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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fisher Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Warner Chilcott Inc. submits this petition in accordance with 21 CFR §10.20 and §10.30 regarding the acceptance for filing, review, and approval by the Commissioner of Food and Drugs (the "Commissioner") of abbreviated new drug applications ("ANDAs") for estradiol vaginal cream products that rely on ESTRACE® (Warner Chilcott) estradiol vaginal cream, USP, 0.01% as the reference listed drug, and where the bioequivalence data for these applications are based on pharmacokinetic blood level data alone or another showing of bioequivalence other than a well-controlled clinical end-point bioequivalence trial that demonstrates equivalent safety and therapeutic effect.

As described in detail below, this action is requested to ensure that there are sufficient data within the application to demonstrate the true pharmaceutical equivalence and bioequivalence of a generic drug product of estradiol vaginal cream, 0.01%, to determine it therapeutically equivalent with ESTRACE vaginal cream.

A. Action Requested

By this petition the undersigned requests that the Commissioner stay final approval and/or effective date of final approval of any estradiol vaginal cream ANDAs unless the applications contain data to address the special bioequivalence and therapeutic equivalence issues raised by such products, in accordance with the applicable bioequivalence requirements in the statute, regulations and guidance documents, specifically, Section 505(j)(8) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 CFR §320, and the 2003 Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation. Complete bioequivalence testing ensures the generic version has the same clinical effect and

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is as safe as the innovator product. Bioequivalence programs for locally acting vaginal estradiol drug products that do not include clinical studies in a target population should be considered only partial substantiation for bioequivalence to the innovator product. Only those applications that include well-controlled clinical end-point bioequivalence trials demonstrating equivalent safety and therapeutic effect should be considered for review.

Our requested action to uphold the accepted and pivotal standards of bioequivalence prior to approval of a generic estradiol vaginal cream, 0.01%, is based on the following:

- ESTRACE, estradiol vaginal cream, 0.01%, is absorbed and acts locally via estrogen receptors located in the vaginal mucosa and is intended for local treatment of vaginal symptoms associated with vulvar and vaginal atrophy. The intended mechanism of ESTRACE vaginal cream action is in local vaginal tissue, and any effect on serum estradiol levels in the bloodstream is secondary to the local therapeutic effect seen with ESTRACE vaginal cream treatment. Therapeutic equivalence of a generic vaginal estradiol cream product should therefore be based on demonstrated safety and efficacy at the local site of estradiol absorption.
- In order for a generic product to be therapeutically equivalent and therefore substitutable with ESTRACE vaginal cream, the generic product should also demonstrate efficacy in the treatment of symptoms of vulvar and vaginal atrophy as per the 2003 Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation.
- Efficacy in treating clinical endpoints associated with vulvar and vaginal atrophy is dependent on both the inactive ingredients and the active ingredients in a drug product formulation. Differences in the inactive ingredients of the generic formulation could impact the ability of the generic product to effectively treat local clinical endpoints. Lack of efficacy in treating these will not be identified in a bioequivalence trial based on estradiol and/or metabolite(s) blood level data alone.
- Different inactive ingredients contained in the formulation of a generic estradiol cream product could alter the adverse effect profile that is observed with ESTRACE vaginal cream. Formulation dependent adverse events that may occur with the use of the generic product will not be identified in bioequivalence studies that rely on estradiol and/or metabolite(s) blood level data alone.
- Estradiol levels in the blood are not a complete measure of the biologic effects of a local vaginal estradiol product to treat vulvar and vaginal atrophy. For example, FSH levels in the blood can differ with nominally similar products, which do not show measurable estrogen absorption. For this reason safety and efficacy must be demonstrated using clinical endpoints.

The above listed points are explained more fully below.

B. Statement of Grounds

I. ESTRACE Vaginal Cream Background

1. Approved Products

The innovator product, ESTRACE, estradiol vaginal cream, USP 0.01%, received FDA approval in January 1984 for the treatment of vulvar and vaginal atrophy. The majority of the products approved for the treatment of symptoms related to estrogen deficiency that occurs with women as they enter menopause are intended to be absorbed into the bloodstream and exert their therapeutic effects via systemic action. Estrogen products approved for local vaginal treatment instead act directly via estrogen receptors located in the local vaginal mucosa. These products include; VAGIFEM[®] (estradiol vaginal tablets, 25 µg), ESTRING[®] (estradiol vaginal ring) and ESTRACE[®] (estradiol vaginal cream, 0.01%) (Attachment 1).

