



MAR 17 2000

1613 '00

Food and Drug Administration
Rockville, MD 20857
MAR 17 10 33 50

Sharon W. Brown
Associate Director, Drug Regulatory
Berlex Laboratories, Inc.
340 Changebridge Road
Montville, NJ 07045

Mary Mathisen
Regulatory Specialist
3M Pharmaceuticals
3M Center
Building 260-6A-22
Pharmaceutical Regulatory Affairs
St. Paul, MN 55144-1000

Re: Docket No. 98P-0434/CP1 and PSA1

Dear Ms. Brown and Ms. Mathisen:

This responds to your citizen petition and supplements¹ (Petition) and petition for stay of action (PSA), both dated June 12, 1998, submitted on behalf of Berlex Laboratories and 3M Pharmaceuticals. The Petition requests that the Food and Drug Administration (FDA) refuse to approve an abbreviated new drug application (ANDA) for a transdermal estradiol patch that relies on Climara as its reference listed drug unless certain scientific, medical, regulatory, and legal criteria are met. The Petition requests that FDA:

1. Require, using the "best available method," a demonstration of rate and extent of absorption consistent with good medicine and science and FDA's own previous scientific and medical opinion.
2. Require a demonstration that skin adhesion is at least as good with the generic patch as with Climara.
3. Require a demonstration that the results of skin irritation and sensitization studies in humans are at least as good with the generic patch as with Climara.
4. Require a demonstration of the safety of the inactive ingredients as set forth in section 505(j)(4)(H) of the Federal Food, Drug, and Cosmetic (the Act) and 21 CFR 314.127(a)(8).

¹ The Agency received supplements to the Petition dated August 7, 1998; December 22, 1998; January 8, 1999; March 10, 1999; March 24, 1999; May 12, 1999; May 14, 1999; and June 14, 1999.

98P-0434

PDN1

5. Require an ANDA applicant relying on Climara as the reference listed drug to provide evidence that its product is bioequivalent at both sites of application.
6. Require an ANDA relying on Climara to have labeling that is identical to that of Climara.
7. Convene a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Advisory Committee for Pharmaceutical Science to develop standards that relate to the approval of estrogens, multi-day extended-release products, and transdermal delivery systems.
8. Validate the above standards with both the FDA Medical Policy Coordinating Committee and the FDA Biopharmaceutics Coordinating Committee.
9. Require a 505(b)(2) application, rather than an ANDA, for a generic drug product relying on Climara as the reference listed drug.

The PSA requests that FDA stay the approval of a generic transdermal estradiol patch until after the Agency has responded to the Petition or, if the Petition is denied, stay or suspend any such approval until the completion of judicial review of the Agency's decision. In reaching its decision, FDA has considered the information in the Petition, the supplements, the comments, the information in the docket related to the Petition, as well as other information available to the Agency as identified in this response. For the reasons set forth below, the Petition is granted in part and denied in part, and the PSA is denied.

I. Climara Transdermal Delivery System

A transdermal delivery system is a dosage form that delivers the drug at a constant rate through the skin to the blood stream and then to the site of action in the body. Climara is a transdermal delivery system that delivers a constant amount of estradiol over a period of 7 days. Climara is one of several estradiol transdermal delivery systems that have been approved by the FDA. Climara is approved for application to the abdomen or the buttocks in three different delivery rates: 0.05 mg/24 hours, 0.075 mg/24 hours, and 0.1 mg/24 hours. Transdermal administration of estradiol provides slow, sustained-release of the hormone, systemic distribution, and more constant blood levels than are obtained with oral doses.

Climara is used for hormone replacement therapy. It is indicated for the relief of symptoms associated with menopause, including vasomotor symptoms (hot flashes) and vulval and vaginal atrophy. It is used to treat low estrogen levels due to hypogonadism, castration, or primary ovarian failure. In addition, Climara is indicated for treatment of abnormal uterine

bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

II. Statutory and Regulatory Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process.² The showing that must be made for an ANDA to be approved is quite different from what is required in a new drug application (NDA). An NDA applicant must prove that the drug product is safe and effective. An ANDA does not have to prove the safety and effectiveness of the drug product because an ANDA relies on the finding FDA has made that the reference listed drug is safe and effective. Instead, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the reference listed drug (21 U.S.C. 355(j)(2)(A)(iv)).³ The scientific premise underlying the Hatch-Waxman Amendments is that in most circumstances bioequivalent drug products may be substituted for each other.

A generic drug is bioequivalent to the listed drug if "the rate and extent of the absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses" (21 U.S.C. 355(j)(8)(B)(i)).⁴

III. Standard Bioequivalence Testing

The standard bioequivalence study for a transdermal system is conducted in a crossover fashion in a small number of volunteers, usually 24-36 healthy normal adults.⁵ Single applications of the test and reference transdermal systems are applied to these volunteers, and the blood or plasma levels of the drug are measured over time. Characteristics of these concentration-time

² The goal of the amendments was to allow more expeditious approval and marketing of lower priced generic versions of previously approved innovator drugs.

³ A generic drug that establishes bioequivalence as well as pharmaceutical equivalence is rated as therapeutically equivalent to the reference drug in FDA's *Approved Products with Therapeutic Equivalence Evaluations*, commonly referred to as the *Orange Book*.

⁴ See also 21 CFR 320.1(e) and 320.23(b).

⁵ The Office of Generic Drugs (OGD) has reviewed and approved a number of generic transdermal products, including transdermal delivery systems for nicotine and nitroglycerin.

curves, such as the area under the curve (AUC) and the peak or maximum blood or plasma concentration (C_{max}), are examined by statistical procedures. C_{max} is the characteristic of the concentration-time curve that FDA uses to represent the rate of absorption. AUC is the characteristic of the concentration-time curve that the Agency uses to determine the extent of absorption.

Generic applicants should analyze the AUC and C_{max} data for the test and reference products statistically and should demonstrate that they meet FDA's statistical criteria for a determination that the products are bioequivalent. Specifically, the log transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80 to 125 percent of the reference product using the 90 percent confidence interval. In addition, ANDAs for transdermal products are requested to submit skin irritation, skin sensitization studies, and adhesion tests between the reference listed drug and the proposed generic version of the transdermal system. The results are considered when determining whether the product is bioequivalent.

