

AMENDED CITIZEN PETITION

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The undersigned, Endo Pharmaceuticals Inc. ("Endo"), submits this Amended Citizen Petition under section 505 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355, and 21 C.F.R. § 10.30. Endo requests that the Commissioner of the Food and Drug Administration ("FDA") require sponsors of Abbreviated New Drug Applications ("ANDAs") or 505(b)(2) applications referencing Lidoderm[®] (lidocaine) topical patch, 5%, to conduct clinical endpoint studies to establish bioequivalence, until the Agency has taken the actions requested in this Petition.

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ACTION COMPLAINED OF

By letter dated October 5, 2006,² FDA's Office of Generic Drugs ("OGD") broke with FDA's longstanding precedent requiring bioequivalence studies with clinical endpoints for locally acting topical drug products. For generic versions of Lidoderm[®] (lidocaine) topical patch, 5%, OGD instead recommended a standard pharmacokinetic bioequivalence study used for systemically acting drugs. OGD did not offer any data or explanation to justify its departure from two decades of established precedent, according to which OGD has 1) determined that pharmacokinetics are not suitable to demonstrate bioequivalence to topical drug products and therefore 2) generally required clinical endpoint studies to establish bioequivalence for topical products.

OGD has not made publicly available any data to support its decision. Furthermore, there is no publicly available information suggesting that OGD's pharmacokinetic method for demonstrating bioequivalence to Lidoderm has been validated to correlate with relevant clinical effects of the drug. Finally, OGD offered its recommendations to private parties without submitting the recommendations, the data, and an accompanying rationale for public review by scientific experts and other interested parties.

ACTIONS REQUESTED

OGD's bioequivalence recommendations for Lidoderm[®] (lidocaine) topical patch, 5% lack scientific validity, conflict with statutory provisions and regulations regarding bioequivalence, and violate administrative law. Therefore, Endo respectfully requests that the Agency:

1. Withdraw the lidocaine topical patch, 5% bioequivalence recommendations contained in October 2006 controlled correspondence from OGD³;
2. Convene a joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee ("DODAC") and Advisory Committee for Pharmaceutical Science ("ACPS") to discuss development of the appropriate method(s) for demonstrating bioequivalence for drug products with patch dosage forms and local routes of administration;
3. Decline to approve or stay the approval of any ANDA or 505(b)(2) application referencing Lidoderm that does not contain studies with clinical safety and efficacy endpoints that demonstrate bioequivalence to Lidoderm; and,
4. If the Agency contemplates an alternative to bioequivalence studies with clinical endpoints for Lidoderm, only develop such method through a valid public process, with input from FDA advisory committees, including DODAC and ACPS.

² Letter from Dale Conner, Director of Bioequivalence, OGD (Oct. 5, 2006) [hereinafter Lidoderm Bioequivalence Recommendations] (attached as Ex. 1)

³ See *Id.*

STATEMENT OF GROUNDS

1. Factual Background

1.1. Overview of Post-Herpetic Neuralgia and Treatment Options

Post-herpetic neuralgia (“PHN”) is defined as pain that persists for more than one month after the expiration of an acute herpes zoster phase. The pathogenesis of PHN is related to the nerve and skin damage that occurs during the acute herpes zoster phase and accompanying healing process. PHN develops in the same area as the initial pain and rash of herpes zoster, though PHN may occur in an area slightly larger or smaller than the area of the herpes zoster pain and rash. PHN pain differs from patient to patient, variously described as sharp, burning, throbbing, piercing, stabbing, and/or highly sensitive to touch and temperature. PHN is associated with damaged cutaneous “a” and “c” nerve fibers subject to excessive and disorderly neuronal discharge.

PHN cannot be cured. Moreover, antiviral agents are ineffective because the virus causing herpes zoster is no longer present once the herpes zoster rash has abated. Consequently, treatment of PHN focuses on relief of pain. Although many drug products have been used to treat PHN, Lidoderm was the first product approved by FDA for the indication of treating PHN pain and remains the only FDA-approved topical product for treating PHN pain.

1.2. Lidoderm is a Topical Product not a Transdermal Product

Lidoderm is a topical dermatological product approved for the local treatment of pain associated with PHN.⁴ It uses an occlusive dressing, or “patch,” to promote permeation of lidocaine through the stratum corneum. Lidoderm provides local pain relief at the site of patch application.

FDA classifies Lidoderm as having a “topical” rather than “transdermal” route of administration.⁵ Unlike transdermal products, topical products do not depend upon systemic absorption as a component of administration.⁶ Rather, topical products are designed to maximize local drug concentration in the skin and minimize drug transport across the skin into systemic circulation.⁷

⁴ LIDODERM PACKAGE INSERT (2006) (Indication and Usage section), *available at* <http://www.fda.gov/cder/foi/label/2006/020612s008lbl.pdf>. *See also* VINOD P. SHAH, DONALD HARE, SHRIKANT V. DIGHE, AND ROGER L. WILLIAMS, *Bioequivalence of Topical Dermatological Products* 394, in *TOPICAL DRUG BIOAVAILABILITY, BIOEQUIVALENCE, AND PENETRATION* at 393-412 (V.P. Shah & H.I. Maibach, eds. 1993) (attached as Ex. 2) (identifying local anesthetics as one of the U.S. topical dermatological product categories).

⁵ OFFICE OF GENERIC DRUGS, FDA, *APPROVED DRUGS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS* 3-227 (27th ed. 2007) [hereinafter *ORANGE BOOK*], *available at* <http://www.fda.gov/cder/orange/obannual.pdf>.

⁶ *See, e.g.*, Center for Drug Evaluation and Research (“CDER”), FDA, *DATA STANDARDS MANUAL: DRUG NOMENCLATURE MONOGRAPHS*, Monograph No. C-DRG-00301 (Route of Administration) (2006), *available at* <http://www.fda.gov/cder/dsm/DRG/drg00301.htm> (defining the “topical” route of administration as “[a]dministration to a particular spot on the outer surface of the body,” while defining the “transdermal” route of administration as “[a]dministration through the dermal layer of the skin to the systemic circulation by diffusion.”).

⁷ *See, e.g.*, CHARAN R. BEHL ET AL., *In Vivo and In Vitro Skin Uptake and Permeation Studies: Critical Considerations and Factors Which Affect Them*, in *TOPICAL DRUG BIOAVAILABILITY, BIOEQUIVALENCE, AND PENETRATION*, *supra* note 4, at 226 (attached as Ex. 3) (contrasting transdermal products, which “are designed to

1.3. Lidoderm Illustrates the Complex Interaction Between the Formulation of a Topical Drug and the Local Environment in the Skin.

Herpes zoster viral infection and the subsequent healing process change the microenvironment of the peripheral nerve fibers in PHN patients. Accordingly, while the herpes zoster surface rash has abated by the time PHN patients use Lidoderm to relieve PHN pain (note that Lidoderm must be applied to “intact” skin), residual pathophysiological changes persist in PHN patients as evidenced by neuronal dysfunction in the periphery. In addition, studies with the Lidoderm patch revealed differences in systemic absorption of lidocaine between healthy subjects and PHN patients, some of this difference likely related to subject age.⁸

The vehicle used in any topical formulation of lidocaine significantly affects the rate at which the active drug substance of lidocaine can leave the formulation, migrate across the stratum corneum, pass into the upper (papillary) and lower (reticular) dermis, and then into diseased subcutaneous tissue.⁹ While vehicle and excipient effects are pronounced in normal, healthy skin tissue, damaged dermal tissue in PHN patients presents a unique environment of even greater complexity. Both the active drug substance and the vehicle interact with epidermal and dermal cells, matrix proteins, chemokines, secretory glands, blood vessels, and peripheral nerves in ways that are not yet known or able to be predicted. Plasma concentrations obtained downstream of this complex site of action have not been shown to correlate with changes in the rate and extent of absorption of the drug at the site of action in the dermis. Moreover, topical applications of comparable doses of lidocaine have different clinical effects while in some cases yielding comparable plasma concentration profiles.¹⁰

1.4. The Rate and Extent of Absorption of Lidoderm at the Local Site of Action Is Not Dependent Upon Systemic Absorption.

Clinical studies of Lidoderm suggest that Lidoderm selectively interferes with cutaneous “a-delta” and “c” fiber functions, as evidenced by reductions in pain and cold sensation, while leaving the heavy myelinated “b” fibers largely unaffected, as evidenced by continued sensation of light touch and warmth.¹¹

deliver a particular drug into the systemic circulation to achieve a systemic therapeutic effect” with an objective of “obtain[ing] the maximum possible drug transport across the skin into the blood with minimal drug buildup and metabolism in the skin,” with dermatological products, which are “designed to obtain a local effect in diseased skin by topical application on the skin surface” with an objective of “localiz[ing] maximal drug concentration in the desired skin layer with a minimal net drug transport across the skin.”)

⁸ Bryan J. Campbell et al., *Systemic Absorption of Topical Lidocaine in Normal Volunteers, Patients with Post-Herpetic Neuralgia, and Patients with Acute Herpes Zoster*, 91 J. PHARM. SCI. 1343 (2002) (attached as Ex. 4).

⁹ See, e.g., ERIC W. SMITH ET AL, *The Human Skin Blanching Assay for Topical Corticosteroid Bioavailability Assessment*, in TOPICAL DRUG BIOAVAILABILITY, BIOEQUIVALENCE, AND PENETRATION, *supra* note 4, at 155 (attached as Ex. 5) (“[I]t is now well established that incorporating identical concentrations of the same drug into two different topical vehicles (chemical equivalency) does not necessarily produce topically bioequivalent dosage forms.”).

¹⁰ See *infra* Section 1.7.

¹¹ See, e.g., William T. White et al., *Lidocaine Patch 5% With Systemic Analgesics Such as Gapapentin: A Rational Polypharmacy Approach for the Treatment of Chronic Pain*, 4 PAIN MED. 321, 327 (2003) (attached as Ex. 6) (“Findings also suggest that treatment with the lidocaine patch 5% provided effective analgesia without local anesthesia.”); Arnold A. Gammaitoni et al., *Pharmacokinetics and safety of continuously applied lidocaine patches 5%*, 59 AM. J. HEALTH-SYS. PHARM. 2215 (2002) (attached as Ex. 7) (“The patch facilitates lidocaine diffusion

The amount of lidocaine available systemically following use of the Lidoderm patch to create this local effect is far below the levels associated with the systemic administration of lidocaine for the relief of neuropathic pain. The mean peak plasma concentration of lidocaine after application of three Lidoderm patches for 12 hours in healthy volunteers has been shown to be roughly 0.13 µg/ml.¹² In PHN patients, the mean peak plasma concentration of lidocaine after application of three Lidoderm patches for 12 hours was even lower at 0.052 µg/ml.¹³ This is almost 20 times lower than the blood levels of lidocaine required to relieve pain in patients with PHN and other forms of neuropathic pain.¹⁴

1.5. FDA Did Not Rely on Pharmacokinetics to Establish Bioavailability as Part of its Review and Approval of Lidoderm.

Because Lidoderm acts locally, systemic pharmacokinetics cannot easily be correlated to availability of the drug at the site of action and were therefore not used by FDA as a basis for approval of Lidoderm. The pharmacokinetic study¹⁵ submitted as part of the Lidoderm New Drug Application (“NDA”) determined the total lidocaine exposure (AUC) and maximum concentrations (C_{max}) in plasma in 51 individuals at the maximum recommended dose of three patches for 12 consecutive hours.¹⁶ Results indicated that systemic exposure of lidocaine was minimal, about 3% of the dose applied. The mean peak plasma concentration was approximately one tenth of that known to induce systemic toxicity. After three days of repeated dosing, there was no evidence of accumulation of systemic concentrations. Neither PHN patients nor patients

across the skin, where the drug binds to sodium channels that are present in abnormally high numbers on hyperactive or damaged nociceptors. When bound to these sodium channels, lidocaine reduces the abnormal ectopic discharges produced by damaged and dysfunctional peripheral nerves and interrupts conduction of the pain signal, thus alleviating pain. This system prevents lidocaine from entering the plasma in any clinically meaningful concentrations.”); *id.* at 2219 (“[T]hese data are consistent with the belief that the mechanism of action of the patch involves the delivery of a low dose of lidocaine to block sodium channels on activated nociceptors without producing concentrations sufficiently high to block sensory fibers.”); Michael C. Rowbotham et al., *Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia*, 41 *NEUROLOGY* 1024 (1991) (attached as Ex. 8) (“In experimentally damaged peripheral nerve, spontaneously active fibers and evoked activity in A-delta and C fibers are inhibited by intravenous lidocaine at concentrations much lower than required to block normal axonal conduction.”).

¹² LIDODERM PACKAGE INSERT, *supra* note 4 (Clinical Pharmacology section).

¹³ Campbell, *supra* note 8.