2. Systemic Absorption

Depending on dose, vaginal estrogen products may be well absorbed through the vaginal mucosa, and as a result bypass the liver and produce higher parent serum concentrations and lower metabolite concentrations compared to some oral estrogen replacement products (Attachment 2). Products that act via local absorption of estrogenic compounds have shown to have less estrogen-induced liver effects on renin substrate, thyroxine binding globulin, sex hormone binding globulin, cortisol binding globulin, and lipid profile than products that act through the systemic circulation (Attachment 2).

Absorption notwithstanding, the mechanism of action of vaginal estrogen products is local, as discussed further below. The effect that local estrogen drug products intended for vaginal absorption have on circulating blood levels of estradiol is still being investigated. A study evaluating the systemic absorption of local vaginal estradiol tablets show a pattern of absorption that is dose dependent and more significant following the initial dose of estradiol than after 14 days where absorption was significantly less (Attachment 3). Additionally, a study evaluating the blood levels of estrogens following the administration of estriol cream and vaginal suppositories showed a high degree of interindividual variation in absorption (Attachment 4). According to the label for ESTRING (estradiol vaginal ring), systemic exposure to estradiol and estrone from ESTRING is low and decreases with repeat dosing. The low overall systemic exposure to estradiol and estrone resulting from therapy with this locally acting estrogen product is expected to result in a reduced amount of estrogen-dependent effects (Attachment 5).

II. Establishing Bioequivalent Efficacy in Treating Local Symptoms

21 CFR §320.24 outlines the types of evidence that are recommended to measure bioavailability or establish bioequivalence, and states in this section that applicants should use the most accurate, sensitive, and reproducible approach available. The following in vivo and

in vitro approaches are listed as acceptable for determining bioavailability or bioequivalence. These methods are listed in descending order of accuracy, sensitivity, and reproducibility:

1. Blood/Plasma/Serum drug concentration measurement in humans
2. Urinary excretion in humans
3. *In vivo* pharmacological effect
4. Well-controlled clinical trials
5. *In vitro* test
6. Any other approach deemed adequate by FDA

Locally acting estrogen products administered intravaginally are not intended to deliver the active moiety to the bloodstream. The mechanism of action of these products is through the direct interaction of the estradiol administered to the target tissues of the lower genitor-urinary tract where estrogen receptors are located and respond to estrogen therapy.

According to 21 CFR §320.24(b)(4), of the above outlined methods for determining bioavailability or bioequivalence, the approach that is considered sufficiently accurate for measuring the bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, as with topical preparations for the mucous membrane, is through well-controlled clinical trials that establish the safety and effectiveness of the drug product. A clinical end-point bioequivalence trial is considered an accurate method for dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution. The other methods listed in 21 CFR §320.24 are not an option for demonstrating bioequivalence since ESTRACE vaginal cream is not intended to deliver the active moiety, estradiol, to the bloodstream for systemic distribution. Additionally, there is no current in vitro standard or pharmacodynamic measure for the bioavailability of estrogen when administered intravaginally to the local site of action. Therefore, following the recommendations set forth in 21 CFR §320.24, the most accurate, sensitive and reproducible method for evaluating the bioequivalence of locally acting estradiol vaginal cream products is through well-controlled clinical trials that establish the safety and effectiveness of the drug product.

The preface to FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") outlines the criteria for classifying drug products as therapeutic equivalents, and provides as one of the criteria for therapeutically equivalent drug products; "they are bioequivalent in that a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard". As described in 21 CFR §320.33(f)(1), well-documented pharmacokinetic evidence that "the active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part from a localized site" is a factor that may present problems when assessing the bioequivalence of two pharmaceutical products that may not be bioequivalent drug products. As described previously, local vaginal estradiol products are absorbed into local vaginal tissue, and therefore present a known bioequivalence problem in evaluating the bioequivalence of two

pharmaceutical products. Following the guidelines set forth in the Orange Book, bioequivalence should then be based on an appropriate standard other than estradiol concentrations in the blood. For these reasons, clinical trials are the most appropriate and present the most accurate method for demonstrating bioequivalence in locally acting vaginal estrogen products.

Establishing bioequivalence standards for drugs that are not intended to be absorbed into the bloodstream (some estradiol from ESTRACE vaginal cream may be absorbed into the bloodstream but that is not the intended mode of action) has been a complex issue that the FDA has struggled with ever since promulgation of the bioavailability/bioequivalence regulations. The lack of established bioequivalence standards for non-systemic drug products resulted in Congress adding a new statutory provision (Pub. L. 108-173 amending section 505(j)(8) of the FDCA) that allows the FDA to assess the bioavailability of non-systemic drug products by using "scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action." The FDCA was further amended by the following:

"For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."

