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

CITIZEN PETITION

The undersigned, Endo Pharmaceuticals Inc. ("Endo"), submits this Citizen Petition under section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act") (21 U.S.C. § 355 (2006)) and FDA regulations 21 C.F.R. §§ 10.20, 10.30, 320.1, and 320.22-24 (2006).

Endo respectfully requests that the Food and Drug Administration ("FDA") apply bioequivalence requirements consistent with 21 C.F.R. § 320.24(b)(4) (comparative clinical efficacy trials appropriate for topical products) to any abbreviated new drug application (ANDA) seeking regulatory approval of a generic drug product that references Endo's product Lidoderm® (lidocaine topical patch, 5%) as its reference listed drug (RLD). Recently FDA incorrectly

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established plasma concentrations of lidocaine as the key measure for demonstrating bioequivalence of all generic lidocaine topical patch, 5% products to Endo's Lidoderm®.¹

While plasma levels of a drug are appropriate for transdermal patch products, which produce their effect only once the active pharmaceutical ingredient is systemically available, such levels are inapplicable to topical products such as Lidoderm®. As Dr. Dale Conner, the Director of the FDA Division of Bioequivalence and author of the "Dear Applicant" letter previously acknowledged, "[p]lasma concentrations are not an accurate measure of drug availability at the site of activity" for topical products, and "surrogate measures may not always adequately reflect availability at the site of activity."²

Lidoderm® exerts its analgesic effect locally at the site of application without a complete sensory block.³ Any generic version of Lidoderm® must also reflect this characteristic. Most importantly, because the labeling for any generic product must be the same as that of the RLD, a demonstration that a generic version of Lidoderm® provides the same local analgesia without complete sensory block is required to ensure the generic labeling is the same as that of Lidoderm®.⁴ However, this effect cannot be demonstrated via clinical studies with only pharmacokinetic endpoints. Accordingly, requiring generic manufacturers to conduct comparative clinical efficacy trials to demonstrate bioequivalence is necessary to ensure that any generic lidocaine topical patch, 5% product is as safe and effective and produces the same unique

¹ See Letter from Dale Conner, Director of Division of Bioequivalence, FDA (Oct. 5, 2006) (the "Dear Applicant letter"). [Tab A]

² See FDA Advisory Committee for Pharmaceutical Science (March 2003), available at http://www.fda.gov/OHRMS/DOCKETS/ac/03/slides/3926S1_19_Conner_files/frame.htm.

³ Lidoderm® Package Insert, *Clinical Pharmacology*.

⁴ See 21 U.S.C. § 355(j)(2)(A)(v) (requires ANDA applicant to show "that the labeling proposed for the new drug is the same as the labeling approved for the listed drug"); 21 C.F.R. § 314.94(a)(8)(iii) (requires ANDA applicant to submit statement that proposed labeling is the same as RLD labeling).

analgesic effect without complete sensory block as Lidoderm[®], and moreover, to comply with FDA's own regulations.

FDA's new methodology for establishing bioequivalence between a generic lidocaine patch, 5% product and Lidoderm[®], essentially via pharmacokinetic measures is improper. Instead, as FDA regulations provide, comparative clinical efficacy trials are the only appropriate method for a generic Lidoderm[®] applicant to prove bioequivalence.

I. ACTIONS REQUESTED

This petition requests the following:

That FDA amend its October 5, 2006 Dear Applicant letter and any similar document addressed to any other company regarding the standard for establishing bioequivalence for products using Lidoderm[®] as the RLD to include, in addition to the requirements set out in the Dear Applicant letter, the following requirements:

1. An applicant attempting to demonstrate its product's bioequivalence with Lidoderm[®] must conduct comparative clinical studies demonstrating identical safety and efficacy between its product and Lidoderm[®].

2. An applicant relying on Lidoderm[®] as its RLD must show that its product produces the same local analgesic effect as Lidoderm[®] without producing a complete sensory block, in order to assure that the generic product has the same labeling, efficacy and safety profile as Lidoderm[®].

II. STATEMENT OF GROUNDS

Permitting generic ANDA applicants to rely primarily on plasma concentrations of lidocaine to demonstrate bioequivalence between their products and Lidoderm[®] is unsound for several reasons:

- First, we show that while plasma levels of a drug may be appropriate for determining bioequivalence of transdermal patch products, Lidoderm[®] is a topical patch product that produces its effect locally and must be applied directly over the painful site.⁵ FDA cannot simply adopt the standard for transdermal patch products that act systemically for generic versions of Lidoderm[®], which acts locally, simply because Lidoderm[®]'s dosage form is also a patch. To do so would be contrary to FDA's own regulations.
- Next, we establish that plasma concentrations of lidocaine, the active pharmaceutical ingredient, are an improper metric for demonstrating that a generic version of Lidoderm[®] produces the same local analgesic effect without the complete sensory block that Lidoderm[®] produces. Because such a demonstration is necessary to both scientifically establish bioequivalence in terms of efficacy and to comply with the FDCA and FDA regulations that require generic labeling to be the same as that of the RLD, evidence from comparative clinical trials is necessary.
- Finally, we demonstrate that plasma levels of lidocaine, the active pharmaceutical ingredient, are a scientifically poor indicator of bioavailability, and therefore are an improper measure of bioequivalence, for topical patch products that act locally such as Lidoderm[®]. Using such pharmacokinetic measures as the key component to establishing bioequivalence runs contrary to the FDCA and FDA's own regulations.