IV. Bioequivalence Testing and Analysis for Generic Estradiol Transdermal Drug Delivery Systems

The Petition states that because transdermal products are unique and Climara is unique among transdermal products, the standard bioequivalence study performed for an ANDA is not adequate to assess the bioequivalence of a generic estradiol transdermal delivery system. Accordingly, the Petition sets out a number of requirements and asserts that the Agency must require a generic applicant to meet these requirements to show that its drug product is bioequivalent to the reference listed drug.⁶ The Petition asserts that a multiple-dose study as well as a single-dose study must be conducted to establish bioequivalence (Petition at 7). In addition, the Petition asks that the Agency consider a number of pharmacokinetic parameters

⁶ The Petition asserts that the Agency has tried for years to develop a guidance for the approval of generic transdermal products but has been unable to develop criteria that will ensure the safety and efficacy of generic estradiol transdermal patches. The Agency strongly disagrees with this assertion. The absence of a guidance document does not mean that the Agency has not determined the proper criteria for the approval of generic estradiol transdermal drug delivery systems. One of the Agency's primary goals is to ensure that only safe and effective products are approved for use by the public. Accordingly, OGD exercises the utmost care in assessing any generic drug application that is submitted for review and approval. OGD is primarily responsible for the review of ANDAs and postapproval supplements and has only limited resources to devote to the development of guidance for industry. The absence of a published guidance for a specific product does not preclude the Agency from accepting, reviewing, and approving ANDAs that meet the statutory requirements.

*other than C_{max} and AUC to determine whether the generic transdermal system is bioequivalent. The specific parameters requested by the Petition will be discussed below.*⁷

A. The Need for a Multiple-Dose Study

As set forth in the regulations, an ANDA for a generic estradiol transdermal drug delivery system must demonstrate that the rate and extent of absorption of the proposed product does not show a significant difference from the reference listed drug when administered at the same molar dose of active moiety under similar experimental conditions, either single dose or multiple dose (21 CFR 320.23(b)).

The Petition asserts that the generic applicant must perform both a single dose and a multiple-dose study.

The Agency does not agree that a multiple-dose study is necessary before a generic estradiol transdermal drug delivery system may be determined to be bioequivalent. Multiple-dose studies are performed to achieve and measure the drug substance (e.g., active ingredient) at its steady-state level in blood or serum. A steady-state concentration will eventually be achieved when a drug is administered at a constant rate. At the point the drug reaches steady state, the rate of elimination (output) of the drug will equal the rate of drug availability (input).

The Petition argues that because transdermal products are extended-release dosage forms, the Agency must treat them like oral extended-release drug products and require ANDAs for estradiol transdermal systems to include a multiple-dose bioequivalence study (Petition at 7).

FDA agrees that transdermal products are extended-release products. However, FDA's position is that these drug products have many properties that differentiate them from oral extended-release products. Because of the unique properties, a multiple-dose study is not necessary. For example, transdermal products can be designed to deliver drug into the systemic circulation at a constant rate over a prolonged period, such as 7 days. However, an oral extended-release dosage form may be given once per day. A person takes the tablet in the morning, and the tablet passes through the gastrointestinal system and is eliminated during the course of 1 day. For this type of product, it may take several doses before steady state is reached.⁸

⁷ The Petition, with its eight supplements, raises more than 50 issues.

⁸ The guidance entitled *Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing* sets forth the current FDA recommendations for establishing bioequivalence of oral extended-release products.

The Climara transdermal system is applied to the skin and is not removed during the course of 7 days. It is designed to release a constant rate of drug to the blood stream through the skin. FDA's position is that constant blood levels are achieved within this 7-day time frame, that is, the levels of drug in the blood and/or plasma reach steady state during the first application of the product.⁹ Because Climara reaches steady-state in less than 1 day, the FDA has determined that a multiple-dose study is unnecessary to determine bioequivalence.

FDA has approved numerous estradiol transdermal drug delivery systems as well as other dosage forms of estradiol, including tablets and injections. The Agency relied on its extensive experience with estradiol and specifically with estradiol transdermal drug delivery systems to determine the necessary criteria for approval of a generic estradiol transdermal drug delivery system. A review of the information regarding the approvals of NDAs for transdermal estradiol systems convinced the Agency that steady-state plasma concentrations of estradiol are achieved well within the 7-day single-dose application period of Climara. The Biopharmaceutics Coordinating Committee met on January 22, 1998, considered the available information, and determined that a single 7-day application of the estradiol transdermal system is appropriate to document bioequivalence and that a multiple-dose study for a generic estradiol transdermal system would provide no more information necessary for approval than a single-dose study. Furthermore, requiring a multiple-dose study would expose human subjects to unnecessary testing in violation of the principle set out in 21 CFR 320.25(a).

The Petition cites a statement in an FDA review of the Esclim 50 estradiol transdermal system that "serum levels of estradiol and estrone reached steady-state by the second week of treatment with Esclim" to support its contention that a multiple-dose study is necessary (December 22, 1998, supplement at 2-3). Esclim 50 is an estradiol transdermal product that has a unique dosing schedule in which patches are alternately applied for 3 and 4 days. The initial determination of the reviewer that steady state for Esclim 50 was not reached until the second week was confounded by the alternating periods of application. When the C_{min} s observed after the 3-day applications are compared with the C_{min} s observed after the 4-day applications, it becomes apparent that the drug reaches steady state within 3 days. Thus, after closer examination of the data for the Esclim 50 NDA as well as the data supporting the approval of other estradiol transdermal systems, it is clear that steady state for an estradiol transdermal system such as Climara is achieved within 1 day.

⁹ The Agency believes that steady state is reached during one application of a Climara due to the elimination half-life (the amount of time it takes the body to eliminate 50 percent of the drug) of estradiol. The half-life of estradiol is approximately 4 hours as stated in the approved labeling for Climara. Steady state is typically attained after approximately four half-lives. Thus, for estradiol, it would take approximately 16 hours to reach steady state. Since the transdermal system is applied for 7 days (168 hours), there is more than ample time for the drug to achieve steady state in the blood and/or plasma before the second dose must be applied.

The Petition also cites a March 10, 1999, comment by Bernard E. Cabana, Ph.D., in support of its contention that a multiple-dose study should be required of generic applicants. Dr. Cabana asserts that a single-dose study is inadequate for estradiol transdermal products because of the great variability of endogenous estradiol and estrone at baseline following a 1-week washout period. According to Dr. Cabana, in one clinical study, endogenous estradiol levels in individual subjects varied from 50 percent to 154 percent higher at baseline than in the previous week (March 10, 1999, supplement). Dr. Cabana does not provide the data or a reference to the study that he cites. Assuming that his assertions regarding baseline variability of as much as 154 percent for estradiol are correct, this represents a very small magnitude of variability when plasma levels resulting from transdermal estradiol are analyzed. For example, the baseline estradiol concentrations in postmenopausal women are approximately 0.4 picogram(pg)/millileter(mL). If the variability around this is ± 150 percent, this results in a magnitude of ± 0.6 pg/mL. After administration of transdermal estradiol, peak plasma concentrations of approximately 165 pg/mL are achieved. The magnitude of baseline variation of ± 0.6 pg/mL when added to concentrations of 165 pg/mL yields an increase in variability of only ± 0.4 percent, a negligible increase. In addition, the Agency has further addressed this concern by recommending a washout period of 2 weeks to ensure that the effects from the first dose are eliminated before the second dose is administered.

