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VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Citizen Petition to Establish Appropriate Approval Standards for Generic Clonidine Transdermal Products

Dear Sir or Madam:

CITIZEN PETITION

We submit this petition on behalf of our client, Boehringer Ingelheim Pharmaceuticals, Inc. ("BI"), under 21 C.F.R. § 10.30 and Federal Food, Drug, and Cosmetic Act ("FFDCA" or "Act") Sections 505(b) and 505(j), 21 U.S.C. §§ 355(b) and 355(j). BI is the developer and marketer of Catapres-TTS® clonidine transdermal therapeutic systems (hereinafter, "the BI patch"). This petition is prompted in part by a "paragraph IV" notice letter received by BI from Elan Pharmaceutical Research Corp. ("Elan") that describes a purported generic copy of the BI patch that, from the letter's description, appears very different from the BI patch. In this petition, BI requests that the Food and Drug Administration ("FDA") take the following actions:

A. Action Requested

1. Elan has stated in its paragraph IV notice letter that the Elan product: a) is substantially different than the BI patch; b) does not perform substantially the same function, in substantially the same way, to accomplish substantially the same result as the BI patch; c) contains differing inactive ingredients that are not equivalent to those in the BI patch; and d) unlike the BI patch, contains no controlled-release mechanism. If these statements are true, the Elan product is not appropriate for submission or approval pursuant to an abbreviated new drug application ("ANDA"). Petitioner requests that FDA deny such application for approval.

01P-0470

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2. Petitioner asks that FDA not approve any new or pending ANDA or application filed under Section 505(b)(2) of the Act for a generic clonidine transdermal product that has a controlled-release mechanism or inactive ingredients that differ from those in the BI patch, in the absence of a showing that that mechanism or those ingredients do not affect the safety or effectiveness of the products.

3. Petitioner requests that FDA not approve any new or pending ANDA or application filed under Section 505(b)(2) of the Act for a generic clonidine transdermal product that does not meet the bioequivalence testing requirements proposed in this petition.

4. The bioequivalence requirements set out in this petition are those that petitioner performed at the direction of FDA when petitioner sought to change manufacturing sites for its product. If FDA denies Request No. 3, petitioner asks that FDA provide an explanation of how failing to require generic manufacturers to satisfy the same testing requirements is consistent with FDA's contention that the public has equal assurance of the safety and effectiveness of generic drugs as is provided for innovator products.

5. Petitioner asks that FDA not approve any generic clonidine transdermal product that contains a reservoir substantially larger than that of the corresponding BI patch.[1]

6. Petitioner asks that FDA determine whether 180-day exclusivity is applicable with respect to generic clonidine transdermal products and, if so, to whom that exclusivity belongs, and announce its conclusion.

B. Statement of Grounds

1. Background on Clonidine

Clonidine is a centrally acting alpha agonist and is an antihypertensive agent. It is available in both oral and transdermal dosage forms. Clonidine stimulates alpha

[1] BI has no information about the reservoir size for the Elan patch but raises this issue because larger reservoirs have apparently been considered by other generic applicants in the past.

adrenoreceptors in the brain stem, resulting in reduced sympathetic outflow from the central nervous system and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Because it is a chronically administered drug for the control of hypertension, it is critical that the dosage of clonidine be predictably consistent over time. The pharmacologic response of blood pressure reduction measured by the physician in the first three months of therapy should be maintained over years for a transdermal antihypertensive, such as transdermal clonidine, to be safe and effective.

2. The BI Patch

BI markets Catapres-TTS® clonidine transdermal therapeutic systems. The BI patch provides continuous systematic delivery of clonidine (base form) for seven days at an approximately constant rate.

The BI patch is available in three strengths that deliver different amounts of clonidine per day: Catapres-TTS®-1 (0.1 mg clonidine per day); Catapres-TTS®-2 (0.2 mg per day); and Catapres-TTS®-3 (0.3 mg per day). The surface area of the skin covered by these systems is 3.5, 7.0, and 10.5 cm^2, respectively, and the amount of drug released is thus directly proportional to the surface area of the product. The composition per unit area of all three dosages is equal. To ensure constant release of drug over seven days, the total drug content of the system is sufficiently greater than the total amount delivered that the concentration of drug in the reservoir and the skin-contact adhesive is above saturation during the seven-day application period.

The BI patch incorporates proprietary reservoir technology developed by the Alza Corporation. It consists of a four-layer system that is applied to the skin. Proceeding from the visible surface toward the surface attached to the skin, the four layers are:

1. a backing layer of pigmented polyester film ("layer 1");

2. a drug reservoir of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide ("layer 2");

3. a microporous polypropylene membrane containing mineral oil that controls the rate of delivery of clonidine from the system to the skin surface ("layer 3"); and

4. an adhesive formulation of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide ("layer 4").

Prior to use, a protective siliconized polyester liner that covers the fourth layer is removed. The polyester backing layer (i.e., layer 1 above) protects the system contents from environmental influences.

Following system application to intact skin, clonidine in the adhesive layer (layer 4) saturates the skin site below the system. Clonidine from the drug reservoir (layer 2) then begins to flow through the mineral oil contained in the rate-controlling membrane (layer 3) and the adhesive layer of the system (layer 4) into the systemic circulation via the capillaries beneath the skin. Therapeutic plasma clonidine levels are achieved two to three days after initial application of the BI patch.