⁵ See Lidoderm[®] Package Insert, *Dosage and Administration*.

Accordingly, in addition to the requirements set forth in the Dear Applicant letter, FDA must require generic manufacturers to conduct comparative clinical efficacy trials to demonstrate bioequivalence both to ensure that any generic lidocaine topical patch, 5% product is indeed bioequivalent to Lidoderm[®] and to comply with the FDCA and FDA regulations.⁶ The direction FDA provides in its Dear Applicant letter for establishing bioequivalence between Lidoderm[®] and a generic topical patch product is incomplete, and thus is contrary to the scientific evidence, inconsistent with the governing law, and could result in the approval of products without proven safety and efficacy.

A. Lidoderm[®] is a Topical Patch Product and Generic Versions of Lidoderm[®] Cannot be Approved Using Bioequivalence Standards for Transdermal Patch Products.

In its October 5, 2006 Dear Applicant letter, FDA adopts a measurement of bioequivalence for generics of Lidoderm[®] that is appropriately used for transdermal patch products. Among other things, FDA recommends that the generic applicant conduct studies measuring and comparing plasma concentrations of lidocaine as the primary means of demonstrating bioequivalence of its product to Lidoderm[®].

Lidoderm[®] (lidocaine topical patch, 5%) is a topical product approved for the local treatment of pain associated with post-herpetic neuralgia.⁷ On the other hand, transdermal patch products such as fentanyl patch, nitroglycerine patch, and clonidine patch, are formulated to produce systemic effects.⁸ While Lidoderm[®] must be applied at the site of pain in order to

⁶ See 21 U.S.C. § 355(j); 21 C.F.R. § 320, *et seq.*

⁷ See Lidoderm[®] Package Insert, *Indication and Usage*.

⁸ See Galer, B.S., *Topical Medications*, in *BONICA'S MANAGEMENT OF PAIN* 1736-41 (J.D. Loeser ed. Lippincott, Williams & Wilkins 2001). [Tab B]

produce its intended analgesic effect,⁹ transdermal patch products may be applied anywhere on the body and still produce their intended effects. In contrast to the intended extensive systemic absorption of the active pharmaceutical ingredient from transdermal patch products, application of Lidoderm[®] results in minimal systemic absorption of lidocaine, the active pharmaceutical ingredient—only $3 \pm 2\%$ of the applied dose is absorbed.¹⁰ It necessarily follows from this that plasma concentrations as the primary measure of the equivalent efficacy for a generic Lidoderm[®] are of no utility.

FDA regulations require that bioequivalence for topical products be measured at the site of drug action. The regulations define bioequivalence as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical alternatives becomes available at the site of drug action.”¹¹ The site of action for Lidoderm[®] is at the location that the patch is applied; as such, the relevant metric for demonstrating bioequivalence should focus on the effect of a generic lidocaine patch, 5% product at the site of application rather than the presence in the blood of the active pharmaceutical ingredient. On the other hand, for transdermal patch products, for which the site of action is systemic, the proper metric for determining bioequivalence is presence in the bloodstream of the active pharmaceutical ingredient. It would be unlawful for FDA to ignore its own rules and apply

⁹ See Rowbotham, M.C., et al., *Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia*, 65 PAIN 39, 43 (1996). [Tab C] See also discussion at Section II.B.2.a, *infra*.

¹⁰ See Lidoderm[®] Package Insert, *Clinical Pharmacology* (“When Lidoderm[®] is used according to the recommended dosing instructions, only $3 \pm 2\%$ of the dose applied is expected to be absorbed.”).

¹¹ 21 C.F.R. § 320.1 (2006) (emphasis added).

bioequivalence standards appropriate for systemically-acting transdermal patch products to Lidoderm[®], a locally-acting topical patch product.¹²

While FDA has some discretion in determining study design and methods for demonstrating bioequivalence for generic products, the FDCA affords FDA no discretion in requiring that generic companies demonstrate bioequivalence.¹³ The pharmacokinetic requirements that FDA sets forth in its October 5, 2006 Dear Applicant letter as the primary measure for establishing bioequivalence of generic lidocaine topical patch products with Lidoderm[®] are merely the standard for proving bioequivalence for an entirely different dosage form that has a different site of action. Because the site of action for Lidoderm[®], a topical patch, is different from that of transdermal patch products, applying the transdermal standard for a generic version of Lidoderm[®] will not ensure that the generic product is bioequivalent. As a result, FDA's proposed standard does not meet the statutory requirement, and using this standard to determine bioequivalence between a generic lidocaine topical patch, 5% product and Lidoderm[®] is unlawful.¹⁴

¹² See, e.g., *Cherokee Nation of Okla. v. Norton*, 389 F.3d 1074, 1087 (10th Cir. 2004) (agencies must follow their own rules); *Steenholdt v. Fed. Aviation Admin.*, 314 F.3d 633, 639 (D.C. Cir. 2003) (stating the same).