¹⁴ Clinical studies of the efficacy of systemically-administered lidocaine in patients with post-herpetic neuralgia have demonstrated that plasma concentrations of less than 1 µg/ml are not associated with meaningful pain relief. See Rowbotham, *supra* note 11, at 1027. Similar results were found in clinical studies of systemically administered lidocaine in patients with other forms of neuropathic pain as well as in healthy volunteers with experimentally-induced neuropathic pain. See Ivo W. Tremont-Lukats et al., *Systemic Administration of Local Anesthetics to Relieve Neuropathic Pain: A Systematic Review and Meta-Analysis*, 101 *ANESTHESIA & ANALGESIA* 1738 (2005) (attached as Ex. 9).

¹⁵ See Dan Wang, Ph.D., FDA, *Clinical Pharmacology and Biopharmaceutics Review* (Nov. 29, 1996), in CDER, FDA, APPROVAL PACKAGE FOR LIDODERM, NDA No. 20-612 (Mar. 19, 1999) [hereinafter LIDODERM APPROVAL PACKAGE], available at <http://www.fda.gov/cder/foi/nda/99/20612.htm>.

¹⁶ *Id.* Lidoderm (lidocaine patch, 10 cm x 14 cm, 700 mg lidocaine or 5%) was tested in a single, multi-part study. Part one tested 16 healthy volunteers given a single application of three patches (2,100 mg of lidocaine) for 12 hours and then multiple applications of three patches for 12 hours over three days. Parts two and three studied 22 acute herpes zoster patients and 13 post-herpetic neuralgia patients, who were given a single application of three patches for 12 hours. Lidocaine blood levels were measured for up to 72 hours.

with acute herpes zoster showed increased lidocaine absorption. FDA thus concluded that systemic levels of lidocaine obtained in clinical endpoint studies were “not an approvability issue in this case.”¹⁷

1.6. Unlike Other Lidocaine Products, Including Other Lidocaine-Containing Patch Products, the Cutaneous Concentration of Lidocaine Resulting From Application of Lidoderm Provides Analgesic Relief Without Complete Sensory Block.

Beginning with the initially approved and marketed labeling and continuing to the present day, the Lidoderm package insert states:

The penetration of lidocaine into intact skin after application of LIDODERM is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.¹⁸

Numerous clinical studies support this finding. Lidoderm’s ability to produce an analgesic effect without complete sensory block has been demonstrated in PHN patients¹⁹ as well as in healthy volunteers²⁰ and patients with other forms of pain.²¹ These studies used multiple applications of Lidoderm, and all consistently showed that sensation to light touch and pinprick was maintained, indicating that Lidoderm does not cause a complete sensory block. Patients treated with Lidoderm continue to experience normal skin sensation while experiencing reduced neuropathic pain resulting from post-herpetic neuralgia.

Lidoderm’s ability to produce an analgesic effect without complete sensory block distinguishes Lidoderm from other topical lidocaine products. The package insert for EMLA[®] Cream, for instance, cautions patients that EMLA Cream “may be accompanied by the block of all sensations in the treated skin.” Consequently, “the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.”²² The Synera[®],²³ Lidosite[®] Topical System,²⁴ and lidocaine

¹⁷ Dan Wang, Ph.D., FDA, *Clinical Pharmacology and Biopharmaceutics Review* (Aug. 17, 1998), in LIDODERM APPROVAL PACKAGE, *supra* note 15.

¹⁸ LIDODERM PACKAGE INSERT, *supra* note 4 (Clinical Pharmacology section).

¹⁹ See White, *supra* note 11.

²⁰ See Gammaitoni, *supra* note 11, at 2218-19.

²¹ See, e.g., White, *supra* note 11; Gammaitoni, *supra* note 11; F. Burch et al., *Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients*, 12 OSTEOARTHRITIS AND CARTILAGE 253 (2004) (attached as Ex. 10); Bradley S. Galer et al., *Topical lidocaine patch 5% may target a novel underlying pain mechanism in osteoarthritis*, 20 CURRENT MED. RES. AND OPINION 1455 (2004) (attached as Ex. 11); Joseph Gimbel et al., *Lidocaine Patch Treatment in Patients with Low Back Pain: Results of an Open-Label Nonrandomized Pilot Study*, 12 AM. J. OF THERAPEUTICS 311 (2005) (attached as Ex. 12).

²² EMLA PACKAGE INSERT (2006) (Precautions: Information for Patients subsection), available at <http://www.fda.gov/cder/foi/label/2006/019941s018lbl.pdf>.

²³ SYNERA PACKAGE INSERT (2005) (Precautions: Information for Patients subsection), available at <http://www.fda.gov/cder/foi/label/2005/021623lbl.pdf> (product use “may lead to diminished or blocked sensation in the treated skin”).

²⁴ LIDOSITE PACKAGE INSERT (2004) (Precautions: Information for Patients subsection), available at http://www.fda.gov/cder/foi/label/2004/21504_lidoSite_lbl.pdf (“[T]he patient should be aware that block of all sensations in the treated skin may occur.”).

ointment²⁵ package inserts contain similar cautionary statements that product application can dramatically impair sensation.

By contrast, the Lidoderm label does not contain any precautionary information about sensory loss or sensation blocking because Lidoderm does not cause such complete sensory block.

1.7. Plasma Concentrations of Lidocaine Do Not Reflect Rate and Extent of Absorption of Lidoderm at the Local Site of Action.

Lidoderm's ability to provide analgesic relief without complete sensory block and the concomitant safety concerns is dependent upon a complex interaction of both rate and extent of absorption at the site of action. The Lidoderm patch delivery system is designed to offer pain relief over a sustained period by enabling lidocaine to be available *in the dermis* over an extended period. Lidocaine can be available at the local site of action on a sustained basis only by providing a continual influx of lidocaine to the affected area. However, because lidocaine is known to cause complete sensory block when applied topically, lidocaine that is made available at a sufficiently high level or rapid rate of release can result in complete or near-complete sensory block.

Despite the different clinical effects of lidocaine associated with different dosing regimens and vehicles, Endo is aware of no evidence to support a correlation between plasma concentrations and these varied effects. For instance, when 60g of EMLA Cream were applied to 400 cm² of intact skin (3.75 mg/cm²) in healthy volunteers and then covered by an occlusive dressing and left in place for 3 or 24 hours, peak plasma concentrations of lidocaine were 0.12 µg/ml or 0.28µg/ml, respectively.²⁶ These peak plasma concentrations of lidocaine are similar to those observed in healthy volunteers after application of three Lidoderm patches (2,100 mg applied to 420 cm², equivalent to 5 mg/cm²) for 12 hours (0.13 µg/ml²⁷). However, these comparable plasma concentrations of lidocaine do not reflect the differing clinical effect regarding sensory loss.

Further, the C_{max} of 0.12 µg/ml lidocaine observed with EMLA Cream was reached one hour post a three-hour exposure, while the C_{max} of 0.12 µg/ml lidocaine was not observed with Lidoderm until after eleven hours of continuous exposure to the patch. Also observed in these studies were differences in the absolute amount of lidocaine absorbed over a 24-hour period. While both products were applied in similar amounts over similar skin areas and left in place for the same 12-hour period, at 24 hours following start of treatment 16 percent of the applied lidocaine dose in EMLA Cream was absorbed and only three percent of the lidocaine dose in Lidoderm was found to be absorbed. Consequently, it is clear that changes in dosage form and formulation may significantly impact both the rate and extent of absorption of a topical lidocaine product. Importantly, these data demonstrate that no clear correlation between plasma levels of lidocaine and observed clinical effect can be found in the available data.

²⁵ LIDOCAINE OINTMENT PACKAGE INSERT (2006) (Precautions: Information for Patients subsection), *available at* <http://dailymed.nlm.nih.gov/dailymed/fdaDrugXsl.cfm?id=1905&type=display> (“[T]he patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. . . . Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma.”).

²⁶ EMLA PACKAGE INSERT, *supra* note 22 (Clinical Pharmacology section).

²⁷ LIDODERM PACKAGE INSERT, *supra* note 4 (Clinical Pharmacology section).

Accordingly, no available pharmacokinetic data have been shown to accurately and sensitively detect lidocaine concentrations in the dermis, where Lidoderm's clinical efficacy may be aided by a cutaneous reservoir of drug concentration that accumulates around affected nerves. Although lidocaine accumulating in this cutaneous reservoir may eventually be absorbed into systemic circulation, there is no evidence to suggest that downstream plasma concentrations reflect the local concentrations essential to produce analgesic effect without complete sensory loss.

2. Establishing Bioequivalence for Topical Products

Because Lidoderm is a locally acting topical product, bioequivalence for Lidoderm should be evaluated in the context of OGD's standards for bioequivalence for topical products. These standards become clear from a review of the regulatory history and public statements by FDA pertaining to the evaluation and review of topical products.

2.1. Overview of Statutory and Regulatory Framework

2.1.1. Therapeutic Equivalence

An ANDA sponsor seeking approval for a generic version of a drug must show that its drug product is bioequivalent to a reference listed drug ("RLD"),²⁸ as well as being pharmaceutically equivalent to the listed drug (i.e., having the same active ingredient(s), the same route of administration, dosage form, and strength).²⁹

Drugs that are determined to be pharmaceutically equivalent and bioequivalent and that satisfy certain labeling and manufacturing requirements are recognized by FDA as therapeutically equivalent.³⁰ Thus, though ANDA sponsors are not required to submit clinical study data establishing independent safety and efficacy claims, therapeutically equivalent products are considered *interchangeable* with their RLDs because they "can be expected to have *the same clinical effect and safety profile* when administered to patients under the conditions specified in the labeling."³¹

2.1.2. Bioequivalence for Drugs Intended to be Absorbed into the Bloodstream

Bioequivalence is defined generally as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available *at the site of drug action* when administered at the same molar dose under similar conditions in an appropriately designed study."³² Bioequivalence must be shown using evidence obtained by "the most accurate, sensitive, and reproducible

²⁸ 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.94(a)(7).

²⁹ 21 C.F.R. § 314.94(a)(5)-(6).

³⁰ ORANGE BOOK, *supra* note 5, at vi; CDER, FDA, GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE FOR ORALLY ADMINISTERED DRUG PRODUCTS – GENERAL CONSIDERATIONS 5 (2003) [hereinafter ORALLY ADMINISTERED DRUG PRODUCTS GUIDANCE] ("Together with the determination of pharmaceutical equivalence, establishing BE [bioequivalence] allows a regulatory conclusion of therapeutic equivalence.").

³¹ ORANGE BOOK, *supra* note 5, at vi (emphasis added).

³² 21 C.F.R. § 320.1(e) (emphasis added). *Accord* 21 U.S.C. § 355(j)(8)(B); 21 C.F.R. § 320.23(b).

approach available among” several permissible approaches.³³ Pharmacokinetic studies are the preferred method for drugs intended to be absorbed systemically unless a pharmacokinetic measurement is not feasible.³⁴

2.1.3. *Bioequivalence for Drugs Not Intended to be Absorbed Into the Bloodstream*

Statutory and regulatory provisions allow the use of alternative methods besides pharmacokinetics to establish bioequivalence for locally acting drugs, including topical drug products.³⁵ Alternative tests must be “scientifically valid” and must be “expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.”³⁶ As stated in the Orange Book:

Alternative study methods, such as in-vitro studies or equivalence studies with clinical or pharmacodynamic endpoints, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays and *topical products applied to the skin*).³⁷

Drugs that are not intended to be absorbed systemically are *not* required to use pharmacokinetics simply if such measurements are feasible. Rather, a pharmacokinetic study is only suitable to establish bioequivalence if it is the most accurate, sensitive and reproducible method of showing bioequivalence.³⁸

As described in more detail below, OGD’s longstanding interpretation of these regulations, as confirmed in numerous public statements by FDA officials, has been that current science does not support using pharmacokinetics to establish bioequivalence for topical products, even where plasma concentrations are detectable and measurable.

2.2. **OGD Has Rejected Automatic *in Vivo* Waivers, *in Vitro* Tests Without *in Vivo* Correlation, and Pharmacokinetic Tests as Suitable Methods of Demonstrating Bioequivalence for Topical Products.**

OGD’s current standards for demonstrating topical bioequivalence reflect an “evolution of scientific thinking”³⁹ regarding the complexity of the skin and suitable methods to compare bioavailability of drug products that act locally within the skin. Prior to 1984, generic versions of pioneer topical products could be approved merely by demonstration of *in vitro* bioequivalence. Although regulations issued subsequent to the Drug Amendments of 1962⁴⁰ required *in vivo*

³³ 21 C.F.R. § 320.24(a).

³⁴ 21 C.F.R. § 320.24(b)(3)-(4).

³⁵ 21 U.S.C. § 355(j)(8)(C); 21 C.F.R. § 320.24(b).

³⁶ 21 U.S.C. § 355(j)(8)(C).

³⁷ ORANGE BOOK, *supra* note 5, at viii (emphasis added).

³⁸ 21 C.F.R. § 320.24(a).