The BI patch is designed to release clonidine at an approximately constant rate for seven days of treatment. The energy for drug release is derived from the concentration gradient existing between a saturated solution of drug in the system and the much lower concentration prevailing in the skin. Clonidine flows in the direction of the lower concentration at a constant rate, limited by the rate-controlling membrane (layer 3), so long as a saturated solution is maintained in the drug reservoir. The rate-controlling membrane is a microporous membrane that maintains a constant rate per unit area of release for all three dosage strengths of the BI patch.

After seven days, the patch is removed and another patch is applied to a different spot on the skin.[2] The clonidine in the saturated skin at the area of the earlier application then enters the systemic circulation as the skin under the new patch is becoming saturated. Thus, the sequential use of the BI patch results in predictably consistent blood levels of clonidine.

If the BI patch is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about eight hours after system removal and then decline

[2] The "different spot on the skin" should be consistent with the approved labeling instructions of the BI patch systems as studied in MacGregor TR, Matzek KM, Keirns JJ, et al. Pharmacokinetics of transdermally delivered clonidine. Clin Pharm Ther 1985, 38, 278-284 (Exhibit K to this Petition).

slowly over several days. During this time period, blood pressure returns gradually to pre-treatment levels.

3. An ANDA Applicant Seeking Approval of a Product Containing Different Inactive Ingredients Than the Innovator Must Show That Those Inactive Ingredients Do Not Undermine Safety or Effectiveness

The FFDCA requires FDA to deny approval of an ANDA if "the composition of the drug is unsafe under [the prescribed] conditions [of use] because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." FFDCA Section 505(j)(4)(H), 21 U.S.C. § 355(j)(4)(H) (emphasis added). FDA's regulations, 21 C.F.R. § 314.127(a)(8), implement that provision. FDA has made clear its position that an ANDA product fails this test if its inactive ingredients affect efficacy as well, because:

> an inactive ingredient that increases or decreases an active ingredient's efficacy may affect the safety of the drug product as well. If a drug is not achieving its therapeutic purpose, the drug may be unsafe for use.

63 Fed. Reg. 64,222, 64,223 (Nov. 19, 1998).[3]

Recently, in its response to a citizen petition filed by 3M/Berlex concerning a transdermal estrogen patch, FDA re-affirmed its commitment to scrutinize changes in inactive ingredients carefully, stating: "An ANDA *will not be approved if there are any safety issues raised by the presence of an inactive ingredient.*" FDA Response to Docket No. 98P-0434/CP1 and PSA1 (March 17, 2000) (hereinafter "Estrogen Patch Petition Response") (Exhibit A to this Petition) at 19. Similarly, we believe FDA will agree that the *absence* of an inactive component (such as a rate-controlling membrane for a transdermal product) may compromise the safety of a product.

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[3] FDA has proposed to amend 21 C.F.R. § 314.127(a)(8) to state the efficacy requirement specifically, but made it clear that doing so would simply "clarify that, consistent with current FDA policy, the applicant must show that different inactive ingredients would not affect a product's efficacy," in addition to its safety. 63 Fed. Reg. 64,222, 64,223 (Nov. 19, 1998).

a. Safety and Efficacy Concerns Raised by a Patch with a Different Controlled-release Mechanism

FDA has recognized that, in evaluating changes in inactive ingredients between innovator and generic versions of transdermal patches, the combination of those ingredients must produce an equivalent controlled-release mechanism for the generic to be able to claim the safety and efficacy of the innovator. See 21 C.F.R. § 314.127(a)(8)(ii)(A): "Examples of the changes that may raise serious questions of safety include .... (5) The use of a delivery or a modified release mechanism never before approved for the drug." Thus, as FDA has stated, patches *"have to have the same controlled release mechanism, or they are not going to be considered as pharmaceutically equivalent."* Statement of Don Hare, Transcript of December 14, 1990 Meeting of Generic Drugs Advisory Committee, at 173 (emphasis added) (Exhibit B to this Petition).[4]

The BI Patch has a microporous polypropylene membrane (layer 3 above) which provides an upper limit on the rate at which clonidine can be released from the reservoir (layer 2 above) and into the skin. This membrane therefore acts as a safety mechanism for preventing delivery of clonidine at too high a rate. Elan's paragraph IV certification notice asserts that the Elan product does not infringe U.S. Patent No. 4,559,222, because it does not contain "elements identical or equivalent to each claimed element of the patented invention." Letter from Barry S. White to Professor Rolf Krebs and Ernest Mario, Ph.D., August 1, 2001 (hereinafter "Elan notice") (Exhibit C to this Petition) at 9. U.S. Patent No. 4,559,222 contains claims directed specifically to the rate-controlling membrane feature of the BI patch. (See claims 8 and 9, Exhibit D to this Petition.) Elan argues in its paragraph IV certification notice that its product does not "perform substantially the same function, in substantially the same way, to accomplish substantially the same result as each element of the claims" in the innovator patent (i.e., U.S. Patent No. 4,559,222). Elan notice at 9.

[4] Since, as Elan admits, the Elan product does not have the same controlled release mechanism, FDA accordingly should not consider it to be pharmaceutically equivalent to the BI patch. Thus, even if it were determined to be bioequivalent, it cannot be rated as therapeutically equivalent to the BI patch in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the *Orange Book*. Compare Estrogen Patch Petition Response at p. 3, footnote 3.