¹³ See 21 U.S.C. § 505(j) (requires ANDA applicant to show bioequivalence).

¹⁴ See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (FDA may not promulgate regulations that run contrary to FDCA requirements); *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (setting forth the standard for finding an agency action arbitrary and capricious); *Perales v. Sullivan*, 948 F.2d 1348, 1354 (2d Cir. 1991) (agency action is arbitrary and capricious if it fails to meet statutory requirements); *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. Ruckelshaus*, 719 F.2d 1159, 1164 (D.C. Cir. 1983) ("[a]gency action is arbitrary and capricious if the agency has failed to meet statutory ... requirements").

B. FDA's Reliance on Plasma Concentrations of Lidocaine as the Key Measure for Approving a Generic Version of Lidoderm® is Improper.

1. Any Generic Version of Lidoderm® Must Establish that it Provides an Equivalent Local Analgesic Effect Without Causing a Complete Sensory Block.

Lidoderm® is uniquely characterized as providing an analgesic effect without causing a complete sensory block.¹⁵ FDA's October 5, 2006 Dear Applicant letter does nothing to address this important effect that Lidoderm® produces, and as such a generic applicant would be unable to mirror Lidoderm®'s labeling. Evidence from a comparative clinical trial is needed to prove that a generic version of Lidoderm® replicates this effect of local analgesia without complete sensory block.

- a. Lidoderm® Has the Unique Effect of Producing Analgesia Without Complete Sensory Block.

The FDA-approved Lidoderm® product labeling expressly states that "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."¹⁶ It should also be noted that skin numbness or other terms that may reflect a complete sensory blockade at the patch application site are not listed in the Adverse Reactions section of the approved Lidoderm® product labeling. A generic version of Lidoderm® must also demonstrate this unique effect.

In addition to the data provided in the NDA and reflected in the approved product labeling, further clinical studies support Lidoderm®'s ability to produce analgesia without causing a complete sensory block. These findings have been demonstrated in patients with post-

¹⁵ See Lidoderm® Package Insert, *Clinical Pharmacology*.

¹⁶ *Id.* (emphasis added).

herpetic neuralgia¹⁷ as well as in healthy volunteers¹⁸ and patients with other forms of both neuropathic and nociceptive pain.¹⁹ The studies used multiple applications of Lidoderm[®], and all consistently showed that in the vast majority of subjects, sensation to light touch and pinprick was maintained, indicating that Lidoderm[®] does not cause a complete sensory block.²⁰

These data, along with those submitted with the NDA, clearly differentiate the product from topical gels and creams like EMLA[®] (lidocaine/prilocaine cream) and the lidocaine/tetracaine patch (Synera[®]). As demonstrated below, these formulations produce a local sensory block. Lidoderm[®] is unique in that patients continue to experience normal skin sensation while experiencing reduced neuropathic pain resulting from post-herpetic neuralgia. Such a distinction is of importance to the safety of the patient using the product. It is obvious and well understood that patients with areas of skin numbness resulting from a complete sensory block may injure themselves seriously but be unaware of the injury.²¹ Indeed, the package inserts for EMLA[®] and Synera[®] alert patients to be aware that use of the products may block all sensation to the treated skin, and therefore inadvertent trauma to the treated area could result from scratching, rubbing, or exposure to extreme hot or cold temperatures.²² In contrast, there is

¹⁷ White, W.T., et al., *Lidocaine Patch 5% With Systemic Analgesics Such as Gabapentin: A Rational Polypharmacy Approach for the Treatment of Chronic Pain*, 4 PAIN MED. 321 (2003). [Tab D]

¹⁸ Gammaitoni, A.R., et al., *Pharmacokinetics and Safety of Continuously Applied Lidocaine Patches 5%*, 59 AM. J. HEALTH-SYS. PHARMACY 2215, 2219 (2002). [Tab E]

¹⁹ See White et al., *supra* note 16. Gammaitoni et. al, *supra* note 17. See also, Burch F., et al., *Lidocaine Patch 5% Improves Pain, Stiffness, and Physical Function in Osteoarthritis Pain Patients*, 12 OSTEOARTHRITIS AND CARTILAGE 253 (2004) [Tab F]; Galer, B.S., et al., *Topical Lidocaine Patch 5% May Target a Novel Underlying Pain Mechanism in Osteoarthritis*, 20 CURRENT MED. RES. AND OPINION 1455 (2004) [Tab G]; Gimbel, J., 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). [Tab H]

²⁰ *Id.*

²¹ EMLA[®] Package Insert, *Information for Patients*; Synera[®] Package Insert, *Information for Patients*.

²² *Id.*

no similar language in the Lidoderm® package insert because there is no complete sensory block at the site of application.

b. Plasma Concentrations of Lidocaine Cannot be Used as a Surrogate for Demonstrating Equivalence to Lidoderm®'s Property of Causing Local Analgesia Without Complete Sensory Block.