It should also be noted that the Agency would not require multiple-dose studies to establish the bioequivalence of estradiol transdermal systems approved through the NDA process. If Berlex/3M wanted to change an aspect of Climara that made it necessary to demonstrate bioequivalence, it would be asked to perform a single-dose bioequivalence study using one 7-day application of its new product compared to its former product to establish that the new product was bioequivalent to the former product.

The Petition notes that there are special concerns with multi-day dosing of a transdermal product, specifically drug accumulation and the possibility of drug retention in the skin. In addition, the Petition expresses concern about the fact that sex hormone binding globulin (SHBG) increases with continuous estradiol dosing (Petition at 7). Accordingly, the Petition asserts that a generic applicant must perform a multiple-dose study to address these concerns.

The Agency's position regarding drug retention in the skin and the increase in SHBG after long-term treatment with an estradiol transdermal drug delivery system follows. After application of a transdermal product to the skin, the drug released from the transdermal system attains an equilibrium concentration within the skin under the patch. This skin concentration of drug remains relatively constant and is related to the rate of drug released from the patch. When the patch is removed from the skin, the drug remaining in the skin, which is a comparatively small amount compared to the drug currently in the body or in the patch, is absorbed into the systemic circulation. If two products are bioequivalent, there should be no

difference in the amount of drug substance retained in the skin. Furthermore, the equivalent amounts of drug released into the body resulting in equivalent drug plasma concentrations should yield equivalent effects on SHBG. Thus, the Agency does not believe that a multiple-dose study is necessary to address these concerns.

B. Pharmacokinetic Parameters

The Petition proposes that FDA use a host of measures other than C_{max} and AUC to evaluate the bioequivalence of a generic estradiol transdermal delivery system. These measures include C_{min} , $C\tau$, T_{max} , partial AUC, occupancy time, and percent fluctuation. The Petition also proposes sampling times and procedures, specific comparisons, and other aspects of a bioequivalence protocol. The specific recommendations will be addressed below.

1. C_{max} and AUC

The Petition argues that C_{max} alone is an insufficient measure of the rate of absorption and that C_{max} and AUC are not sufficient to establish bioequivalence (Petition at 6).

The Agency believes that C_{max} is the best parameter available for the evaluation of rate in determining bioequivalence. FDA has always accepted, and continues to accept, systemic exposure measures such as C_{max} and AUC to indicate comparability in rate and extent of absorption. The Agency has carefully explored alternatives such as partial areas and AUC/C_{max} as the parameter for absorption rate. After a great deal of simulation and examination of the available data, the Agency has come to the conclusion that C_{max} and AUC are the best parameters available for evaluating bioequivalence.¹⁰

The Agency monitors and evaluates many pharmacokinetic parameters in addition to C_{max} and AUC. The Agency does not apply strict statistical criteria to these other pharmacokinetic parameters due to their variability. These parameters are monitored during review of the bioequivalence study. If one of the monitored parameters appears to be anomalous, the reviewer will consult with the team leader. If the team leader considers the anomaly to be a concern, the issue may be discussed with other team leaders. The discussion may be elevated to higher levels if it is deemed necessary. If, in the opinion of the experts in the Agency, the deviation of the parameter may impact either the safety or the efficacy of the drug product, the issue may be raised with a medical officer in the appropriate review division within the Agency.

¹⁰ Bois et al., "Bioequivalence: Performance of Several Measures of Extent of Absorption" and "Bioequivalence: Performance of Several Measures of Rate of Absorption" in *Pharmaceutical Research*, Vol. 11, Nov. 5 and 7, 1994.

2. C_{min} , $C\tau$, and T_{max}

The Petition asserts that C_{min} is important because it is more sensitive to product performance, and that C_{min} should have to meet the same strict 90 percent confidence interval criteria as the AUC and C_{max} (December 22, 1998, supplement at 3-4).

The Agency agrees that C_{min} is an important parameter. C_{min} is monitored during the evaluation of the steady-state study, but the strict 90 percent confidence interval criterion is not applied. This approach is based on the voluminous data the Agency has on many steady-state studies for extended-release dosage forms as well as studies on estradiol transdermal systems. From these data, the Agency observed that C_{min} is variable for all drug products and thus concluded that it is not prudent to place a statistical criterion on it. A substantial increase in the number of test subjects would be needed to provide sufficient statistical power to use a 90 percent confidence interval for C_{min} . This would make it much harder for *any* drug product to be approved. Furthermore, applying the 90 percent confidence interval to C_{min} is not necessary because FDA and the scientific community consider C_{max} and AUC to be the primary indicators of rate and extent of absorption for bioequivalence purposes.

The Petition also advocates the use of $C\tau$ and T_{max} to evaluate bioequivalence. The petition defines $C\tau$ as the absorption rate at the end of the application interval and T_{max} as the time C_{max} is reached (Petition at 7-8).

The Agency defines $C\tau$ as the concentration in the blood or plasma at the end of the dosing interval and, under most circumstances, considers $C\tau$ to be the same as C_{min} . The Agency monitors this parameter but does not apply statistical criteria to it. The Agency also considers T_{max} so variable that it does not apply strict statistical criteria to this parameter.

3. Occupancy Time

The Petition asks that the Agency look at occupancy time. The Petition defines occupancy time as the time period the serum level remains within 75 percent of C_{max} (Petition at 8).

The Agency's position is that this concept is unvalidated as a reliable measure of bioequivalence. Thus, FDA has never used it for bioequivalence determinations. Furthermore, using C_{max} and AUC and monitoring C_{min} , the Agency accomplishes the same objective without requiring an additional and unvalidated parameter.

4. Serum Sampling

The Petition states that transdermal patch content and construction vary so much from product to product that measuring the daily absorption rate is particularly important (Petition at 10-11). The petitioner asserts that FDA must rely on a serum-sampling schedule that is sufficiently sensitive to detect potential differences in rate and extent of absorption each day of the patch application period, especially days 4 to 7 (Petition at 9). Thus, the Petition proposes that blood samples be drawn every 6 hours over the entire 7-day period. The Petition also asserts that equivalency of rate and extent of absorption must be established for each day, that both peak concentration values need to be tested,¹¹ and that partial AUC values should be calculated and compared daily (Petition at 10). Furthermore, the Petition asks that multiple serum samples, at least four daily, be collected every day of the application period and that the principles of the Wagner-Nelson drug absorption equations be used to show the rate of absorption change per day (Petition at 10.)

