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Department of Health and Human Services
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March 12, 2012

RE: Docket No. FDA-2006-P-0346-0006 (formerly 2006P-0522)

AMENDMENT

Endo Pharmaceuticals (Endo) hereby amends the above-referenced petition pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 355), 21 C.F.R. Part 314, and 21 C.F.R. § 10.30, as described more fully below.

The issues raised in this amendment fall into two broad categories.

First, nothing has arisen since this petition was filed in 2006 to demonstrate that FDA's pharmacokinetic (PK) bioequivalence (BE) method can ensure generic lidocaine patch products equivalent to Endo's Lidoderm® (lidocaine patch 5%). On the contrary, the scientific consensus continues to be that the evidence for this approach has yet to be established:

- Since Endo filed this petition in 2006, scientific experts and FDA officials have repeatedly and publicly acknowledged that PK has not yet been validated as a BE method for drugs like Lidoderm that act in the skin. (pp. 8-10)

- Since it began recommending PK to demonstrate the BE of generics to Lidoderm in 2006, FDA's Office of Generic Drugs (OGD) has declined to discuss the method publicly and has not used PK as a BE method for any other locally acting topical drug.

- OGD has yet to advance any data demonstrating PK is sensitive enough to ensure generic lidocaine patches will replicate Lidoderm's labeled clinical effects of analgesia without complete sensory block.

- Scientific experts have delineated the additional studies needed to test whether OGD's PK hypothesis for Lidoderm generics is sufficiently accurate and sensitive to identify generic products that do not produce analgesia without complete sensory block. (pp. 13-14).

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Second, in addition to OGD's unvalidated PK method, generic applicants that claim to copy Lidoderm are also confronted with several additional issues:

- Measuring PK after only a single patch application and removal (as called for in OGD's 2007 Draft Lidocaine Guidance[1]) has not been established as clinically relevant to the actual use conditions of Lidoderm, i.e., repeated, daily patch application and removal at the same diseased skin sites. To ensure that differences in generic patch formulations do not alter drug delivery (the 2007 Draft Lidocaine Guidance permits, e.g., generic patches to be more adhesive than Lidoderm) bioequivalence testing must account for changes to the skin associated with the repeated, same-site patch application and removal actually used by Lidoderm patients. (pp. 16-24)

- FDA may have neglected to require submission of failed BE studies on generic lidocaine patches, according to at least one OGD official. This omission would have violated new FDA regulations promulgated in 2009. Without access to failed BE studies, FDA cannot make approval decisions. In addition, data integrity concerns at a contract laboratory specializing in topical BE studies underscore the importance that all data must be submitted to ensure proper FDA review of Lidoderm generics. (pp. 25-35)

- FDA has not met its legal obligation to publish bioequivalence requirements for generic copies of Lidoderm, instead only publishing nonbinding draft recommendations. Approval of generic lidocaine patches based on anything other than Orange Book-listed bioequivalence requirements would violate the law. (pp. 35-39)

- FDA may have violated multiple laws and regulations by privately answering this petition and modifying its 2007 Draft Lidocaine Guidance, as asserted by at least one generic applicant, Watson Pharmaceuticals. If FDA selectively disclosed such material facts then it has violated multiple laws and regulations, and is foreclosed from relying on the methods recommended in the draft guidance to approve Lidoderm generics. (pp. 40-42)

Based on these and other grounds described further below, Endo amends this petition to add the following Additional Actions Requested:

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[1] FDA, OFFICE OF GENERIC DRUGS, DRAFT GUIDANCE ON LIDOCAINE, p.1 (May 2007, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf [hereinafter, *2007 Draft Lidocaine Guidance*].

ADDITIONAL ACTIONS REQUESTED

Endo hereby requests that, in addition to the actions it has already requested in this petition and previous amendments thereto, FDA take the following additional actions:

I. Not review or approve any generic lidocaine patch 5% product[2] as bioequivalent to Lidoderm based in whole or in part on pharmacokinetic testing unless and until:

a. Clinical studies sufficient to validate the pharmacokinetic and pharmacokinetic/pharmacodynamic relationships for each of Lidoderm's endpoints—analgesia and absence of complete sensory block—have been conducted. Such studies should utilize simultaneous measurement of dermal and plasma concentrations, validate the linearity and dose-proportionality of dermal and plasma exposure and evaluate the dose- and concentration-response relationships of analgesia and absence of complete sensory block; and

b. A validated pharmacokinetic test demonstrates under the same repeated patch application conditions under which Lidoderm is used that drug absorption, rate and extent of drug delivery at the site of action, and rate and extent of delivery to the blood are not different between the generic lidocaine patch 5% product and Lidoderm.

II. Not review or approve any generic lidocaine patch 5% product unless and until a quality test for patch adhesion has been validated to link adhesive performance of the patch to in-use wear characteristics including site location, repeated applications to the same anatomical sites, duration of use, time between patch applications, effect of patch cutting, and changes in skin architecture under chronic use conditions.

III. Not review or approve any generic lidocaine patch 5% product unless and until a quality test for patch irritation has been validated to link patch performance to in-use wear characteristics including site location, repeated applications to the same anatomical sites, duration of use, time between patch applications, effect of patch cutting, and changes in skin architecture under chronic use conditions.

IV. Not review or approve any generic lidocaine patch 5% product unless it passes the performance tests identified in Requests II and III.

V. Not review or approve any generic lidocaine 5% patch products based on bioequivalence methods other than clinical endpoint studies unless and until such alternate methods have been validated to the satisfaction of FDA's Advisory Committees for Pharmaceutical Science and Clinical Pharmacology and Dermatologic and Ophthalmic Drugs.

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[2] The terms "generic lidocaine patch 5% product", "generic lidocaine patch product", "generic lidocaine product", "generic product" and similar terms as used herein mean any product for which FDA approval is sought in an abbreviated new drug or 505(b)(2) application which references Lidoderm®.

VI. Confirm that any abbreviated new drug or 505(b)(2) application seeking to demonstrate bioequivalence to Lidoderm (lidocaine patch 5%) must contain, and will not be reviewable or approvable unless it contains, either a summary report or a complete report of all bioavailability and bioequivalence studies[3] (including all in vivo, animal, and in vitro studies to assess the bioavailability, bioequivalence, delivery rate or penetration rate of drug into/through the skin of any test product relative to either an RLD or any other lidocaine-containing topical product) conducted during the development of the drug product, to include bioavailability and bioequivalence studies on all experimental formulations that are pharmaceutically equivalent to the formulation intended to be marketed to be the same as the RLD, Lidoderm (lidocaine patch 5%).

VII. Not review or approve any lidocaine patch 5% ANDA or 505(b)(2) application as bioequivalent to Lidoderm (lidocaine patch 5%) unless FDA has verified that all bioavailability and bioequivalence studies (including all in vivo, animal, and in vitro studies to assess the bioavailability, bioequivalence, delivery rate or penetration rate of drug into/through the skin of any test product relative to either an RLD or any other lidocaine-containing topical product) on all experimental formulations that are pharmaceutically equivalent to the formulation that is the subject of the application have been submitted to FDA. Such verification should include, but not be limited to:

a. Requesting each lidocaine patch 5% applicant to submit all bioavailability and bioequivalence studies (including all in vivo, animal, and in vitro studies to assess the bioavailability, bioequivalence, delivery rate or penetration rate of drug into/through the skin of any test product relative to either an RLD or any other lidocaine-containing topical product), including complete pharmacokinetic profiles for each study subject, conducted by or on behalf of the applicant on all formulations that are pharmaceutically equivalent to the product that is the subject of the application, and provide the names and contact information of all third parties, including but not limited to contract research organizations, that were associated with such studies;

b. Contacting any third parties, including but not limited to contract research organizations, that FDA believes or has reason to believe may have been associated with the studies described in Action Requested VII(a), and request from such third parties summaries of all such studies as described in Action Requested VII(a); and

c. Reviewing all studies conducted by Cetero Research on any lidocaine patch 5% product or experimental pharmaceutical equivalent thereof, given Cetero's particular expertise in patch products and FDA's recent concerns regarding the data

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[3] As used in this document, the term "all bioavailability and bioequivalence studies" means all studies designed and executed for the purpose of assessing the bioavailability or bioequivalence of the drug regardless of outcome, including "pilot" studies. Any failed study for which the basis for failure is in whole or part suggested to involve data integrity or other issues related to the conduct and analysis of the study should be included as part of any ANDA filing. FDA can then make an independent assessment of whether the study failed for data integrity reasons, or whether in fact the test product failed in an otherwise well-conducted study.

integrity of bioanalytical studies conducted by Cetero between April 2005 and August 31, 2009.

VIII. Obtain, if FDA concludes that a generic lidocaine patch 5% product should be approvable despite the existence of any failed bioavailability or bioequivalence studies (including all in vivo, animal, and in vitro studies to assess the bioavailability, bioequivalence, delivery rate or penetration rate of drug into/through the skin of any test product relative to either an RLD or any other lidocaine-containing topical product), the concurrence of FDA's Advisory Committees for Pharmaceutical Science and Clinical Pharmacology and Dermatologic and Ophthalmic Drugs, prior to final approval of the generic lidocaine patch application, with FDA's conclusion that the application can be approved despite the existence of such failed studies.

IX. Develop and publish an analysis of the information submitted on failed bioavailability and bioequivalence studies (including all in vivo, animal, and in vitro studies to assess the bioavailability, bioequivalence, delivery rate or penetration rate of drug into/through the skin of any test product relative to either an RLD or any other lidocaine-containing topical product) on topical and transdermal patch product ANDAs and 505(b)(2) applications and, based thereon, establish parameters for the types of formulation differences that might have a material impact on FDA's assessment of bioequivalence for patch products, including lidocaine patch 5% products.

X. Commit Generic Drug User Fee Act funds, should they become available, to determining whether plasma pharmacokinetics can be validated as a method for determining the bioequivalence of generic lidocaine patch 5% products to Lidoderm.

XI. Not review or approve any generic lidocaine patch 5% product until FDA has published bioequivalence requirements in the Orange Book for lidocaine patch 5% products and the generic lidocaine patch 5% product has demonstrated it meets such bioequivalence requirements.

XII. Confirm that since the filing of this petition in December 2006 no FDA employee has disclosed to Watson Pharmaceuticals, Inc. or any other generic lidocaine patch applicant in communications not available to the general public that anything other than clinical endpoint BE studies could be acceptable to demonstrate the bioequivalence of generic lidocaine patch 5% products to Lidoderm.

XIII. Confirm that FDA has not, in communications not available to the general public, modified the bioequivalence method described in FDA's draft bioequivalence guidance for lidocaine patch 5% products, and is not, in the review of generic lidocaine patch 5% ANDAs or 505(b)(2) applications, relying on any bioequivalence method other than the method described in the draft guidance or clinical endpoint bioequivalence studies.

XIV. Not approve any generic lidocaine patch 5% product if FDA has disclosed information to any applicant for any such product that would indicate whether or how FDA may answer this petition prior to issuing a full written response to this petition.

All parties, including patients, physicians, FDA, Endo, and ANDA applicants would benefit from a transparent, data-driven discussion of the scientific and legal bases for approval of generic lidocaine patch products. In the hope that FDA will begin this process, Endo amends this petition.[4]

I. Lidoderm® and the Complexity of Delivering Drug From Topical Patches Applied to Diseased Sites in the Skin

Lidoderm® (lidocaine patch 5%) is a patch applied to locations on the skin where patients are experiencing the pain of post-herpetic neuralgia (PHN). Patch formulations of drug products present many complexities. Indeed, Lidoderm is a particularly challenging formulation because unlike most other FDA-approved patch products, it is not a transdermal but rather designed solely to deliver active ingredient to the skin. Thus, in addition to the many challenges and uncertainties surrounding patch technologies, demonstrating bioequivalence to Lidoderm requires an evidence-based answer to the outstanding scientific issues of measuring the rate and extent of drug delivery to the site of action in the skin. This is an issue acknowledged by FDA as being shared by all locally acting topical drug products regardless of indicated use of the product.