Thus, if the statements made by Elan in its paragraph IV certification notice are true, then Elan is admitting not only that its product has different individual inactive ingredients, discussed below, but that the combination of those inactive ingredients produces an entirely new controlled-release mechanism. That mechanism has not been shown to be safe and/or effective. We submit that it cannot be so shown without clinical trials, making the Elan product inappropriate for an ANDA.

b. Specific Potential Safety and Efficacy Concerns Posed by the Substantially Differing Inactive Ingredients Present in the Elan Product

Elan freely admits that its ANDA product "does not contain mineral oil, polyisobutylene or colloidal silicon dioxide... in any amount, much less in the... percentages or ratios" claimed in the innovator's patent and used in the BI patch. Elan notice at 3. Elan also freely admits that its product contains no equivalents to any of those inactive ingredients. Id. at 11-12.

The Elan notice also makes it clear that its product's individual inactive ingredients differ significantly from those in the BI patch. Elan states that "Elan's clonidine transdermal system uses a silicon [silicone] adhesive for the drug reservoir, not a matrix of mineral oil and polyisobutylene." Id. at 11. That silicone adhesive "is prepared by reacting polydimethylsiloxane polymer with a soluble trimethylsiloxy resin, hydroxy end-blocked silicate resin and stabilized by reaction with trimethylsilyl reagent." Id. at 12. Elan states that its "silicone adhesive composition is a polymeric matrix that has physical and chemical properties that are *very different from mineral oil.*" Id. (emphasis added).

The following describes some of the specific potential safety and efficacy concerns posed by these differences. See generally, as to the functions and importance of the inactive ingredients the Elan patch lacks, Declaration of Robert M. Gale (Exhibit E to this Petition).

Absence of Polyisobutylene and Mineral Oil

Elan freely admits that the matrix in the BI patch employs polyisobutylene, which the Elan product lacks. Polyisobutylene is employed because it is a contact adhesive (i.e.,

it is not a permanent adhesive and can be peeled off the skin after wearing) and because it is extremely bio-compatible with skin. This latter property of polyisobutylene is important due to the poor irritation/sensitization profile of clonidine.

Mineral oil provides three benefits. First, it promotes adhesion to the skin of the polyisobutylene. Second, because clonidine diffusion is relatively slow within polyisobutylene, the mineral oil facilitates migration of the active ingredient out of the patch. Third, the mineral oil provides a conduit for passage of clonidine from the reservoir through the microporous membrane at the designed rate (hence the rate control concept). The result of this combination is that the surface area of contact of drug product to skin in the BI patch is well defined and rate-controlled to deliver drug at the appropriate dose throughout the use of the patch. Further, the membrane provides protection from drug overdosing due to increased skin temperature or blood flow, such as from fever or exercise. By contrast, the silicone adhesive used in the Elan product is not as bio-compatible and clonidine is readily soluble in the adhesive, compared to the polyisobutylene. This substitution of ingredients, along with the lack of rate control due to the admitted absence of a rate-controlling membrane will thus likely have a substantial impact on the degree of irritation/sensitization, and particularly the rate of drug delivery.

The rate of drug delivery for the BI patch is relatively low, 0.1 mg. per day,[5] so that steady state blood concentrations are not reached until approximately day 6. Based upon the ready solubility and diffusivity of clonidine in the silicone adhesive employed by Elan, and the lack of need for a migration enhancer, it may be presumed that the irritation/sensitization and the rate and extent of absorption may be drastically increased in the Elan product.

Absence of Rate-controlling Membrane

Elan freely admits that its product "uses a silicon [silicone] adhesive for the drug reservoir, not a matrix of mineral oil and polyisobutylene." Elan notice at 11. Elan further admits that this silicone adhesive is comprised of a resin that is used to tackify the silicone polymer to transform it into a pressure-sensitive adhesive. Id. at 12. Thus, the product appears to have a "reservoir" of drug that is part of the silicone adhesive that is to

[5] Here, and at other points where we refer to rate of delivery, the reference is, for convenience, to the lowest strength patch.

be applied directly to the skin, and the Elan patch thus contains no rate-controlling membrane. Id.

By contrast, as Elan states, the BI patch contains a "drug reservoir layer and an adhesive layer, ...[a matrix]... and a drug release rate-controlling membrane disposed between said reservoir and adhesive. . . ." Id. at 3. This rate-controlling membrane (layer 3 noted above) is a safety feature, as it imposes an upper limit upon the delivery and flow of clonidine through the skin and into the bloodstream. Elan's patch appears not to have that safety feature.

As noted above, due to the presence of the rate-controlling membrane and matrix, the daily dosage delivered by the BI patch corresponds to 0.1 mg per day. See package insert for the Catapres-TTS® products (Exhibit F to this Petition). This serves to maintain the drug delivery relatively slow and constant and guards against the potential for sudden unintended spikes in drug delivery that might result from a product without such a rate-controlling membrane or matrix, such as Elan's.

The importance of this safeguard should not be underestimated. Without it, the effective dose delivered can be expected to vary with the rate of blood flow to the skin. Many factors can result in increased blood flow, and thus an effective unintended overdose, if no rate-limiting barrier is used: "Variations in cutaneous blood flow of 40% have been observed during sleep and the awake state because of blood flow redistribution to transport oxygen to the skeletal muscles of movement." Lowenthal et al. (1988).[6] In addition, temperature and exercise have been shown to affect cutaneous blood flow. Id. Thus, without a rate-controlling barrier, a patient would be expected to experience significant variations in absorption of this potent drug. The safety of a product that may produce such variations cannot simply be assumed to be the same as that of the BI patch, whose controlled-release mechanism would prevent such variations.