The Agency does not agree that the proposed serum sampling schedule is warranted and notes that there is no clinical data supporting the Petition's request.¹² Bioequivalence can be determined without the frequent serum sampling recommended by the Petition. The Agency recommends that a generic applicant collect blood samples twice before the initiation of the study to determine baseline estradiol levels and then collect samples every 6 hours on the first day after the transdermal estradiol system is applied in order to establish C_{max} . However, once the steady-state plasma levels of estradiol are reached, the generic applicant need only collect blood every 24 hours. When the blood estradiol level is at steady state and is not changing, a blood sample collection every 24 hours is sufficient. Additional blood samples are recommended after the removal of the transdermal system. This sampling schedule is frequent enough to characterize the plasma concentration profile and show whether a generic estradiol transdermal system maintains steady-state levels of estradiol throughout the 7-day dosing period because the blood estradiol levels from transdermal estradiol systems such as Climara remain almost constant as stated in the approved labeling of Climara (over 50 pg/ml from 11 hours to 168 hours).

The Petition asks that ANDA applicants measure serum levels of estradiol, estrone, and estrone sulfate. In addition, the Petition states that the most sensitive and precise analytical assays be

¹¹ According to the Petition, "Climara has two peak concentration values, because estradiol absorption from Climara first increases to a peak level then slows, then increases to a second and higher peak level, and then declines thereafter" (Petition at 10).

¹² The Agency also notes that Berlex/3M did not use the recommended serum sampling schedule when conducting the clinical trials that supported their NDA for Climara.

Docket No. 98P-0434/CP1 and PSA1

used to measure estrogenic moieties and asserts that available GC-MS methods should be required as they are the most precise. Finally, the Petition asks that all pharmacokinetic bioequivalence comparisons be performed with and without background subtraction of endogenous levels (Petition at 11).

The Agency agrees that the parent moiety and its pharmacologically active metabolite(s) should be measured. For estradiol, the Agency recommends that applicants measure the parent compound, estradiol, and the products of its metabolism: unconjugated estrone and total estrone (estrone sulfate + glucuronide + unconjugated estrone). These are the same analytes that the Agency recommends be measured during the bioequivalence studies of all oral estradiol products. The Agency's practice is not to recommend a specific assay and/or method, but to inform applicants that the most sensitive assay method should be used. The Agency agrees that all pharmacokinetic bioequivalence comparisons should be performed with and without background subtraction of endogenous levels.

The Petition asks that serum sampling be continued after the patch is removed to determine if there is any retention of drug in the skin due to a unique component of the dosage form and to calculate the terminal elimination rate constant of the drug (Petition at 8-9).

FDA advises applicants to monitor blood levels for at least 12 hours after the patch is removed. Applicants should calculate $t_{1/2}$ (half-life) and K_e (elimination rate constant) based on this information. These parameters are monitored by the Agency.

5. Percent Fluctuation

The Petition asks that bioequivalence measures be included that are sensitive to the variability in the serum levels over the entire 7-day application period; that the average 7-day coefficient of variation of the serum levels be compared between products in all studies; and that percent fluctuations should be included as a bioequivalence parameter in the multiple-dose study (Petition at 10).

FDA's position is that the variability of the 7-day plasma concentration profile parameters (AUC and C_{max}) is accounted for through the 90 percent confidence interval calculations and the criteria used to assess bioequivalence. Large variability in these parameters will result in a wider 90 percent confidence interval and a lower probability of passing the 80 to 125 percent bioequivalence criteria. Therefore, the current bioequivalence criteria make this additional analysis and criteria for other measures of variability unnecessary.

6. Penetration Enhancers

The Petition asks that the effect of penetration enhancers be considered.

The Agency does not prohibit the use of penetration enhancers. However, as expressed by the petitioners, penetration enhancers may cause increased bioavailability and skin irritation. These concerns are generally addressed during the review of the bioequivalence and skin irritation studies.

C. Relevance of Certain Documents

The Petition asks that FDA rely on bioequivalence guidelines developed for extended-release products to establish bioequivalence standards for generic estradiol transdermal drug delivery systems (Petition at 4-6). The Petition proposes that each of the following four FDA publications be relied on by the Agency to develop the bioequivalence criteria for generic transdermal drug delivery systems: (1) a 1984 guidance by Dr. Jerome Skelly entitled Division Guidelines for the Evaluation of Controlled Release Drug Products,¹³ (2) a 1985 "Report of the Workshop on Controlled-Release Dosage Forms: Issues and Controversies,"¹⁴ (3) a 1986 document entitled "Regulatory Aspects Pertinent to the Development of Transdermal Drug Delivery Systems,"¹⁵ and (4) a 1990 workshop report entitled "In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms."¹⁶ Based on the petitioners' interpretation of these documents, the Petition proposes that certain approval criteria be applied by the Agency (Petition at 4-6).

The specific proposals are discussed below.¹⁷ It is important to note that the documents relied on by the Petition are at least 10 years old. Over the past 10 years, the Agency has gained considerable experience with estradiol and transdermal drug delivery systems on which to base

¹³ This guidance was written for NDA submissions for controlled release solid oral dosage forms.

¹⁴ The workshop recommendations were also intended for NDA submissions for controlled release solid oral dosage forms.

¹⁵ While this document was written specifically for transdermal drug delivery systems, it makes no recommendations regarding single-dose versus multiple-dose studies or applicable statistical criteria.

¹⁶ This document primarily addressed oral drug delivery systems.

¹⁷ The Petition states that this 1984 guidance supports all of the Petition's proposals for approval criteria, except that the Petition did not advocate a food effect study (Petition at 4-5). As all of the proposals in the Petition are addressed elsewhere in this response, they will not be addressed again in this section.

its determination of the necessary criteria for the approval of a generic estradiol transdermal delivery system.

The Petition argues that the Agency should rely on these documents to require a generic applicant to establish a relationship between plasma levels of estradiol and clinical response.

FDA does not agree that it is necessary for a generic applicant to conduct a study to establish the relationship between plasma levels and clinical response. This relationship, whether direct or indirect, has already been established through the NDA approval process and does not need to be repeated by an ANDA applicant.

The Petition also argues that the generic applicant should be required to match the blood level profiles of the reference listed drug and, if the profiles diverge, the generic applicant should be required to perform clinical studies.

The Agency's position is that matching of plasma concentration profiles of the parent drug or metabolites is not currently used as a regulatory method or criterion for the approval of ANDAs for any drug product approved by FDA. The variability of individual plasma concentration measurements due to assay and subject variability makes this approach extremely difficult to perform without using very large numbers of subjects. The current clinical and scientific opinion is that profile comparison is unnecessary to determine the bioequivalence of two pharmaceutically equivalent products.¹⁸ Furthermore, there is currently no generally accepted and validated method for carrying out a scientifically rigorous comparison of two profiles. As discussed above, the Agency's position is that C_{max} and AUC are the appropriate criteria by which to evaluate bioequivalence (Sections III and IV.B.1). These criteria are valid for virtually all systemically absorbed drug products.

The Petition relies on the 1990 workshop report to support its contention that the Agency must require a multiple-dose study. The 1990 workshop report stated: "While this guideline is designed primarily with oral drug delivery systems in mind, the general principles are applicable to other controlled-release drug delivery routes, e.g., transdermal, intramuscular, intranasal, etc." (Report at 976).