A. FDA Has Acknowledged the Complexity of Lidoderm

FDA's Office of Generic Drugs (OGD) recognized the scientific challenge of locally acting topical products in its "Critical Path Opportunities for Generic Drugs" in May 2007. OGD generated this document to address the "scientific challenges unique to the development of generic drugs".[5] One of the scientific challenges identified by OGD as needing further investigation was the development of bioequivalence methods other than clinical studies for topical products.[6] OGD expressed the hope that:

> Based on the analysis of the mechanisms for topical drug delivery, it may be possible to identify a limited number of key factors that determine product performance and to employ this understanding in the development of rational bioequivalence standards that are much more efficient [than clinical endpoint BE studies].[7]

A month later, FDA acknowledged the "complex issues" raised in this petition regarding the demonstration of bioequivalence for generic products that reference Lidoderm. FDA

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[4] Endo recognizes that any "change in or review of the requirements for approval" of generic lidocaine patch products resulting from this petition will preclude forfeiture of the 180-day exclusivity period afforded the first ANDA applicant, in this case Watson Pharmaceuticals, Inc. (Watson). 21 U.S.C. § 355(j)(5)(D)(i)(IV).

[5] FDA, OFFICE OF GENERIC DRUGS, CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS, §1 (May 1, 2007), http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm [hereinafter, *Critical Path*].

[6] *Id.* § 4.

[7] *Id.* § 4.3.3.

explained that it had "been unable to reach a decision on [Endo's] petition because it raises complex issues requiring extensive review and analysis by Agency officials."[8]

The complex issues raised in this petition requiring FDA's "extensive review and analysis" include:

- PK has never been validated as a BE method for locally acting topical drugs
  - Numerous statements from FDA and OGD concur[9]
- The utility of PK for locally acting topical drugs is limited to a safety assessment, i.e., to ensure toxic blood levels are not reached[10]
- No data demonstrate PK is sufficiently accurate and sensitive to detect whether or not generic patches will, like Lidoderm, produce a local analgesic effect without complete sensory block[11]
- Until sufficient data are generated to validate a correlation between blood PK and clinical activity and ensure that PK is capable of discriminating between formulations with respect to both analgesia and degree of sensory block, the only scientifically justified BE approach for generic lidocaine patches will remain clinical endpoint studies[12]
- EMLA, OGD's lone approval of a locally acting topical product based on PK, is not an appropriate model for Lidoderm:[13]
  - EMLA did not include data demonstrating PK has been validated for use in assessing BE of locally acting topical drugs
  - Unlike Lidoderm, which is repeatedly applied to the same skin sites for pathological pain associated with PHN, EMLA is a single use topical cream used to prevent pain associated with dermal procedures like venipuncture and skin grafts by anesthetizing a single skin site for 3-4 hours
  - EMLA produces a complete sensory block, unlike Lidoderm, which has demonstrated the unique property of inducing analgesia without producing complete sensory block
  - OGD does not discuss or present data supporting its use of PK to approve generic copies of EMLA, including at scientific meetings where the discussion topics include alternatives to clinical endpoint BE for locally acting topical products

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[8] Letter from Jane Axelrad, CDER, to Endo Pharmaceuticals, *re: Docket No. 2006P-0522/CP1*, Docket No. FDA-2006-P-0346-0005 (Jun. 13, 2007) [hereinafter, *Axelrad Letter*].

[9] *See, e.g.,* Citizen Petition Amendment from Endo Pharmaceuticals to FDA, Docket No. 2006P-0522 (Aug. 29, 2007) pp. 8-15, 17-19 [hereinafter, *Endo August 2007 Petition Amendment*].

[10] *See, e.g., id.* at 14, 19-21.

[11] Lidoderm® Package Insert, Clinical Pharmacology, p. 1 (Apr. 2010) ("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."); *Endo August 2007 Petition Amendment* at 22-25.

[12] *See, e.g., Endo August 2007 Petition Amendment passim.*

[13] *See, e.g., id.* at 18-19, 27, Appendix C.

- At scientific meetings, OGD speakers reiterate the general rule of clinical endpoint BE for topical products and highlight vasoconstriction (skin blanching) for topical corticosteroids as the only exception to this rule[14]

B. FDA Continues to Search for Alternatives to Clinical Endpoint BE Studies for Drugs Like Lidoderm

Lacking answers to the complex questions surrounding PK and other potential alternatives to clinical endpoint BE studies for drugs like Lidoderm, FDA has, since this petition was filed in 2006, continued to seek the advice of outside experts to foster the development of science and regulation in this area. The continuing theme, as evidenced by OGD's persistent reiteration of the longstanding rule that clinical endpoint BE is required, is that most questions remain unanswered because the necessary science has yet to be developed.

For example, FDA funded work in 2007 that surveyed the level of evidence for BE methods other than clinical studies for topical drugs and concluded that:

> to evaluate the bioavailability and bioequivalence of topical drug products . . . [f]or the present . . . with the exception of the vasoconstriction assay for corticosteroids, and despite the diversity of efforts which have been made, clinical studies are obligatory.[15]

Similarly, FDA's 2009 response to a citizen petition reiterated once again that PK is not appropriate for locally acting drugs like Lidoderm:

> [F]or products that are intended to be systemically absorbed, bioequivalence is typically established by measuring the concentration of the active ingredient . . . in some biological fluid (such as blood) as a function of time. [But when a product, like Lidoderm] acts locally and is not intended to be systemically absorbed, bioequivalence must be measured by another method.[16]

As another example, in 2009 FDA asked its Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) to take the initial step of simply trying to define the many open questions and areas in need of further research and development in order to ensure appropriate regulation of patch technologies.[17] The Committee's discussion was wide-ranging and underscored the many uncertainties in this area.[18]

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[14] *See, e.g., id.* at 14-16.

[15] Christophe Herkenne, et al., *In Vivo Methods for the Assessment of Topical Drug Bioavailability*, 25 PHARMACEUTICAL RES. 87, 99 (2008). *Exhibit 1.*

[16] Letter from Janet Woodcock, CDER, FDA, to Hill Dermaceuticals, Inc., *re: Docket No. FDA-2004-P-0215*, Docket No. FDA-2004-P-0215-0038, p. 15 (Mar. 29, 2009) (emphasis added).

[17] *See* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Meeting Transcript for Topic 2: Challenges in the Development of Transdermal Drug Delivery Systems, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting, pp. 66-159 (Aug. 5, 2009).

[18] *See id.*

In 2011, two FDA experts in locally acting topical drug BE from FDA's Office of Clinical Pharmacology once again reiterated the current state of the science, i.e., that plasma pharmacokinetics cannot serve to measure bioavailability but can be useful to assess safety:

> [P]lasma levels of topically applied, locally acting agents are not reflective of true bioavailability...at the site of action. Rather, systemic absorption of topical drugs may elicit unwanted pharmacological and/or toxicological effects in unintended organ tissues and thus may raise safety concerns.[19]

Again with respect to the general difficulties of assessing the performance of patch technologies, FDA recently co-sponsored a two-day meeting devoted to improving "All Aspects of the Design, Development, Manufacturing, and Regulation of Transdermal Drug Delivery Systems."[20] The meeting announcement made clear the challenges that continue to face this field:

> The first US transdermal drug delivery system (TDDS) was approved by the FDA more than 30 years ago. Despite this length of time and the advancement of science in many other pharmaceutical fields, little has changed or evolved in the development, control and regulation of these products. Over the years, various product quality problems have been reported by patients and practitioners. Some of these quality problems have safety and efficacy implications that have led to the recall of numerous batches of products and, in some cases, the temporary or permanent removal of the product from the market.[21]

FDA again revisited bioequivalence standards for topical products such as patches in an October 2011 roundtable at the annual meeting of the American Association of Pharmaceutical Scientists (AAPS).[22] As multiple speakers made clear, with the established exception of skin blanching for topical corticosteroids, BE methodology for topical products remains limited to comparative clinical endpoint studies. Several approaches that may offer promise as alternatives to clinical endpoint bioequivalence studies for topical products were discussed, including micro-dialysis, tape stripping, in vitro release testing and in vitro skin penetration. No speaker (there were two OGD scientists on the panel), however, brought up PK as a BE method for locally acting topical products.

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[19] Seongeun Cho & Edward D. Bashaw, *Clinical Pharmacology for Development of Topical Dermatological Products: Present and Future Opportunities for Safety and Efficacy*, 89 CLINICAL PHARMACOLOGY & THERAPEUTICS 167, 167 (2011). *Exhibit 2.*

[20] FDA & THE DRUG INFORMATION ASSOCIATION, Jointly Sponsored Conference: Improved Development and Regulation of Transdermal Systems, p. 1 (Sep. 15-16, 2011). *Exhibit 3.*

[21] *Id.*

[22] AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS, Bioequivalence Standards for Topicals (BEST) Classification: Efficient Methods for Evaluating the BEST Drug Products, 2011 Annual Meeting and Exposition (Oct. 24, 2011). *Exhibit 4.*

At this roundtable, OGD's Robert Lionberger indicated that there is more work to be done to obtain FDA approval of any of these methods. The necessary data must be generated and published, and experience with the alternate methods must be gained through use in the research and development context.[23] The alternative methods must be commercially available, and gain acceptance by pharmaceutical scientists, the medical community, and patients.[24]

Finally, it bears mention that the generic drug industry also recognizes that many scientific questions regarding BE testing for topical drugs still need to be addressed. For example, in January 2012 generic manufacturers and FDA announced their joint commitment to use monies from the recently proposed Generic Drug User Fee Act (GDUFA) to fund research in this area.[25]

C. FDA Practice Since the Filing of Endo's Petition Further Confirms that Clinical Endpoint BE is Necessary for Locally Acting Topical Products

Since Endo's petition was filed, FDA has not adopted PK as a BE method for any other locally acting topical products. As explained above, pharmaceutical science has not been sufficiently developed to establish PK as a valid BE measure for drugs like Lidoderm that act locally in the skin. Indeed, since this petition was filed, FDA has recommended clinical endpoint BE studies for other topical products with local effects.[26]

In sum, the field of bioequivalence science for topical products does not appear to have developed much beyond the early stage identified by OGD in its 2007 Critical Path document. Moreover, FDA's frequent role in sponsoring and participating in scientific meetings on this topic substantiates the seriousness with which the Agency continues to view the need to address the many open questions and build on the limited information currently available regarding patch technologies and how to assess the bioequivalence of locally acting topical products. Until the many open issues have been satisfactorily addressed, there will be no scientific basis for PK or any other alternate to clinical endpoint BE for generic lidocaine patch 5% products.

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[23] AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS, Presentation by Robert Lionberger, Ph.D., FDA: Regulatory Perspective, Bioequivalence Standards for Topicals (BEST) Classification: Efficient Methods for Evaluating the BEST Drug Products, 2011 Annual Meeting and Exposition (Oct. 24, 2011). *Exhibit 5*.

[24] *Id.*

[25] FDA, Draft Letter *re: Generic Drug User Fee Act Program Performance Goals and Procedures,* p. 18, http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf [hereinafter, *GDUFA Letter*].

[26] *See, e.g.,* FDA, OFFICE OF GENERIC DRUGS, DRAFT GUIDANCE ON ADAPALENE, p.1 (Nov. 2009), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM191958.pdf; FDA, OFFICE OF GENERIC DRUGS, DRAFT GUIDANCE ON CLOTRIMAZOLE, p.1 (Mar. 2010) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204388.pdf; FDA, OFFICE OF GENERIC DRUGS, DRAFT GUIDANCE ON DICLOFENAC SODIUM, p.1 (Jan. 2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM240969.pdf.

II. Experts Have Determined the Additional Research Needed to Assess the Feasibility of Plasma PK as a BE Method for Locally Acting Topical Drugs

For topically applied drug products intended to produce effects locally in the skin (i.e., not meant for systemic absorption), clinical endpoint studies are, with one exception, the BE method of choice. This petition originally arose because OGD switched from clinical endpoint BE to the pharmacokinetic approach for generic copies of Lidoderm, as described in OGD's draft guidance for lidocaine patch 5% generic products, without data to validate the PK method for use with this locally acting topical product.[27]

A. The Biorelevance of PK Measures for the BE of Locally Acting Topical Drugs Has Not Been Established

Although topically applied drug products provide high concentrations of drug at the site of action in the epidermis and dermis, the concentrations in blood are often too low to measure. With the advent of highly sensitive mass spectrometry methods, it is now possible to measure extremely low concentrations of drugs in plasma, after the application of very high topical doses over large surface areas.

In 2006-07, OGD began signaling that systemic drug concentrations may be used to assess BE of locally acting topical lidocaine patch products.[28] However, as explained above, it is widely accepted that the relevance of systemic concentrations to the activity of locally acting topical drug products remains unknown, and these concentrations have not been correlated to those at the site of action.