The new statutory standard focuses the FDA to use scientifically valid methods and measurements to assess the bioequivalence of non-systemic drug products, such as ESTRACE vaginal cream, to assure equivalent safety and therapeutic effect.

III. Demonstrated Bioequivalence in Clinical Efficacy

The 2003 Draft Guidance for Industry for Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation lists five symptoms that are associated with vulvar and vaginal atrophy. These symptoms are as follows:

- A) Vaginal dryness
- B) Vaginal and/or vulvar irritation/itching
- C) Dysuria
- D) Vaginal pain associated with sexual activity
- E) Vaginal bleeding associated with sexual activity

The draft guidance recommends that randomized, double blind studies of 12-week duration be conducted for these associated symptoms. The co-primary endpoints that should be studied and demonstrate a statistically significant improvement for the treatment of vulvar and vaginal atrophy include;

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her,
- Mean change from baseline to week 12 in vaginal pH,
- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).

As stated in the Orange Book, therapeutically equivalent drug products must have the same "clinical effect and safety profile when administered to patients under the conditions specified in the labeling". In order for a generic product to be determined therapeutically equivalent to ESTRACE vaginal cream, it should therefore demonstrate efficacy in treating the five associated symptoms of vulvar and vaginal atrophy that are associated with the menopause. **Blood level concentrations of estradiol following local vaginal estrogen treatment are not indicative of the effectiveness in treating local symptoms of vulvar or vaginal atrophy, and therefore should not be the basis for establishing bioequivalence.** Instead, demonstrated bioequivalence in treating the endpoints as defined in the 2003 Draft Guidance for Industry for Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation should be shown. However, comparability of estradiol blood levels between a generic estradiol vaginal cream and ESTRACE vaginal cream should be demonstrated to assure that systemic absorption, as an additional measure of safety, is equivalent.

IV. Bioequivalence of Adverse Event Profile

As stated in the Orange Book, therapeutically equivalent drug products must have the same "clinical effect and safety profile when administered to patients under the conditions specified in the labeling". In order for a generic estradiol vaginal cream to be determined therapeutically equivalent to ESTRACE vaginal cream, the pattern of adverse events that occur with use of the generic product should be no worse than those observed with the use of ESTRACE vaginal cream. The safety profile of a generic estradiol vaginal cream product should be evaluated in clinical studies where the generic drug product is administered under the same conditions that are specified in the product labeling. This is necessary because similar adverse events cannot be expected to result from products that differ in formulation, even when the formulation differences are only in the inactive ingredients. This is demonstrated by studies described below that evaluate both systemic and local observed adverse effects that occur in local vaginal estrogen products with differing formulations.

1. Systemic Adverse Effects

Symptoms of vulvar and vaginal atrophy may be more appropriately treated with local estrogen therapy as opposed to oral or a parenteral form of estrogen therapy because local therapy is known to have the advantage of avoiding enterohepatic circulation, inactivation by hepatic metabolism of the active moiety and unwanted systemic effects (Attachment 6). Potential advantages of local vaginal estrogen products over estrogen products that deliver the active ingredient through the systemic circulation are that systemic adverse effects such as

bleeding, breast tenderness and endometrial stimulation are typically avoided with the use of local estrogen therapy (Attachment 7). While these same adverse effects are listed in the ESTRACE vaginal cream package insert, they are associated more with class labeling for estrogen therapy than with actual reports with the use of ESTRACE vaginal cream. The availability of a locally applied product provides an option for estrogen therapy that avoids the potential harmful systemic effects for many women who wish to avoid systemic exposure to exogenous estrogens. However, because systemic effects can be seen with the use of local estrogen products, it is important to monitor the adverse effects associated with local estrogen therapy to ensure that systemic effects do not compromise the safety associated with the use of these products.

2. Local Adverse Effects

The safety profiles of several vaginal estrogen products were also evaluated in the above mentioned review article, and show that although different local vaginal estrogen preparations may be equally effective in treating the signs and symptoms of vaginal atrophy, the preparations studied differ in their adverse event profiles (Attachment 4). The table below summarizes some of the observed adverse effects reported in studies comparing different types of local vaginal estrogen treatments.