³⁹ Dale Conner, Pharm.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science 167 (Mar. 12, 2003) [hereinafter ACPS Meeting (Mar. 12, 2003)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf>).

⁴⁰ Pub. L. 87-781, 76 Stat. 780.

demonstrations of bioavailability for all new drug applications, FDA was permitted to waive the *in vivo* bioequivalence requirement in situations where bioavailability was considered “self evident or not necessary for the product to achieve any of its intended purposes.”⁴¹ This applied to a “drug product [that] is a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect.”⁴² Even in the absence of this topical drug-specific waiver, topical *in vivo* bioequivalence could be waived for topical products simply if FDA believed an *in vitro* test was acceptable.⁴³

According to Dale Conner, Pharm.D., currently Director of Bioequivalence for OGD, the assumption underlying this approach was that “these [topical] products are very simple” and that it was not necessary “to worry too much about the clinical effectiveness of these products as long as they have some fairly superficial similarities.”⁴⁴ FDA presumed that the skin was a simple, homogenous tissue and that pharmaceutical equivalents would behave in identical fashion. Consequently, prior to 1984 and the enactment of Hatch/Waxman, *in vivo* waivers were granted for most if not all new topical products. Basic *in vitro* tests to establish pharmaceutical equivalence were sufficient for FDA to determine therapeutic equivalence.

Dr. Conner describes the scientific assumptions supporting this outdated regulatory approach as a “naïve view. . . . [B]y today’s understanding this is not a simple situation and the skin is not a simple organ nor are these products simple, uncomplicated products.”⁴⁵ Indeed, Dr. Conner notes that the development of a pharmacodynamic assay for comparing corticosteroid products revealed “that many of the steroid products on the market that were allegedly bioequivalent were, indeed, not bioequivalent or therapeutically equivalent.”⁴⁶

Clinicians had already observed that supposedly therapeutically equivalent products were in fact not equivalent. As Jonathan Wilkin, M.D., Director of FDA’s Dermatologic and Dental Drug Products Division, said, “most dermatologists will have experienced squirting an innovator [topical product] on one hand and a generic topical on another hand and perceiving noticeable

⁴¹ 21 C.F.R. § 320.22(b) (1977).

⁴² 21 C.F.R. § 320.22(b)(2) (1977).

⁴³ See Bioavailability and Bioequivalence Requirements, 42 Fed. Reg. 1624, 1627 (Jan. 7, 1977) (“Preferably, the *in vitro* test should be an *in vitro* bioequivalence standard, i.e., an *in vitro* test that has been correlated with human *in vivo* data. If an *in vitro* bioequivalence standard does not exist, however, the Commissioner believes that a solution to a bioequivalence problem is to require an FDA-specified *in vitro* test not correlated with human *in vivo* data); 21 C.F.R. § 320.22(d) (1977) (“For certain drug products bioavailability may be demonstrated by evidence obtained *in vitro* in lieu of *in vivo* data. The Food and Drug Administration shall waive the requirement for the submission of evidence obtained *in vivo* demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria: . . . (5) The drug product contains the same active drug ingredient or therapeutic moiety and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both drug products meet an appropriate test that has been approved by the Food and Drug Administration.”).

⁴⁴ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 168.

⁴⁵ *Id.*

⁴⁶ *Id.* at 169.

differences in the quality of the two products.”⁴⁷ It is therefore not surprising that, as Dr. Conner has said, “dermatologists have a history of not trusting generic drugs or generic drug products.”⁴⁸

Advances in scientific understanding of the complexity of both the skin and topical preparations, including the impact of drug vehicle and excipients,⁴⁹ led FDA to recognize that topical products raised complex issues requiring scientifically valid *in vivo* bioequivalence methods to ensure therapeutic equivalence.

FDA’s greater recognition of the scientific complexities of topical bioequivalence occurred against the backdrop of the requirement introduced by Hatch/Waxman in 1984 that all generic products submit information demonstrating *in vivo* bioequivalence as part of an ANDA.⁵⁰ This meant that, as a legal matter, OGD could no longer freely waive *in vivo* bioequivalence for topical products as it had in the pre-Hatch/Waxman era.⁵¹

Consequently, by the time FDA finished revising its bioavailability and bioequivalence regulations pursuant to Hatch/Waxman in 1992, ANDAs for topical products had to show *in vivo* bioequivalence to an RLD. *In vitro* tests were only suitable as a stand-alone method if such tests had been correlated with *in vivo* safety and efficacy.⁵²

⁴⁷ Jonathan Wilkin, M.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science 206 (Oct. 22, 2003) [hereinafter ACPS Meeting (Oct. 22, 2003)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3996T2.pdf>).

⁴⁸ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 167.

⁴⁹ See, e.g., A. Rougier and C. Lotte, *Predictive Approaches I: The Stripping Technique*, in TOPICAL DRUG BIOAVAILABILITY, BIOEQUIVALENCE, AND PENETRATION, *supra* note 4, at 167 (attached as Ex. 13) (“In recent years, increasing attention has been paid to the influence that the components of a vehicle may have on enhancing or hindering the movement of a drug product through the skin. Interest in biopharmaceutics, for instance, has stimulated the investigation of problems concerned with the formulation of vehicles for use in dermatology and their effect on the activity of the drug. It is now well known that substances added to preparations as excipients, and other factors such as the physical form of the drug, affect not only the release and absorption of the drug, but also its action. Unfortunately, few techniques can be used routinely to elucidate rapidly the role that a vehicle or a component in a vehicle may have on the overall absorption of a drug *in vivo*.”).

⁵⁰ 21 U.S.C. § 355(j)(2)(A)(iv).

⁵¹ Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28882-83 (proposed July 10, 1989) (“Before enactment of the 1984 Amendments, the agency deferred or waived the requirement for the submission of evidence of *in vivo* bioavailability for various drugs for a number of reasons. For example, FDA deferred the requirement if adequate methodology were not available for *in vivo* testing. However, section 505(j)(2)(A)(iv) of the act requires that the applicant provide information to show that its drug product is bioequivalent to the listed drug referred to by the applicant. Thus, there is no statutory provision for deferral of the requirement. Therefore, in those situations where methodology for *in vivo* testing is not available, the applicant is required to develop adequate methodology for such testing, or to carry out clinical studies to assess therapeutic equivalence, unless the agency determines that *in vitro* methods can be used to demonstrate bioequivalence.”).

⁵² *Id.* at 28912 (“The agency has no evidence to show that *in vitro* data alone are regularly sufficient to assure bioequivalence. *In vitro* testing can be used for drugs where there is a known *in vivo/in vitro* correlation, and has been used for pre-1962 drugs not suspected of having, or not likely to have, a bioavailability problem. For all other drug products, an *in vivo* bioequivalence study on the product is required to support at least one strength of a product.”) (emphasis added); Abbreviated New Drug Applications, 57 Fed. Reg. 17976 (Apr. 28, 1992) (“In general, the submission of *in vivo* data is required to support a new product unless there is a known *in vivo/in vitro* correlation, in which case *in vitro* data alone may be sufficient.”).

Since the enactment of Hatch/Waxman and implementation of regulations, developing bioequivalence methods for topical drugs has proven elusive. At a March 2003 ACPS Meeting, Ajaz S. Hussain, Ph.D., FDA's Deputy Director of the Office of Pharmaceutical Science, stated, "[w]e have struggled for the last 12 years trying to develop a method for assessing the bioequivalence of drugs applied to the skin and we have not been successful in trying to move the decision forward in a consensus way."⁵³

As discussed below, one thing has been clear amidst the struggle to develop topical bioequivalence methods since enactment of Hatch/Waxman. ***Although pharmacokinetic studies are generally viewed as the favored test for systemic drug products, OGD has repeatedly affirmed that traditional pharmacokinetics are not suitable for demonstrating bioequivalence to most topical products.***

Shortly after FDA implemented its Hatch/Waxman regulations, several FDA officials published a book chapter on the current state of demonstrating bioequivalence for topical products.⁵⁴ These officials stated that, with the exception of topical corticosteroids, pharmacokinetic and pharmacodynamic measures as well as *in vitro* testing were not suitable for demonstrating bioequivalence of topical products.⁵⁵ Although these officials conceived that plasma concentrations of topical products are sometimes detectable and *theoretically* might be used to assess bioequivalence, they explained that pharmacokinetic methods would have to be modified to accommodate the impact of topical formulations and be clinically correlated with effects at the local site of action. Accordingly, the authors noted that "at this time, approval of a generic topical dermatological product based on systemically absorbed drug concentrations has not been allowed in the United States."⁵⁶

In other public statements since implementation of the Hatch/Waxman regulations, OGD has repeatedly affirmed that pharmacokinetic tests are not applicable to topical products.

In March 1998, FDA's Deputy Director of CDER and the Chair of the Biopharmaceutics Coordinating Committee, Roger L. Williams, M.D., described how OGD was trying to develop three bioequivalence documents, including one for topical dermatological products.⁵⁷ Dr. Williams described bioequivalence for topical products as especially challenging because "we cannot rely on blood levels as our surrogate for release or safety and efficacy."⁵⁸

⁵³ Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 51.

⁵⁴ SHAH ET AL., *supra* note 4, at 393-412.

⁵⁵ *Id.* at 411.

⁵⁶ *Id.* at 404-05.

⁵⁷ Roger L. Williams, M.D., Remarks at the Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee 16 (Mar. 19, 1998) [hereinafter DODAC Meeting (Mar. 19, 1998)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3402t1.pdf>). The three guidance documents under development were eventually published as CDER, FDA, GUIDANCE FOR INDUSTRY (DRAFT): BIOAVAILABILITY AND BIOEQUIVALENCE FOR NASAL AEROSOLS AND NASAL SPRAYS FOR LOCAL ACTION (2003) [hereinafter NASAL AEROSOLS AND NASAL SPRAYS DRAFT GUIDANCE]; ORALLY ADMINISTERED DRUG PRODUCTS GUIDANCE, *supra* note 30; and CDER, FDA, GUIDANCE FOR INDUSTRY (DRAFT): TOPICAL DERMATOLOGICAL DRUG PRODUCT NDAS AND ANDAS—IN VIVO BIOAVAILABILITY, BIOEQUIVALENCE, IN VITRO RELEASE, AND ASSOCIATED STUDIES (1998) [hereinafter TOPICAL DERMATOLOGICAL DRUG PRODUCTS DRAFT GUIDANCE]. The latter draft Guidance was eventually revoked; see section 2.5 below.

⁵⁸ Roger L. Williams, M.D., Remarks at DODAC Meeting (Mar. 19, 1998), *supra* note 57, at 17.

In his March 2003 discussion of topical bioequivalence, OGD's Dr. Conner explained *why* pharmacokinetic studies were generally inapplicable to topical products. Dr. Conner stated that, with systemic drugs, plasma concentrations are attained prior to achieving therapeutic effect, while with topical products the therapeutic effect is achieved before the active ingredients are reflected in plasma. He presented several slides to illustrate the distinction (reproduced in Appendix A).⁵⁹ In his slide depicting the "Model of Oral Dosage Form Performance," Dr. Conner illustrated how a drug product is linearly released from a formulation, dissolved into a solution, absorbed from the gastrointestinal tract into the bloodstream, and then delivered to the site of action for therapeutic effect. Dr. Conner then offered a "Simplistic Model of Topical Dosage Form Performance," according to which a topical drug was linearly released from a formulation, absorbed into the skin and made available at the site of activity for therapeutic effect, and then reflected in systemic circulation.

However, Dr. Conner noted that this depiction of topical dosage forms suggests that "you could just measure the blood and infer back. Even though in our previous scheme the blood acts as an intermediary between what we really want to know and the event we're trying to measure, the blood is later. But perhaps we could still infer back and it would still be okay."⁶⁰ As with FDA's historic approach of granting automatic *in vivo* waivers for topical products, Dr. Conner described the idea that all topical products go through the site of activity and get picked up by the blood as a "naïve view."⁶¹ Dr. Conner therefore offered an alternative model of topical dosage form performance that sought to reflect the complexity of the skin more accurately, particularly the capacity for multiple pathways into and through the skin to affect availability at the site of action.⁶² According to this second model, drugs that are released into the skin may reach the local site by one pathway while another pathway might enable active ingredients to be absorbed into the bloodstream without reaching the local site of activity. Thus, the skin is not "a homogeneous slab with a homogeneous set of layers with only one pathway through each one." Rather, "there are holes in the stratum corneum, there are other routes through the skin." Consequently, pharmacokinetic tests might reflect drug concentration that never reached the local site of activity or only reached the site of activity in some variable amount.⁶³

The complexity of the skin evoked by Dr. Conner was evident in a schematic drawing of the skin presented by Dr. Wilkin, Director of FDA's Dermatologic and Dental Drugs Division (reproduced in Appendix A). This drawing illustrates the complex relationship in the skin between (among other things) multiple pathways, cutaneous nerve endings, and cutaneous blood uptake.⁶⁴

⁵⁹ Dale Conner, Pharm.D., Presentation titled *Bioequivalence of Topical Drugs* at ACPS Meeting (Mar. 12, 2003), *supra* note 39 (slide presentation available at <http://www.fda.gov/ohrms/dockets/ac/03/slides/3926s1.htm>) (.).