One should not confuse the ability to measure systemic concentrations with the ability to measure or predict concentrations in dermal tissues or clinical activity. It cannot be assumed that, in the absence of PK/PD data, as in the case of Lidoderm, the ability to measure systemic levels after topical applications correlates with a local effect on pain and sensory receptors in the skin. Until the biorelevance of non-pharmacologic plasma concentrations is validated and correlated to local tissue concentration of drug and clinical effect, their use in BE assessments is highly suspect.

B. PK for Generic Copies of Lidoderm Fails FDA's Own Standards for Validating Topical BE Methods

Before implementation, it is important to validate any method used to predict clinical outcome of two different locally acting drug products (even if identical in potency and concentration). Historically this has been FDA's approach to validation of BE methods other than clinical endpoint studies for locally acting topical products. For example, this rigorous scientific approach was successfully applied to topical corticosteroids, and

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[27] *2007 Draft Lidocaine Guidance.*

[28] In the fall of 2006, OGD issued controlled correspondence letters outlining PK as a method for generic lidocaine patches to demonstrate BE to Lidoderm, and in 2007 FDA reissued this method in a draft BE guidance. *See 2007 Draft Lidocaine Guidance.*

resulted in the vasoconstriction assay as a generally accepted, well-established alternative to clinical endpoint BE studies for that class of locally acting topical drugs.[29]

Similarly FDA's own 1998 FDA Draft Guidance for Industry titled "Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies" (also known as the dermatopharmacokinetics guidance, hereinafter DPK Guidance) provided relevant background on bioavailability (BA) and BE issues which remains important today.[30] The DPK Guidance restated the generally accepted concept that measurement of active drug in blood "is not regarded as an acceptable measurement of BA/BE for dermatological drug products,"[31] although these levels may be used to measure systemic exposure for the purpose of assessing product safety. The guidance also emphasized the need to assess performance and validation of the method including variability (precision), dose-response, and accuracy (e.g., ability to measure a 25% difference in strength).[32]

Shah (2001) described three aspects of validation needed to provide confidence in the ability of a novel BE methodology to predict topical bioequivalence, in this case the DPK:

- Relevance to clinical efficacy
- Ability to differentiate between strengths and formulations
- Reliability and reproducibility[33]

It was further emphasized that "acceptance of any new methodology for a product approval would require information about its relevance to clinical data."[34]

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[29] *See, e.g.,* C. Herkenne, *supra* note 15 at 88 (2008). The vasoconstrictor method measures vasoconstriction in skin microvasculature, which is related to the amount of drug entering the skin and becoming available at the site of action. This PD method was approved only after years of experience and validation showed that it was accurate, precise and could discriminate effective from ineffective products. Validation of this assay method was based on an understanding of the basic PD relationships between dose and the PD response; this validation included a demonstration of linearity (dose or concentration versus response), accuracy, precision and sensitivity. Gur Jai Pal Singh, et al., *Development of In Vivo Bioequivalence Methodology for Dermatologic Corticosteroids Based on Pharmacodynamic Modeling.* 66 CLINICAL PHARMACOLOGY & THERAPEUTICS 346, 347 (1999). *Exhibit 6.*

[30] This is particularly so given that extensive data on topical lidocaine were generated as part of the DPK initiative. FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, TOPICAL DERMATOLOGICAL DRUG PRODUCT NDAS AND ANDAS—IN VIVO BIOAVAILABILITY, BIOEQUIVALENCE, IN VITRO RELEASE, AND ASSOCIATED STUDIES (Jun. 1998), http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3661b1c.pdf [hereinafter, *DPK Guidance*]. Unfortunately, the DPK Guidance was withdrawn due to concerns regarding reproducibility of the DPK methodology. *See*, Draft Guidance for Industry on Topical Dermatological Drug Product NDAs and ANDAs—In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies; Withdrawal, Notice, 67 Fed. Reg. 35122 (May 17, 2002).

[31] *DPK Guidance* at 3.

[32] *See id.* at 11-12.

[33] Vinod P. Shah, *Progress in Methodologies for Evaluating Bioequivalence of Topical Formulations*, 2 AM. J. CLINICAL DERMATOLOGY 275, 277-78 (2001). *Exhibit 7.*

[34] *Id.* at 277.

OGD's 2007 Draft Lidocaine Guidance recommends the use of systemic plasma concentration data to evaluate the bioequivalence of generic lidocaine patches to Lidoderm.[35] Since the Agency promotes science-based regulation, one would assume that this new draft guidance was based on hard scientific data validating the PK method pursuant to the standards FDA itself enunciated in the context of the DPK experience.

OGD's six-year silence, however, suggests that OGD developed the guidance in the absence of data. FDA should therefore require that OGD, before it can rely on the PK method described in the 2007 Draft Lidocaine Guidance to review or approve generic lidocaine patches, must adhere to FDA's scientific standards and publish data demonstrating the biorelevance of systemic lidocaine concentrations to clinical effectiveness, as well as data validating the method to be accurate, precise, specific, and capable of discriminating between two or more lidocaine patch formulations with respect to both of Lidoderm's two different PD endpoints. [36]

C. Recent Work Delineates the Data Needed to Validate PK as a BE Method for Generic Copies of Lidoderm

Since issuing its BE recommendation of PK for lidocaine patch products, there has been no discussion by OGD of the data, if any exist, that were relied upon as the basis for the method. Recent work by Noonan and colleagues, however, examined the validation requirements and data needed to demonstrate that systemic concentrations attained after application of a topically applied drug product will accurately predict clinical outcome in a localized tissue.[37] Pharmacokinetic and pharmacodynamic models were used as tools to demonstrate the complexity of local concentration versus response data. Care was taken to investigate assumptions leading to any conclusion of bioequivalence between a generic product and Lidoderm and that BE endpoints demonstrate that two patch products have equivalent effects on Lidoderm's two different local PD endpoints: (1) analgesic effect on pain, and (2) the absence of a complete sensory block.

This work demonstrated that the ability to discriminate between inequivalent formulations of topical lidocaine patch products requires knowledge of the accuracy and

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[35] *2007 Draft Lidocaine Guidance* at 1.

[36] It may be claimed that FDA's Office of New Drugs (OND) has endorsed PK as an appropriate BE measure for generic copies of Lidoderm. Given the insufficiency of data to support this approach, it is unclear how OND truly could have endorsed it. A full review of available data and a determination that such data validate a sufficiently sensitive correlation between plasma PK and Lidoderm's two PD endpoints of analgesia and complete sensory block would have been required, but as discussed above available evidence would not support such a determination. This is confirmed by the recent statement of OND experts that "plasma levels of topically applied, locally acting agents are not reflective of true bioavailability because they do not represent concentrations at the site of action." Cho & Bashaw, *supra* note 19 at 167 (2011).

[37] AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS, Poster by Patrick K. Noonan, Ph.D., et al.: Can Systemic Plasma Concentrations Predict Dermal Analgesia and Sensory Blockade after Topical Administration of Local Anesthetics?, 2010 Annual Meeting (Mar. 17-20, 2010). *Exhibit 8*; AMERICAN ASSOCIATION FOR PHARMACEUTICAL SCIENTISTS, Poster by Patrick K. Noonan, Ph.D., et al.: Evaluation of the FDA Draft Guidance on the BE Assessment of Topical Lidocaine Patches for Post-Herpetic Neuralgia (PHN) Using PK & PD Modeling, 2010 Annual Meeting (Nov. 14-18, 2010). *Exhibit 9.*

reproducibility of concentration versus response relationships. Among other things, to develop plasma PK as a validated BE method for generic lidocaine patches, it was shown that FDA would need to:

- Demonstrate the biorelevance of PK parameters (C_{max} and AUC) using systemic blood and dermal samples
- Establish concentration–response and/or dose-response relationships to pain ratings and sensory block at the site of application
- Evaluate the shape and variability of the:
    - Systemic and dermal concentration vs. pain relief curve, and
    - Systemic and dermal concentration vs. sensory blockade curve
- Define the separation and variability between the threshold concentrations, E_{max} and EC_{50} values for pain relief and sensory blockade
- For a stand-alone BE approach using systemic lidocaine concentrations, validate that the method is capable of discriminating between topical patches that do not provide equivalent clinical effects (i.e., pain relief and absence of complete sensory blockade)
- Validate certain assumptions on which the use of plasma concentrations to assess BE of locally acting topical drug products would rely, including:
    - that plasma and dermal PK are linear and dose proportional
    - that plasma concentrations predict relevant clinical endpoints
    - validated, sensitive, accurate and reproducible PK/PD relationships for each clinical endpoint

The work of Noonan and colleagues, by highlighting the many open issues and data insufficiencies, demonstrates that the use of systemic plasma concentrations to determine BE of locally acting, topically-applied drugs (e.g., local anesthetics and analgesics) remains an unvalidated hypothesis. Additional research in this area is required for further model development and to validate the applicability of using plasma concentrations to predict BE of locally acting compounds.

Specifically, clinical trials to verify modeling assumptions and concentration-response data are required to evaluate and validate the PK and PK/PD relationships for each clinical endpoint (i.e., pain and sensory blockade). These clinical trials should utilize simultaneous measurement of dermal and plasma concentrations, validate the linearity and dose-proportionality of dermal and plasma exposure, and evaluate the dose- and concentration-response relationships of pain and sensory blockade.

III. Europe's Requirement of Clinical Endpoint Studies for Generic Versions of EMLA Undermines PK as a BE Measure for Lidoderm Generics

Endo has previously explained how OGD's 2003 approvals of generic versions of EMLA, a topical lidocaine-containing cream for local anesthesia in the skin, were based on PK as the BE measure despite the lack of a scientific basis for this approach. As Endo explained, the PK-based approval of generic versions of EMLA required OGD management to overrule OGD's own primary reviewer, who rightly maintained that PK

was "not appropriate" and that instead a clinical endpoint BE study should be conducted.[38]

A. OGD's Discomfiture With Its Own Generic EMLA Approvals

OGD's discomfiture with the lack of science in support of its generic EMLA approvals is profound. Even while using PK to approve generic EMLAs in 2003, OGD's Director of Bioequivalence was saying publicly that PK was "not suitable" for this purpose.[39] Dr. Conner made this representation to none other than FDA's Advisory Committee for Pharmaceutical Science, and further informed the Committee that only "if we really developed this idea [of PK for topical BE] and got a lot more data, our ideas may change in this area".[40]

OGD's failure to acknowledge, let alone discuss, its use of PK to approve EMLA generics has continued to the present. In numerous presentations since approving generic EMLAs based on PK a decade ago, OGD never mentions its generic EMLA approvals or PK as a validated BE tool for approval of locally acting topical products.

OGD's silence is telling. It would be a true scientific breakthrough to have validated PK as a BE measure for locally acting topical products. If OGD really had the scientific evidence to back it up, then PK would have (and should have) become a widespread approach to demonstrating BE for locally acting topical products, and OGD would regularly raise and discuss the method at scientific meetings.

B. Clinical Endpoint BE—Not PK—Was Used for European Generic EMLA Approvals

Subsequent European experience approving EMLA generics confirms that PK is not an acceptable BE measure for locally acting topical products at the present time. Several years after OGD approved EMLA generics based on PK, Europe approved EMLA generics based on clinical endpoint bioequivalence studies.[41] In vitro skin penetration data were evaluated as part of the approval process and, in combination with adverse event reporting from the clinical study, provided the basis for evaluation of local and systemic toxicity of the generic product.[42]

If the Europeans had thought there was sufficient evidence supporting the use of PK or some other alternative to clinical endpoint BE, then presumably they would not have subjected 70 children to a clinical endpoint study just to demonstrate a generic drug was

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[38] *Endo August 2007 Petition Amendment,* Appendix C at 44-45.
[39] *Id.* Appendix C at 47.
[40] *Id.*
[41] EUROPEAN UNION, HEADS OF MEDICINES AGENCIES, PUBLIC ASSESSMENT REPORT, SCIENTIFIC DISCUSSION, TAPIN CREAM, LIDOCAINE 25 MG/G + PRILOCAINE 25 MG/G, DK/H/1520/001/MR, (Oct. 22, 2009). *Exhibit 10.*
[42] *Id.* at 4-5.

bioequivalent to EMLA. Instead, consistent with the state of the science, they determined that for the relatively less complex EMLA formulation – a cream (not a patch) used to produce local anesthesia (i.e., complete sensory block, an effect Lidoderm does not, and thus generics must be shown not to, induce) in preparation for venipuncture and superficial surgical intervention of the skin (not, like Lidoderm, treatment of chronic disease-based pain) – clinical endpoint studies were required to establish BE.