Product	AE (other)
Estradiol vaginal ring	Vaginal burning ¹ Urinary incontinence ¹ Breast enlargement ¹ Edema ¹ Migraine ¹
Estriol pessary ²	Vaginal itching Breast enlargement Breast pain
Vaginal estradiol tablets	Vaginal itching ³ Breast pain ³ Paresthesia ³ Uterine bleeding ⁴ Perineal pain ⁴

The events described above do not constitute a complete listing of events that occur with the use of local vaginal estrogen products. However, it does illustrate the importance of evaluating first hand the adverse effects associated with product use so patients and physicians can be aware of potential side effects that are specific to a particular product formulation and prescribe treatment based on this information (The Henriksson 1994, Dugal 2000, and Rioux 2000 studies are included as Attachment 8, Attachment 9, and Attachment 10, respectively).

¹ Observed adverse event associated with 2 mg 17 β -estradiol vaginal ring. Reported in Henriksson et al 1994

² Observed adverse events associated with 0.5 mg estriol pessary. Reported in Henriksson et al 1994.

³ Observed adverse events associated with 25 μ g 17 β -estradiol tablet. Reported in Dugal et al 2000.

⁴ Observed adverse events associated with 25 μ g 17 β -estradiol tablet. Reported in Rioux et al 2000.

V. Clinical Endpoints Depend on Inactive and Active Ingredients

The effects of local vaginal estrogen treatment are not the same for products with different formulations. Product formulation can affect the observed clinical effects as well as the subjective effects the drug product has on treating symptoms that occur with treatment of vulvar or vaginal atrophy. Other product characteristics such as variation in application, dispersion at treatment site and other formulation dependent factors can also influence the local efficacy of a vaginal estrogen drug product.

1. Objective Measures of Efficacy

One efficacy measure of local vaginal estradiol products in treating vulvar and vaginal atrophy is the ability of the drug product to cause maturation of the vaginal epithelium. Low doses of estradiol given intravaginally are readily absorbed into an atrophic vaginal epithelium, but as the epithelium becomes more mature estradiol is less well absorbed. Products approved for local treatment exert their clinical effect through direct action on the vaginal epithelium, and therefore changes in the formulation, including changes in the inactive ingredients, could impact the observed effect of the drug product. A blood level study will not effectively evaluate the equivalence of two locally administered vaginal estradiol products in achieving the observed maturation of the vaginal epithelium because; (1) the observed effect of the vaginal estradiol product to stimulate maturation of the vaginal epithelium is substantially a local effect of the estradiol on the vaginal epithelium rather than a result of systemic action and, (2) the amount of estradiol absorbed from a local vaginal estradiol product is entirely dependent on the degree of vaginal atrophy, which varies among woman and also individually as atrophic epithelium is treated and becomes more mature.

Other effects that have been observed with the use of local vaginal estrogen products include a lower incidence of urinary tract infections in women using a local vaginal estradiol treatment versus placebo, and an increase in lactobacilli indicating the reestablishment of a normal vaginal flora pattern with the use of local vaginal estrogen products (Attachment 4). The effects of local vaginal estrogen products rely on attributes of the drug products that are not associated with estradiol absorption into the bloodstream. A generic applicant must therefore demonstrate equal efficacy in treating the objective measures of vulvar and vaginal atrophy through clinical trials.

2. Subjective Measures of Efficacy

Subjective symptoms such as vaginal dryness, dyspareunia, urinary urgency, dysuria and pruritus vulvae all contribute to the overall effectiveness of local vaginal estrogen therapy (Attachment 6). These subjective measures in addition to acceptability factors such as, leakage of the medication, discharge associated with use of the product, and comfort of the product, all affect the overall acceptability and patient preference for a product. A study that evaluated subjective differences between treatment with vaginal estradiol ring use and estriol

nessary use reports that equivalence between the products was not shown in the relief of dyspareunia, occurrence of dysuria, or symptoms of urinary urgency (Attachment 8). Inactive ingredients in the generic product formulation could impact the pharmaceutical elegance of the drug product and could have profound effects on the acceptability and correct use of the drug product. Vaginal cream products are associated with a high degree of medication leakage when compared to other vaginal estrogen treatment (Attachment 4). The comparability of pharmaceutical elegance, leading to patient compliance, would not be evaluated by a blood-level bioequivalence study.

The equivalence of a generic product in treating subjective endpoints as well as meeting equivalent acceptability measures as the innovator product is highly important and should be taken into account when evaluating the bioequivalence and therapeutic equivalence of two local vaginal estrogen products. A generic estradiol vaginal cream product that is therapeutically equivalent and substitutable should be equivalent in the acceptability and subjective efficacy in treating symptoms of vulvar or vaginal atrophy as well as in safety and objective efficacy.

VI. Further Considerations

In addition to the above specified considerations for why an ANDA for estradiol vaginal cream that references ESTRACE vaginal cream as the innovator product should demonstrate bioequivalence to ESTRACE vaginal cream through clinical studies that evaluate local endpoints, the petitioner would like to further comment as to why the design of bioequivalence studies that rely on blood level data alone are not applicable to locally acting estradiol products.