When FDA made this recommendation in 1990, there was limited information on estradiol transdermal products. Therefore, the Agency initially took a very conservative approach and requested multiple dose studies to demonstrate bioequivalence for transdermal estradiol

¹⁸ Bois et al., "Bioequivalence: Performance of Several Measures of Extent of Absorption" and "Bioequivalence: Performance of Several Measures of Rate of Absorption" in *Pharmaceutical Research*, Vol. 11, Nov. 5 and 7, 1994.

products. However, based on the currently available information, it is clear that multiple dose studies are unnecessary for demonstrating bioequivalence.

The Petition also cites a non-FDA document entitled "Points to Consider on Hormone Replacement Therapy" by the Committee for Proprietary Medicinal Products of the European Commission's European Agency for the Evaluation of Medicinal Products (CPMP) (Petition at 6). The Petition asserts that FDA's policy not to require steady-state studies of transdermal drug products goes against the CPMP's recommendation that the bioequivalence of transdermal hormone replacement therapy pharmaceutical products be determined at steady state (December 22, 1998, supplement at 3).

The CPMP recommends that bioequivalence should be determined at steady state, and AUC, C_{max} , and C_{min} should be statistically evaluated. In addition, the document recommends that the 90 percent confidence interval criterion of 80-125 percent should be applied to AUC, that the upper confidence limit for C_{max} should be less than 125 percent, and that the lower confidence limit for C_{min} should be greater than 80 percent.

The Agency agrees with the CPMP that the bioequivalence of transdermal estradiol products should be determined under steady-state conditions. As discussed above, because steady state is reached within the 7-day single dosing interval of Climara, a multiple-dose study is not needed to determine bioequivalence under steady state conditions. FDA has established bioequivalence criteria that are different than the criteria adopted by the CPMP. A generic estradiol transdermal delivery system must meet the 90 percent confidence interval for AUC and C_{max} for unconjugated estradiol, free estrone (major metabolite), and total estrone (unconjugated plus conjugated). The Agency believes that these criteria are adequate measures of bioequivalence.

V. A Generic Estradiol Transdermal Product Can Be Approved in an ANDA

The Petition sets forth a number of arguments asserting that a generic estradiol transdermal delivery system cannot be approved with an ANDA, but rather the applicant must file an NDA. The Petition suggests that there may not be a well-defined relationship between plasma concentration of the drug and active metabolites, and clinical response; therefore, it would not be scientifically credible to assume that certain blood levels will be an adequate bioequivalence

surrogate for clinical safety and efficacy studies (Petition at 12).¹⁹ These arguments are addressed below.

The Agency's position, which is the position outlined in the Hatch-Waxman Amendments, on the contrary, is that the determination of bioequivalence through the measurement of an accessible biological matrix such as blood, plasma, and/or urine to indicate the release of the drug substance from the drug product into the systemic circulation is a well-established scientific principle. This approach rests on an understanding that measuring the active moiety and/or ingredient at the true site of action is generally not possible and, furthermore, that some predetermined relationship between safety and efficacy has already been established relative to the concentration of active moiety and/or ingredient and/or its important metabolite or metabolites in the systemic circulation. Therefore, it is not necessary to reestablish this relationship for each systemically absorbed drug that is the subject of an ANDA. FDA has previously approved estradiol tablets through the ANDA process based on a bioequivalence study with pharmacokinetic endpoints. This type of bioequivalence study is a surrogate for a clinical study and is often much more sensitive to product differences than a comparative clinical trial to determine bioequivalence.

The Petition also suggests that an impediment to the use of serum levels of estradiol as indicators of biological activity is that levels of estradiol and estrone in target tissues can differ from serum levels (Petition at 12).

The Agency agrees that this may be true. It is important to note that there is a difference between serum levels and target tissue levels for *all* drugs. The significant point is that the two levels are in equilibrium. It is not feasible to measure estradiol in human target tissues without an invasive biopsy, which would be unnecessary. The principles of pharmacokinetics establish that the amount of drug measured in the blood is representative of the amount of drug that reaches the target tissues because the blood supplies the target tissues.

The Petition suggests that another impediment to predicting biological activity based on estradiol levels is that multiple active metabolites of estradiol exist that will not be reflected in

¹⁹ The Petition discusses FDA's experience with Menorest, a twice-weekly transdermal estradiol patch, to suggest that "there might not be a well-defined relationship between serum estradiol levels and clinical effect for transdermal products" (Petition at 12). The Petition points to the medical officer's recommendation not to approve the two lower strengths of Menorest. In fact, these two strengths had shown efficacy during the first and second weeks of the study, but those effects were not statistically significant. The study did not have enough subjects for the lower strength patches to show a statistically significant effect, although the effect can be considered clinically significant. The lower strengths were approved by the Agency without additional clinical studies because the blood levels achieved during the study were above the range that was shown to be effective for estradiol.

simple estradiol and estrone measurements, and thus estradiol administration may have far reaching effects that have little relationship to serum levels of estradiol (Petition at 13).

FDA does not find this suggestion credible. If a drug substance is administered to the body and transported by way of the blood to its site or sites of activity, then the plasma or blood concentrations will have a relationship to pharmacologic activity. This principle is well accepted by pharmacokinetic scientists. If this were not true, the equivalent amounts of drug absorbed into the body from dosage units given on different days or from two different lots of an innovator product could not be relied on to yield a consistent and reliable effect.

The Petition argues that FDA should treat a generic estradiol transdermal delivery system as it did Cenestin, a synthetic conjugated estrogen, and require an applicant to submit a 505(b)(2) application rather than an ANDA (June 14, 1999, supplement at 1-2).

The Cenestin example is not applicable to this situation. FDA required the sponsor of Cenestin to submit a 505(b)(2) application rather than an ANDA because the active ingredients in the reference listed drug had not been characterized.²⁰ There is no similar problem in characterizing the active ingredient in Climara (i.e., estradiol). The appropriate application for a generic is an ANDA submitted under section 505(j), not a 505(b)(2) application.²¹

VI. Skin Adhesion

The Petition requests that FDA require a demonstration that skin adhesion is at least as good with the generic patch as with Climara (Petition at 14). Furthermore, the Petition asks that skin adhesion be assessed in a separate study under real world conditions (Petition at 15) and provides specific details on the appropriate sample size to require for such a study (December 22, 1998, supplement at 1).

The Agency's position is that equivalent skin adhesion is a criterion for approval of a generic transdermal product, and FDA will not approve a generic transdermal product that fails this comparison. However, the purpose of studying adhesion is simply to make sure the generic patch stays on as well as the reference listed drug. There is no reason that this observation and measurement cannot be accomplished while the generic patch is being tested on human subjects for other purposes. Accordingly, FDA asks generic applicants to test adhesion during the 7-

²⁰ The reference listed drug was Premarin, a conjugated estrogen in tablet form. The active ingredients in Premarin are extracted from the urine of pregnant mares.