Neither PK, in vitro testing, nor any other alternative method was considered sufficiently developed to ensure the bioequivalence of this locally acting topical product. Thus the European experience with generic copies of EMLA is another confirmation that clinical endpoint studies remain the only method to demonstrate the BE of generic lidocaine 5% patches to Lidoderm.

Should OGD ever choose to end its silence, an explanation of the scientific basis for its generic EMLA approvals would be an interesting (although presumably data-light) read. In the interim, approval of generic versions of EMLA based on clinical endpoint BE in Europe reinforces the scientific isolation surrounding OGD's use of PK as a BE measure for generic versions of EMLA and subsequent 2007 Draft Lidocaine Guidance proposing the same method for Lidoderm.

IV. The Skin Irritation/Sensitization and Adhesion Methods in OGD's Draft Lidocaine Patch Guidance Enable Generic Products that are Not Bioequivalent to Lidoderm

PK is not a viable BE method for generic copies of Lidoderm, as Endo, scientific experts, FDA's own personnel (OGD and OND) and the European regulatory authorities have all made clear. But even assuming, hypothetically, that a BE method relying on PK might someday be validated as an alternate BE approach for generic lidocaine patches, it would not look like the method in OGD's 2007 Draft Lidocaine Guidance. Any eventual alternative BE method for the lidocaine patch would need to evaluate a number of patch properties as well as plasma kinetics of lidocaine following repeated patch applications to the same anatomical site(s)—i.e., the same conditions under which Lidoderm is actually used.

A. Patients Repeatedly Apply and Remove Lidoderm at the Same Skin Sites

Postherpetic neuralgia (PHN) is a complication of shingles. Most cases of shingles clear up in a few weeks, but when the pain continues after the shingles blisters clear, the condition is called PHN.[43] The pain of PHN is chronic, difficult to treat, and can last for months, years and even indefinitely.[44] Treatment of PHN is therefore focused on pain control, and pain therapy may include several interventions, including topical

[43] The Mayo Clinic, Postherpetic Neuralgia, Definition, http://www.mayoclinic.com/health/postherpetic-neuralgia/DS00277. *Exhibit 11.*

[44] *Id.*; Seth J. Stankus, et al., *Management of Herpes Zoster (Shingles) and Postherpetic Neuralgia*, 61 AM. FAM. PHYSICIAN 2437, 2441 (2000). *Exhibit 12.*

medications such as Lidoderm.[45]

Lidoderm's labeling reflects the chronic nature of the disease it treats. Lidoderm patches are repeatedly applied to, and removed from, the same skin sites over significant periods of time. Lidoderm's labeling specifies that this is to be done by applying Lidoderm patches "to intact skin to cover the most painful area . . . only once for up to 12 hours within a 24-hour period."[46] Lidoderm was evaluated for two weeks using this labeled regimen (i.e., patch application—12 hours on—patch removal—12 hours off—patch re-application, etc.) and determined to be effective for "[t]he constant type of pain" associated with PHN.[47]

Importantly, the adhesiveness, or "tack", of the Lidoderm patch is sufficiently gentle such that it does not irritate the sensitive, damaged PHN skin sites where patients repeatedly apply it. Nor does repeated daily patch application and removal result in increased systemic levels of lidocaine that might be associated with increased toxicity. Rather, with Lidoderm it has been shown in clinical trials and post-approval use that both clinical outcome and safety are unaffected by repeated patch applications, including for multi-year periods.[48]

In sum, the ability to repeatedly apply and remove the Lidoderm patch and maintain the safety and efficacy of the product for the treatment of chronic pain associated with PHN is a relevant property of Lidoderm. Consequently, this property must also be demonstrated by any generic product in order for it to be considered equivalent to Lidoderm.

B. OGD's 2007 Draft Lidocaine Guidance Permits Generic Patch Formulations to Differ from Lidoderm, But Does Not Assess Whether Repeated Same Site Application Will Render Generic Lidocaine Patches BioINequivalent

OGD's 2007 Draft Lidocaine Guidance permits generic lidocaine patches to be deemed BE to Lidoderm based on plasma PK in healthy volunteers who apply patches for a single

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[45] S. Stankus, et al., *supra* note 44 at 2441 (2000).

[46] Lidoderm®, Package Insert, Dosage and Administration, p. 2 (Apr. 2010); *see also*, Lidoderm®, Package Insert, Indications and Usage, p. 1 (Apr. 2010) (Lidoderm "should be applied only to **intact skin**") (emphasis in original); Lidoderm® Package Insert, Clinical Pharmacology, Pharmacodynamics, p. 1 (Apr. 2010) ("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."). Without multiple applications, it is unknown whether a more adhesive generic patch would make the skin no longer intact. By contrast, this has not been an issue with Lidoderm during years of use in PHN patients. Bradley S. Galer, et al., *More Then 7 Years of Consistent Neuropathic Pain Relief in Geriatric Patients*, 163 ARCHIVES INTERNAL MED. 628 (2003). *Exhibit 13*.

[47] Lidoderm® Package Insert, Clinical Studies, p. 1 (Apr. 2010).

[48] *See e.g.,* Lidoderm® Package Insert, Clinical Pharmacology: Pharmacokinetics (Apr. 2010); Arnold R. Gammaitoni & Matthew W. Davis, *Pharmacokinetics and Tolerability of Lidocaine Patch 5% with Extended Dosing,* 35 ANNALS PHARMACOTHERAPY 236, 238 (2002), *Exhibit 14*; A.R. Gammaitoni et al., *Safety and Tolerability of the Lidocaine Patch 5%, a Targeted Peripheral Analgesic: A Review of the Literature,* 43 J. CLINICAL PHARMACOLOGY 111 (2003). *Exhibit 15*; B. Galer, *supra* note 46 at 628 (2003).

12 hour period.[49] Thus OGD assumes blood levels seen after a single use will accurately represent blood levels seen under the repeated, daily, same site application and removal conditions under which patients actually use the Lidoderm patch. OGD does not offer data in support of or otherwise seek to justify this extrapolation. OGD's data-free extrapolation is flawed.

1. Patch Adhesion Differences Can Change Bioavailability and Therefore Bioequivalence

It is well-established that disruption in the stratum corneum (the primary barrier to drug absorption across the skin) can increase permeability to chemicals.[50] Removal of multiple cell layers can increase total absorption. Clinical trials have shown that skin stripping prior to application of EMLA topical cream (which contains the same active ingredient as Lidoderm) leads to a modest increase in the effectiveness of EMLA for relieving the pain associated with venipuncture.[51]

The amount of stratum corneum removed by skin stripping is highly variable depending on the adhesive, the user, and the speed/strength of removal.[52] This variability is evident in the literature addressing the use of skin stripping as a method of establishing BE for topical products (dermatopharmacokinetics—DPK).[53]

At the September 2011 FDA/DIA meeting, H. Michael Wolff, the Director/Science Expert for UCB Biosciences, alluded to this issue. He specifically addressed the potential of a stronger adhesive damaging the skin and affecting overall drug absorption in a transdermal patch.[54]

These same factors would contribute to skin barrier disruption and irritation associated with use of a topical lidocaine-containing patch. In the absence of adhesion testing demonstrated to be sensitive enough to detect small differences in adhesion between lidocaine patch products that could alter the bioavailability and therefore the BE of a generic patch following repeated same-site application, BE could only be established

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[49] *2007 Draft Lidocaine Guidance* at 1.

[50] *See, e.g.,* Eva Benfeldt et al., *Effect of Barrier Perturbation on Cutaneous Salicylic Acid Penetration in Human Skin: In Vivo Pharmacokinetics Using Microdialysis and Non-Invasive Quantification of Barrier Function*, 140 BRIT. J. DERMATOLOGY 739 (1999). *Exhibit 16.*

[51] Adam J. Singer et al., *Cutaneous Tape Stripping to Accelerate the Anesthetic Effects of EMLA Cream: a Randomized, Controlled Trial*, 5 ACAD. EMERGENCY MED. 1051 (1998). *Exhibit 17.*

[52] C. Herkenne et al., *supra* note 15 at 91 (2008).

[53] *See e.g.,* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Meeting Transcript, Advisory Committee for Pharmaceutical Science Meeting, pp. 31-61 (remarks of Lynn Pershing and Tom Franz regarding the "bioequivalence assessment of three 0.025 percent tretinoin gel products" with the DPK method) (Nov. 29, 2001); W.L. Au et al., *Comparison of Tape Stripping with the Human Skin Blanching Assay for the Bioequivalence Assessment of Topical Clobetasol Propionate Formulations,* 13 J. PHARMACY PHARMACEUTICAL SCI. 11 (2010). *Exhibit 18.*

[54] DRUG INFORMATION ASSOCIATION, Presentation by H. Michael Wolff, UCB Biosciences: Quality and Safety of TDDS: Formulation Aspects, Improved Development and Regulation of Transdermal Systems Meeting (Sep. 15, 2011). *Exhibit 19.*

using PK if the test were conducted following multiple applications and removal of a patch applied to the same anatomical sites.

2. OGD Permits Generic Lidocaine 5% Patches to Have Greater Adhesion than Lidoderm without Considering the Effect on Bioequivalence Associated with Repeated Same Site Applications

OGD's 2007 Draft Lidocaine Guidance permits approval of generic patches as equivalent to Lidoderm even though they adhere more strongly to the skin. The 2007 Draft Guidance permits generics to be considered equivalent to Lidoderm based on a "single application" of the patch.[55] After that single application, the generic patch "must adhere at least as well as" Lidoderm.[56] The "at least as well as" standard thus permits generic patches which adhere more strongly than Lidoderm.

OGD's draft adhesion test is designed to document that a generic lidocaine 5% patch does not detach more than Lidoderm. It is insensitive to the effect of repeated patch application on the barrier function of the skin. Consequently it would fail to differentiate generic patches which, under the cumulative effect of repeat application and removal from the same anatomical sites, result in a different degree of disruption (including irritation) to the stratum corneum and the consequent difference in drug absorption across the skin.

OGD's test also ignores the potential for repeated patch application to the same anatomical site to decrease adhesion of subsequently applied patches. This could include changes to the skin associated with repeated patch removal (e.g., changes in hydration of the skin) or deposition of adhesive residue, resulting in increased patch detachment and the potential loss of efficacy.

3. Transdermal Patch Experience Demonstrates the Importance of Assessing the Effect of Repeated Patch Applications on Drug Bioavailability and Bioequivalence

Differences in drug absorption induced by differences in patch formulation over repeated application can have serious negative effects on patients. Previous experience with transdermal patches makes this clear.

For example, it has been well documented in the case of fentanyl patches that formulation differences between RLD and generic patches resulted in differences in the amount of drug absorption associated with repeated same-site application of the patch. Differences in adhesives between products and irritation associated with repeated same site application of the patch were thought to contribute to this observation.[57] The solution to

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[55] *2007 Draft Lidocaine Guidance* at 4.

[56] *Id.*

[57] *See, e.g.,* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, APPROVAL PACKAGE FOR FENTANYL TRANSDERMAL SYSTEM, ANDA No. 76-258 (Nov. 21, 2003), Memorandum from Sharon Hertz, Medical

this problem was to require rotation of the patch application site:

> *Remove a DURAGESIC® patch after wearing it for 3 days (72 hours) (see Disposing a DURAGESIC® Patch). Choose a **different** place on the skin to apply a new DURAGESIC® patch...Do not apply the new patch to the same place as the last one.*[58]

The labeling for many transdermal patch products contains similar language warning against repeated patch applications on the same skin site.[59] For example:

> Methylphenidate patches: *Apply Daytrana to a different hip each day.*[60]

> Clonidine patches: *After one week, remove the old patch and discard it...After choosing a different skin site, repeat instructions...for the application of your next CATAPRES-TTS patch.*[61]

In sum, many transdermal patches must be applied to new skin sites every time a new patch is applied.