⁶⁰ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 177.

⁶¹ *Id.*

⁶² Dale Conner, Presentation at ACPS Meeting (Mar. 12, 2003), *supra* note 59.

⁶³ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 177.

⁶⁴ Jonathan Wilkin, M.D., Presentation titled *DPK & Alternative Methodologies: Issues and Opportunities*, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Advisory Committee for Pharmaceutical Science (Nov. 17, 2000) [hereinafter DODAC/ACPS Meeting (Nov. 17, 2000)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3661t1a.pdf> and

Thus, the problem with pharmacokinetic tests for topical products is not simply one of whether it is technologically feasible to systemically measure drugs that are applied topically.⁶⁵ Rather, even assuming that drug products are sufficiently absorbed into systemic circulation (though unintentionally or undesirably), detectable plasma concentrations may not actually reflect bioavailability in the skin. Consequently, as FDA stated in draft Guidance, “measurement of the active moiety(ies) in blood or urine is not regarded as an acceptable measurement of BA/BE for dermatological drug products.”⁶⁶ As Dr. Conner explains, the complex structure of the skin and potential for multiple pathways “all of a sudden says that if I measure blood, I have some confounding sources of drug which may not relate back to drug bioavailability to the site of activity.”⁶⁷

Therefore, FDA has allowed that measurable plasma concentrations from topical products “may be used to measure systemic exposure” as a safety consideration.⁶⁸ However, plasma concentrations have not been sufficient to demonstrate comparative bioavailability at local sites of action in the skin.⁶⁹

2.3. OGD Requires Studies with Clinical Endpoints or Validated Pharmacodynamic Tests to Demonstrate Bioequivalence for Topical Products.

Because pharmacokinetic methods are inapplicable to demonstrating bioequivalence for topical products, FDA has repeatedly affirmed that the default bioequivalence standard for topical products is clinical trials, except in those cases where pharmacodynamic studies are suitable. For instance:

- In 1993, OGD’s Vinod P. Shah, Ph.D. and other FDA officials published an analysis of topical bioequivalence, stating that “comparative clinical studies between the generic and pioneer products are now required by the FDA to document bioequivalence” for topical products.⁷⁰
- In May 1997, Dr. Williams, ACPS Chair and CDER Deputy Director, stated that “the general challenge of establishing sameness is a very deep and difficult scientific challenge” and that demonstrating bioequivalence was particularly challenging for topical products because “you don’t get a useful measurement of bioavailability/bioequivalence by looking at the blood level.”⁷¹

<http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3661t1b.pdf> (slide presentation available at http://www.fda.gov/ohrms/dockets/ac/00/slides/slides/3661s1_03/index.htm).

⁶⁵ TOPICAL DERMATOLOGICAL DRUG PRODUCTS DRAFT GUIDANCE, *supra* note 57.

⁶⁶ *Id.* at 3.

⁶⁷ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 178.

⁶⁸ TOPICAL DERMATOLOGICAL DRUG PRODUCTS DRAFT GUIDANCE, *supra* note 57, at 3.

⁶⁹ *See, e.g.*, NASAL AEROSOLS AND NASAL SPRAYS DRAFT GUIDANCE, *supra* note 57, at 4-6 (distinguishing “local delivery” bioequivalence concepts and “systemic exposure” bioequivalence requirements, and providing that pharmacokinetics are suitable only for systemic safety assessments while requiring clinical endpoint studies to demonstrate local delivery bioequivalence).

⁷⁰ SHAH ET AL., *supra* note 4, at 411.

⁷¹ Roger L. Williams, M.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science 64 (May 7, 1997) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/97/transcript/3296t1.pdf>).

- In March 1998, Dr. Shah stated that “at present [OGD] require[s] the clinical efficacy studies for the bioequivalency determinations of dermatological products other than glucocorticoids.”⁷²
- In March 2003, FDA’s Dr. Wilkin recounted that “[t]he historical difficulties [relating to topical products] have circled around [21 C.F.R. §] 320.24(b)(4) which says that for topical products one uses clinical trials.”⁷³
- In March 2003, OGD’s Dr. Conner stated that because pharmacokinetic studies are not suitable for topical products, “what we’re left with with this type of scheme is that we really need to measure a PD [pharmacodynamic endpoint] or a clinical response to determine what’s really happening, how that drug from that product is available to the site of activity within the skin.”⁷⁴
- In April 2004, OGD chemist Robert Lionberger, Ph.D., indicated that “[t]he current state of topical bioequivalence is that . . . for almost all locally acting dermatological products, clinical trials are necessary to demonstrate bioequivalence.”⁷⁵
- In October 2004, OGD Director of Science Lawrence Yu, Ph.D., stated that “for systemic drugs, the plasma concentration usually relates to the safety and efficacy of drugs, while for locally acting drugs, the plasma concentration is not usually relevant to local delivery of bioequivalence. Because of that, we have to rely on other alternative methods; for example, pharmacodynamic method [or] . . . in vivo clinical comparisons.”⁷⁶
- In May 2007, Dr. Lionberger affirmed that demonstrating bioequivalence for locally acting drugs presents the “most challenging scientific issues” and that clinical studies have been the default requirement or fallback method, because “all drugs have a clinical benefit” and bioequivalence can be shown without having precise scientific understandings of the mechanism of action. By contrast, *in vitro* and pharmacodynamic approaches to demonstrating bioequivalence depend on a “scientific understanding” of the mechanism of action that must be validated.⁷⁷
- OGD’s current thinking on the difficulties associated with establishing bioequivalence for topical products is provided in a May 2007 report titled “Critical Path Opportunities for

⁷² Vinod P. Shah, Ph.D., Remarks at DODAC Meeting (Mar. 19, 1998), *supra* note 57, at 114-15.

⁷³ Jonathan Wilkin, M.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 205.

⁷⁴ Dale Conner, Pharm.D., Remarks at the ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 178.

⁷⁵ Robert Lionberger, Ph.D., Presentation titled *Topical Bioequivalence Update* at the Meeting of the Advisory Committee for Pharmaceutical Science (Apr. 14, 2004) [hereinafter ACPS Meeting (Apr. 14, 2004)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.pdf>) (slide presentation available at <http://www.fda.gov/ohrms/dockets/ac/04/slides/4034s2.htm>).

⁷⁶ Lawrence Yu, Ph.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science 218 (Oct. 20, 2004) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T1.pdf>).

⁷⁷ Robert Lionberger, Ph.D., Remarks at the American Association of Pharmaceutical Scientists Workshop, *BE, BCS, and Beyond* (May 23, 2007) [hereinafter AAPS Workshop (May 23, 2007)] (unofficial transcript on file with Endo).

Generic Drugs.”⁷⁸ In this most recent discussion of the issues, OGD states that, with the exception of pharmacodynamic skin blanching for corticosteroids, clinical studies are recommended for topical products other than solutions “because no alternative methods have been developed.”⁷⁹ With specific reference to the value of pharmacokinetics in the current assessment of bioequivalence for topical products, OGD states that while for many products the amount of drug reaching the systemic circulation can be detected and compared “its relationship to local delivery is still unknown.”⁸⁰

Precisely *because* clinical studies were generally required and standard pharmacokinetic measurements were inapplicable for topical products, OGD set out to develop and implement alternative methods consistent with the FDCA and FDA regulations.

2.4. Pharmacodynamic Studies are Acceptable Only if Based on a Clearly Established and Validated Correlation Between Pharmacodynamic Effect and Bioavailability at the Local Site of Action.

OGD has successfully established an alternative bioequivalence method for one class of topical dermatological products. Based on valid science and developed through an open public process, OGD’s efforts culminated in a pharmacodynamic approach (vasoconstrictor assay) rather than clinical endpoint studies for demonstrating bioequivalence to topical corticosteroid products.

The vasoconstrictor assay does not directly measure bioavailability at the site of action within the skin. However, the pharmacodynamic effect measured by the assay is directly dependent upon the drug becoming available at the site of action. As explained in FDA’s Guidance for these products,⁸¹ this pharmacodynamic approach is based on a clearly documented property of corticosteroids in producing blanching or vasoconstriction in the microvasculature of the skin. FDA indicates that “this property presumably relates to the amount of drug entering the skin and thus becomes a possible basis for the comparison of drug delivery from two potentially equivalent topical corticosteroid formulations.”⁸² Prior to being accepted by OGD, the vasoconstriction method was demonstrated to be reliable and used by industry to measure bioavailability and show bioequivalence.⁸³ Furthermore, FDA implemented this approach only after allowing for public notice and comment and revising its Guidance based on scientific evaluation of the comments received.⁸⁴

⁷⁸ OGD, FDA, CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS (May 1, 2007), available at <http://www.fda.gov/oc/initiatives/criticalpath/reports/generic.html>.

⁷⁹ *Id.* at 4.3.3.

⁸⁰ *Id.*

⁸¹ CDER, FDA, GUIDANCE: TOPICAL DERMATOLOGICAL CORTICOSTEROIDS: *IN VIVO* BIOEQUIVALENCE (1995) [hereinafter TOPICAL CORTICOSTEROIDS GUIDANCE].

⁸² *Id.* at 2.

⁸³ See, e.g., SMITH ET AL., *supra* note 9, at 155 (noting that “[t]he human skin blanching assay (often called the vasoconstrictor assay) has been used for nearly 30 years as a means of qualitatively assessing the topical availability and potency of corticosteroids”).

⁸⁴ FDA disseminated interim guidance for topical corticosteroids in July 1992. This interim guidance, which preceded FDA’s codified Good Guidance Practices, provided opportunity to comment. Public evaluation of FDA’s proposed method helped demonstrate that the initially-proposed methods were inadequate, as evidenced by FDA’s decision to revise the initial interim guidance with a substantially revised pharmacodynamic assay, which eventually issued as a final guidance in 1995. See TOPICAL CORTICOSTEROIDS GUIDANCE, *supra* note 81.

OGD's reliance on a vasoconstrictor assay for topical corticosteroids does not provide support for the use of pharmacokinetic studies to establish bioequivalence for topical lidocaine patches such as Lidoderm. As previously discussed, systemic plasma concentrations have never been correlated with Lidoderm's active ingredient reaching Lidoderm's site of action in the dermis. Further, absent some measure of local effect at the site of action such as electrophysiological studies of nerves or some other yet-to-be-identified action of lidocaine, for Lidoderm there is no comparable pharmacodynamic marker of activity similar to corticosteroid skin blanching.

2.5. OGD Has So Far Been Unable to Establish a Broadly-Applicable Bioequivalence Method to Replace the Requirement for Clinical Trials or Validated Pharmacodynamic Studies.

In the mid-1980s, OGD began developing what it hoped would be a universally applicable method to establish bioequivalence for topical products.⁸⁵ Between 1989 and 1998, OGD participated in numerous major meetings to discuss a skin-stripping technique for measuring drug concentration in the stratum corneum, termed dermatopharmacokinetics ("DPK").⁸⁶ OGD issued draft Guidance in June 1998 ("DPK Guidance") recommending use of the DPK method for virtually all topical dermatological products.⁸⁷

Despite devoting considerable time and resources to developing the DPK test, OGD's attempt to develop a universally applicable method comparable to pharmacokinetic measurements for systemically acting drugs ultimately was unable to satisfy regulatory standards or demonstrate scientific validity. As a result, OGD withdrew the draft DPK Guidance in 2002. The extensive work and debates on the DPK method nonetheless help illustrate the complexity of the skin and further underscore why pharmacokinetics presently are not suitable for topical bioequivalence. In particular, the deliberations over the DPK method highlight the critical importance of ensuring that any alternative method for demonstrating topical bioequivalence must be validated to correlate with relevant clinical effects.

As explained in more detail in Appendix B, OGD's withdrawal of the draft DPK Guidance is significant because it highlights the complexity of the skin and the need for correlating a topical bioequivalence method with drug performance *at the local site of*

⁸⁵ See Vinod P. Shah, Ph.D., Remarks at the Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Advisory Committee for Pharmaceutical Science 18-19 (Oct. 23, 1998) [hereinafter DODAC/ACPS Meeting (Oct. 23, 1998)] (transcript available at <http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3461t1.pdf>); Lynn Pershing, Ph.D., Remarks at DODAC/ACPS Meeting (Oct. 23, 1998), *supra*, at 202.