²¹ FDA regulations provide that the Agency may refuse to file a 505(b)(2) application for a product that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Act (21 CFR 314.101(d)(9)).

day bioequivalence study and the 21-day skin irritation/sensitization study, using a test method and scoring similar to those outlined in the Petition. A separate skin adhesion test is not needed as it is simply a comparison of the adhesive properties of the two transdermal products, which can be observed and measured during the bioequivalence study and during the skin irritation study. Real world conditions are included in these tests because the subjects in the studies lead normal lives, including bathing, while participating in the study. The Agency requests that the sample size of the study be sufficient to yield acceptable power for the statistical analysis.

The Petition also asks that no overlays be used and that if a subject's patch comes off, the subject receive a new patch and continue the study (Petition at 14-16).

The Agency agrees with the petitioner. The Agency generally does not permit a generic drug product to use overlays during the conduct of the bioequivalence and skin irritation and sensitization studies. This does not mean that the Agency would preclude an ANDA applicant from providing optional overlays with its marketed product for patient convenience. Likewise, the Agency would not preclude an ANDA applicant from eliminating an optional overlay from its marketed product. However, FDA does not agree with the petitioner that a subject who loses a patch during the bioequivalence study should continue in the study with a new patch. The Agency recommends that such a subject be withdrawn from the study. Taking a subject out of the study increases the chance of failure of both the bioequivalence and adhesion studies because of the lower statistical power in the bioequivalence evaluation and a negative result in the adhesion analysis. The Agency believes its procedure is stricter and more scientifically sound than the procedure suggested by the petitioner.

VII. Skin Irritation and Sensitization

The Petition states that separate studies are needed to assess irritation and sensitization and that these studies should not be combined with pharmacokinetic bioequivalence studies (Petition at 16).

FDA requests that applicants submit skin irritation and sensitization studies, or a combined skin irritation/sensitization study, with ANDAs for transdermal drug products to ensure that the performance of the generic product is similar to that of its reference listed drug.²² A firm

²² See FDA's guidance for industry, *Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* (1999). The guidance describes a scientifically rigorous study to evaluate comparative skin irritation/sensitization for a new transdermal product versus the reference listed drug. The Agency reviewed and considered the Petition's comments during the comment period for the draft guidance as well as in responding to this Petition.

may submit a combined skin irritation and sensitization study. These studies are generally conducted separate from the bioequivalence study. The skin irritation and sensitization data provided by a generic applicant should show acceptable contact sensitization and no significant difference in the mean or cumulative irritation scores of the reference listed drug and the generic.

VIII. Inactive Ingredients

The Petition asks FDA to make sure that different inactive ingredients in a generic estradiol transdermal delivery system do not affect the safety of the product and asserts that a generic applicant must identify and characterize the inactive ingredients and provide information to demonstrate that the inactive ingredients do not affect the safety of the product (Petition at 16-18). The Petition notes that while certain substances may be safe toxicologically when examined alone, transdermal products are complex and each active and inactive ingredient in a transdermal system has an effect on the other components and on the performance of the overall system (May 14, 1999, supplement).

A. Statutory and Regulatory Standards

There is no requirement in the Act or in FDA regulations that a transdermal drug product approved in an ANDA contain inactive ingredients that are identical to the reference listed drug.²³ However, section 505(j)(4)(H) provides that an ANDA will not be approved if “information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.” FDA regulations provide that an applicant must “identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product” (21 CFR 314.94(a)(9)(ii)).

B. Evaluation of Inactive Ingredients in a Generic Transdermal System

When an ANDA is submitted, the information regarding the inactive ingredients is examined during the initial review for completeness before the application is filed. If it is determined that additional information is needed to support the use of an inactive ingredient in the drug

²³ The Petition alludes to the requirements at 21 CFR 314.94(a)(9)(iii) and (v) for inactive ingredients in parenteral and topical drug products. These regulations do not apply to transdermal products.

product, the application is not filed until the applicant submits this information. The Agency reviews the components and composition of the drug product during the review of the application.

FDA maintains an internal database of approved inactive ingredients, which the reviewer accesses during the review of an application to determine whether all inactive ingredients have been previously approved for use in a drug product administered by the same route of administration at the same concentration. If there are any questions regarding the type or quantity of inactive ingredients used in the drug product, the Office of Generic Drugs (OGD) may request additional information regarding the inactive ingredient and/or consult with pharmacology and toxicology reviewers within the Agency. An ANDA will not be approved if there are any safety issues raised by the presence of an inactive ingredient.

The Petition expresses concern that different inactive ingredients in a generic estradiol transdermal drug delivery system may influence the presence in the product reservoir of other estrogenic compounds with pharmacologic activity and the profile of the estrogenic compounds in systemic circulation due to changes in the rate of estradiol absorption or altered micro-metabolism at the skin site (Petition at 16-18).

The Agency obtains this type of information from stability studies that are conducted on the generic product. The active ingredient and the finished drug product are thoroughly examined during the review of the chemistry, manufacturing, and controls data submitted by the applicant. Any alteration of the drug substance estradiol by inactive ingredients would be detected during this review. If the inactive ingredients affected the absorption of the drug substance, it would be evident during the review of the bioequivalence study.²⁴

IX. Chemistry, Manufacturing, and Controls (CMC)

The Petition asks that no new estradiol transdermal product be approved until sufficient evaluation of the CMC information has been completed to ensure the safety and the efficacy a generic estradiol transdermal delivery system (May 14, 1999, supplement at 1).

²⁴ The May 14, 1999, supplement refers to the proposed rule published on November 19, 1998, "Bioavailability and Bioequivalence Requirements; Abbreviated Applications; Proposed Revisions," that proposes to amend current § 314.94(a)(9) to recognize the possibility that the use of different inactive ingredients may affect efficacy as well as safety. As stated in the preamble, this proposed rule is intended to amend the regulations to reflect existing Agency policy and to improve the accuracy and clarity of the regulations. If the use of a different inactive ingredient by a generic applicant affected the efficacy of the generic, it would be detected in the bioequivalence study. By establishing bioequivalence to its reference listed drug, a generic product shows that it is as effective as the reference listed drug.

The Agency notes that the CMC section of an ANDA undergoes a thorough review to ensure the safety of the generic drug product. Transdermal products often contain high molecular weight polymeric excipients (e.g., adhesives and backing) that are unlikely to penetrate the skin. The Agency ensures that the monomers and additives in the polymeric excipients are controlled within safe levels by setting adequate specifications for these excipients for both NDAs and ANDAs. The safety of all components is determined by checking whether the components were previously approved for the same route of administration. The Agency also determines whether the concentration of each component is within the range previously approved. Impurities and degradation products are analyzed by validated analytical methods and specifications. Impurities and degradation products that may be present in the generic drug product are limited to acceptable levels to ensure the safety of the drug product.