Patch rotation, however, is not an option with Lidoderm. Lidoderm patches must be applied repeatedly to the skin sites where PHN pain occurs. This has implications for assessing whether generic products are BE to Lidoderm. As the use of Lidoderm does not allow for rotation of the application site because patches are applied repeatedly to the same painful sites in the skin, any BE methodology must account for changes in drug absorption that could occur as a result of repeated same site patch application.

Officer, Division of Anesthetic, Critical Care, and Addiction Drug Products, FDA, pp. 4-5 (Aug. 15, 2002) ("The differences in frequency of these adverse events between the Duragesic and Mylan patches may have been due to a [sic] either a difference in bioequivalence, or alternatively, reflected a greater degree of enhanced bioavailability due to local skin irritation.") and Recommendations for Skin Irritation and Sensitization Studies for Generic Fentanyl Transdermal Systems from Dena Hixon, Associate Director for Medical Affairs, OGD, FDA, p. 4 (Sep. 18, 2002) ("The data submitted...demonstrated that repeated same-site applications of the lowest approved dose of Duragesic transdermal system, 25 μ g/hr, may produce dangerously high serum fentanyl levels despite Naltrexone blockade. This may be due at least in part to increased absorption of fentanyl in skin that is irritated by the repeated same-site applications.").

[58] Duragesic® Medication Guide, Instructions for Applying a Duragesic Patch, p. 5 (Jul. 2009) (emphasis in original).

[59] *See, e.g.,* Duragesic® Package Insert, Information for Patients, p. 4 (Jul. 2009) ("each patch should be applied on a different skin site from the previous location"); Catapres-TTS® Package Insert, Dosage and Administration, p. 13 (Apr. 2010) ("Each new application of Catapres-TTS transdermal therapeutic system should be on a different skin site from the previous location"); Daytrana® Package Insert, § 2.1: Dosage and Administration, Application, p. 4 (Oct. 2010) ("place on the opposite hip at a new site if possible"); Exelon® Package Insert, Patient Information, p. 17 (Aug. 2010) ("Change your application site every day to avoid skin irritation.").

[60] Daytrana® Medication Guide, How Should I Use Daytrana?, p. 3 (Oct. 2010).

[61] Catapres-TTS® Patient Instructions, p. 12 (Apr. 2010).

4. OGD Has Not Established Standards for Patch Adhesion, Irritation, or Sensitization

OGD's 2007 Draft Lidocaine Guidance is tentative; even if finalized it would only represent OGD's "current thinking".[62] For patch adhesion, irritation, and sensitization, the draft guidance reflects the significant level of uncertainty and open questions regarding how best to assess these parameters for topically applied patches.

As the 2007 Draft Lidocaine Guidance indicates, OGD has withdrawn its *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products,* a document originally issued in 1999.[63] Nonetheless, OGD's recommendations in the 2007 Draft Lidocaine Guidance for skin irritation, sensitization, and adhesion testing are largely based on this withdrawn guidance, and reflect the uncertainties that led to its withdrawal.

In the withdrawn guidance, OGD recognized the need to fully evaluate skin irritation and sensitization caused by generic drugs as compared to an RLD because "the condition of the skin may affect the absorption of a drug from a transdermal system".[64] The methodologies and study designs for assessing irritation and sensitization recommended by OGD for use in evaluation of generic transdermal drugs were based on the assumption that testing represents "conditions of maximal stress" and therefore provides the most sensitive scenario for detecting differences between the RLD and generic product with respect to irritation and sensitization.[65]

For generic lidocaine 5% patches, however, "conditions of maximal stress" are not ensured. Clinical use of Lidoderm entails repeated, daily application of the patch to the same anatomical sites for a period of several weeks or longer in a 12 hour on/off cycle, but OGD permits PK assessment for BE after only a single 12 hour patch application.[66] Similarly, for irritation, OGD recommends continuous patch wear for three weeks, with the patch replaced three times per week followed by a two-week rest period and a single 48 hour challenge for sensitization testing. This methodology is insensitive to how the repeated same site application and removal of the patch at 12-hour intervals might disrupt the architecture or barrier function of the skin and lead to changes in drug absorption over time or exacerbate irritation or sensitization associated with actual use conditions of Lidoderm.

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[62] *2007 Draft Lidocaine Guidance* at 1 ("This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternate approach if the approach satisfies the requirements of the applicable statutes and regulations.").

[63] *Id.* at 6.

[64] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, SKIN IRRITATION AND SENSITIZATION TESTING OF GENERIC TRANSDERMAL DRUG PRODUCTS, p. 1 (Dec. 1999) http://www.fda.gov/ohrms/dockets/98fr/990236Gd.pdf.

[65] *Id.*

[66] *2007 Draft Lidocaine Guidance* at 1.

Adding to the uncertainty is the fact that OGD does not appear to know how to analyze the data from these studies to reach a bioequivalence determination. This is characterized by OGD's statement in the 2007 Draft Lidocaine Guidance that OGD is "currently evaluating the appropriate statistical tests that should be used to analyze clinically meaningful differences between products with regard to skin irritation, sensitization and adhesion".[67]

Absent data demonstrating that the studies recommended in OGD's 2007 Draft Lidocaine Guidance would discriminate between different formulations on parameters of adhesion, irritation, and sensitization under actual use conditions, there is little basis for the extrapolation of these withdrawn transdermal tests for use in establishing BE of a lidocaine patch product.

C. OGD's Option to Combine Study Adhesion Together with Irritation and Sensitization Further Demonstrates the Flaws in OGD's Approach

In addition to the stand-alone single patch application adhesion test, OGD's 2007 Draft Lidocaine Guidance also provides that generic lidocaine patch 5% applicants may study adhesion during the irritation/sensitization study. For this combination study, OGD recommends that:

> One-fourth of a test patch and one-fourth of the reference patch should be applied to the same individuals simultaneously for 21 days during the induction phase of the study. The patches should be applied continuously to the same sites and replaced with a new one-fourth patch three times weekly.[68]

and then follows that:

> Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate for the intended induction of skin irritation and sensitization...[69]

The adhesion properties of generic lidocaine patches will fail to match the reality of chronic Lidoderm use unless they demonstrate equivalence to Lidoderm with an appropriate test mimicking the continued application of Lidoderm to the same site(s). Following the above protocol would not accurately address this, as Lidoderm is labeled for 12 hours of patch application followed by a 12-hour rest period, followed by repetitive reapplications to the same site.

The above recommendations would not accurately reflect any changes to the skin from the repeated removal and reapplication of a new patch every 24 hours, as there may be

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[67] *Id.* at 6.
[68] *Id.* at 2.
[69] *Id.* at 4.

changes in the patch adhesion if patches are applied repeatedly to the same skin area. This may be due to variation in skin hydration brought about by the previous patch application before a new patch is applied to the same skin site, trace residue deposition, or other perturbations to the skin over repeated use that impact adhesion of subsequently applied patches.

OGD's 2007 Draft Lidocaine Guidance further provides:

> Cutting patches to a smaller size is likely to change the shape as well as the size of the patch and may change adhesive performance of the patch. Therefore, adhesion data may not be adequate to demonstrate that your to-be-marketed patch adheres as least as well as the RLD. Therefore, you should consider collecting adhesion data during your PK bioequivalence study...[70]

However, the Lidoderm package insert makes clear that "patches may be cut into smaller sizes with scissors".[71] The specific adhesive properties of Lidoderm include the property that cutting the patches is an acceptable method of applying the patch. Any generic lidocaine patch should have similar adhesive properties when cut into smaller pieces in order to be equivalent to Lidoderm.

The final adhesion recommendation in OGD's 2007 Draft Lidocaine Guidance is to collect the adhesion data concurrently during the PK bioequivalence study.[72] As mentioned above, the PK bioequivalence study as suggested will not accurately portray bioequivalence. If the adhesion study is done concurrently with a PK study, adhesion should at the very least be assayed to ensure that changes to skin properties from repeated skin stripping and exposure do not adversely affect the adhesive properties of a patch. However, if an "at least as well as"[73] metric were employed in this regard, the issue of variance from skin stripping due to relatively greater adhesion of a generic patch would not be reflected. The only accurate way to ensure that the relative adhesive strengths of two patches do not significantly alter BE is to perform a clinical endpoint study.

D. OGD's Guidance Lacks Guidelines for Anatomical Placement of Generic Lidocaine Patches

The 2007 Draft Lidocaine Guidance contains no specifications for the location of patch application, and does not specify whether differing sites should be tested to ensure adhesion is consistent regardless of anatomical placement.

Lidoderm, however, is a locally acting topical patch, and as such, the application of the patch is dependent on the site of pain. Adhesion and drug absorption can be dependent on the site of application due to variations in skin hydration and stratum corneum

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[70] *Id.*
[71] Lidoderm® Package Insert, Dosage and Administration, (Apr. 2010).
[72] *2007 Draft Lidocaine Guidance* at 4.
[73] *Id.*

thickness.[74] As discussed above, repeated application of lidocaine patches to differing anatomical locations may disrupt skin architecture differently and exacerbate differences in both drug absorption and patch adhesion. For example, a generic patch may adhere "at least as well as" Lidoderm in one anatomical location, even after repeated exposure, but not in another.

E. If PK Were a Valid Method for Lidocaine Patch BE, it would Include Multiple Same Site Patch Applications

As explained in Endo's previous filings to this petition, Lidoderm is a unique lidocaine-containing product providing two clinical responses: (1) analgesia (2) without complete sensory block. It is postulated that lidocaine delivered from the Lidoderm patch accumulates in the dermis or epidermis of PHN patients where it acts on the dermal pain receptors.[75] As Lidoderm was tested for chronic use, and has been continually used for more than a decade, it is clear that repeated same-site application does not affect the two clinical responses.

As discussed above, if a generic patch does not have the same adhesive strength and skin stripping properties as Lidoderm, then drug absorption across the skin may be altered, and this difference would become more significant as a function of application/removal cycles. This is another basis (in addition to the other grounds Endo has advanced in this petition) for concluding that the PK measurement recommended in the 2007 Draft Lidocaine Guidance is deficient. Only a repeat exposure test mimicking real world usage would ensure that levels of lidocaine achieved by generic patches are the same as those found with Lidoderm and as a consequence, analgesic efficacy without complete sensory block is maintained with generic products.

Moreover, if patients are unaware that a generic version of Lidoderm could cause complete sensory block with chronic use, they may be harmed by unknowing, inadvertent trauma. Because currently there is no demonstrated correlation between plasma levels of lidocaine and Lidoderm's two independent clinical effects, any repeat exposure comparison assessing the bioequivalence of generic products to Lidoderm should be performed using clinical trials.

Generic lidocaine patch products should not be approved until the impact of differences between generic and RLD formulations that could alter bioavailability of the drug at the site of action as a function of repeat patch application to the same skin site have been fully characterized and justified. Specifically, the changes in skin architecture from repeated removal and reapplication of the Lidoderm patch under conditions of actual use and their role in irritation, adhesion and drug delivery should be investigated further, as discussed above.

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[74] Lyn Margetts & Richard Sawyer, *Transdermal Drug Delivery: Principles and Opioid Therapy,* 7 CONTINUING EDUC. ANESTHESIA CRITICAL CARE & PAIN 171 (2007). *Exhibit 20.*

[75] FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, APPROVAL PACKAGE FOR LIDODERM, NDA No. 20-612 (Mar. 19, 1999), Medical Officer's Review from Rosemarie Neuner, Clinical Reviewer, Division of Anesthesia, FDA, p.5 (Oct. 11, 1996).

V. No Generic Lidocaine Patch Product will be Approvable until All of Its Failed Bioavailability and BE Studies Have Been Submitted and Analyzed

In 2009 FDA began requiring submission of failed BE studies on ANDA products. However, OGD's implementation of the requirement to submit failed BE studies has lagged with respect to topical products like generic copies of Lidoderm. Moreover, a contract research organization specializing in BE studies for topical products has recently experienced serious data integrity issues. Consequently, it is critical both that FDA hold lidocaine patch ANDA applicants to FDA's new regulations requiring submission of all failed BE studies and analyze those studies as part of ANDA reviews in order to avoid improper ANDA approvals.

A. FDA Regulations Now Require Generic Applicants to Submit All Bioavailability and Bioequivalence Studies

New drug application (NDA) sponsors traditionally have been required to submit to FDA the results of failed studies on their drug product candidates, including failed bioavailability and bioequivalence studies.[76] Thus, applicants under section 505(b)(2) of the FDCA seeking approval of lidocaine patch 5% products are required to submit all of their BA and BE studies, both passing and failed.