Absence of Silicon Dioxide

The silicon dioxide component of the BI patch is present to prevent cold flow (i.e., oozing over time) of the clonidine-containing adhesive in layers 2 and 4 of the BI

[6] Lowenthal DT, Matzek KM and MacGregor TR. Clinical Pharmacokinetics of Clonidine. Clinical Pharmacokinetics 1988, 14(5), 287-310 at 296 (Exhibit Q to this Petition) (citation omitted).

patch. If the adhesive in layers 2 and 4 of the BI patch were to exhibit cold flow, there would be a tendency for the adhesive to ooze out of the patch and onto the inside of the foil pouch. This could lead to getting the clonidine-containing adhesive on the patient's fingers when opening the pouch and removing the patch therefrom. This could result in a potentially dangerous condition for the patient resulting from rubbing one's eyes with contaminated hands, causing pupil dilation and/or blurred vision which in turn could present dangerous conditions while driving, operating machinery or exercising. See Declaration of Ernest Gurwich, Pharm.D., ¶ 3 (Exhibit G to this Petition). As noted, apparently the Elan product has an adhesive reservoir which apparently contains no silicone dioxide, and thus may be subject to increased incidence of cold flow and the attendant safety concern of clonidine hand contamination.

Other Differing Inactive Ingredients and the Effect Upon Sensitization

Transdermally administered clonidine causes allergic sensitization reactions in many patients. (See Package Insert (Exhibit F to this Petition) under section entitled "Adverse Reactions.")[7] Allergic sensitization is very different from ordinary skin irritation. See, for example, U.S. Patent No. 5,049,387 at column 1, line 38 to column 2, line 6 (Exhibit M to this Petition). This type of sensitization, also known as contact dermatitis, often is not evident until a patch has been worn for many weeks.[8] If it does occur, it can become progressively more severe with repeated exposure. If sensitization occurs, the patient must discontinue the therapy, often permanently. See Declaration of Dr. Gurwich, ¶ 3 (Exhibit G to this Petition).

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[7] The Merck Manual notes the following with respect to transdermal clonidine:

> Clonidine is available for transdermal administration in 2.5-, 5-, or 7.5-mg impregnated patches applied once weekly, delivering respectively 0.1, 0.2, or 0.3 mg/day. This unique dosage form seems to be as effective as the oral route with fewer adverse effects. However, about 20% of patients develop cutaneous reactions at the site of application, requiring discontinuation of the drug in this form.

Merck Manual Section 16, Chapter 199, Arterial Hypertension (Exhibit P to this Petition).

[8] Catapres-TTS® patch package insert, Adverse Reactions: Clinical trial experience with Catapres-TTS® (Exhibit F).

Many materials commonly employed as inactive ingredients in patch products are known to potentiate significantly the occurrence of allergic sensitization. In view of the high allergic topical sensitization profile of clonidine, it is therefore essential that, in addition to any skin irritation and sensitization/adhesion testing performed by Elan,[9] a longer term study be considered to determine whether the Elan product's use of differing inactive components, listed above or otherwise, may have the effect of potentiating such sensitization to a level greater than that experienced with the BI patch.

Certainly, under FDA regulations, Elan or any other ANDA applicant would bear the burden of showing that its new delivery system and its new and different inactive ingredients would not affect the safety or effectiveness of the ANDA drug. It is possible that Elan could prove that its apparently fundamentally different product is safe and effective if it performs and submits the clinical safety and effectiveness investigations necessary for approval of a full NDA. Certainly, however, this apparently different product should not be considered a generic version of the BI patch that may be approved under an ANDA.

4. Legal and Policy Issues Presented by Bioequivalence Testing Requirements

Legal and policy concerns support adoption of the *in vivo* bioequivalence testing requirements set out below in this petition for two reasons. First, the law and the need to protect the public require that approval of a generic drug be based on a showing of bioequivalence by a scientifically adequate procedure, and this petition sets out the minimum standards that must be included for a bioequivalence protocol to be considered scientifically adequate. Second, the law and good public policy require that generic drugs be required to meet at least the standards imposed, in analogous situations, on the innovator products that they copy.

[9] We assume that FDA will require all generic applicants to conduct a cumulative skin irritation study that meets the requirements of FDA's Guidance on "Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products" (December 1999) (hereafter "FDA Skin Testing Guidance"). See 65 Fed. Reg. 5353 (Feb. 3, 2000). If FDA is not intending to do so, this petition specifically requests that that Guidance be applied to any purported generic version of the BI patch.

a. Showing of Bioequivalence by an Adequate Test Method

The Act requires that an ANDA applicant demonstrate that its product is bioequivalent to the reference listed drug. FFDCA Section 505(j)(2)(A)(iv), 21 U.S.C. § 355(j)(2)(A)(iv). To demonstrate bioequivalence, the applicant must show that "the rate and extent of absorption of the drug do not show a significant difference" from that for the listed drug. FFDCA Section 505(j)(8)(B)(i), 21 U.S.C. § 355(j)(8)(B)(i).[10]

The paradigm for bioequivalence testing is the measurement of blood levels after administration of an oral product to determine the rate and extent of absorption of the therapeutic moiety of that product. While clonidine transdermal products have characteristics in common with oral products in that systemic absorption can be measured, they differ in that the release mechanism of the product, as well as skin-related absorption characteristics, may affect systemic absorption. Accordingly, the unique aspects of transdermal products must be considered in defining approval requirements for generic products.