Topical products containing lidocaine do not replicate Lidoderm®'s effect in avoiding complete sensory block even where they produce plasma concentrations similar to those produced by Lidoderm®. Accordingly, plasma concentrations are not an appropriate or valid surrogate for demonstrating this effect.

Topical products containing lidocaine, other than Lidoderm®, are approved as topical anesthetics to provide local skin analgesia in connection with needle insertion or superficial surgical procedures.²³ When 60g of EMLA® were applied to 400 cm² of intact skin in healthy volunteers and then covered by an occlusive dressing (consistent with dosage instructions to provide dermal analgesia prior to dermal procedures) and left in place for 3 or 24 hours, peak plasma concentrations of lidocaine were 0.12µg/mL or 0.28µg/mL, respectively.²⁴ At such concentrations, there was complete sensory block.²⁵ These plasma concentrations of lidocaine are similar to those seen in healthy volunteers after application of three Lidoderm® patches for 12 hours (mean peak plasma concentration, 0.13µg/mL²⁶). However, application of Lidoderm® is not associated with any sensory loss.²⁷ Application of Synera® topical patch containing 70mg of lidocaine and 70mg of tetracaine provides a contrasting example. For Synera®, mean peak

²³ EMLA® Package Insert, *Indications and Usage*; Synera® Package Insert, *Indications and Usage*.

²⁴ EMLA® Package Insert, *Clinical Pharmacology*.

²⁵ EMLA® Package Insert, *Indications and Usage*.

²⁶ Lidoderm® Package Insert, *Clinical Pharmacology*.

²⁷ See *id.*, Gammaitoni, et al., *supra* note 17.

plasma lidocaine concentrations of just 0.0017 µg/ml, a level that is about one hundredth of that produced by Lidoderm[®], resulted in local dermal anesthesia for superficial venous access procedures.²⁸ Thus, the fact that these products have different local effects at the same or significantly lower plasma concentrations as Lidoderm[®] shows that plasma concentrations of lidocaine are not reflective of activity at the site of application.

- c. The FDCA and FDA Regulations Require Any Generic Version of Lidoderm[®] Produce an Analgesic Effect Without Sensory Block at the Site of Action.

As discussed above, pharmacokinetic data cannot establish whether a generic lidocaine topical patch, 5% product will mimic the local analgesia without complete sensory block effect of Lidoderm[®]. Without evidence proving that a generic version of Lidoderm[®] replicates this effect, a generic manufacturer cannot include a claim that the product does have that effect in its labeling; to do so would be false and render the product misbranded. However, Section 505(j) of the FDCA requires that the labeling of a generic product be the same as that of the reference listed drug.²⁹ Because the measures of bioequivalence FDA has proposed will not provide evidence sufficient to support a claim that the generic applicant must include in its labeling, that methodology is insufficient to permit generic applicants to meet their statutory obligations and cannot be used. Moreover, section 505(j) also requires that the method used to prove bioequivalence of drugs that act locally must detect any significant difference in the safety or therapeutic effect of the generic version. As the standard FDA has proposed will not establish whether a generic version of Lidoderm[®] produces the local analgesia with complete sensory

²⁸ Synera[®] Package Insert, *Clinical Pharmacology*.

²⁹ See 21 U.S.C. § 355(j)(2)(A)(v).

block effect, the statute forbids FDA from relying on plasma concentrations and must require comparative clinical studies.

(i) Comparative Clinical Trials are Necessary to Ensure Identical Labeling for a Generic Version of Lidoderm®.

A generic product's label must be the same as that of the RLD it purports to rely on.³⁰ As such, any generic manufacturer of a lidocaine topical patch, 5% product using Lidoderm® as its RLD must be able to include in its labeling a statement that its product produces local analgesia without causing a complete sensory block, as does Lidoderm®.³¹ Simple measurement of plasma lidocaine levels and an evaluation of the amount of lidocaine delivered, combined with requiring a patch of the same size will not ensure that this analgesia-without-complete sensory block effect at the site of application is actually occurring. Skin sensitization/irritation studies will also not suffice to ensure that a generic Lidoderm® product is producing the necessary analgesic effect without causing a complete sensory block. However, to ensure that the labeling is not false, FDA must require that the applicant of any generic lidocaine topical patch, 5% product has submitted evidence demonstrating that its product produces this same effect.³²

While the requirements set forth in the October 5, 2006 Dear Applicant letter are all necessary aspects of establishing that a generic product is the same as Lidoderm®, as demonstrated above, a determination of whether a generic version produces an analgesia without complete sensory block effect can only be accomplished by requiring the generic applicant to conduct comparative clinical efficacy studies. Thus, in order for the generic labeling to be the

³⁰ See 21 U.S.C. § 355(j)(2)(A)(v) (requires ANDA applicant to show "that the labeling proposed for the new drug is the same as the labeling approved for the listed drug") (emphasis added); 21 C.F.R. § 314.94(a)(8)(iii) (requires ANDA applicant to submit statement that proposed labeling is the same as RLD labeling).