In recent years, FDA promulgated regulations extending to ANDA sponsors the requirement to submit all BA and BE studies.[77] ANDA sponsors are now required:

> to submit data from all BE studies the applicant conducts on a drug product formulation submitted for approval, including studies that do not demonstrate that the generic product meets the current bioequivalence criteria.[78]

For complex dosage forms like the lidocaine patch 5%, FDA construes the requirement for submission of all BA and BE studies to encompass:

> submission of either a summary report or a complete report of all bioavailability or bioequivalence studies conducted during the development of the drug product.[79]

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[76] 21 C.F.R. § 314.50(d)(3). As FDA noted when it promulgated the regulations requiring ANDAs to contain all BA and BE studies, "NDA applicants and NDA holders are already required to submit failed BE studies. Section 314.50(d)(3) of FDA regulations requires an NDA to contain a description of all bioavailability and pharmacokinetic studies in humans performed by or on behalf of the applicant. The requirement to submit bioavailability studies includes reports of any bioequivalence studies performed by or on behalf of the applicant." Requirements for Submission of Bioequivalence Data, Final Rule, 74 Fed. Reg. 2849, 2852 (Jan. 16, 2009).

[77] Requirements for Submission of Bioequivalence Data, Final Rule, 74 Fed. Reg. 2849 (Jan. 16, 2009); Requirements for Submission of Bioequivalence Data, Proposed Rule, 68 Fed. Reg. 61640 (Oct. 29, 2003).

[78] FDA, OFFICE OF GENERIC DRUGS, DRAFT GUIDANCE FOR INDUSTRY, SUBMISSION OF SUMMARY BIOEQUIVALENCE DATA FOR ANDAS, p. 1 (Apr. 2009), http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2009-D-0126-gdl.pdf, citing Requirements for Submission of Bioequivalence Data, Final Rule, 74 Fed. Reg. 2849 (Jan. 16, 2009).

The reason FDA requires submission of all BA and BE studies for complex dosage forms is because:

> limited information is available regarding quantitative and qualitative changes that could have a significant impact on the bioavailability of the product. Because of this lack of information, [FDA] consider[s] all experimental formulations that are pharmaceutically equivalent to the formulation of the complex dosage form product intended to be marketed to be the same as the RLD.[80]

In sum, FDA has extended the longstanding requirement for NDA applicants to submit all BA and BE studies to ANDA applicants as well. Any ANDA applicant seeking to demonstrate bioequivalence to Lidoderm must submit all bioequivalence studies on both the formulation for which it seeks marketing approval, and any pharmaceutical equivalents to that product.

B. Without Failed BE Studies, FDA Cannot Approve Generic Products

FDA needs all failed BE studies in order to make ANDA approval decisions informed by the totality of the available evidence. To achieve this goal, FDA decided to change its regulations and require generic drug applicants to submit failed BA and BE studies because such applicants had "generally not submitted the results of the nonpassing study or studies to FDA".[81] By changing its regulations to require submission of all BA and BE studies, FDA ended the former practice where:

> ANDA applicants [were] only required to submit one BE study (or two, if a fed study is required). Based on one or two studies, FDA might conclude that the product is bioequivalent to its RLD. If the agency receives other BE studies conducted by the applicant, and these studies failed to show bioequivalence, the agency might make a different decision about whether to approve the ANDA than it would have if the agency had received only the passing study. In such a case, receipt of additional BE studies will be critical to FDA's determination as to whether a generic product is equivalent to its RLD.[82]

In sum, without failed BE studies, FDA cannot approve generic products. To be approvable, generic products must demonstrate bioequivalence.[83] And "[u]nless FDA

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[79] FDA, OFFICE OF GENERIC DRUGS, GUIDANCE FOR INDUSTRY, SUBMISSION OF SUMMARY BIOEQUIVALENCE DATA FOR ANDAS, p. 9 (May 2011) (emphasis added), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf.

[80] *Id.* at 9. By asking for a much wider scope of information than it requests for orally administered, systemically absorbed products, FDA highlights the high level of uncertainty around locally acting BE; pharmaceutical science has yet to develop for locally acting drugs anything akin to the limited parameters of Cmax and AUC established (based on extensive evidence and experience) for oral systemic drugs.

[81] Requirements for Submission of Bioequivalence Data, Final Rule, 74 Fed. Reg. 2849, 2850 (Jan. 16, 2009).

[82] *Id.* at 2851.

[83] 21 U.S.C. § 355(j)(2)(A)(iv).

receives all BE studies on the same drug product formulation, it is not possible for the agency to make an informed, scientifically based decision about bioequivalence."[84] Thus, absent submission to FDA of all failed BA and BE studies on experimental formulations that are pharmaceutically equivalent to each generic lidocaine patch 5% product intended to be marketed to be the same as Lidoderm, no such products can be approved.

C. FDA is Not Enforcing the Failed Studies Rule

Unfortunately, FDA's regulations and guidance do not provide adequate assurance that failed BA and BE studies will actually be submitted. In the preamble to its final rule requiring ANDAs to contain all BA and BE studies, FDA stated that no additional enforcement mechanism was necessary because (1) no such mechanism was provided to enforce the requirement for submission of failed BA/BE studies for NDAs; (2) noncompliance might be considered a violation of the 18 U.S.C. § 1001 prohibition on making misstatements of material fact to the government; and (3) FDA "has a variety of different enforcement and oversight mechanisms that [it uses] to ensure compliance with data submission requirements."[85]

These assurances are insufficient, particularly in light of FDA's past statements and recent findings.

First, the analogy to NDAs is imperfect because it fails to account for the more robust NDA data package versus the relatively modest dossier of an ANDA. Without controlled clinical safety and efficacy studies, bioequivalence studies furnish the principal data basis for approval of an ANDA product as safe and effective. BE studies, therefore, are more salient and critical for ANDAs than they are in the NDA context. Because the BE requirement for ANDAs essentially takes the place of – rather than supplements – full clinical safety and effectiveness data, there is a greater need in the ANDA context to ensure that an applicant's asserted demonstration of bioequivalence is valid and reliable.

Second, reliance on 18 U.S.C. § 1001 is unlikely to enhance compliance to an acceptable level. Although the preamble to FDA's new rule requiring submission of failed studies in ANDAs states that "in certain circumstances" noncompliance "could be considered" a violation of 18 U.S.C. § 1001, the prohibition on making untrue statements existed prior to FDA's new rule requiring ANDAs to include failed BE studies but, as FDA has conceded, did little to ensure that ANDA applicants would submit their failed studies.

Indeed, before the new rule requiring ANDAs to contain failed BE studies, OGD's Director of Bioequivalence Dale Conner had already stated publicly that under the FDCA's prohibition on untrue statements of material fact, selective reporting of only positive data is not acceptable, and failure to report failed studies could constitute

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[84] Requirements for Submission of Bioequivalence Data, Final Rule, 74 Fed. Reg. 2849, 2851 (Jan. 16, 2009).
[85] *Id.* at 2856.

selective reporting.[86] However, Dr. Conner also indicated that this was merely a "legal opinion" presented by FDA lawyers to OGD as "things to think about" and represented "one way of thinking" about the issue.[87] Similarly, while FDA's new failed studies rule indicates that selective reporting *could* violate the prohibition on material misstatements of fact, it does not provide any increased certainty of its applicability beyond Dr. Conner's speculative statements.

Third, FDA's assertions about the effectiveness of its existing enforcement mechanisms to ensure compliance with data requirements are not substantiated by FDA's own public statements. By FDA's own admission, ANDA sponsors generally did not submit failed study information prior to the final rule. As Dr. Conner stated in 2000, "it is more than often, it is most of the time they choose not to submit these studies."[88] The failure of voluntary submission of failed BE studies meant that "[o]ftentimes or most of the time, the FDA [was] blissfully ignorant of the existence of these studies."[89]

D. Despite the New Rule, Few Failed Studies Are Being Submitted to FDA

FDA's blissful ignorance of failed BE studies does not appear to have changed, despite the new rule requiring submission of all bioavailability and BE studies. A June 2011 FDA analysis of failed BE studies submitted under the new rule indicates that while roughly 800 ANDAs were approved during the first two years since the rule became effective, only 40 ANDAs included information on failed BE studies. Moreover, these 40 ANDAs accounted for a total of 73 failed studies, with a range of 1 to 11 studies per ANDA.[90]

"Blissful ignorance" is indeed the appropriate term to describe any notion that only some 40 out of 800 ANDA products – roughly five percent – failed a BA or BE study. Anyone familiar with pharmaceutical development would be hard-pressed to accept the notion that 95% of ANDA products avoided a BA or BE test failure in the course of their development, even excluding studies on formulations that are not the "same" as the to-be-marketed formulation (as is permitted for non-complex drug products).[91]

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[86] *See* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Meeting Transcript, Advisory Committee for Pharmaceutical Science and Advisory Committee for Ophthalmic Drugs Joint Meeting, pp. 187-88 (remarks of Dale Conner) (Nov. 16, 2000) [hereinafter, *Joint Advisory Committee Meeting*].

[87] *Id.* at 187, 201.

[88] *Id.* at 185.

[89] *Id.*

[90] OMICS GROUP CONFERENCES, Presentation by Ethan Stier, Ph.D., OGD, 2nd World Congress on Bioavailability and Bioequivalence, (Jun. 6, 2011) [hereinafter, *2nd World Congress on BA and BE*]. *Exhibit 21.*

[91] Information from failed BE studies is particularly important given heightened concerns about manufacturing compliance by generic drug manufacturers and a general skepticism about generic drug quality and safety. FDA's discovery of "significant deviations from U.S. Current Good Manufacturing Practice (cGMP) Regulations" at two of Ranbaxy's biggest plants revealed that voluntary compliance with applicable regulations may be inadequate to ensure that all drugs are safe and effective. *See* Warning Letter from Richard Friedman, FDA, to Malvinder Mohan Singh, CEO and Managing Director, Ranbaxy Laboratories Limited (Sept. 16, 2008), http://www.fda.gov/ICECI/EnforcementActions/

Three months after reporting that only 5% of ANDAs include failed BA or BE studies, OGD authors presented a poster that analyzed the reasons why the failed studies that were submitted had failed.[92] The lead author stated the poster did not include ANDAs for topical dosage forms, such as ANDAs seeking to copy the Lidoderm patch.[93] He also indicated that topical products are not subject to the failed BE studies rule. This plainly inaccurate statement may indicate a belief that the rule only requires submission of failed BE studies on solid oral dosage forms intended for systemic distribution, which of course is not true.

The OGD author's comments are nonetheless disturbing. If in fact OGD is not applying the rule requiring submission of failed BA and BE studies to generic products – like ANDAs referencing Lidoderm – because they are not solid oral dosage forms for systemic distribution, then OGD is misapplying FDA's regulations. Consequently, this petition amendment contains new Actions Requested designed to ensure that OGD correctly applies FDA's new Failed Bioequivalence Studies rule to all ANDAs, including ANDAs referencing Lidoderm.

E. FDA Should Track Both ANDA Applicants and Contract Research Organizations to Ensure Submission of All Lidocaine Patch 5% Bioequivalence Studies

FDA's inspection process is not equipped to uncover withheld BE study information. OGD's Dr. Conner made this plain in recounting how one ANDA sponsor failed to submit a BE study report that would have prevented approval had FDA known of it. In fact, the existence of the failed study came to light only due to probing from foreign regulatory agencies from which the ANDA sponsor was also seeking approval.[94] FDA's ignorance of the data led FDA to approve the ANDA, while the subsequent revelation of a failed BE study prompted remedial regulatory action.

WarningLetters/2008/ucm1048134.htm. Ranbaxy was subsequently barred from importing 30 drug products into the U.S., and FDA was forced to impose further, more severe restrictions due to evidence of falsified data, when it invoked its Application Integrity Policy on one of the two plants, halting review of all pending or future drug applications that rely on data generated by the plant. *See* Letter from Janet Woodcock, CDER to Malvinder Mohan Singh, CEO and Managing Director, Ranbaxy Laboratories Limited (Feb. 25, 2009), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm118418.pdf.