⁸⁶ See Vinod P. Shah, Presentation titled *Dermatopharmacokinetics Perspectives from Bioequivalence Viewpoint: Historical Development of Dermatopharmacokinetics and Overview of the Guidance*, DODAC/ACPS Meeting (Nov. 17, 2000) (slide presentation available at <http://www.fda.gov/ohrms/dockets/ac/00/slides/slides/3661s1.htm>) (providing chronology of meetings and workshops, including AAPS/FDA meetings in May 1989, March 1990, and December 1991; FDA/Industry conference in March 1992; GDAC Advisory committee April 1992; Bio-International conference in May 1992; AAPS/FDA meeting May 1993; EUFEPS/Nuremburg conference December 1995; Bio-International Tokyo April 1996; AAPS/FDA BE topicals September 1996; Trade association meetings in April 1997 and December 1997; ACPS December 1997; DODAC March 1998).

⁸⁷ TOPICAL DERMATOLOGICAL DRUG PRODUCTS DRAFT GUIDANCE, *supra* note 57.

action. Of course, these are the same reasons why OGD historically has not applied pharmacokinetic measurements to topical products. Any effort to introduce pharmacokinetic measurements for topical bioequivalence would therefore have to surmount the same types of issues raised recently and in substantial detail in the discussion of the proposed DPK method.

2.6. OGD's Public Statements Indicate that Pharmacokinetic Measurements Remain Unacceptable as a Method of Demonstrating Bioequivalence for Topical Products.

OGD expected its DPK method to be a universally applicable method for topical drug products. With the withdrawal of the DPK Guidance, there is presently no generally applicable guidance document expressly relating to topical drug products. Rather, OGD's policy is apparent directly from its bioequivalence regulations and supported by numerous public statements, which clearly state that clinical safety and efficacy endpoint studies are required for topical products except where there exists an appropriately validated pharmacodynamic study or *in vitro/in vivo* correlation.

Subsequent to the withdrawal of the draft DPK Guidance, OGD has reiterated that pharmacokinetic tests are not suitable for demonstrating bioequivalence for topical products, given currently available data. Endo is not aware of any public forum where OGD has explained how it is appropriate to rely on a pharmacokinetic test to demonstrate bioequivalence for topical products without other types of testing to assess bioequivalence at the local site of action. To the contrary, in March 2003, OGD's Director of Bioequivalence Dr. Conner dismissed suggestions that detectable plasma concentrations of topical products could be inferred back to the local site of action as an acceptable method for demonstrating bioequivalence.⁸⁸ OGD's Associate Director of Medical Affairs, Dena Hixon, M.D., similarly stated that "certainly for these locally acting drugs [including topical drugs] . . . the pharmacokinetic studies are not adequate to establish bioequivalence."⁸⁹

These statements, like those in section 2.3 above, plainly indicate that OGD's regulatory interpretation and scientific policy remain consistent with some two decades of public affirmation that pharmacokinetic studies are not suitable for demonstrating bioequivalence for topical products. In the words of OGD's recent (May 2007) Critical Path document, the relationship between blood levels of a topical drug and local delivery "is still unknown."⁹⁰

⁸⁸ As part of his original presentation, Dr. Conner stated that "[p]lasma concentrations, at least in our current way of understanding, are not suitable for looking at drug availability at the site of activity." Dr. Conner further suggested that "if we really developed this idea and got a lot more data," OGD might change its approach, but that "at our current level of understanding, it just doesn't really look like a good approach." Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 183. During the question and answer period, Leon Shargel, Ph.D., R.Ph., asked whether "there [was] data available" to show that "equivalent blood levels" were correlated with bioequivalent topical products. Leon Shargel, Ph.D., R.Ph., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 184-85. Dr. Conner replied that "it [pharmacokinetics] doesn't look good with our current level of data and understanding." Dr. Conner suggested that OGD welcomed new data to provide a basis for using pharmacokinetics. Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 185.

⁸⁹ Dena Hixon, M.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 189.

⁹⁰ CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS, *supra* note 78, at 4.3.3.

2.7. OGD Approved Generic Versions of a Lidocaine/Prilocaine Cream Product Based on Pharmacokinetics While Simultaneously Disavowing in Public that There are Any Data to Support Using Pharmacokinetics in Such a Manner.

Endo is aware of only one locally acting topical product for which OGD has approved ANDAs based on pharmacokinetics rather than pharmacodynamic or clinical endpoint studies to demonstrate bioequivalence—generic versions of EMLA[®] Cream (lidocaine 2.5%; prilocaine 2.5%). While OGD may claim this as precedent to justify using pharmacokinetics for topical bioequivalence recommendations, OGD's approvals of generic copies of EMLA violated FDA's own rules and publicly stated policy and were inconsistent with FDA's prior approval of an NDA submitted by the sponsor of EMLA Cream. Furthermore, OGD offered no science-based validation that pharmacokinetics could be used to reflect the rate and extent of absorption at the local site of action in the dermis. OGD's generic EMLA approvals therefore furnish no precedent for the development of topical bioequivalence standards for Lidoderm. On the contrary, it serves as a warning against using pharmacokinetic bioequivalence for Lidoderm.

As described in detail in Appendix C, in 2002 FDA received an ANDA proposing pharmacokinetic tests to establish bioequivalence for EMLA Cream. The primary reviewer in the Division of Bioequivalence indicated that pharmacokinetic tests were not suitable for topical products and instead recommended that the applicant conduct a clinical endpoint study.⁹¹ However, the division team leader overruled the primary reviewer's recommendation and permitted the ANDA sponsor to establish bioequivalence through pharmacokinetics.⁹² The principal "data" used to support the team leader's decision related to OGD's prior acceptance of pharmacokinetic tests for two other ANDA sponsors for copies of EMLA Cream. However, the team leader failed to provide any scientifically valid basis to support using pharmacokinetics for topical products such as EMLA Cream.⁹³

Significantly, OGD's decision to overrule the primary reviewer and accept pharmacokinetic tests directly contradicted contemporaneous public statements by OGD's Director of Bioequivalence that OGD did not have any data to support using pharmacokinetics to establish bioequivalence for topical products.⁹⁴ OGD's decision also stands in conflict with FDA's own biopharmaceutics assessment of EMLA products. In the late 1990s, AstraZeneca, the innovator manufacturer of EMLA, submitted a supplemental new drug application ("SNDAs") for a patch version of its EMLA cream. FDA converted the application to an NDA because AstraZeneca's patch product constituted a new dosage form.⁹⁵ FDA required AstraZeneca to submit clinical studies to

⁹¹ Surendra P. Shrivastava, Ph.D., OGD Division of Bioequivalence, FDA, *Division of Bioequivalence Review* (Dec. 30, 2002), in CDER, FDA, APPROVAL PACKAGE FOR ANDA No. 76-453 (Aug. 18, 2003) [hereinafter *GENERIC EMLA APPROVAL PACKAGE*], available at <http://www.fda.gov/cder/foi/nda/2003/076453.pdf>.

⁹² Shrinivas G. Nerurkar, Ph.D., OGD Division of Bioequivalence, FDA, *Division of Bioequivalence Review* (Feb. 24, 2003), in *GENERIC EMLA APPROVAL PACKAGE*, *supra* note 91.

⁹³ See *infra* Appendix C.

⁹⁴ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 183.

⁹⁵ Memorandum from Cynthia McCormick, M.D., Director, Division of Anesthetic, Critical Care and Addiction Drug Products, FDA, to File NDA #19-941/SLR-004 and Paula Botstein, M.D., Director of Office of Drug Evaluation III, FDA (Jan. 5, 1998), in CDER, FDA, APPROVAL PACKAGE FOR EMLA ANESTHETIC DISC, NDA No. 20-962 (Feb. 4, 1998) [hereinafter *EMLA DISC APPROVAL PACKAGE*], available at <http://www.fda.gov/cder/foi/nda/98/20962.pdf>.

demonstrate equivalent efficacy to EMLA Cream rather than permit the company to rely on pharmacokinetics.⁹⁶

To obtain approval for the EMLA Disc, AstraZeneca submitted five clinical endpoint studies.⁹⁷ The Biopharmaceutics review stated that pharmacokinetic studies showing comparable blood levels of lidocaine and prilocaine delivered by the two dosage forms would be inadequate for approval.⁹⁸ The sponsor did show that the release rates from EMLA Anesthetic Disc and EMLA Cream were equivalent in a skin permeation study.⁹⁹ However, this study was only supportive of approval and FDA required clinical endpoint trials to determine efficacy, a local effect on the skin.¹⁰⁰ Thus, unlike OGD's review of generic copies of EMLA, FDA's review of EMLA itself was consistent with OGD's longstanding position that bioequivalence for locally acting drugs is not able to be established by pharmacokinetic studies alone.¹⁰¹

Because OGD's approval of generic copies of EMLA did not comport with OGD's publicly-held policy regarding topical bioequivalence, these approvals should not be viewed as a relevant standard for demonstrating topical bioequivalence or as informing any discussion regarding the utility of pharmacokinetics in establishing the bioequivalence of topical products.

2.8. OGD's Recent Efforts to Establish Alternative Bioequivalence Methods Suggest that Pharmacokinetics Are Suitable Only to Assure Safe Levels of Systemic Exposure—Not to Establish Equivalence in Local Delivery

OGD apparently continues to try to develop a sufficient scientific basis for its withdrawn DPK Guidance. However, Dr. Hussain has explained that OGD has "stepped back" from the idea of using DPK to be a surrogate for deeper penetration or clinical trials.¹⁰² Instead, OGD now focuses on applying DPK to drug products where the stratum corneum is more directly relevant.¹⁰³ Moreover, rather than try to develop a single universally applicable method such as DPK, OGD has indicated it is "starting fresh"¹⁰⁴ and focusing on "a mechanistic understanding of the topical drug absorption process."¹⁰⁵

⁹⁶ *Id.*

⁹⁷ *Id.* See also Suresh Doddapaneni, Ph. D., Clinical Pharmacologist, DPE II/OCBP, *Clinical Pharmacology and Biopharmaceutics Review* (Dec. 15, 1997), in EMLA DISC APPROVAL PACKAGE, *supra* note 91.

⁹⁸ Suresh Doddapaneni, *Clinical Pharmacology and Biopharmaceutics Review*, *supra* note 97.

⁹⁹ *Id.*

¹⁰⁰ Memorandum from Cynthia McCormick, *supra* note 157 ("The systemic levels seen after EMLA Cream application are substantially low and it would be expected that the levels seen after the Disc application would be just as low. Thus, formal bioequivalence studies were not practical for this new dosage form. Therefore, clinical efficacy studies were submitted by the sponsor in which the Anesthetic Disc was compared to EMLA cream and provided equivalent results.").

¹⁰¹ FDA's review of label changes regarding EMLA Cream in 1998 and 2000 were similarly consistent in requiring clinical studies rather than pharmacokinetics. See FDA, APPROVAL PACKAGE FOR NDA NO. 19-941/S-008 (Feb. 4, 1998), available at http://www.fda.gov/cder/foi/nda/98/019941s008_emla.pdf; FDA, APPROVAL PACKAGE FOR NDA NO. 19-941/S-011 (Jan. 28, 2000), available at <http://www.fda.gov/cder/foi/nda/2000/19-941S011.pdf>.

¹⁰² Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 202.

¹⁰³ *Id.* at 202-203

¹⁰⁴ Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting (Apr. 14, 2004), *supra* note 75, at 247.

¹⁰⁵ Robert Lionberger, Ph.D., Remarks at ACPS Meeting (Apr. 14, 2004), *supra* note 75, at 228.

In the absence of pharmacokinetic tests or an acceptable DPK test, in the last several years OGD has moved toward what it describes as a “portfolio approach”¹⁰⁶ for demonstrating topical bioequivalence. By “portfolio approach” OGD means using a collection of tests, any one of which would be inadequate on its own to demonstrate bioequivalence but which taken in combination might be a sufficient basis to demonstrate bioequivalence. OGD suggests it will develop a collection of tests that can be used in various combinations for particular drugs.¹⁰⁷

OGD has frequently indicated that pharmacokinetic tests can be part of a portfolio approach even though they cannot be a stand-alone method for bioequivalence. Thus, as Dr. Yu stated in October 2003, while “systemic plasma profile is not a very good surrogate for locally acting drugs,” OGD may seek to “rely on additional as well as alternative tests to establish bioequivalence.”¹⁰⁸ In developing portfolio methods to show bioequivalence, Dr. Yu has further emphasized that OGD “want[s] to try and provide a scientific basis” demonstrating the validity of non-clinical bioequivalence tests for any generic topical product.¹⁰⁹ OGD has not, however, indicated that there is any scientific basis for using pharmacokinetic tests to reflect rate and extent of absorption at topical sites of action.

OGD has identified the following as candidates for a portfolio approach to bioequivalence:

- *in vitro* diffusion cell tests – to measure the rate at which a drug leaves a formulation and crosses an artificial membrane into receptor fluids;
- *in vitro* rheology tests – to measure how the formulation flows and spreads on the skin;
- *in vivo* DPK; and
- *in vivo* microdialysis.¹¹⁰

Dr. Lionberger describes this as “the whole list of tests”¹¹¹ relevant for bioequivalence of topical drug products. Noticeably absent from this list is any reference to pharmacokinetic studies. Presumably this reflects OGD’s longstanding approach that pharmacokinetics are not suitable to detect significant differences in rate and extent of absorption at local sites of action in the skin.