Before an ANDA is approved, it is audited by the director of the appropriate division of chemistry in OGD with respect to formulation, specifications for the drug substance, and specifications for drug products as part of OGD's quality assurance procedures. The director audits the proposed specifications of the drug product and determines whether they are acceptable. In addition, the first application for a generic version of a drug product undergoes an additional quality assurance audit by the OGD's Associate Director for Chemistry.

X. An ANDA is not required to demonstrate bioequivalence at both application sites.

The Petition asserts that an ANDA applicant must show bioequivalence at both sites of application because the bioequivalence of a generic product to Climara at one site of application is insufficient to show that the generic product will also be bioequivalent at the other site of administration (Petition at 18-20). The Petition presents pharmacokinetic data on Climara showing that when the patch was applied to the buttock site, C_{max} and AUC_t were respectively 25 percent and 17 percent higher than when the patch was applied to the abdomen site. Corresponding figures for C_{max} and AUC_t for two other transdermal estradiol drug products, Menorest and Fempatch, were higher--5 percent and 9 percent higher for Menorest and 19 percent and 17 percent higher for Fempatch. C_{max} and AUC_t values for another transdermal estradiol drug product, Estraderm^R, were 5.4 percent and 3.5 percent lower when the patch was applied on the buttock. The Petition asserts that because the bioavailability of estradiol is different on the abdomen site and on the buttock site, a generic estradiol transdermal delivery system must demonstrate bioequivalence at both sites.

The Agency has approved Climara for application to both the buttock and abdomen sites. Differences in pharmacokinetic parameters when the transdermal systems are applied to different areas of the body as demonstrated in the data above do not mean that there is a question regarding the bioequivalence of a generic transdermal system when applied to either the abdomen or buttock. The reason that bioavailability of the transdermal estradiol products

is different when applied to the abdomen as opposed to the buttock is due to the inherent differences in absorption at the two sites (application to the buttocks results in higher C_{max} and C_{avg} values - as stated in the labeling of Climara). The observed difference is not the result of a property of Climara or of any of the other estradiol patches. If a bioequivalent product is placed on the same site as the reference listed drug product, it will yield equivalent plasma concentrations. If these same two products are placed on an alternate site on the body, different plasma concentrations may result, but the products will still yield equivalent plasma concentrations.

The Agency notes that an ANDA is required to show that the generic product is bioequivalent (i.e., has the same rate and extent of absorption) to the reference listed drug. There is nothing in the Act or FDA regulations that requires a transdermal product to demonstrate bioequivalence at multiple test sites. Nor is there a scientific reason to require such testing. The Agency's scientific opinion and practice is that two transdermal products shown to be bioequivalent at one site are also bioequivalent at an alternate site. For example, 3M's bioequivalent and therapeutically equivalent AB-rated generic version of Nitrodur (Key Pharmaceuticals), a generic nitroglycerin transdermal system, was approved based on a bioequivalence study performed at one site. However, the labeling allows for use of the product at "any area of the body except the extremities below the knee or elbow." FDA did not require 3M to repeat bioequivalence studies at all possible sites of application. Furthermore, if Berlex/3M wanted to change an aspect of Climara that made it necessary to demonstrate bioequivalence, it would only be required to demonstrate bioequivalence at one site of application.

The Agency's position is that an applicant for a generic estradiol transdermal system that demonstrates bioequivalence to Climara by a bioequivalence study at one site of application establishes that its product is bioequivalent to Climara.²⁵ Furthermore, to require an unnecessary bioequivalence study at the second site would be in violation of the principle that no unnecessary human research should be done (21 CFR 320.25(a)(1)).

²⁵ The Petition argues that the "same labeling" requirement (21 U.S.C. 505(j)(2)(A)(v) and 21 CFR 314.94(a)(8)) requires an ANDA that relies on Climara to be labeled for administration at both sites and that because an ANDA has to be labeled for use at both sites of administration, the ANDA must provide evidence that it is bioequivalent to Climara at both sites of administration (Petition at 19-21). While the Agency requires all ANDAs to comply with the applicable labeling requirements, the Agency does not agree that the labeling requirements require bioequivalence testing at both sites of administration. As discussed above, a generic drug product that is determined to be bioequivalent at one site of administration will also be considered to be bioequivalent at a second site of administration and will be labeled for use at both sites of administration.

XI. Validation of Approval Criteria

The Petition requests that the Agency adopt approval criteria before approving an ANDA for a generic estradiol transdermal system (Petition at 3).

There is no statutory or regulatory requirement that FDA issue, in advance of approval of a generic drug, a guidance specific to that drug.²⁶

The Petition asks FDA to convene a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Advisory Committee for Pharmaceutical Science, with industry participation, to examine the relevant data and information relating to estrogens, multi-day extended-release products, and transdermal drug delivery systems for the purpose of developing appropriate and consistent standards for the approval of new generic products (Petition at 2). The Petition also asks that FDA validate with both the Medical Policy Coordinating Committee and the Biopharmaceutics Coordinating Committee the scientific and medical appropriateness of the approval standards for a generic multi-day transdermal estradiol patch (Petition at 2).

The Agency has stated that the Biopharmaceutics Coordinating Committee's responsibility is to establish policies and procedures that govern bioavailability and bioequivalence reviews in the Office of Clinical Pharmacology and Biopharmaceutics and OGD to ensure high quality scientific review and promote consistency. If new bioequivalence issues arise during the course of review of an ANDA, they may be presented to the Biopharmaceutics Coordinating Committee to discuss the issues and obtain a consensus opinion. The bioequivalence requirements for 7-day estradiol transdermal systems were discussed before the Biopharmaceutics Coordinating Committee in January 1998. The Biopharmaceutics Coordinating Committee carefully reviewed the information available to the Agency and concluded that a multiple-dose study was unnecessary because steady-state plasma concentrations are achieved after a single application of the transdermal system (7 days' duration). This issue was not referred to the Medical Policy Coordinating Committee since it was strictly a bioequivalence issue. If the Biopharmaceutics Coordinating Committee Members believed that input was necessary from the Medical Policy Coordinating Committee, the issue would have been referred to that committee. FDA does not routinely consult an advisory committee on the many issues that arise in the course of approving drugs, and there was no need to do so in this case.

²⁶ Even if the Agency issued a guidance document setting out the recommendations for generic estradiol transdermal systems, an applicant would not be required to follow the guidance if the Agency determined that another method of satisfying the statutory and regulatory requirements for an ANDA was feasible. The Agency permits applicants to use any means that are scientifically persuasive to meet the bioequivalence requirements of the Act.

XII. Procedural Issues

A. The Docket Is Complete.

The Petition expresses concern that five letters in support of the Petition sent to the Office of the Commissioner had not initially been made a part of the docket (January 8, 1999, supplement at 1-2).