³¹ *Id.*

³² Indeed, if the drug caused numbness, the labeling would need to include a statement similar to those found in the EMLA® and Synera® Package Inserts. See notes 20-21 and accompanying text.

same, manufacturers of generic versions of Lidoderm[®] must be required to conduct comparative clinical efficacy studies to prove their products replicate Lidoderm[®]'s effect, in addition to the meeting the other requirements set forth in the October 5, 2006 Dear Applicant letter. FDA's failure to require generic manufacturers to conduct studies designed to demonstrate this effect of analgesia without a complete sensory block would be contrary to the statutory requirement and unlawful.³³

- (ii) The Standard Proposed by FDA Will Not Detect a Potential Significant Difference in Therapeutic Effect or Safety Profile of a Generic Version of Lidoderm[®].

The standard FDA proposes in the Dear Applicant letter violates the statute for another reason. An ANDA applicant under 505(j) is required to prove bioequivalence of its product to a reference listed drug.³⁴ Under section 505(j)(8)(C), for drugs not intended to be absorbed into the bloodstream, FDA "may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."³⁵ Because, as discussed above, the active ingredient in Lidoderm[®] is not intended to be absorbed into the bloodstream in therapeutically meaningful amounts, FDA must adopt an alternative means of establishing bioequivalence that will detect any difference in the safety and therapeutic effect of a generic version. Because plasma concentrations of lidocaine combined with the other parameters specified in the October 5, 2006 Dear Applicant letter cannot demonstrate whether a generic version of Lidoderm[®] has the same effect of local analgesia without complete sensory block,

³³ See *Brown and Williamson*, 529 U.S. at 139; *Perales*, 948 F.2d at 1354; *Ruckelshaus*, 719 F.2d at 1164.

³⁴ 21 U.S.C. § 355(j).

³⁵ 21 U.S.C. § 355(j)(8)(C) (emphasis added).

those measures alone are insufficient to meet the statutory requirement. Instead, FDA must require clinical trials as contemplated by its own regulations.

As established above, the standard proposed by FDA would not detect a significant difference in the therapeutic effect of a generic version of Lidoderm[®] with respect to the effect of local analgesia without complete sensory block as the statute requires. Moreover, because application of Lidoderm[®] does not result in a complete sensory block, demonstrating this effect is also crucial for establishing that the safety profile of any generic product does not differ from that of Lidoderm[®]. Safety concerns would arise for a generic product that does not produce the same analgesia-without-complete sensory block effect as Lidoderm[®] if a patient using the generic product experienced skin numbness in addition to relief of localized neuropathic pain. For example, as noted above, the labeling for other lidocaine topical anesthetic products caution patients about possible inadvertent trauma while experiencing complete sensory block. A generic version of Lidoderm[®] must therefore demonstrate it does not produce complete sensory block to ensure that the generic version would not have a different safety profile than Lidoderm[®]. Because plasma concentrations cannot detect that difference in safety profile, under the FDCA, plasma concentrations are an improper primary measure of bioequivalence.³⁶

2. Plasma Concentrations are a Scientifically Improper Measure for Proving Bioequivalence of Locally-Acting Topical Products Such as Lidoderm[®].

FDA's Dear Applicant letter provides that the key measure for proving bioequivalence of a generic version of Lidoderm[®] is the plasma concentration of lidocaine. However, clinical data establish that plasma concentrations of lidocaine are irrelevant for proving the efficacy of a generic version of Lidoderm[®] topical patch product. Accordingly, using plasma concentrations

³⁶ 21 U.S.C. § 355(j)(8)(C).

is an inadequate basis of proving bioequivalence.³⁷ Because such proof is required under the statute and FDA regulations, FDA's reliance on plasma levels as the key measure for establishing bioequivalence for generic versions of Lidoderm® is unlawful.

- a. Clinical Evidence Shows that Lidoderm® Acts Locally Rather than Systemically, Rendering Plasma Concentrations of Lidocaine an Inaccurate Measure of Efficacy for Purposes of Showing Bioequivalence.

Clinical studies have demonstrated that the mean peak plasma concentration of lidocaine after application of three Lidoderm® patches for 12 hours in healthy volunteers is 0.13µg/mL.³⁸ In patients with post-herpetic neuralgia, the approved indication for Lidoderm®, the mean peak plasma concentration of Lidoderm® after application of three patches for 12 hours was lower at 0.052µg/mL.³⁹

In contrast, clinical studies of the efficacy of systemically-administered lidocaine in patients with post-herpetic neuralgia have demonstrated that plasma concentrations of lidocaine less than 1µg/mL (approximately 20x higher than those recorded in patients following application of three Lidoderm® patches) are not associated with meaningful pain relief.⁴⁰ Thus the low plasma concentrations of lidocaine achieved following application of Lidoderm® in accordance with the approved package insert are completely inconsistent with plasma

³⁷ Data regarding the concentration of lidocaine is of course relevant to establish the safety of a generic to Lidoderm®. Endo does not challenge FDA's requirement that a generic applicant provide such data in support of a showing of safety.

