevertheless, other substances in the environment, both anthropogenic and natural, are known to have estrogenic properties, and thus the scientific literature on the overall cumulative impacts of estrogenic substances in the environment should be monitored and reanalyzed as needed.

F. Comments

Based on the review of the submitted EA and available information, no significant adverse environmental impacts are expected from the approval of this NDA for BZA/CE in DUAVEE tablets. As indicated above, however, estrogenic moieties are introduced into the environment from the use of several other drug products. Therefore, a cumulative assessment of estrogenic and/or otherwise hormonally active introductions from all sources, as well as an assessment of break-down products, while not mandated for this NDA under current FDA regulations, would provide a fuller and more confident analysis of the potential impacts. Such an assessment would benefit from the monitoring and collection of scientific literature for potential environmental impacts due to cumulative effects and break-down products.

G. Conclusions

The EA is adequate for approval of the NDA. It contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and supporting reports, and of the scientific validity of the “no significant effects” conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA for DUAVEE tablets.

Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

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/s/

JAMES P LAURENSEN
08/26/2013

NAKISSA SADRIEH
08/26/2013

Finding of No Significant Impact

NDA 022-247

**DUAVEE™—Bazedoxifene Acetate/Conjugated Estrogens
(BZA/CE) Film-coated Tablets**

**Food and Drug Administration
Center for Drug Evaluation and Research**

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc. (Wyeth or sponsor) requests approval of NDA 022-247, DUAVEE (BZA/CE) for the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of moderate to severe vulvar and vaginal atrophy associated with menopause, and prevention of postmenopausal osteoporosis. In support of its application, Wyeth prepared an environmental assessment (EA; attached), in accordance with 21 CFR Part 25, which evaluates the potential environmental impact from the use and disposal of this product. FDA had required this EA because of “extraordinary circumstances” that indicated that at the expected level of exposure, there was the potential for serious harm to the environment (see 21 CFR 25.21 and Docket # FDA-2010-P-0377).

The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and other information and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review and information available to date, FDA has determined that approval of the present application for DUAVEE (BZA/CE) is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachment: July 26, 2013, Environmental Assessment

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/s/

JAMES P LAURENSON
08/26/2013

NAKISSA SADRIEH
08/26/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: July 15, 2013
From: James P. Laursen
OPS/IO/SRS
To: Samantha Bell
OPS/OND
Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS
Subject: Environmental Assessment for NDA 22-247, Bazedoxifene Acetate/Conjugated Estrogens (BZA/CE) Film-coated Tablets

Review of Supplemental Document No. 47, Quality/Response to Information Request, Section 1.11.1 Quality Information Amendment (hereafter referred to as Environmental Assessment (EA) Proposal), Submitted 7/3/2013, and associated Testing Strategy to Support the Environmental Assessment of Bazedoxifene/Conjugated Estrogens, submitted March 29, 2013

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc. (hereafter referred to as Wyeth)
235 East 42nd St
New York, New York 10017

Background

Wyeth has filed a new drug application, NDA 22-247, to gain approval for Bazedoxifene Acetate/Conjugated Estrogens (BZA/CE) film-coated tablets. The proposed indications include:

- 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

BZA is a new molecular entity (NME). CEs are used in Wyeth Premarin products. IMS 2012 drug use database estimates total use of CEs at (b) (4) with Pfizer/Wyeth products at (b) (4)



(Information Request COR-NDAIR-01, March 18, 2013). Following subsequent discussions, including the June 26, 2013 Late Cycle Meeting (LCM), Wyeth submitted the subject proposal for conducting an EA for BZA/CE. This memo provides our review of that proposal.

Summary of this Review

The Wyeth EA Proposal is acceptable subject to several clarifications that can be addressed in the EA. Below is suggested text to transmit to the applicant:

We reviewed your environmental assessment (EA) proposal submitted on July 3, 2013 and have the following comments, which must be addressed in the EA to ensure it contains sufficient information and analysis to enable us to determine whether the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(a)) and ultimately whether we will prepare an environmental impact statement (EIS) or a finding of no significant impact (FONSI) (21 CFR 25.40(a)). Therefore, in the EA please:

1. Provide clear justification for marker selection, addressing potential potency, environmental concentration, and other relevant factors for each of the BZA/CE components;
2. Account for the up to approximately (b) (4) of unidentified CE products, which is based on (a) lower end estrone and 17 β -dihydroestradiol data in your March 29, 2013 testing strategy and (b) the NMT (not more than) (b) (4) for 17 β -estradiol in your July 3, 2013 EA proposal, which should be used as a starting point in the EA instead of the (b) (4) average batch concentration;
3. Provide supporting information for the use of any depletion mechanisms (metabolism, WWTP degradation) in the development of estimated environmental concentrations; and
4. Estimate individual and cumulative risk to the environment (a) for the representative CE components in the formulation; (b) across both BZA and CE in the formulation and (c) for all marketed CEs by Wyeth.