[92] AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS, Presentation by Patrick E. Nwakama, Devrat T. Patel, Ethan Stier, Dale P. Conner, and Barbara M. Davit, OGD: The Regulatory Impact of Failed Studies in Bioequivalence Determination: A Review of Abbreviated New Drug Applications (ANDAs) Submitted after Implementation of the "All BE Studies" Rule, 2011 Annual Meeting and Exposition (Oct. 23-27, 2011). *Exhibit 22.*

[93] AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS, Discussion between Patrick E. Nwakama and petitioner's outside counsel, 2011 Annual Meeting and Exposition (Oct. 23-27, 2011).

[94] *See Joint Advisory Committee Meeting* at 218 (remarks of Dale Conner) ("An inspector, unless they were rifling through everyone's file cabinets in the company, would never have found that even by chance probably. You know, the sponsor, for a variety of reasons, finally submitted it to us based on some requests from foreign regulatory agencies, I believe, and they discovered it again and decided to do the right thing and submit it. That is how we found out about it.").

FDA's new rule requiring submission of all BA and BE studies in ANDAs will remain a paper tiger unless failed studies are actually submitted. More importantly, as FDA itself stated when promulgating the new rule, without submission of all BA and BE studies, FDA won't be able to make bioequivalence decisions – or, consequently, approve generic drugs.[95]

Thus, to continue approving ANDAs, FDA needs to ensure that all BA and BE studies are submitted. To facilitate this process in the case of generic applicants seeking to demonstrate BE to Lidoderm, Endo requests that FDA require generic applicants to provide the names and contact information of all third parties, such as contract research organizations (CROs), that were associated with any BA or BE studies that are required to be submitted. Endo also requests herein that FDA itself contact any such third parties, such as CROs, that FDA believes or has reason to believe may have been associated with BA or BE studies on the product that is the subject of the application or any pharmaceutical equivalents thereof, and request from such third parties summaries of all such studies.

It is common practice in the generic drug industry to use CROs for BA and BE studies. Consequently, CROs are an obvious, independent source of information and verification regarding failed BA and BE studies, and should therefore be part of FDA's approach to ensuring failed studies are actually submitted. Indeed, FDA itself has acknowledged that CROs are likely the best source of information about the actual percentage of failed BE studies in practice.[96]

F. Data Integrity Concerns Regarding Cetero and Watson

Few CROs possess significant expertise in testing patch products. One of them is Cetero Research. Cetero claims "extensive experience" in this area.[97] Indeed, Cetero's Executive Medical Director is an expert and inventor in the field of skin penetration.[98]

Cetero illustrates why FDA should seek BA/BE information from third parties, such as CROs, in addition to generic sponsors themselves. Under FDA's new rule requiring submission of all such studies, any Cetero BA or BE study on a lidocaine patch 5% product must be submitted to FDA. To the extent ANDA applicants do not submit studies

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[95] FDA cannot approve an ANDA if it does not contain evidence demonstrating that the ANDA product is bioequivalent to the listed drug it references. 21 U.S.C. § 355(j)(4)(F). "Unless FDA receives all BE studies on the same drug product formulation, it is not possible for the agency to make an informed, scientifically based decision about bioequivalence." Requirements for Submission of Bioequivalence Data, 74 Fed. Reg. 2849, 2851 (Jan. 16, 2009).

[96] *See Joint Advisory Committee Meeting* at 203 (remarks of Dale Conner) (Nov. 16, 2000).

[97] Cetero Research, What We Offer, Dermatology, http://www.cetero.com/home/what-we-offer/therapeutic-and-specialty-areas/dermatology ("Cetero Research offers comprehensive *in vitro* and *in vivo* bioavailability, bioequivalence and safety testing services, from preclinical formulation assessments to early phase human studies, for both topical products and transdermal delivery systems."). *Exhibit 23.*

[98] *Id.* ("The Franz diffusion cell and the finite dose model, which were invented by Dr. Thomas Franz, our Executive Medical Director, have become the industry standard for evaluating the performance of topical and transdermal dosage forms.").

as required, information obtained from CROs provides an obvious means to cross-check whether the full array of studies that must be submitted have in fact been sent to FDA.

Given Cetero's particular expertise in patch products, Cetero's recent travails may also have compromised the integrity of lidocaine patch 5% product applications. To wit, all applicants who relied on Cetero for a generic lidocaine patch 5% product were recently advised by FDA to "either repeat the bioequivalence testing done by Cetero or retest drug samples using a different test laboratory or contractor."[99] FDA has concluded that Cetero engaged in a multi-year pattern of misconduct serious enough to raise questions about the integrity of the data Cetero generated for its clients.[100]

Indeed, Watson Pharmaceuticals, Inc., the lead applicant seeking approval of a generic copy of Lidoderm, engaged Cetero to conduct at least one bioequivalence study. Watson explains that the study did not fall within the date range of concern to FDA.[101] It is not clear whether Cetero was involved in any other studies on Watson's generic lidocaine patch. FDA's new regulations requiring submission of all studies would, of course, require submission of all Cetero studies (as well as those from any other source), passing or failed, once they have been appropriately analyzed.[102]

Moreover, Cetero is not the first CRO serving the generic industry whose data have been found wanting by FDA. In 2007, for example, FDA determined that there were "significant concerns about the validity of the reported results" of BE studies conducted by MDS Pharma Services for 140 ANDA products already on the market.[103]

FDA officials continue to acknowledge that there is widespread skepticism about generic drug quality, which has led FDA's Office of Generic Drugs to make boosting overall

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[99] FDA, Notification to Pharmaceutical Companies: Change in Timeframe for Cetero Studies Requiring Reevaluation, http://www.fda.gov/Drugs/DrugSafety/ucm265559.htm.

[100] *Id.* ("FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or 'prep' run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding 'prep' runs that prevented [Cetero] from conducting an adequate internal investigation to determine the extent and impact of these violations.").

[101] *See* THOMSON REUTERS STREETEVENTS, Edited Transcript: WPI – Q4 2011 Watson Pharmaceuticals Earnings Conference Call, Statement by Watson President and CEO, p. 13 (Feb. 14. 2012) (The situation involved a biostudy on Lidoderm performed at Cetero. The study was performed -- when the Cetero issue first happened, there was a date range provided by the agency. That date range was subsequently narrowed. The biostudy question now falls outside of the range of concerns that the FDA has about Cetero..."). *Exhibit 24.*

[102] Cetero's data integrity problems do not permit a generic applicant (like Watson) or FDA itself to ignore studies that have been conducted. Rather, all studies must be submitted and assessed in order to review Watson's, or any other ANDA applicant's, ANDA. Cetero's data integrity problems merely necessitate that affected applicants re-run properly stored samples from, or re-do entirely, affected BE studies. Cetero's travails cannot be an excuse simply to ignore the studies in question.

[103] Untitled Letter, Joanne Rhoads, CDER to MDS Pharma Services (Dec. 21, 2004), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm054655.pdf.

public confidence in generic drugs an office priority.[104] Submission of information from all BA and BE studies will enable FDA to evaluate whether sponsors are being appropriately proactive in response to failed BE study results and thereby help promote increased confidence in generic drugs.

G. FDA Should Require Complete PK Profiles for Each Study Subject

OGD acknowledges that it has "limited information . . . regarding quantitative and qualitative changes that could have a significant impact on" bioavailability for complex dosage forms.[105] OGD therefore requests reports on *all* BA and BE studies conducted on any formulations that are pharmaceutically equivalent to the to-be-marketed formulation.[106]

OGD's approach does not go far enough. At present OGD will permit submission of study reports for complex products in the same summary format used for standard oral dosage form products, about which there is much greater information on quantitative and qualitative changes that may affect BA or BE than exists for complex dosage forms. This summary report format, however, is ill-equipped to provide the information FDA needs for complex dosage forms like patches because it was plainly designed for oral dosage forms. (Hence, e.g., the repeated references to "Tab./Cap./Susp" and the inclusion of a table for In Vitro Dissolution Studies that designates "Tablet" and "Capsule" as the dosage forms.[107])

In addition, according to the standard tables for the suggested summary report, ANDA sponsors need only provide aggregate data such as median C_{max}, T_{max} and AUC along with confidence interval ranges. While they may be adequate for OGD to determine whether more detailed information in a full report is necessary, such aggregate data are not sufficient for complex dosage forms. Instead, complete pharmacokinetic profiles for each subject should be included for complex dosage forms.

In sum, OGD rightly states that more information is needed to determine which formulation changes for complex products might have a potential impact on

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[104] *See, e.g.,* FDA, Welcome Letter from the Director, Office of Generic Drugs, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119433.htm.

[105] FDA, OFFICE OF GENERIC DRUGS, GUIDANCE SUBMISSION OF SUMMARY BIOEQUIVALENCE DATA, p. 9 (May 2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf.

[106] *Id.*

[107] FDA, Generic Drugs: Information for Industry, Model Bioequivalence Data Summary Tables, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf. In one instance, OGD has recognized that the suggested summary report is not adequate for all types of products. In the case of aqueous nasal spray products, OGD has provided independent BE Summary Tables for in vitro BE studies. FDA, Generic Drugs: Information for Industry, Bioequivalence Summary Tables For Aqueous Nasal Spray Products, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf.

bioavailability. But simple aggregate data will not provide the type of information required.

H. FDA Should Use Information from Failed Topical Patch BE Studies to Reduce Uncertainty and Increase Reproducibility in BE Methods

Submission of information on failed studies is also important because it "will increase [FDA's] understanding of how changes in components, composition, and methods of manufacture may affect formulation performance" and thereby "promote further development of science-based bioequivalence policies" for complex dosage forms.[108] In light of the uncertainties regarding patch products and locally acting drugs, this is the prudent course.

The existence of failed BE studies raises critical questions about a core requirement of demonstrating BE: that ANDA sponsors should use "the most accurate, sensitive, and *reproducible*" BE approach.[109] The importance of reproducibility is evident in FDA's decision to withdraw its proposed DPK skin stripping BE method for topical drug products in 2003.[110] In that case, conflicting test results from different laboratories precluded a judgment that FDA's proposed method was sufficiently reproducible.

Similarly, FDA's acknowledgment that one ANDA sponsor submitted 11 failed BE studies as part of an ANDA reveals that FDA must develop criteria to evaluate whether a BE methodology is sufficiently reproducible.[111] FDA did not indicate whether it has decided to approve the ANDA that included 11 failed studies. However, an ANDA with failed BE studies should not be approved unless FDA has developed criteria to evaluate whether the failed studies are easily explained consistent with the various factors that can yield a failed BE study. If only 1 study out of 12 was "passable," was the method sufficiently reproducible?

Although reproducibility of the PK method used for oral drugs may not be called into question by failed BE study results given the evidence-based validity of the method for use with these drugs, conflicting results from PK studies used to evaluate BE of topical drug products could reinforce the lack of understanding about relating plasma concentrations to local activity in the skin. Criteria for evaluating failed studies are thus particularly important for a complex dosage form such as the lidocaine topical patch 5%.

At present, FDA is unable to define the scope of minor changes that *might* influence BE determinations for topical patch products because it has no ability to know what

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[108] Requirements for Submission of Bioequivalence Data, Proposed Rule, 68 Fed. Reg. 61640, 61640-41 (Oct. 29, 2003).
[109] 21 C.F.R. § 320.24(a) (emphasis added).
[110] *See* FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, Problem Statement by Lawrence Yu, Ph.D.: Research for Generics - Bioequivalence of Topical Products, Advisory Committee for Pharmaceutical Science Meeting (Sep. 22, 2003), http://www.fda.gov/ohrms/dockets/ac/03/briefing/3996B1_18_Yu-Bioequiv%20of%20Topical%20Products.htm.
[111] *2nd World Congress on BA and BE.*

formulation differences have an effect at all. The relative lack of understanding about the relationship between central compartment PK and local activity in the skin requires proactive analysis of information gleaned from failed BE studies conducted on locally acting topical patch products.

As OGD indicated in its 2007 Critical Path Opportunities for Generic Drugs report,[112] the relationship between central compartment pharmacokinetics and local activity in the skin "remains unknown."[113] OGD identified pharmacokinetic studies as one potential path for further development to enhance BE methods for topical drugs. However, OGD has not provided any evidence of progress in its understanding of the relevance of PK data to assessing BA/BE at local sites of activity or how such data may be used to support BE determinations for locally acting patch products. The submission of failed BA/BE studies provides an opportunity for FDA to further this Critical Path initiative by disclosing information that might illuminate the relationship between local and central activity.