³⁸ Lidoderm® Package Insert, *Clinical Pharmacology*.

³⁹ Campbell et al., *Systemic Absorption of Topical Lidocaine in Normal Volunteers, Patients with Post-Herpetic Neuralgia, and Patients with Acute Herpes Zoster*, 91 J. PHARMACEUTICAL SCI. 1343 (2002). [Tab I] It should be noted that the number of patches applied has no therapeutic consequence relating to increasing the amount of systemically available lidocaine, but rather the number of patches is solely related to completely covering the painful area. There was no evidence that steady-state plasma concentrations increase with repeated application of patches in accordance with the approved package insert dosing recommendations.

⁴⁰ Rowbotham, M.C., et al., *Both Intravenous Lidocaine and Morphine Reduce the Pain of Postherpetic Neuralgia*, 41 NEUROLOGY 1024 (1991). [Tab J]

concentrations achieved following effective doses of systemically administered lidocaine in the same patient population. 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.⁴¹

These data indicate that Lidoderm[®] is not producing its effects based on the amount of lidocaine reaching the systemic circulation. Rather, Lidoderm[®] can only be exerting its effect locally. As a result, plasma concentrations of lidocaine following application of Lidoderm[®] are an improper measure of the bioavailability of lidocaine at its site of action. Because plasma concentrations are insufficient to reflect the local bioavailability of lidocaine following application of Lidoderm[®], such a measure is also improper as a measure of bioequivalence. As such, it is improper to apply the bioequivalence standards FDA has proposed to lidocaine topical patch, 5% products.

b. The Proposed Bioequivalence Standard for Lidoderm[®] is Contrary to FDA Regulations.

FDA's regulations explicitly recognize that plasma concentrations are an inadequate measure for demonstrating bioavailability, and thus, bioequivalence for topical products.⁴² Section 320.23(a)(1) of the C.F.R. states, "for drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action."⁴³ Thus, bioavailability, and by inference, bioequivalence, for topical products must be measured locally. Further, section 320.24(b)(4) provides for the use of "appropriately designed

⁴¹ Summarized in Tremont-Lukats et al., *Systemic Administration of Local Anesthetics to Relieve Neuropathic Pain: A Systematic Review and Meta-Analysis*, 101 ANESTHESIA & ANALGESIA 1738 (2005). [Tab K]

⁴² See 21 C.F.R. §§ 320.23(a)(1), 320.24(b)(4).

⁴³ 21 C.F.R. § 320.23(a)(1) (emphasis added).

comparative clinical trials for the purposes of demonstrating bioequivalence.... of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes..."⁴⁴ Endo's Lidoderm[®] falls squarely into the category of products contemplated by section 320.24(b)(4). Thus, any 505(j) applicant referencing Lidoderm[®] as its RLD must follow the requirements of that section in demonstrating bioequivalence.

The administrative history of this regulation supports this conclusion.⁴⁵ In its discussion of the scope of the rule, FDA contemplated situations where plasma concentrations would not be the proper measurement of bioequivalence. FDA provided alternative avenues for a generic applicant by saying "when other, or accurate, sensitive, and reproducible testing methods are not available, FDA will accept appropriately designed comparative clinical trials for purposes of demonstrating in vivo bioequivalence."⁴⁶ As noted above, the final rule states that comparative clinical trials are appropriate for determining bioequivalence in topical products because plasma concentrations do not adequately measure local activity.⁴⁷

FDA also indicated in its administrative history that methods for determining bioequivalence for locally acting drugs must be determined on a case-by-case basis depending on the drug under study.⁴⁸ The metrics for assessing bioequivalence for a generic version of Lidoderm[®], then, must be tailored to that drug to reliably demonstrate bioequivalence.

⁴⁴ 21 C.F.R. § 320.24(b)(4) (emphasis added).

⁴⁵ See Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950 (Apr. 28, 1992) (codified at 21 C.F.R. §§ 320, *et. seq.*).

⁴⁶ *Id.* at 17,973.

⁴⁷ 21 C.F.R. § 320.24(b)(4).

⁴⁸ See Abbreviated New Drug Application Regulations, 57 Fed. Reg. at 17,972 (emphasis added).

Lidoderm®'s effect of analgesia without causing a complete sensory block demands that FDA require comparative clinical efficacy trials for generic versions of this drug.

Based on its own regulations, FDA's use of plasma levels to prove bioequivalence is erroneous. The regulations contemplate comparative clinical efficacy studies for demonstrating bioequivalence of topical products, and FDA must give effect to its own rules.⁴⁹ The failure of an agency to follow its own rules invalidates its action as being arbitrary and capricious.⁵⁰

c. FDA's Prior Statements Confirm that Plasma Concentrations are an Inappropriate Basis for Showing Bioequivalence to Lidoderm®.