As recently as May 2007, Dr. Lionberger provided an update regarding developments in topical bioequivalence. Despite OGD’s longstanding interpretation that pharmacokinetic measurements are not suitable for demonstrating topical bioequivalence, Dr. Lionberger suggested it *may* be possible to demonstrate bioequivalence through plasma concentration profiles in cases where “you knew that the plasma concentration actually reflects the delivery to the site of action.”¹¹² Dr. Lionberger said that in cases where plasma concentration is achieved only by the active ingredient’s passage through the site of action, plasma concentrations may either be a suitable method for demonstrating bioequivalence or part of a method of demonstrating bioequivalence.

¹⁰⁶ Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 277; Jonathan Wilkin, M.D., Remarks at *id.* at 252.

¹⁰⁷ Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 277.

¹⁰⁸ Lawrence Yu, Ph.D., Remarks at ACPS Meeting (Oct. 22, 2003), *supra* note 47, at 149.

¹⁰⁹ *Id.*

¹¹⁰ Robert Lionberger, Ph.D., Presentation at ACPS Meeting (Apr. 14, 2004), *supra* note 75.

¹¹¹ Robert Lionberger, Ph.D., Remarks at ACPS Meeting (Apr. 14, 2004), *supra* note 75, at 158.

¹¹² Robert Lionberger, Ph.D., Remarks at AAPS Workshop (May 23, 2007), *supra* note 75.

To the extent that Dr. Lionberger intended only to convey that pharmacokinetic tests may be used to establish systemic exposure for topical products in conjunction with other tests that establish bioequivalence at the site of action, his statement is consistent with OGD's longstanding approach. Indeed, Dr. Lionberger offered only one example of using pharmacokinetic measurements for locally acting products: a combination test for nasal sprays and aerosols. In that case, OGD recommends including pharmacokinetic tests only for systemic exposure safety profiling, not for bioequivalence at the local site of action.¹¹³ Dr. Lionberger did not, however, identify any example of where a pharmacokinetic measurement "actually reflects" local delivery nor provide any data to support how pharmacokinetic data would be sufficient to support bioavailability at local sites of action.

Given that Dr. Lionberger's presentation took place nearly four years *after* OGD approved generic versions of EMLA Cream based upon pharmacokinetic studies rather than clinical endpoint bioequivalence studies, it would have been appropriate for him to identify ANDAs referencing EMLA Cream as a noteworthy example if OGD wanted to claim that pharmacokinetics may be used to demonstrate local bioequivalence rather than merely assess systemic exposure. However, he did not discuss EMLA; neither, apparently, has any other employee of OGD. OGD's failure to acknowledge its approval of generic copies of EMLA Cream during subsequent discussions of topical bioequivalence can best be interpreted as an indication that OGD recognizes that it did not have sufficient data to justify its review and therefore is unwilling to use it as an example to support a new publicly-promulgated topical bioequivalence method.

Thus, to the extent that studies with pharmacokinetic endpoints have any role in OGD's evolving "portfolio approach," it is limited to systemic exposure safety concerns rather than local bioequivalence. Endo is not aware of any public forum in which OGD has suggested that it intends to embrace pharmacokinetics as a method to establish local delivery for topical bioequivalence or mentioned the existence of data to support such an approach.

3. Notwithstanding FDA's Rules and Publicly Stated Policy Regarding the Inapplicability of Pharmacokinetics to Establish Bioequivalence for Topical Products, OGD has Proposed Using Pharmacokinetics to Establish Bioequivalence to Lidoderm.

As described above, OGD has devoted considerable resources trying to develop alternatives to bioequivalence studies with clinical endpoints to demonstrate bioequivalence for topical products. However, OGD has yet to validate such a method that could supplant the need for clinical trials for a locally acting topical product such as Lidoderm. Nonetheless, OGD apparently has decided to apply the bioequivalence recommendations for systemically acting transdermal patches to Lidoderm.

In its October 2006 letter,¹¹⁴ OGD recommended two studies "to establish bioequivalence of a lidocaine topical patch."¹¹⁵ The two studies consisted of: 1) "[a] single-dose fasting *in-vivo*

¹¹³ See NASAL AEROSOLS AND NASAL SPRAYS DRAFT GUIDANCE, *supra* note 57, at 4-5.

¹¹⁴ Lidoderm Bioequivalence Recommendations (Oct. 5, 2006), *supra* note 2.

¹¹⁵ *Id.* at 1.

bioequivalence study” to obtain a “pharmacokinetic profile of lidocaine for bioequivalence assessment based on the 90% confidence interval criteria”; and 2) a comparative skin irritation/sensitization study (also to include assessment of skin adhesion).¹¹⁶ Although OGD devoted more than seven pages of commentary to delineate how to conduct the skin irritation/sensitization study,¹¹⁷ OGD offered only a few comments on how to conduct an acceptable pharmacokinetic study. OGD instructed that the study should include a 24-hour post-dose sampling time, that only lidocaine rather than its metabolites should be measured, that an apparent dose delivered should be calculated based on the amount of product remaining in the patch, that a lower limit of quantification of 0.20 ng/ml should be achieved, and that *in vitro* dissolution should be assessed based on the USP method for transdermal products.

OGD thus recommended an approach for Lidoderm virtually identical to the set of tests generally used for transdermal products: pharmacokinetics (including *in vitro* dissolution), skin irritation/sensitization, and skin adhesion.¹¹⁸ However, while OGD offered extensive detail regarding the precise parameters for assessing skin irritation, sensitization, and adhesion, OGD offered no explanation for whether or how its proposed pharmacokinetic study could address the local delivery dimension of bioequivalence rather than simply assess systemic exposure for safety considerations.

4. There is No Scientific Basis for OGD’s New Bioequivalence Test for Lidoderm.

OGD’s October 2006 letter containing bioequivalence recommendations for Lidoderm fails to offer any data or rationale for its departure from clinical endpoint bioequivalence studies for Lidoderm. This explanatory void is not surprising. Endo is unaware of any data or rationale that would justify OGD’s new approach.

4.1. Currently Available Data Do Not Support Using Pharmacokinetic Measurements as a Suitable Method for Demonstrating Bioequivalence to Lidoderm.

As noted above, an ANDA sponsor must ensure that its product has the same labeling as the RLD.¹¹⁹ The safety and efficacy claims contained in the RLD labeling are the ultimate benchmark of the types of significant differences that a suitably-designed bioequivalence study must be capable of detecting. For generic products seeking to reference Lidoderm, pharmacokinetic studies cannot at this time sufficiently detect, predict, or reflect significant differences in rate and extent of lidocaine absorption at the site of action in the dermis where low levels of lidocaine selectively interfere with affected nerve fibers of PHN patients. Thus, pharmacokinetics presently cannot ensure that generic products will result in the analgesia without complete sensory block for which Lidoderm is labeled and used.

¹¹⁶ *Id.*

¹¹⁷ *Id.* at 2-9.

¹¹⁸ See ANDA CHECKLIST FOR CTD or eCTD FORMAT FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING (updated Oct. 10, 2006), available at http://www.fda.gov/cder/ogd/anda_checklist.pdf (identifying in-vivo pharmacokinetic study, adhesion study, and skin irritation/sensitization study as the appropriate studies for Transdermal Delivery Systems).

¹¹⁹ 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8).

4.1.1. No Evidence Suggests that Systemic Blood Measurements are Sufficiently Sensitive or Accurate to Detect BioINequivalent Products with Respect to Producing an Analgesic Effect without Complete Sensory Block.

It appears OGD failed to consider fully aspects of Lidoderm that raise questions regarding the utility of using systemic blood levels of lidocaine for detection of a bioINequivalent lidocaine topical patch. The relevant clinical actions of Lidoderm, as stated in its labeling, include both a local analgesic action (relief of pain associated with PHN) and the lack of complete sensory block (anesthesia) associated with other topical lidocaine-containing products. Simply stated, Lidoderm relieves the pain associated with PHN without producing numbness. It is likely that this observed treatment effect is at least in part determined by the rate and extent of lidocaine release from the Lidoderm patch and the associated penetration and local distribution of the drug in the skin.

The mechanism(s) of action and local tissue concentration of drug associated with the observed clinical effects of Lidoderm are poorly defined. It is not currently known what threshold concentration of lidocaine in the skin is required to produce pain relief or what concentration is required to produce a sensory block. It seems likely, however, that Lidoderm's ability to produce an analgesic effect without complete sensory block results from achieving local concentrations of lidocaine in skin that fall within a range that is sufficient to block pain but insufficient to produce sensory block. In other words, the clinical effect of Lidoderm and the differentiation of Lidoderm from other lidocaine-containing topical products involve two independent dose-response relationships (one for control of pain and the other for sensory loss). To date, neither of these dose-response relationships has been defined for Lidoderm or other topical lidocaine preparations.

In order to consider using systemic blood levels of lidocaine as a downstream surrogate marker of local tissue concentration of drug in skin and of clinical efficacy for the purpose of establishing bioequivalence, several issues would have to be adequately addressed. First, the relationships between applied dose, local tissue concentration of lidocaine in the skin, and observed clinical effect for both anesthesia and sensory block need to be established. These dose-response relationships are a necessary first step in that they would define the range of lidocaine concentrations at the site of action that are associated with the clinical properties of producing an analgesic effect without complete sensory block.

Once this concentration range is determined, one can ask whether measurement of lidocaine in blood reflects this same dose-response relationship and, importantly, whether blood measurements of lidocaine are a sufficiently sensitive and accurate indicator of differences in local skin concentrations that could result in different clinical effects. For example, is blood a sufficiently sensitive surrogate to discriminate between local lidocaine concentrations that may relieve pain without resulting in local sensory block (numbness) and drug levels that produce a sensory block along with relief of pain?

It is estimated that when used at the maximum labeled dose, approximately three percent of the applied dose of a Lidoderm patch is absorbed through the skin and cleared by systemic

circulation.¹²⁰ This results in very low levels of lidocaine to be measured in blood. To date, blood levels of lidocaine associated with use of the Lidoderm patch have been measured to ensure safety of the product and establish the lack of potentially toxic levels of lidocaine in the blood. It is unclear whether the sensitivity, precision, and accuracy of these methods are sufficient to detect differences in systemic blood levels that correlate with differences in therapeutic response. Endo is unaware of any data generated to date that has defined the dose-response for topical lidocaine (in any preparation) with respect to analgesia or sensory block using systemic blood level monitoring.

The potential impact of vehicle and excipients on the rate and extent of absorption of topical products is well documented. It is not known to what extent qualitative or quantitative changes to the Lidoderm patch might alter local concentrations of the drug or change the interaction of the drug with the target. It is possible that excipients modify both the local pattern of drug distribution within the heterogeneous complex environment of the skin as well as modify the response of the target nerves to lidocaine. Excipients may also inhibit or enhance the uptake of the drug by nerve fibers. Excipient-associated differences in local patterns of drug distribution, uptake by nerves, local metabolism, and clearance of lidocaine may all potentially alter the therapeutic profile of a lidocaine-containing topical patch. These excipient-associated changes may not be reflected in integrated downstream sampling of systemic lidocaine in blood. Endo is not aware of data that would support OGD's apparent assumptions that local changes in the distribution, concentration or activity of topical lidocaine caused by drug excipients that could impact on clinical efficacy would be reflected in measurable differences in systemic blood levels.

In sum, the available science does not seem sufficient to support what OGD has done. Most of the important questions have not been answered, and what little data are available are not supportive of OGD's action.

4.1.2. Cmax and AUC Are Not Reliable Indicators of Bioequivalence for Topical Drug Products Such as Lidoderm.

Lidoderm relies upon a slow onset of clinical effect sufficient to produce analgesia without complete sensory block rather than rapid onset of analgesic effect associated with other topical lidocaine products.

Pharmacokinetic measurements are particularly unsuitable for this type of drug where clinical effect is tied directly to absorption rate. It is well documented that pharmacokinetics are limited in their ability to assess rate of absorption.¹²¹ As FDA has acknowledged:

Both direct (e.g., rate constant, rate profile) and indirect (e.g., Cmax, Tmax, mean absorption time, mean residence time, Cmax normalized to AUC)

¹²⁰ LIDODERM PACKAGE INSERT, *supra* note 4 (Clinical Pharmacology section).