FDA has discretion to determine the best method for establishing bioequivalence, but its decisions in this area must be "reasonable and scientifically supported." Schering Corp. v. Sullivan, 782 F.Supp. 645, 651 (D.D.C. 1992), vacated as moot, 995 F.2d 1103 (D.C. Cir. 1993); accord, Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 218 (D.D.C. 1996); cf. A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1491 (D.C. Cir. 1995) ("reasoned decisionmaking" required in FDA decisions on bioequivalence issue). Petitioner respectfully submits that the test outlined below in this petition is reasonable and scientifically supported and that material deviations from what is proposed would be difficult to justify on scientific grounds.

b. Treating Generics and Innovators Alike

FDA has consistently taken the position that generic drugs are not approved on the basis of less rigorous scientific testing requirements than are imposed on the

[10] If an applicant were to seek approval of "505(b)(2) NDA" in reliance on data concerning the BI patch, it would also need to show that its product was bioequivalent to the BI patch in order to justify extrapolation of data for that drug.

innovator drugs they copy.[11] Here, when petitioner changed the manufacturing site for the BI patch, FDA required it first to complete an *in vivo* bioequivalence test. (See Exhibit H to this Petition.) BI performed a test of the type described in this petition and FDA approved the change on the basis of the test. This requirement was imposed – we believe appropriately – even though all aspects of the patch, such as its inactive ingredients, design, etc., remained the same. There can be no justification for requiring a less rigorous test to approve a generic competitor that may have different inactive ingredients, a different design, or even potentially a different amount of active ingredient in the patch.

We believe this point is self-evident and will be accepted by the FDA as consistent with an appropriate policy of fairness and evenhandedness. Failure to apply the same standards would, however, violate the law. See, e.g., Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 28 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious"); Allergan, Inc. v. Shalala, No. 94-1223 at 8 (D.D.C. Nov. 10, 1994) ("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the [Administrative Procedures Act]"). Accord, Etelson v. Office of Personnel Management, 684 F.2d 918, 926 (D.C. Cir. 1982) ("Government is at its most arbitrary when it treats similarly situated parties differently").

5. Testing Requirements for Generic Clonidine Transdermal Products

More than three years ago, on May 21, 1998, BI submitted to FDA a proposed Guidance setting out parameters for a bioequivalence study for transdermal clonidine patches. This petition describes the study proposed in that Guidance (which is the same testing that BI performed to qualify a new manufacturing site at FDA's direction). FDA has never responded to BI's proposal and has never issued a guidance for transdermal clonidine patches or even a guidance that specifically addresses bioequivalence testing for transdermal drugs generally.

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[11] In fact, FDA recently reaffirmed this position in its Estrogen Patch Petition Response, noting that it would require an ANDA applicant to meet the same standards required of the innovator in the NDA process and would likewise require the innovator to meet the same standards to establish bio-equivalence in connection with a change to its own product. Id. at 7 and 21.

FDA did issue a guidance for orally administered products that is described as "generally applicable to non-orally administered drug products where reliance on systemic exposure measures is suitable to document BA [bioavailability] and BE [bioequivalence] (e.g., transdermal delivery systems ...)."[12] FDA has also addressed the requirements for bioequivalence testing of one type of transdermal patch in the Estrogen Patch Petition Response. These two documents suggest that FDA accepts several key points in the BI proposal. As the following discussion illustrates, however, there are certain points specific to clonidine patches that must be addressed.[13] See generally, Declaration of Thomas R. MacGregor, Ph.D. (Exhibit J to this Petition).

a. *In Vivo* Bioequivalence Study

Generic transdermal clonidine products should be required to undergo a two-way, crossover study designed to test both the reference and test product for the full seven-day therapeutic period in each healthy volunteer.

i. Test Design

The test should be a two-way, crossover study between the reference and test products conducted as an open-label, randomized design in 24 healthy, normotensive volunteers. Consistent with the labeling for the BI patch, each transdermal system should be applied to a hairless area of the upper outer arm or upper chest, avoiding areas of scars, calluses, cuts, abrasions, or irritations. The selected area should be washed with soap and water, rinsed, and thoroughly dried with a tissue before placement of the system.

Subjects should wear a single unit of the reference or test product for seven days, followed by a seven-day washout period. Following that washout period, they should wear the alternative system to the first week for seven days. As discussed below, measurements during the entire seven-day therapeutic period, and for three days

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[12] Guidance for Industry: "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" (Oct. 2000) [hereafter "Oral Product Guidance"] at 1 (Exhibit I to this Petition). Petitioner believes a separate guidance for transdermal products should be developed.

[13] As FDA recently acknowledged, "the bioequivalence studies that would be needed for a particular transdermal drug product ... will vary according to the active ingredient in the product." FDA Skin Testing Guidance at 1 n.2.

thereafter, are important in order to compare how the test and reference products reach and maintain steady-state concentrations. Thus, although the agency generally discusses bioequivalence testing as involving either single-dose or multiple-dose studies, with even a multiple-dose study lasting only a few days, a single dose of the BI patch is applied over seven days and clonidine delivered by the patch remains in the skin for two or three additional days. Thus, the full ten-day test period is required to address the rate and extent of absorption of each product.[14]

The FDA's Oral Products Guidance (page 9) requires calculation of total exposure through "the last time point with measurable concentration for individual formulation." In the FDA response to the transdermal Estrogen Patch Petition, it agreed to measurement "*at least* 12 hours after the patch is removed," presumably reflecting the point at which meaningful blood levels (above background body level of estradiol) could be measured. Estrogen Patch Petition Response at 11 (emphasis added). For clonidine, meaningful measurements can be made three days after patch removal.

To determine bioequivalence, blood samples and total urine should be collected for clonidine determination over days 1 through 10 and 15 though 24 and tested as discussed below. Following seven days of wear, the used systems should be returned to the lab and assayed for residual clonidine in order to estimate the dose delivered.