In addition to the statements made by Dale Conner quoted above, other high-ranking scientific officials of FDA have made similar, recent statements confirming that plasma concentrations are not an appropriate means for proving bioequivalence of topical products like Lidoderm®. For example, Lawrence Yu, the Director of Science at the FDA Office of Generic Drugs, stated in an October 2004 Advisory Committee presentation 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 ... bioequivalence. Because of that, we have to rely on other alternative methods; for example, pharmacodynamic method [or] ... in vivo clinical comparisons...."⁵¹ Further, Robert Lionberger, a chemist at the FDA Office of Generic

⁴⁹ See, e.g., *Cherokee Nation of Okla.*, 389 F.3d at 1087 ("Agencies ... must follow their own rules and regulations"); *Steenholdt*, 314 F.3d at 639 (agencies must follow their own rules).

⁵⁰ *Cherokee Nation*, 389 F.3d at 1078, 1087. Further, FDA's decision to permit using a combination of plasma levels, apparent dose measurements, and patch design as determinants of bioequivalence between a generic lidocaine topical patch product and Lidoderm®, rather than a requiring comparative clinical efficacy trials as contemplated by the regulations, is also an unlawful amendment of the regulations that violates the Administrative Procedures Act (APA) requirement of public notice and opportunity for comment. See 5 U.S.C. § 553; *Sugar Cane Growers Co-op of Fla. v. Veneman*, 289 F.3d 89 (D.C. Cir. 2002) (stating that an utter failure to comply with notice and comment is not harmless); *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 547 (D.C. Cir. 1983) (agency must "fairly appraise interested persons" of any rulemaking).

⁵¹ Presentation by Lawrence Yu, FDA Advisory Committee for Pharmaceutical Sciences Transcript (October 2004), available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4078T1.htm>.

Drugs, indicated that “[t]he current state of topical bioequivalence is that ... for almost all locally acting dermatological products clinical trials are necessary to determine bioequivalence.”⁵² Dena Hixon, the Associate Director for Medical Affairs at FDA Office of Generic Drugs stated in a presentation to an FDA Advisory Committee that for “locally acting drugs, ... the pharmacokinetic studies are not adequate to establish bioequivalence.... [M]ost of our locally acting drugs require clinical endpoint studies to determine bioequivalence.”⁵³ Given these repeated statements by FDA officials that plasma concentrations are an insufficient and improper primary measure of bioequivalence for topical products, FDA’s recent decision to suggest such an improper metric for demonstrating bioequivalence between a generic lidocaine topical patch, 5% product and Lidoderm[®] lacks any foundation and would be arbitrary and capricious.⁵⁴

d. There is No One-Size-Fits-All Standard for Proving Bioequivalence in Topical Products.

In a 2003 letter to the Pharmaceutical Science Advisory Committee members, Helen Winkle, the Acting Director for the Office of Pharmaceutical Science at FDA stated that “determining bioequivalence for approving generic . . . topical dermatological products has been complicated. . . . FDA has researched methods for determining bioequivalence for topical products, . . . but has been unable to specifically identify a method which adequately addressed therapeutic equivalence of the products.”⁵⁵ In the absence of any other adequate method for

⁵² Presentation by Robert Lionberger, FDA Advisory Committee for Pharmaceutical Sciences Transcript (April 2004), available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4034T2.htm>.

⁵³ Presentation by Dena Hixon, FDA Advisory Committee for Pharmaceutical Sciences Transcript (March 2003), available at <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.htm>.

⁵⁴ In addition to these statements, the FDA has even recently represented to a court that plasma concentration data may not be appropriate for establishing bioequivalence for topical products. See *Alpharma v. Leavitt*, 460 F.3d 1, 5-7 (D.C. Cir. 2006).

⁵⁵ Letter from Helen Winkle to Advisory Committee for Pharmaceutical Science members (Feb. 11, 2003), available at http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926B1_01_A-FDA-Winkel%20Cover%20Letter.htm (emphasis added).

demonstrating bioequivalence of topical products, it is evident that performing comparative clinical studies remains the most reliable method for demonstrating bioequivalence.

The difficulty in establishing a one-size-fits-all surrogate standard for measuring bioequivalence for topical drugs is also evident in FDA's past issuance and withdrawal of guidance documents recommending studies designed to measure bioequivalence of topical products.⁵⁶ In each of those guidances, FDA sought to establish surrogate methods for demonstrating bioavailability and bioequivalence in topical products in order to circumvent the requirement that a generic manufacturer undertake comparative clinical efficacy studies. FDA later withdrew those guidances because they set forth insufficient measures for assessing bioequivalence.

In April 2006, FDA acknowledged the inappropriateness of using pharmacokinetic measures to demonstrate bioequivalence in a topical product, mesalamine delayed-release tablets.⁵⁷ With respect to a proposed generic mesalamine delayed-release tablet, FDA indicated that "[s]ince mesalamine delayed-release tablets act locally within the GI tract, a bioequivalence study with clinical endpoints is more appropriate" than pharmacokinetic measures for demonstrating bioequivalence.⁵⁸ One of the factors FDA considered in its decision to require clinical studies was that plasma concentrations of mesalamine "do not reflect drug efficacy – i.e., the pharmacologic response to drug availability at the enterocytes of the colon."⁵⁹ Only seven

⁵⁶ See, e.g., FDA Draft Guidance for the Industry, Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies, 1998; FDA Draft Guidance for the Industry, Interim Guidance for Documentation of *In Vivo* Bioequivalence of Albuterol Aerosols (Metered-Dose Inhalers), 1994; FDA Draft Guidance for the Industry, Bioequivalence Study for Topical Antifungal Products, 1990.