¹²¹ Rodney P. Basson et al., *Tmax: An Unconfounded Metric for Rate of Absorption in Single Dose Bioequivalence Studies*, 13 PHARM. RES. 324 (1996) (Cmax reflects extreme drug exposure rather than rate of absorption) (attached as Ex. 14); Rajeev M. Menon et al., *Effect of the Rate of Niacin Administration on the Plasma and Urine Pharmacokinetics of Niacin and Its Metabolites*, 47 J. CLIN. PHARM. 681 (2007) (plasma concentrations failed to detect differences in dosing rates) (attached as Ex. 15).

pharmacokinetic measures are limited in their ability to assess rate of absorption.¹²²

FDA also states that an early exposure measure may be suitable in circumstances “that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect).”¹²³ In such situations, FDA recommends a partial AUC to establish early exposure values. Thus, FDA has acknowledged that the C_{max} metric is an imperfect indicator for a rate-sensitive product.¹²⁴

4.1.3. *OGD Should Follow the DPK Precedent and Withdraw its Pharmacokinetic Bioequivalence Recommendations for Lidoderm.*

The DPK experience illustrated that the largely uncharacterized complexity of the skin, its diseases, and the mechanisms of action of drugs used to treat them place a heavy data burden on those who propose something other than clinical endpoints to demonstrate bioequivalence to these agents. After more than a decade of open, public process, OGD could not meet this burden for DPK.

Unlike DPK, OGD has conducted no public process, offered no data, and supplied no rationale for its recommendation that generic applicants use pharmacokinetics to demonstrate bioequivalence to Lidoderm. Because the much more robust DPK effort itself could not meet the heavy burden required for abandoning clinical studies, it is highly unlikely that OGD’s Lidoderm recommendation could pass muster.

4.2. **OGD Inappropriately Proposed to Apply the Bioequivalence Standards for Systemically-Acting Transdermal Patches to Locally-Acting Topical Patches.**

Lidoderm is a topical patch, but OGD’s proposed recommendations for generic copies of Lidoderm are virtually identical to the studies required for systemically-acting transdermal patches.¹²⁵ OGD has failed to explain why it is appropriate to apply bioequivalence methods for systemically acting products to locally acting products.

¹²² ORALLY ADMINISTERED DRUG PRODUCTS GUIDANCE, *supra* note 30, at 8. *Cf.* Letter from Steven K. Galson, M.D., M.P.H., Acting Director, CDER, to Susan P. Rinne, Vice President, Regulatory Affairs, ALZA Corporation 7 (Jan. 28, 2005) (consolidated response to four citizen petitions, Docket Nos. 2004P-0506, 2004P-0472, 2004P-0540, and 2004P-0340) (“C_{max} is affected by the rate of absorption and is considered to be a surrogate for the rate of absorption.”).

¹²³ ORALLY ADMINISTERED DRUG PRODUCTS GUIDANCE, *supra* note 30, at 8-9.

¹²⁴ *See, e.g.*, Letter from John M. Taylor, III, Associate Commissioner for Regulatory Affairs, FDA, to James H. Schafer, D.V.M., Response to Citizen Petition, Docket No. 02P-0489, at 2 (Dec. 31, 2003), *available at* <http://www.fda.gov/ohrms/DOCKETS/dailys/04/jan04/010904/02P-0489-PDN00001-vol1.pdf> (“[W]e agree that C_{max} is not a pure measure of absorption rate, but rather reflects both rate and extent of absorption. In addition, peak concentrations will also be affected by drug-specific attributes such as the rate and extent of intercompartmental exchange as well as the rate of drug elimination. Therefore, variability attributable to each of these sources impacts the true C_{max} value. Compounding this problem is that C_{max}, as defined by model-independent methods, is highly dependent upon drug sampling time. Nevertheless, in the majority of situations, FDA continues to consider C_{max} a highly informative metric upon which to compare the *in vivo* performance characteristics of a dosage form.”).

¹²⁵ FDA has approved generic versions of three transdermal patches: Climara (estradiol), Duragesic (fentanyl), and Nitro-Dur (nitroglycerin). In each case, FDA required that the ANDA sponsors demonstrate bioequivalence

Transdermal patches are intended to introduce drugs into systemic circulation. As a result, FDA's bioequivalence Guidance for orally administered drug products is "generally applicable" to transdermal patch products because "reliance on systemic exposure measures is suitable to document" bioequivalence for such products.¹²⁶ However, consistent with longstanding policy, the Guidance does not propose pharmacokinetics for locally acting products. Rather, the Guidance proposes "studies with clinical efficacy and safety endpoints and/or suitably designed and validated in vitro studies, if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study."¹²⁷ Once again, OGD's private recommendations of pharmacokinetics for Lidoderm bioequivalence are at odds with the Agency's publicly stated policies.

4.3. OGD's Proposed Recommendations Do Not Constitute a Sufficient "Portfolio" of Bioequivalence Tests Because None of OGD's Proposed Tests Are Capable of Evaluating Local Delivery.

OGD's proposed Lidoderm bioequivalence recommendations indicate that, in addition to measurement of lidocaine levels in the blood, the sponsor should determine levels of lidocaine remaining in the patch following use and measure the amount of lidocaine associated with adhesive residue left on the skin following removal of the patch. While an assay of lidocaine remaining in the patch following use will provide information regarding gross differences between products that may raise safety concerns, the amount of lidocaine in the patch relative to the levels of lidocaine at the site of action and associated with clinical effect differs by orders of magnitude. Moreover, there is no evidence of any correlation between residual drug in the patch and blood levels, local concentration of drug at the site of action, or clinical effect of lidocaine from the Lidoderm patch. In addition, clinical experience with the Lidoderm patch suggests no adhesive residue is associated with use of the product so it is difficult to understand the basis for OGD's suggestion of adhesive residue analysis. As with measurement of residual lidocaine in a used patch, measurement of adhesive residue (if it were present) has not been correlated with any bioequivalence parameters including rate and extent of absorption at the target or blood compartments or the clinical effect of the drug.

through the same combination of studies (standard pharmacokinetic measurements (AUC and Cmax), skin sensitization and adhesion, and dissolution testing) it now recommends for generic copies of Lidoderm. See FDA, APPROVAL PACKAGE OF ANDA NO. 75-182 (estradiol) (OGD required a pharmacokinetic test with standard 90% CI and 80-125% acceptance limits; a 21-day skin sensitization study; dissolution testing), available at http://www.fda.gov/cder/foi/nda/2000/75182_Estradiol.pdf; FDA, APPROVAL PACKAGE FOR ANDA NO. 76-258, available at <http://www.fda.gov/cder/foi/nda/2003/076258.pdf> (fentanyl); FDA, APPROVAL PACKAGE FOR ANDA NO. 89-884, available at http://www.fda.gov/cder/foi/anda/98/089884_nitroglycerin_toc.htm (nitroglycerin).

¹²⁶ ORALLY ADMINISTERED DRUG PRODUCTS GUIDANCE, *supra* note 30, at 1 (The guidance "is also generally applicable to nonorally administered drug products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products)."). FDA explains that the use of pharmacokinetic studies for systemically acting products "rests on an *understanding* that . . . *some relationship exists* between the efficacy/safety and concentration of active moiety and/or its important metabolite or metabolites in the systemic circulation." *Id.* at 6 (emphasis added). No such validated relationship between locally acting topical products applied to diseased skin and systemic circulation has been demonstrated generally or in the specific case of Lidoderm.

¹²⁷ *Id.* at 6.

OGD also recommends that ANDA applicants develop a dissolution method based on the USP method for transdermal products and perform skin irritation/sensitization/adhesion studies. As demonstrated by the DPK deliberations, analysis of *in vitro* release rates cannot provide a mechanism to assess rate and extent of absorption in the dermis due to the potential role of both vehicle and excipients in affecting rate and extent of absorption of active ingredients. Furthermore, skin irritation/sensitization/adhesion studies are performed principally for safety considerations rather than as a mechanism of assessing local delivery.

Consequently, while OGD's proposed parameters might provide some information regarding equivalence of the product particularly as they apply to safety issues associated with product use, there is no evidence that they can appropriately be used as supporting evidence of product bioequivalence relating to local delivery.

4.4. OGD's Approval of Generic Versions of EMLA is Not Legitimate, Reliable, Or Relevant as Precedent for Demonstrating Bioequivalence to Lidoderm.

OGD's approval of ANDAs referencing EMLA Cream was an unjustified departure from FDA regulations and publicly stated policy. OGD's acceptance of pharmacokinetic measurements for generic formulations of lidocaine/prilocaine cream is therefore of no relevance to generic formulations of Lidoderm because there was no scientific basis to support OGD's acceptance of pharmacokinetic measurements for generic copies of EMLA. Appeals to faulty precedent should not be used to perpetuate further erroneous decision-making.

The specifics of Lidoderm also make the EMLA "precedent" inapplicable to Lidoderm. Differential systemic uptake of Lidoderm among PHN patients indicates that Lidoderm acts differently in diseased skin. Consequently, a method for demonstrating bioequivalence of a topical cream applied to healthy skin is irrelevant to determining the proper method to demonstrate bioequivalence of a topical lidocaine patch used to treat pain associated with diseased skin. Also, unlike Lidoderm, EMLA does not create analgesia without complete sensory block. Thus, to the extent OGD actually developed a pharmacokinetic measure for EMLA, the upper limit of permissible blood levels would not have been defined by a correlation with causation of sensory block but rather as a safety parameter.

5. OGD's Lidoderm Bioequivalence Recommendations Violate the Law

The October 2006 bioequivalence recommendations for generic copies of Lidoderm appear to represent a scientific reversal by OGD. The lack of a scientific foundation should be sufficient for FDA to revoke these recommendations immediately. OGD's failure to comply with the law requires the same result.

5.1. OGD's Bioequivalence Recommendations Are Invalid Because OGD Did Not Explain Its Decision or Support it with Substantial Evidence.

Agency actions must be accompanied by a satisfactory explanation, must be supported by substantial evidence, must be consistent with applicable statutes and regulations, and must not be arbitrary, capricious or an abuse of discretion. Federal agency actions that fail to meet any one of

these requirements, or otherwise violate any law, are invalid under the Administrative Procedure Act (“APA”),¹²⁸ and must be set aside.¹²⁹

The correspondence containing OGD’s 2006 recommendations merely recited how to conduct a pharmacokinetic bioequivalence test and a skin sensitization study. No rationale or data were offered in support of these tests, despite their obvious break with Agency precedent.

OGD’s failure to explain its new test was arbitrary and capricious. OGD has not demonstrated that its new test was “based on a consideration of the relevant factors.”¹³⁰ “At a minimum, [OGD] must have considered relevant data and articulated an explanation establishing a ‘rational connection between the facts found and the choice made.’”¹³¹ Because OGD did not “adequately explain its result,”¹³² “provide a reasoned explanation for its decision,”¹³³ “cogently explain why it has exercised its discretion in [this] manner,”¹³⁴ or explain its departure from established precedent,¹³⁵ OGD’s new bioequivalence test for generic copies of Lidoderm must be set aside as arbitrary and capricious.¹³⁶

OGD’s new bioequivalence test for generic copies of Lidoderm was also unaccompanied by any evidence. This violated the requirement of the Administrative Procedure Act which requires that agency actions be supported by “substantial evidence.”¹³⁷ For this additional reason, OGD’s new test must be set aside.¹³⁸

Any explanation or evidence offered in support of OGD’s new pharmacokinetic test for Lidoderm would have to overcome consistent OGD statements that no such data or methods exist. As Dr. Conner put it, plasma concentrations would only be suitable for looking at drug availability at the site of action “if we really developed this idea and got a lot more data.”¹³⁹ And

¹²⁸ 5 U.S.C. § 706(2).

¹²⁹ See, e.g., *Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 48 (1983).

¹³⁰ *Marsh v. Oregon Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotations omitted).

¹³¹ *Biovail Corp. v. FDA*, 2007 U.S. Dist. LEXIS 20238 (D.D.C. Mar. 22, 2007) (quoting *Bowen v. Am. Hosp. Ass’n*, 476 U.S. 610, 626, (1986)).

¹³² *Public Citizen, Inc. v. FAA*, 988 F.2d 186, 197 (D.C. Cir. 1995).

¹³³ *Fox Television Stations, Inc. v. FCC*, Slip Op. at 22 (2d Cir. 2007). See also *Massachusetts v. EPA*, 127 S. Ct. 1438, 1463 (2007) (“EPA has offered no reasoned explanation for its refusal to decide whether greenhouse gases cause or contribute to climate change. Its action was therefore arbitrary, capricious, . . . or otherwise not in accordance with law.”) (internal citations and quotations omitted) (alteration in original).

¹³⁴ *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995) (quoting *State Farm*, 463 U.S. at 48).

¹³⁵ See, e.g., *Drug Plastics & Glass Co. v. NLRB*, 44 F.3d 1017, 1022 (D.C. Cir. 1995) (agency failure to explain departure from precedent resulted in invalidated agency action); *Yale-New Haven Hosp. v. Leavitt*, 470 F.3d 71, 72 (2d Cir. 2006) (agency action based on new rule governing Medicare reimbursement was arbitrary and capricious because the Secretary failed to offer a rationale for changing historical practices); *ANR Pipeline Co. v. Fed. Energy Regulatory Comm’n*, 71 F.3d 897, 901 (D.C. Cir. 1997) (“[W]here an agency departs from established precedent without a reasoned explanation, its decision will be vacated as arbitrary and capricious.”); *Ramaprakash v. FAA*, 346 F.3d 1121, 1125 (D.C. Cir. 2003) (An agency’s “failure to come to grips with conflicting precedent constitutes an inexcusable departure from the essential requirement of reasoned decision-making.”) (citation and internal quotations omitted).