Heparinized blood samples (7-10 mL depending on assay validation) for each treatment should be collected by venipuncture in the morning on days 1 through 10 and 15 through 24 and the date and time recorded. The times at which samples are drawn for each subject should be consistent throughout the study. On days 1 and 15, samples should be drawn immediately prior to transdermal application, and on days 8 and 22, samples should be drawn immediately prior to system removal. Samples should be immediately centrifuged upon collection. Plasma should be removed, aliquoted, and frozen at $\leq$-20°C until analysis.

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[14] One could argue that a test of the clonidine patch should also involve multiple doses, to assure that different patches would not produce different buildups of clonidine in tissue reservoirs that would lead to variations in systemic absorption over time. BI believes that this issue can be addressed by measurement of the amount of drug delivered and excreted in a study testing a single seven-day dose of each product.

On treatment days 1 through 10 and 15 through 24, urine should be collected in a single container for each 24-hour period. After thorough mixing and recording of the volume, aliquots should be frozen for clonidine determination.

ii. Parameters to be Evaluated

The test system should be considered bioequivalent to the reference system only if the rate and extent of absorption of clonidine from the test and reference systems are not significantly different when administered at the same molar dose of clonidine under similar conditions. To assess this, the following parameters should be evaluated and compared for the test and reference product.

(a) Area Under the 9-Day Concentration Time Curve (AUC)

Calculating the area under the curve (AUC) of plasma concentration over a nine-day period permits an assessment of rate of clonidine absorption during and following transdermal application. This time period includes seven days of wear and a 48-hour period after transdermal removal. The intravenous terminal half-life of clonidine is 12 hours. Equivalence of the area under the curve over nine days ensures that the rate of drug absorption from the products is comparable following an initial week of wear. See Declaration of Dr. MacGregor, ¶ 8.

(b) Steady-State Plasma Clonidine Concentrations over Days 4, 5, and 6

As a centrally active antihypertensive drug, clonidine's therapeutic activity and side effect profiles are correlated with steady-state plasma clonidine concentrations. The maximum reduction in blood pressure is reached two to three days after initial application of a transdermal product and is maintained for at least seven days or until the system is removed. Therefore, to determine the equivalence of the rate of drug delivery to the bloodstream between the test and reference product, the steady-state plasma clonidine concentrations at days 4, 5, and 6 must be measured and compared.

The treatment of hypertension is a long-term process. It is assumed that once a therapeutically-effective plasma steady-state concentration of clonidine is reached using a

transdermal system, it will be maintained with subsequent applications of equivalent systems. This assumption was tested (MacGregor et al, 1985)[15] with the BI patch by multiple-system changeover at steady-state with intensive sampling to evaluate clonidine plasma concentrations for the following 24 hours. There were no substantial increases or decreases in concentrations, with the concentrations being of the same magnitude as during studies in which there was no system changeover but intense sampling. In a marketplace in which products would be switched, the increases and decreases in plasma clonidine concentrations should be of a comparable magnitude to the consecutive changes of fresh product from one source. Accordingly, assessment of steady-state concentration is important to ensure equivalence.

iii. Equivalence in Total Drug Delivered

Unlike oral products, transdermal systems require excess drug to drive the delivery rate in a controlled manner. Different system designs with different excipients and release mechanisms may have different total dose loads in the system. Generally, as with the BI patch, not all of the drug in the patch will enter the body before the patch is removed. Thus, unlike the situation when an oral medication is administered, for a transdermal system it is not self-evident how much of the drug actually enters the body.

Even if equivalent blood levels are observed in a short-term (one patch) study, the possibility that two systems will administer different amounts of drug to the body may be important. Such a difference may result in different levels of drug in tissues of the body, in particular the skin, that would form a reservoir that could affect long-term drug levels.

As noted above, treatment of hypertension is a long-term process. Boekhorst and van Tol (1985)[16] demonstrated that steady-state plasma clonidine concentrations after four weeks of therapy with BI patch were maintained after one year of therapy. This study, together with the earlier consecutively-administered study (MacGregor, et al

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[15] MacGregor TR, Matzek KM, Keirns JJ, et al. Pharmacokinetics of transdermally delivered clonidine. Clin Pharm Ther 1985, 38, 278-284 (Exhibit K to this Petition).

[16] Boekhorst JC, van Tol RGL. Catapres Transdermal Therapeutic System (TTS) for Long-Term Treatment of Hypertension. In Weber et al. (eds) Low Dose Oral and Transdermal Therapy of Hypertension, pp. 122-125, Steinkopff, Darmstadt, 1985 (Exhibit L to this Petition).

1985)[17], suggests that once a patient is titrated to a desired the BI patch system size, the plasma clonidine steady-state concentrations achieved will be maintained for an extended period on that regimen.

This therapeutic goal of maintaining plasma clonidine steady-state concentrations for an extended period would not, however, necessarily be achieved if the alternative transdermal system produced a different *in vivo* dose. If the *in vivo* dose was greater than that for the listed product, with extended wear the systemic exposure would be greater (a safety concern); if the *in vivo* dose was less than the listed product, then the systemic exposure would be less (a sub-therapeutic concern).

(a) Amount Excreted Unchanged in the Urine over a 10-Day Total Urine Collection Interval

By measuring the amount of drug excreted unchanged in the urine over a 10-day period (seven days of wear and three days of washout), equivalence of *in vivo* dose released over an initial week of wear can be estimated. See Declaration of Dr. MacGregor, ¶ 9. On average 40% of the released dose from a Catapres TTS® patch is excreted unchanged in the urine during a week of wear, with the remainder being metabolized in the skin and liver. Thus, if the test patch produces essentially the same drug levels in urine as the innovator product, that would be significant evidence that the same dose was being absorbed by both patches. Id.