Detailed Review

The following provides additional detail on our responses to the specific items in the EA proposal:

1. The sponsor proposed submitting EAs for BZA and CE by July 31, 2013. We agree with this schedule.
2. The sponsor proposed submitting an EA for BZA. We agree with the need to submit an EA for BZA and anticipate that this is the EA described in the sponsor's March 29, 2013 Testing Strategy to Support the Environmental Assessment of Bazedoxifene/Conjugated Estrogens (EA testing strategy). In addition, as requested in our April 12, 2013 Information Request, the July 31, 2013 submission should provide the BZA EA in the format recommended in the CDER EA guidance (USFDA, 1998). Furthermore, the cumulative environmental risk of BZA/CE should be assessed using the mode of action (MOA) equivalency/cumulative risk approach, as described in item 3.c below.
3. The sponsor proposed submitting a literature-based EA for CE using available Pfizer ecotoxicity data, along with literature and modeled data. We agree with this approach, with the following clarifications.
 - a. The sponsor outlined the rationale they are using to base the CE EA on three components of CE, as follows:
 - i. The sponsor noted that estrone (E1) and 17 β -dihydroequilin (17 β -Eq) are environmentally relevant markers for the CE product. We agree that these substances are environmentally relevant, but as discussed during the June 26, 2013 late cycle meeting (LCM), it is not clear from the March 29, 2013 testing strategy or the referenced literature exactly how these markers were selected. Therefore, the sponsor needs to clearly articulate in the EA why these two components are being selected and why these components are representative of CEs.
 - ii. The sponsor noted that 17 β -estradiol (E2) and 17 β -Eq represent the two most potent estrogens found in the CE product (based on binding affinity to estrogen receptors (ERs)) and that estrone (E1) is the most abundant estrogen in the CE/BZA product. We note, however, that as described in the literature, in particular Bhavnani (1998) and Dey et al. (2000), which are referenced in the EA proposal and EA testing strategy, and as discussed at the June 26, 2013 LCM, CE is composed of many other estrogenic substances. Some of these substances, such as delta-8-estrone sulfate and its major *in vivo* metabolite delta-8-17 β -estradiol, are "biologically active with potency either equal to or greater than that of the classical estrogens". In addition, several measures of potency, including gene activation and other biological effects, are noted in these references. Depending on the measure, the ranked order potencies of the substances can differ significantly (Bhavnani et al., 2008; Dey et al., 2000). Finally, the relative fractions of these substances within CE, as noted in item 4 below, will affect the relative environmental risk of each substance and thus whether and how much they represent CE. Therefore, the sponsor needs to clearly

describe in the EA the rationale for selecting representative estrogens (markers) for CE, with consideration for these and other relevant factors.

- b. The sponsor briefly described the literature-based approach they plan to use along with modeled data for the CE EA, indicating that the approach will follow the CDER EA Guidance (USFDA, 1998). We agree with the use of the CDER EA Guidance.
 - c. The sponsor stated that the predicted no effect concentration (PNEC) for CE will be based on the most conservative no observed effect concentration (NOEC) from 17β -estradiol effects data and from the fish reproduction and sexual development study currently being conducted for E1 and 17β -Eq under Good Laboratory Practice (GLP) using Japanese medaka (*Oryzias latipes*). While this appears to indicate that a single PNEC will be developed for CE, the proposal goes on to state that the approach will use risk quotients (RQ) using both the E2 PNEC value and the E1 and 17β -Eq PNEC value to support final EA conclusions. This approach is acceptable and appears consistent with the equivalent MOA/cumulative risk approach, based on U.S. Environmental Protection Agency guidance (Callahan and Sexton, 2007). Thus, given BZA's similar MOA as an estrogenic agonist in some tissues, the BZA RQ should be included in this cumulative assessment. That is, add the BZA and CE RQs, and if the sum is greater than 1, more realistic assumptions (e.g., advanced environmental concentration models) can be used and the analysis appropriately refined.
 - d. The sponsor noted that marketing volume (kg of active CE) will be provided for total CE found in all of Wyeth's current product line, five-years post market (2018), including the volume of CE anticipated from the approval of CE/BZA, as well as the volume of CE attributed to CE/BZA alone (2018). We interpret this bullet to mean that total CE across the entire sponsor's product lines, including the amount from approval of the specific application, will be used in estimating environmental concentrations, as described in the CDER EA Guidance.
4. The sponsor clarified that although specifications for E2 (sulfate) are set at not more than (NMT) (b)(4) relative potency in the CE raw material, E2 (as the sodium sulfate) is present at approximately (b)(4) in the sponsor's entire CE product line. We note, however, that as described in our March 18, 2013 Information Request, the literature indicates that E2 ranges from (b)(4) in CE. Therefore, we recommend that the (b)(4) value be used for the EA, at least as a screening assessment step. Furthermore, the sponsor's March 29, 2013 testing strategy notes that E1 comprises (b)(4) of the CE mixture, and that equilin sulfate and 17β -Eq comprise (b)(4) of the CE mixture, respectively, and that these latter two substances will be represented by 17β -Eq due to its greater ER binding affinity and functional activity. Summing the lower (screening assessment assumption) concentrations of these ranges and adding the (b)(4) for E2 accounts for approximately (b)(4) of CE, thus potentially leaving up to about (b)(4) of the CE

constituents unaccounted for. Given the many CE constituents and metabolites, and the potential for some to be highly potent, the sponsor will need to capture the potential effects of all of the CE constituents, such as by assuming that the unknown constituents have the same potency as the most potent known constituent, as described in the CDER EA guidance.

Conclusion

The subject proposal for the BZA/CE EA is acceptable subject to several clarifications that can be addressed in the EA. We have provided language to be transmitted to the applicant.

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- Dey, M., Lyttle, C.R. and Pickar, J.H., 2000. Recent insights into the varying activity of estrogens. *Maturitas*. 34, S25-S33.
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/s/

JAMES P LAURENSEN
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