¹³⁶ 5 U.S.C. § 706(2).

¹³⁷ *Id.*

¹³⁸ *Id.*

¹³⁹ Dale Conner, Pharm.D., Remarks at ACPS Meeting (Mar. 12, 2003), *supra* note 39, at 183.

as recently as May 2007 – months after OGD’s October 2006 recommendation of pharmacokinetic bioequivalence for Lidoderm – OGD stated once again that the relationship of plasma concentration to local delivery “is still unknown.”¹⁴⁰

In sum, there is no connection between the facts about Lidoderm and OGD’s choice to rely on pharmacokinetic measurements of bioequivalence for this agent. OGD’s actions are arbitrary and capricious, and should be set aside.

5.2. OGD’s Bioequivalence Recommendations Are Invalid Because They Have Not Been Shown to be Capable of Demonstrating Bioequivalence.

Bioequivalence can be demonstrated either by showing an absence of significant difference in rate and extent of absorption at the site of drug action or by showing an absence of significant difference in safety and therapeutic effect.¹⁴¹ OGD’s October 2006 recommendations for showing bioequivalence of generic copies to Lidoderm meet neither of these plain legal requirements.

First, OGD’s recommendations do not measure rate or extent of absorption of lidocaine at the site of Lidoderm’s action. As described in detail above, OGD’s recommendations measure lidocaine in the blood pool, not at Lidoderm’s site of action, damaged nerves in the skin. Moreover, Endo knows of no established correlation between the two.

Second, OGD’s recommendations have not been validated to detect significant differences in therapeutic effect. Lidoderm’s key therapeutic effect is to cause analgesia without sensory block. As a result, bioequivalence methods must detect whether a generic test product falls within the range of lidocaine concentrations defined by these two dose-response relationships (analgesia and sensory block). Thus, OGD would first have to define this range. Having done so, OGD would then need to validate a correlation between changes within this range and plasma concentrations of lidocaine. To Endo’s knowledge, neither of these complex tasks has been conducted.

In sum, OGD’s recommendations violate the FFDCA and FDA’s own regulations for demonstrating bioequivalence, and consequently are not in accordance with law, in violation of the APA.¹⁴²

5.3. OGD’s Bioequivalence Recommendations Are Invalid Because They Are Inconsistent with FDA’s Own Regulations.

FDA regulations require that bioequivalence must be shown using evidence obtained by “the most accurate, sensitive, and reproducible approach available among” several permissible approaches.¹⁴³ Agencies, of course, must follow their own regulations.¹⁴⁴

¹⁴⁰ CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS, *supra* note 78, at 5.

¹⁴¹ 21 U.S.C. § 355(j)(8); 21 C.F.R. § 320.

¹⁴² 21 U.S.C. § 355(j)(8); 21 C.F.R. § 320; 5 U.S.C. § 706(2).

¹⁴³ 21 C.F.R. § 320.24(a).

¹⁴⁴ *See, e.g., Doe v. Rumsfeld*, 341 F. Supp. 2d 1 (D.D.C. 2001) (“Although FDA’s scientific expertise is due great deference, it is well within this Court’s scope of authority to ensure that the agency adheres to its own

As demonstrated above, pharmacokinetics are not presently suitable for demonstrating bioequivalence for locally acting topical products such as Lidoderm. Bioequivalence studies with clinical endpoints remain the most accurate, sensitive, and reproducible approach available among the approaches permitted in FDA regulations. Absent a rationale buttressed by substantial evidence to demonstrate how pharmacokinetics are more accurate, sensitive, and reproducible than clinical endpoint bioequivalence studies, OGD's proposed recommendations for Lidoderm are inconsistent with FDA regulations and should therefore be set aside.

5.4. OGD's Bioequivalence Recommendations Are Invalid Because OGD Failed to Provide Public Notice or Opportunity for Comment.

Unlike the public process OGD pursued in proposing alternatives to clinical endpoint bioequivalence in the case of topical corticosteroids and DPK, OGD engaged in no public process when it adopted pharmacokinetics instead of clinical studies as the recommended bioequivalence approach for generic copies of Lidoderm.

As previously explained, FDA's bioequivalence regulations require "the most accurate, sensitive, and reproducible approach available among" several permissible approaches.¹⁴⁵ As also explained above, OGD has identified bioequivalence studies with clinical endpoints as the bioequivalence approach generally applicable to non-solution topical dermatological products such as Lidoderm. Most recently, the DPK effort to move away from clinical endpoints served, by its ultimate failure, to reaffirm such studies as the bioequivalence standard for these agents. Thus, OGD's interpretation of its bioequivalence regulations as they apply to such products is that clinical endpoint studies are "the most accurate, sensitive, and reproducible approach" to establishing bioequivalence for drugs like Lidoderm.

Having interpreted its regulations to require clinical endpoint studies as the bioequivalence standard for drugs like Lidoderm, OGD was required to conduct notice and comment rulemaking when it sought to replace clinical trials with pharmacokinetic measurements. "[N]ew rules that work substantive changes in prior regulations are subject to the APA's procedures."¹⁴⁶ "[W]hen an agency changes the rules of the game . . . more than a clarification has occurred."¹⁴⁷ "[A] legislative or substantive rule is one that does more than simply clarify or explain a regulatory term, or confirm a regulatory requirement, or maintain a consistent agency policy."¹⁴⁸ OGD's Lidoderm bioequivalence recommendations cannot be construed as merely confirming a

procedural requirements."); *Service v. Dulles*, 354 U.S. 363, 377, 380 (1957) (Administrative agencies must comply with their own voluntarily-promulgated regulations, even where Congress has given the agency "absolute discretion" over the administrative action in question); *Steenholdt v. FAA*, 314 F.3d 633, 639 (D.C. Cir. 2003) (Federal agencies are required to "follow their own rules, even gratuitous procedural rules that limit otherwise discretionary actions.") (citing *Accardi v. Shaughnessy*, 347 U.S. 260 (1954)); *Doe v. United States Dep't of Justice*, 753 F.2d 1092, 1098 (D.C. Cir. 1985) (Courts "have long required agencies to abide by internal, procedural regulations . . . even when those regulations provide more protection than the Constitution or relevant civil service laws.").

¹⁴⁵ 21 C.F.R. § 320.24(a).

¹⁴⁶ *Sprint Corp. v. FCC*, 315 F.3d 369, 374 (D.C. Cir. 2003).

¹⁴⁷ *Id.*

¹⁴⁸ *National Family Planning and Reproductive Health Ass'n, Inc. v. Sullivan*, 979 F.2d 227, 237 (D.C. Cir. 1992)).

regulatory term or requirement or maintaining consistent policy. Rather, they “change[] the rules of the game”¹⁴⁹ from studies with clinical endpoints to studies with simple blood level measurements.¹⁵⁰

It would be unavailing for the Agency to seek to avoid the requirement of notice-and-comment rulemaking by claiming that OGD’s new bioequivalence recommendations are somehow not a substantive rule. Once OGD has chosen which particular bioequivalence approach in its regulation applies to a particular product or group of products, that is the only approach applicants may use, because there can only be one approach which is “the most accurate, sensitive, and reproducible.”¹⁵¹ The words of the regulation dictate this result. Furthermore, it is clear from the EMLA experience that OGD views its bioequivalence “recommendations” as “precedent” that it must follow.¹⁵² Thus, OGD’s new bioequivalence recommendations are a substantive rule that would bind future generic applicants seeking to copy Lidoderm.¹⁵³ Consequently, OGD’s failure to promulgate these recommendations through notice-and-comment rulemaking renders them invalid.

5.5. OGD Should Withdraw its Pharmacokinetic Bioequivalence Recommendations for Lidoderm.

OGD should withdraw its pharmacokinetic bioequivalence recommendations for generic copies of Lidoderm because, as demonstrated in this Petition, there is no scientific basis upon which to allow use of pharmacokinetic measurements to demonstrate bioequivalence to Lidoderm and OGD failed to follow the law in advancing its recommendations.

5.6. FDA Should Convene a Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Advisory Committee for Pharmaceutical Science to Discuss Appropriate Bioequivalence Method(s) for Patch Dosage Forms with Local Routes of Administration.

Dermatologists play a key role in the proper analysis of bioequivalence for topical products. They were consulted regarding DPK and were critical to highlighting the extraordinary complexity of the skin and diseased skin conditions and the flaws of the DPK proposal. Had OGD consulted with dermatologists on EMLA like it did on DPK, it is apparent from the DPK deliberations that dermatologists would have been more likely to concur that pharmacokinetic

¹⁴⁹ *Sprint Corp.*, 315 F.3d at 374.

¹⁵⁰ Moreover, once an administrative agency has established a regulatory interpretation, it may only change that interpretation through a public process that includes notice for a proposed change and an opportunity for comment. See, e.g., *Paralyzed Veterans of Am. v. D.C. Arena*, 117 F.3d 579, 586 (D.C. Cir. 1997) (“Once an agency gives its regulation an interpretation, it can only change that interpretation as it would formally modify the regulation itself: through the process of notice and comment rulemaking.”); *Alaska Prof'l Hunters Ass'n v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999) (“When an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment.”).

¹⁵¹ 21 C.F.R. § 320.24(a).

¹⁵² *Nerurkar, Division of Bioequivalence Review*, *supra* note 92.

¹⁵³ *Sprint Corp.*, 315 F.3d at 373 (“[A]n agency’s imposition of requirements that ‘affect subsequent [agency] acts’ and have a ‘future effect’ on a party before the agency triggers the APA notice requirement.”) (quoting *Sugar Cane Growers Coop. v. Veneman*, 289 F.3d 89, 95-96 (D.C. Cir. 2002)).

tests were not a suitable benchmark for bioequivalence for EMLA Cream. Dermatologists' input regarding OGD's new pharmacokinetic approach to Lidoderm bioequivalence would similarly be important. FDA should seek DODAC's input regarding OGD's actions with respect to Lidoderm, EMLA, and other topical lidocaine-containing products.

A joint DODAC/ACPS advisory committee meeting is also needed to properly address bioequivalence standards for topical patches. CDER's classification system distinguishes topical patches from transdermal patches. However, there has been no corresponding consideration of how this classification relates to bioequivalence considerations. FDA has substantially addressed bioequivalence for transdermal patches by indicating that the general Guidance for orally administered drug products applies to transdermal products. But FDA has failed to provide sufficient guidance regarding topical patches. A joint DODAC/ACPS meeting would enable OGD to review the unique features of topical patches and the implications for identifying the most appropriate and validated bioequivalence tests. Convening this type of advisory committee meeting would also be consistent with FDA's Good Guidance Practices,¹⁵⁴ as well as FDA's Citizen Petition regulations,¹⁵⁵ which indicate that FDA may hold public meetings or workshops or present issues to an advisory committee for review.

5.7. FDA Should Stay the Approval or Approvable Status of Any ANDA or 505(b)(2) Application Referencing Lidoderm that Does Not Contain Studies with Clinical Safety and Efficacy Endpoints that Demonstrate Bioequivalence to Lidoderm.

In the absence of an alternative, scientifically valid method promulgated in accordance with the law and FDA's regulations, FDA must adhere to its longstanding interpretation and not approve generic products that have not demonstrated bioequivalence to Lidoderm using studies with clinical endpoints.

5.8. If OGD Contemplates an Alternative to Bioequivalence Studies with Clinical Endpoints for Lidoderm, OGD Should Only Develop Such Method Through a Valid Public Process with Input from FDA Advisory committees, including DODAC and ACPS.

To comply with the law and meet the standards of open science, OGD must use a public process of notice and comment to develop and promulgate any alternative to bioequivalence studies with clinical endpoints for Lidoderm. Failure to do so will invalidate any such alternative approaches.

¹⁵⁴ 21 C.F.R. § 10.115.

¹⁵⁵ 21 C.F.R. § 10.30(h).

6. Conclusion

For all of the above reasons, Endo respectfully requests that the Agency grant the relief requested in this Petition.

ENVIRONMENTAL IMPACT

As provided in 21 C.F.R. § 25.30, Endo maintains that its petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement. Endo is not aware of any extraordinary circumstances that would necessitate an environmental impact statement.

ECONOMIC IMPACT

As provided in 21 C.F.R. § 10.30(b), Endo will submit economic impact information at the request of the Commissioner.

CERTIFICATION

Endo 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 Endo that are unfavorable to the petition.



Mary Alice Raudenbush
Vice President, Regulatory Affairs
Endo Pharmaceuticals Inc.