FDA is aware of its responsibility regarding the maintenance of the docket. Letters that do not reference a citizen petition, are not addressed to the Dockets Management Branch, and do not contain a docket number may not always get into the docket. Furthermore, FDA's policy is not to put a letter from a member of Congress in the docket unless the member specifically requests it. However, the five letters you cited, and all other letters and comments concerning the Petition, have been included in the docket and have been considered by FDA in responding to the Petition.

B. Good Guidance Practices

The Petition asserts that the Agency failed to follow good guidance practices (GGPs) and violated fundamental due process. Specifically, the Petition references three actions by the Agency that are addressed below.

- 1. The petitioner's first concern is the selection of a confidence interval for generic metered-dose inhalers (MDI).²⁷*

The Agency declines to comment regarding this concern because there is a citizen petition pending before the Agency which raises a number of complex issues related to MDIs. These issues are more appropriately addressed in that forum.

- 2. The petitioner objects that on April 27 and May 21, 1998, CDER's guidance web page listed certain biopharmaceutics guidances as withdrawn without giving the public an opportunity to comment (August 7, 1998, supplement at 2).*

FDA notes that it decided to remove many product-specific bioequivalence guidances that were published before the Agency adopted GGPs because these guidances were outdated or inaccurate, and it would have been misleading to industry to retain them. The Federal

²⁷ It is unclear to the Agency what this assertion has to do with the proper criteria for the approval of a generic estradiol transdermal delivery system.

Register notice describing GGP states: “[E]ach quarter, the Agency will publish a Federal Register notice that lists all guidance documents that were issued during that quarter and all guidance documents that have been withdrawn” (62 FR 8961, February 27, 1997). GGPs do not require that the public be given an opportunity to comment before a guidance is withdrawn. Furthermore, the withdrawal of outdated guidances is in keeping with the spirit of GGPs, which is that the Agency accurately communicate to the public its *current* thinking on regulatory matters. FDA intends to replace product-specific guidances with general guidances that can be applied in multiple situations. FDA publishes these guidances in draft and asks for public comment.²⁸

- 3. The petitioner complains that Berlex met with OGD on June 12, 1998, and was not told that OGD would not require applicants for estradiol transdermal products to conduct multiple-dose, steady-state studies (August 7, 1998, supplement at 2-3).*

The Agency notes that at the June 12, 1998, meeting, representatives from Berlex/3M and their consultant presented their viewpoints regarding the concern of physicians when prescribing transdermal therapy, recommendations for pharmacokinetic standards for transdermal estradiol patches, and proposed criteria for skin irritation and adhesion. The Agency carefully considered these viewpoints.

Several weeks later, Dale Conner, OGD’s Director of Bioequivalence, spoke at public conferences on scientific considerations regarding bioequivalence testing. Dr. Conner discussed the status of FDA’s current thinking regarding methods for establishing bioequivalence. Such discussions are a regular part of the Agency’s role in monitoring and reviewing developments in scientific fields that influence FDA’s regulatory activities. FDA is not required to engage in a formal public process as it determines scientific standards for approval of NDAs and ANDAs. Guidance documents are one way of informing the regulated industry of scientific methods and standards that will be acceptable to the Agency in meeting regulatory requirements, but as you know, there may be multiple ways in which an applicant can meet a requirement for approval of an ANDA. Dr. Conner’s comments regarding the acceptability of one approach to establishing bioequivalence did not preclude use of other approaches that are scientifically valid. Dr. Conner’s comments regarding current FDA thinking on establishing bioequivalence for estradiol transdermal systems were fully appropriate.

²⁸ A number of draft bioavailability and bioequivalence guidances are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

XIII. Petition for Stay of Action (PSA)

The PSA requests that FDA refrain from approving an ANDA for a generic estradiol transdermal delivery system relying on Climara as the reference listed drug. The PSA bases the request for a stay "in the absence of evidence that the Agency has established and applied standards for approving generic transdermal estradiol patches" (PSA at 1). As grounds for grant of a stay, the Petition asserts that the public interest would be served by establishing such standards, that the public has an interest in requiring FDA to act lawfully, and that the petitioner's reputation and good will may be destroyed if the composition of a generic transdermal patch raises safety issues or the product's transdermal administration cannot be effectively measured to show therapeutic equivalence (PSA at 2-3).

The Agency notes that the petitioner speculates regarding potential harm to its reputation but presents no evidence in the PSA that the untoward events outlined as possibilities are in fact likely to happen. It presents no evidence that distinguishes the decisions pertaining to a generic estradiol transdermal drug delivery system referencing Climara from those made concerning hundreds of other generic products. Furthermore, the Agency has established standards for approval of generic estradiol transdermal drug delivery systems. The Agency, therefore, is not persuaded that the extraordinary relief requested in the PSA is appropriate. Moreover, it cannot accept that one company's reputation and good will might be destroyed if a consumer uses a product that is manufactured by another company. The PSA does not elaborate on this point. As discussed above, the Agency agrees with many of the approval criteria you have set forth, but finds some of the criteria unnecessary to ensure the safety and efficacy of a generic estradiol transdermal delivery system.

Any approval of a generic estradiol transdermal drug delivery system will be based on sound scientific standards applicable to the review of such a product. It would not be appropriate to deny the public the benefit of a lower priced generic drug product in the absence of scientific evidence that a delay in the approval of an ANDA is necessary to protect the public health. The Petition does not contain evidence that such a delay is necessary. FDA concludes that the Petition has neither demonstrated sound public policy grounds for a stay nor shown that public health interests outweigh the delay resulting from imposition of a stay. For these reasons, FDA denies the PSA.

XIV. Conclusion

The request that FDA refuse to approve an ANDA for a generic drug product relying on Climara as the reference listed drug unless the application meets certain criteria is granted in part and denied in part. The requests concerning the following specific criteria are granted: that FDA require, using the best available method, a demonstration of rate and extent of

absorption consistent with good medicine and science; that FDA require a demonstration that skin adhesion for a generic estradiol transdermal system is as good as Climara's; that FDA require that the results of skin irritation studies for a generic estradiol transdermal system are as good as Climara's; that FDA require skin sensitization tests for generic estradiol transdermal systems; and that FDA require the labeling of a generic estradiol transdermal system to be the same as Climara's. Also, FDA grants the request to validate the approval standards with the Biopharmaceutics Coordinating Committee.

The requests concerning the following specific criteria are denied: that a multiple-dose study be required; that evidence of bioequivalence at both sites of action be required; that FDA convene a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Advisory Committee for Pharmaceutical Science to discuss issues associated with approval of a generic drug product relying on Climara as the reference listed drug; that FDA validate with the Medical Policy Coordinating Committee the approval standards for a generic multi-day estradiol transdermal system; and that a 505(b)(2) application, rather than an ANDA, be required for a generic drug product relying on Climara as the reference listed drug. Finally, FDA denies the PSA.

Sincerely yours,

for 
Dennis Baker
Associate Commissioner
for Regulatory Affairs