(b) The Total Dose Delivered over the 7-Day Period of Wear (Content Uniformity Dose - Residual Amount After Wear)

By measuring the amount of drug remaining in the system after it is removed, an estimate of the *in vivo* dose delivered to the body can be empirically determined. See Declaration of Dr. MacGregor, ¶ 10. This would include drug that could potentially remain in skin reservoirs.

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[17] MacGregor TR, Matzek KM, Keirns JJ, et al. Pharmacokinetics of transdermally delivered clonidine. Clin Pharm Ther 1985, 38, 278-284 (Exhibit K to this Petition).

iv. Confidence Intervals

Confidence intervals (90%) for each of the primary variables should be constructed. Bioequivalence should be considered demonstrated if the 90% confidence interval for each primary variable ratio (test to reference) is wholly contained in the interval 0.80-1.20 (or 0.80-1.25 for log transformed data) and the point estimates for each variable ratio is within 0.90-1.10. This is consistent with FDA's requirements generally.

v. Product to be Tested

In the past, BI has tested the Catapres-TTS®-2 patch, the middle strength of the BI dosage forms. This was done because clonidine's effect in reducing blood pressure makes the administration of the highest dose, Catapres-TTS®-3 patch, inappropriate for normal volunteers. While FDA current practice would require a generic applicant to test the highest strength for which it is seeking approval, we believe a test of the Catapres-TTS®-2 patch dose should be considered appropriate. The generic manufacturer could then seek a waiver of *in vivo* testing of the other strengths if the other strengths are proportionally similar to the *in vivo* tested product in their active ingredients and inactive ingredients (assuming, of course, that the generic manufacturer could demonstrate that the inactive ingredients used by it do not have an effect on the safety or efficacy profile of its transdermal clonidine product), there is a theoretical proportional method of delivery to ensure bioequivalence to the other strengths of the BI patch, and the patches are shown to be dose proportional in dissolution testing.

b. In Vitro Testing

i. Dissolution Testing

The generic applicant should follow the guidelines in USP 24 chapter <724> on Transdermal Delivery Systems-General Release Standards (Exhibit N to this Petition). Release rates equivalent to those of the BI patch should also be demonstrated in accordance with the specific procedure adapted from the USP guidelines set out by FDA experts in a published article.[18]

[18] Shah VP, Tymes NW, Skelly JP. *In Vitro* Release Profiles of Clonidine Transdermal Therapeutic Systems and Scopolamine Transdermal Patches, Pharmaceutical Research, 1989, 6(4) 346-351 (Exhibit O to this Petition).

ii. Content Uniformity Test

Content uniformity of 10 test product dosage units from the lot used in the dissolution testing and the *in vivo* bioequivalence study should be determined and the data should be submitted to the agency along with the dissolution and bioequivalence data.

c. Safety Review

The agency should review the adverse event profile of the generic product during all of the required testing and ensure that it is equivalent to or better than that for the BI patch.

6. A Patch System Containing A Different Amount of Active Ingredient Can Not Be Approved Under an ANDA

FDA's regulations define "pharmaceutical equivalents" as "drug products that contain identical amounts of ... the same therapeutic moiety, in identical dosage forms, ..." 21 C.F.R. § 320.1(c). FDA proposed to change this definition for products "such as prefilled syringes" that utilize a reservoir. That change would permit residual volume in the reservoir to vary. 63 Fed. Reg. 64,222, 64,223 (Nov. 19, 1998). FDA did not, however, finalize that change after receiving public comment and – as applied at least to transdermal patches containing potent drugs like clonidine – it is clear that the proposed change would be inappropriate.

The FDA announced in 1990 that FDA would require, for transdermal patch products, equal amounts of drug in the patch reservoir, plus or minus 10%. See Statement of Don Hare, Transcript of December 14, 1990 Meeting of Generic Drugs Advisory Committee at 173 (Exhibit B to this Petition). FDA has appropriately recognized that a patch that, when used, still retained a significant amount of clonidine posed a safety hazard. The discarded patch, if for example found by a child and chewed on, would be extremely toxic. Thus, a significantly different amount of residual drug in the reservoir than that found in the innovator should disqualify a drug from ANDA approval.

7. FDA Should Determine Whether the 180-Day Exclusivity Provision Applies to Clonidine Transdermal Patches

BI requests that FDA determine whether the 180-day exclusivity provision will delay the effective date of approval of ANDAs for clonidine transdermal therapeutic systems. BI believes that the facts require that FDA determine that an ANDA submission by Hercon Laboratories invokes the exclusivity provision.

a. The Statute

At issue here is the application of the language of FFDCA § 505(j)(5)(B)(iv), 21 U.S.C. § 355(j)(5)(B)(iv), to a straightforward factual situation. Section 505(j)(5)(B) provides that approval of an ANDA should be made effective on the last applicable date determined from multiple provisions, including the following provision known as the "180-day exclusivity provision:"

> (iv) If the application [i.e., an ANDA] contains a certification described in subclause (IV) of paragraph (2)(A)(vii) [a certification that an applicable patent is invalid or not infringed] and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after—
>
> (I) the date the [FDA] receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

The 180-day exclusivity provision is considered to have two triggers for exclusivity to begin: the "commercial-marketing trigger" of subsection (I); and the "court-decision trigger" of subsection (II). BI submits that neither trigger has been satisfied with respect to ANDAs for clonidine transdermal therapeutic systems, and thus that the 180 days have not yet begun to run. FDA should determine whether this interpretation is accurate.