1. Crossover Period Effects

Locally applied estrogen products such as estradiol vaginal cream, are effective in relieving menopausal symptoms associated with vulvar or vaginal atrophy. This effectiveness is due in part to the ability of locally applied estrogen products to induce vaginal mucosal maturation. The design of a study to test the effectiveness of locally applied estrogen products therefore must take into consideration cumulative effects that are observed when locally applied estrogen products are administered. A crossover design study is the typical design for a study testing bioequivalence of two products. This design is not appropriate, however, in evaluating the equivalence of two locally applied estrogen products, where effects from the first product on a treatment group could impact the efficacy of the second product being evaluated. The effect of the first estrogen product on vaginal mucosal maturation would alter the effects of the second estrogen product being evaluated because of carryover effects from the first treatment product on vaginal mucosal maturation.

This "period effect" was observed in a Phase I study of postmenopausal women undergoing treatment with ESTRING (estradiol vaginal ring) for 12 weeks. The initial estradiol peak blood level post-application that was seen after insertion of the first ring to women was about

38% higher than the initial estradiol peak blood level post-application that was observed for the second ring that was administered to the same group of women (Attachment 5). The reduced systemic levels of estradiol following the insertion of the second ring were attributed to the effect of the first ring administration on revitalizing the vaginal epithelium, therefore reducing the amount of estradiol absorbed. Other studies evaluating the effect of local estradiol treatment on vaginal mucosa have showed a similar result (Attachment 3). For this reason a crossover design trial is not an appropriate measure of bioequivalence because the effectiveness of the second treatment would be affected by the first treatment.

2. Multiple Dose Setting

The effectiveness of locally applied estrogen products to treat vulvar or vaginal atrophy are cumulative, and the overall effectiveness of locally acting vaginal estrogen products is dependent on the ability of the drug product to elicit sufficient mucosal maturation. Studies have shown that this effect affects the absorption of low doses of locally applied vaginal estrogen products so that initially increased absorption of estradiol from an atrophic epithelium is seen and, as the epithelium grows, the absorption of estradiol is less pronounced (Attachment 3). This effect is however variable and not reported with all locally applied vaginal estradiol products. Bioequivalence studies of local vaginal estradiol products that evaluate blood levels following only a single dose of the drug product would therefore only evaluate a small part of the overall effect the product has on the vaginal mucosa. Due to the initial peak in estradiol absorption followed by a plateau, a single dose bioequivalence study of an estradiol vaginal cream drug product would not be predictive of the effects that would be seen in clinical practice where the dose of estradiol is given until it reaches steady state and then maintained with doses given less often. Bioequivalence should be determined from the clinical effect the drug has on treating the symptoms of vulvar and vaginal atrophy when dosed as it is recommended in the product labeling.

VIII. Conclusion

Warner Chilcott Inc. requests that the Commissioner refrain from accepting for filing and/or approving ANDAs filed for estradiol vaginal cream, 0.01%, that use ESTRACE vaginal cream as the reference listed drug, where the bioequivalence data presented in the application rely on blood level data alone. Such ANDAs may not be pharmaceutically or therapeutically equivalent to ESTRACE vaginal cream because: (1) ESTRACE vaginal cream is intended for local absorption and therefore bioequivalence should not be based on levels of estradiol that are absorbed into the systemic circulation, (2) a generic drug product should have the same clinical effects as seen with the innovator product, and therefore bioequivalence should be evaluated based on the demonstrated ability of the drug product to treat local clinical endpoints as defined in the 2003 Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation, and (3) inactive ingredients affect both the safety and efficacy of drug products intended for treatment at the local site of administration. In order to assure that a generic product has a comparable efficacy and safety

profile to that of ESTRACE vaginal cream, bioequivalence should be based on efficacy and safety outcomes when the generic product is studied in the clinical setting. Since factors other than estradiol levels after a single administration can be indicative of absorption of the drug product, an appropriate study to evaluate the bioequivalence of a locally acting generic vaginal estrogen using ESTRACE vaginal cream as the RLD should be of parallel design using clinical endpoints, should evaluate multiple doses of the drug product at steady state, and test both the high and low dosage range for bioequivalence.

C. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR §25.31.

D. Economic Impact

Pursuant to 21 CFR §10.30(b), a statement of the effect of requested action on various economic indicators will be submitted only if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,



Anthony Bruno
Executive Vice President
General Counsel

cc Gary Buehler, Director, Office of Generic Drugs