⁵⁷ See Letter from Dale P. Conner, Director of FDA Division of Bioequivalence, to Julie Massicotte, Algorithme Pharma, Inc. (Apr. 3, 2006).

⁵⁸ *Id.*

⁵⁹ *Id.*

months later, on November 7, 2006, FDA recommended that a generic company conduct studies measuring plasma levels of balsalazide and mesalamine, combined with dissolution studies, to establish bioequivalence for a generic locally-acting balsalazide capsule product.⁶⁰ FDA stated that “although neither dissolution nor plasma pharmacokinetics are a complete reflection of drug appearance at the local site(s) of action, these parameters together provide adequate assurance ... to support a demonstration of bioequivalence.”⁶¹

This recent statement, combined with the statement in the October 5, 2006 Dear Applicant letter, suggests that FDA has now adopted plasma concentrations as the key one-size-fits-all measure for proving bioequivalence for all locally-acting products. For the reasons discussed above, there is neither a scientific nor legal basis for this change of course. Indeed, as recently as December 12, 2006, the Agency confirmed in a revision of its Manual of Policies and Procedures that “[a] bioequivalence study with clinical endpoints . . . may be applied to dosage forms intended to deliver the active moiety locally . . . that are not intended to be absorbed”⁶² like Lidoderm®. Even if plasma concentrations combined with other measures can be used in determining whether to approve an ANDA, the measures proposed in the Dear Applicant letter are an incomplete metric for ensuring that a generic version of Lidoderm® is bioequivalent. For FDA to persist in this course of action would be unlawful.⁶³

⁶⁰ See Letter from Dale P. Conner, Director of FDA Division of Bioequivalence (Nov. 7, 2006) (requiring generic company to measure plasma concentrations of balsalazide and mesalamine as the primary measure of bioequivalence for generic versions of Colazol® capsules).

⁶¹ *Id.*

⁶² FDA Office of Generic Drugs, *Manual of Policies and Procedures 5210.4* (Dec. 12, 2006), available at <http://www.fda.gov/cder/mapp/5210.4R.pdf>.

⁶³ See *Brown and Williamson*, 529 U.S. at 139; *Perales*, 948 F.2d at 1354; *Ruckelshaus*, 719 F.2d at 1164. See also, *Alpharma v. Leavitt*, 460 F.3d 1, 6 (D.C. Cir. 2006) (arbitrary and capricious standard requires an agency to explain why it has exercised its discretion in a given manner); *Public Citizen, Inc. v. Mineta*, 340 F.3d 39, 53 (2d Cir. 2003); (agency must “examine the relevant data and articulate a satisfactory explanation for its action”).

* * * * *

Bioequivalence is central for approval of ANDA products, as it is the only real indicator of whether a generic product is actually equivalent to the RLD and, therefore, as safe and effective as the RLD. The lack of a clear showing of bioequivalence therefore has implications on safety, effectiveness, and consumer trust in the pioneer drug manufacturer, the generic drug manufacturer, and FDA. Moreover, the FDCA mandates a showing of bioequivalence as a requirement for ANDA approval.⁶⁴ Because studies measuring plasma concentrations are inappropriate for demonstrating bioavailability of lidocaine from a lidocaine topical patch, 5% product, results of such studies, even in conjunction with the other requirements set forth in the Dear Applicant letter, would fall far short of proving bioequivalence between the generic and reference drug, as the statute requires.⁶⁵ As such, FDA's recommendation that plasma concentrations be used to demonstrate bioequivalence of a generic lidocaine topical patch, 5% product with Lidoderm[®] -- an improper standard for such demonstration -- is a violation of the Act and an impermissible action by FDA.⁶⁶

III. ENVIRONMENTAL IMPACT

As provided in 21 C.F.R. § 25.30, the petitioner believes this petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement. To the petitioner's knowledge, no extraordinary circumstances exist.

⁶⁴ 21 U.S.C. § 355(j)(2)(A)(iv) (lists as one of the ANDA filing requirements, "information to show that the new drug is bioequivalent to the listed drug").

⁶⁵ *Id.*

⁶⁶ See *Brown and Williamson*, 529 U.S. at 139; *State Farm Mut. Auto. Ins. Co.*, 463 U.S. at 43; *Perales*, 948 F.2d at 1354; *Ruckelshaus*, 719 F.2d at 1164; *Cherokee Nation*, 389 F.3d at 1087.

IV. ECONOMIC IMPACT

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

V. CERTIFICATION

Endo certifies, that, to the best of its knowledge and belief, this petition includes all information and views on which the petition relies, except as expressly stated herein, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

Endo Pharmaceuticals Inc.

By: 

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cc: Gary J. Buehler, R. Ph., Director, Office of Generic Drugs
Dale P. Conner, Pharm. D., Director, Division of Bioequivalence

Attachments