b. The Pending ANDAs

As noted, BI markets Catapres-TTS® clonidine transdermal therapeutic system. Alza owns U.S. Patent No. 4,559,222 ("the '222 patent") for "Matrix composition for transdermal therapeutic system" (Exhibit D to this Petition), and that patent is listed in the *Orange Book* as containing claims covering the Catapres-TTS® products. Hercon Laboratories sent a notice of paragraph IV certification to BI and Alza dated July 21, 1989, alleging that the '222 patent was invalid and/or would not be infringed by Hercon's proposed product. BI did not bring a patent infringement suit against Hercon with respect to that patent.[19] BI believes that Hercon's ANDA has not been approved by FDA, but rather is still pending at FDA.[20]

As discussed above, BI and Alza recently received a notice of paragraph IV certification concerning the '222 patent from Elan Pharmaceutical Research Corp. dated August 1, 2001 (Exhibit C to this Petition). BI believes that Elan's ANDA has not been approved by FDA, but rather is still pending at FDA. BI is not aware of any other applicants with pending ANDAs.

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[19] Hercon's notice of paragraph IV certification to BI and Alza dated July 21, 1989, also alleged that U.S. Patent No. 4,201,211 ("the '211 patent"), which has now expired, was invalid and/or would not be infringed by Hercon's proposed product. BI filed a patent infringement suit against Hercon with respect to the '211 patent under 35 U.S.C. § 271(e)(2) in the U.S. District Court for the District of Delaware. BI and Hercon subsequently entered into a confidential settlement agreement under which the lawsuit was dismissed without any decision being reached by the court.

[20] The settlement of the patent infringement litigation over the now expired '211 patent gave BI no access to Hercon's business plans, nor did it involve a commitment by Hercon not to pursue an eventual ANDA approval. BI frankly does not know the status of any Hercon ANDA for this product.

c. Interpretation of the Statute

Following lawsuits against FDA, the agency removed from the regulations implementing the 180-day exclusivity provision, 21 C.F.R. § 314.107, any requirement that the first applicant successfully defend an infringement suit to be eligible for 180-day exclusivity. Rather, FDA stated that it would regulate directly from the statute, and determine any questions about eligibility for 180-day exclusivity on a case-by-case basis. 63 Fed. Reg. 37,890, 37,891 (July 14, 1998); Guidance for Industry, "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act," Procedural Guidance 5 (June 1998).

The appropriate starting place is thus the statute. The statute provides that any subsequent application containing a paragraph IV certification cannot be approved until the earlier of the satisfaction of either the commercial-marketing trigger or the court-decision trigger.

A natural reading of the statute is that Hercon, as the first company to file an ANDA for a clonidine transdermal therapeutic system, is eligible for 180-day exclusivity. Under the FDA Guidance, FDA has determined that the first applicant need not be sued in order to be eligible for 180-day exclusivity. This position has been upheld on judicial review. Purepac Pharmaceutical Co. v. Friedman, 162 F.3d 1201 (D.C. Cir. 1998).

The Elan product may thus not receive effective approval until 180-days after there is a relevant court decision or Hercon markets its product under its ANDA. This reading is supported by the statute for several reasons: First, it is clear that Hercon was the first applicant to file an ANDA with a paragraph IV certification, and thus that Elan and other applicants would constitute subsequent applicants. Second, because neither Hercon nor any other company has marketed a generic product, the commercial-marketing trigger has not been satisfied. Third, there has not been a relevant court decision with respect to the '222 patent certified to by Elan because BI and Alza have not brought any patent infringement suits concerning that patent. [21]

[21] FDA has at times attempted to construe settlement agreements in the context of 180-day exclusivity. The settled litigation between Hercon and BI concerning a different, expired patent is not relevant to 180-day exclusivity even if settlements could be relevant. The 180-day exclusivity provision on its face refers

BI acknowledges that there may be arguments that Hercon may not be eligible for exclusivity. Hercon's paragraph IV certification for its ANDA was filed 12 years ago. One could argue that FDA may deem the certification changed from a paragraph IV certification (warranting exclusivity) to a paragraph III certification (that would not be eligible for exclusivity). There are problems with such an approach, however. FDA previously attempted to deem a paragraph IV certification changed to a paragraph III certification in a situation in which the first generic applicant apparently marketed the product under the innovator company's NDA. That interpretation was recently ruled unreasonable, on the basis that the statute does not provide authority for FDA to change a paragraph IV certification to a paragraph III certification, no FDA regulation provides the basis for such a change, the FDA ruling was based upon a presumption not supported in the case, and the case was distinguishable from prior precedent. Mylan Pharmaceuticals, Inc. v. Thompson, Civ. Action No. 1:01CV23 (STAMP) at 22 (N.D. W.Va. Apr. 18, 2001). Moreover, unlike the situation in the Mylan case, in which it appears that the first applicant was marketing the drug, Hercon is not marketing the product at all.

C. Environmental Impact

This petition requests that FDA not approve certain types of ANDAs, a decision that would result in no effect on the environment. In addition, the petition requests action on a bioequivalence standard. As such, it is subject to a categorical exclusion from the requirement of an environmental impact assessment. See 21 C.F.R. § 25.31(a), (g).

D. Economic Impact

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

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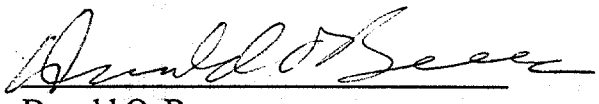
to the exclusivity being based on the patent that is the subject of the certification by the subsequent applicant.

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 that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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