I. FDA Should Seek the Concurrence of the Advisory Committees for Pharmaceutical Science and Clinical Pharmacology and Dermatologic and Ophthalmic Drugs before Approving a Lidocaine Patch 5% ANDA or 505(b)(2) Application that Includes Failed BA or BE Studies

Endo has previously requested that FDA's Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) and Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) convene a joint meeting to discuss development of appropriate BE methods for locally acting patch products like Lidoderm.[114] These advisory committees should also be empaneled to consider any determination by OGD that a generic lidocaine patch should be approved despite the existence of any failed bioavailability or bioequivalence studies.

At the August 5, 2009 ACPS-CP meeting, FDA asked the Committee to identify data gaps and areas in need of further research for patch formulations. As discussed above, the ACPS-CP confirmed that many open issues still need to be addressed, and since that time FDA has continued to acknowledge the limited information available and the need for it to be developed. In this context of significant uncertainty and limited knowledge regarding both patch technologies and BE for locally acting topical products, any FDA decision that a generic lidocaine patch 5% product is approvable despite having failed a BE or BA study (or studies) should not occur in a vacuum.

A return to the ACPS-CP, sitting jointly with the DODAC, should offer a qualified sounding board to double-check FDA's rationale with outside experts. Consideration by these committees would ensure all issues and potential data insufficiencies are addressed. Moreover, to the extent that FDA may consider use of something beyond the basic

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[112] *Critical Path* at § 4.3.3.
[113] *Id.*
[114] *Endo August 2007 Petition Amendment* at 1 (Action Requested No. 2).

pharmacokinetic BE study currently recommended in FDA's 2007 Draft Lidocaine Guidance for generic copies of Lidoderm, these Advisory Committees could help the Agency move forward along that path as well. [115]

Finally, recourse to these Advisory Committees would offer transparency regarding the scientific basis for plasma pharmacokinetics as an appropriate BE method for lidocaine patch 5% generic products, of which to date there has been very little.

VI. FDA's Failure to Publish Bioequivalence Requirements Precludes Approval of Generic Lidocaine Patches

By law, within 30 days of an NDA approval, FDA must publish in the Orange Book whether in vitro and/or in vivo BE testing is required for generic copies of the drug approved in the NDA.[116] The Lidoderm NDA was approved in March 1999. Thus FDA should have published BE requirements for generic copies of Lidoderm in April of that year. FDA failed to do so, a failure which continues to the present, in violation of the law and FDA's regulations.[117]

A. The Law Mandates that FDA Publish Whether In Vitro and/or In Vivo Bioequivalence Testing is Required for Generic Copies of Lidoderm

The law requires FDA to "publish and make public" a list of all approved drugs and indicate, among other things, "*whether* in vitro or in vivo bioequivalence studies, or both such studies, are *required* for [ANDAs] which will refer to the [RLD]".[118] FDA is required to update this list every 30 days, thus capturing any new NDAs approved within the last 30 days.[119]

The clear statutory language requiring publication of BE requirements is supported by legislative history. For example, House Report 98-857, in its section-by-section analysis of the language that was ultimately adopted and is now reflected in 21 U.S.C. § 355 (j)(7)(A)(i)-(ii), explains that:

> [S]ubsection (j) authorizes a program whereby information about listed drugs which could be copied would become available. Within 60 days after

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[115] Endo has previously discussed how the tests proposed in OGD's draft lidocaine patch guidance do not constitute a "portfolio" approach sufficient to ensure the BE of generic copies of Lidoderm. *Endo August 2007 Petition Amendment* at 26-27. Similarly, there is at present insufficient evidence to support coupling OGD's PK test with any BE test other than clinical endpoint studies as a sufficient demonstration of BE for generic copies of Lidoderm. To the extent OGD claims PK plus some test(s) other than clinical endpoint BE would ensure BE for generic lidocaine patches, OGD should obtain the endorsement of that approach from the ACPS-CP and DODAC.

[116] 21 U.S.C. § 355(j)(7)(A)(i)-(iii).

[117] Obviously comparative clinical studies are, as a matter of science, the default BE approach for locally acting topicals, regardless of FDA's failure to publish BE requirements for generic lidocaine patches.

[118] 21 U.S.C. § 355(j)(7)(A)(i)-(iii) (emphasis added).

[119] *Id.*

> enactment of this bill, the FDA is required to publish and make available a list of drugs eligible for consideration in an ANDA...[i]f the drug was approved after 1981, the list must include the date of its approval and its NDA number. The list must specify whether in vitro or in vivo bioequivalence studies, or both, are required for ANDAs. Clause (i). At 30-day intervals thereafter, the FDA must update the list to include drugs that have been approved for safety and effectiveness after enactment of this bill and drugs approved in ANDAs under this subsection. Clause (ii).[120]

FDA's regulations state that "[i]nformation on bioequivalence requirements for specific products is included in the current edition of FDA's publication 'Approved Drug Products with Therapeutic Equivalence Evaluations' and any current supplement to the publication."[121] The regulations define the term "bioequivalence requirement" as (not surprisingly) "a *requirement* imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products *which must be satisfied as a condition of marketing*."[122]

B. FDA Has Not Published Bioequivalence Requirements for Generic Copies of Lidoderm in the Orange Book, a Legal Violation which Precludes Approval of Generic Copies of Lidoderm

FDA has failed to publish BE requirements for generic copies of Lidoderm in the Orange Book.[123] The Agency has therefore violated the plain terms of the law and its own regulations. This is fatal to the approval of generic copies of Lidoderm, because such approvals would be based on FDA's circumvention of the law and regulations.[124]

FDA's legal failure has multiple aspects. First, FDA missed a clear statutory deadline—by some 13 years. FDA did not publish, by the deadline the law requires, whether in vitro, in vivo, or both types of studies are required for generic copies of Lidoderm. As

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[120] H.R. REP. NO. 98-857, pt. 2, at 17 (1984).

[121] 21 C.F.R. § 320.24(a). Note that FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" publication is referred to herein by its commonly known name, the "Orange Book." *See* FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, Preface (32nd ed. 2012).

[122] 21 C.F.R. § 320.1(f) (emphasis added).

[123] Indeed, the only *Orange Book* content conceivably relevant to BE methodologies is therapeutic equivalence codes, but such codes are backward-looking comparisons of generics to brand products which issue only after generics are approved. This is contrary to the statutory language and legislative history which contemplate forward-looking BE requirements, published within 30 days of the RLD's approval, specifying what methods FDA will require if and when generic applications are submitted.

[124] Reviewing courts must "hold unlawful and set aside agency action" if it is "not in accordance with law" or "without observance of procedure required by law." 5 U.S.C § 706(2)(A), (D). *See e.g.*, *Gerber v. Norton*, 294 F.3d 173, 186 (D.C. Cir. 2002) (finding that an agency issued a permit "without observance of procedure required by law" because the agency failed to follow the statutorily mandated procedures of providing opportunity for comment on a developer's permit and making an environmental impact finding of the developer's plan); *Am. Lands Alliance v. Norton*, 242 F. Supp. 2d 1, 8-19 (D.D.C. 2003) (finding an agency's policy to be facially invalid because it was contrary to the plain language of the relevant statute and setting aside Secretary of the Interior's actions that were based on the invalidated agency policy).

explained above, this inaction is a violation of the FDCA, 21 U.S.C. § 355(j)(7)(A)(i) and FDA's implementing regulations, 21 C.F.R. § 320.24.

Furthermore, FDA's failure to publish BE testing requirements in a timely manner is an agency action "unlawfully withheld" or "unreasonably delayed" in violation of the Administrative Procedure Act, 5 U.S.C. § 706(1).[125] In *Norton v. Southern Utah Wilderness Alliance,* 542 U.S. 55, 64 (2004), the Supreme Court ruled that "a claim under 5 U.S.C. § 706(1) can proceed only where a plaintiff asserts that an agency failed to take a discrete agency action that it is required to take." The Court explicitly indicated that statutory deadlines could establish the discrete mandatory action needed to bring a challenge under § 706(1).[126]

Here, FDA violated the statutory deadline to publish BE testing requirements for generic copies of Lidoderm within 30 days of Lidoderm's NDA approval and has thus "unlawfully withheld" mandatory agency action. Even reviewing the instant case under the rubric of "unreasonably delayed," FDA's failure to meet a statutory deadline by thirteen years, when such action was required within *thirty days*, and without any indication by the Agency that action will be taken, plainly violates 5 U.S.C. § 706(1).[127]

Second, FDA has not published or made public bioequivalence requirements for generic copies of Lidoderm. The general public, as well as Endo and other interested parties, has therefore been kept in the dark on this issue. In turn, this impairs the capacity of any party, including Endo, to critique and comment on FDA's bioequivalence requirements for lidocaine patch generics. In sum, FDA's failure to publish undermines the transparency of bioequivalence method development at FDA, an outcome presumably contrary to the intent of the Congress, which mandated publication early on (30 days post NDA approval) such that, had the law been followed, the public would have known of—and had the opportunity to critique—FDA's bioequivalence requirements for generic copies of Lidoderm long ago.

Third, FDA has not met the high standard of developing bioequivalence requirements. Developing BE requirements obligates FDA to identify scientifically valid BE methods that will ensure generic drugs achieve the same rate and extent of drug active ingredient availability at the site of action as the RLD. The Agency's regulations specify that only "the most accurate, sensitive, and reproducible approach" can be used to demonstrate

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[125] *See Saleem v. Keisler,* 520 F. Supp. 2d. 1048, 1059 (W.D. Wis. 2007) (explaining that the phrase "unlawfully withheld" in 5 U.S.C § 706(1) applies to the situation where an agency has failed to meet an explicit statutory deadline, while the phrase "unreasonably delayed," to have any independent meaning, must refer to agency inaction in the absence of a specific deadline); *but see In re Bluewater Network,* 234 F. 3d 1305, 1315-16 (D.C. Cir. 2000) (analyzing agency's failure to meet a statutory deadline under the rubric of unreasonableness using the criteria known as "*TRAC* factors" set forth in *Telecomm. Research & Action Ctr.*, 750 F.2d 70 (D.C. Cir. 1984)).

[126] *See Norton v. S. Utah Wilderness Alliance,* 542 U.S. 55, 71-72 (2004).

[127] *See In re Bluewater Network,* 234 F. 3d at 1315-16 (finding that when faced with a clear statutory mandate, a deadline nine-years ignored, and an agency that has indicated it will do no more, the *TRAC* factors have been met and the agency's delay is unreasonable.)

bioequivalence.[128] FDA's failure to promulgate BE requirements is an abdication of its statutory responsibility to carry out the task of identifying the best BE approach for generic copies of Lidoderm.

Fourth, FDA cannot approve an ANDA unless and until FDA has published bioequivalence requirements. The law requires FDA to issue specific bioequivalence requirements for each RLD. FDA's regulations provide that a bioequivalence requirement is a "requirement...which must be satisfied as a condition of marketing."[129] In other words, generic drugs cannot be approved unless and until they satisfy the BE requirements imposed by FDA for the particular RLD the generics purport to copy. Thus, in the absence of BE requirements for generic copies of Lidoderm, such generic products are not approvable.

Finally, FDA's failure to require particular BE methodology opens the door to generic lidocaine patches approved based on differing BE methods. The legal mandate of BE requirements, however, necessitates uniformity. A BE requirement for generic copies of Lidoderm is a requirement only if all applicants must comply with it. Approval of generics in the absence of BE requirements would permit marketing of generics that were each approved based on a different BE test. This would subvert the law's mandate of uniformity through FDA promulgation of BE requirements applicable equally to each and every generic lidocaine patch ANDA applicant. ANDA approvals based on anything other than requirements would undermine the possibility and purpose of such requirements.

The fact that approval of ANDAs based on anything other than BE requirements would negate the possibility of such requirements also explains the statutory mandate to publish BE requirements within 30 days of NDA approval. Prompt publication within 30 days ensures public clarity regarding what, uniformly, will be the BE requirements for generic copies of a newly approved NDA product.[130]

C. OGD's Draft, Nonbinding BE Guidance for Generic Copies of Lidoderm Contravenes the Law's Mandate to Publish BE Requirements

FDA cannot rely on OGD's 2007 Draft Lidocaine Guidance to meet its legal obligation to publish BE requirements for lidocaine patch ANDA applicants, because the draft guidance, even if finalized, would only contain *recommended* studies. Thus even in final form the 2007 Draft Lidocaine Guidance could not be mistaken for a "bioequivalence requirement". Per FDA's own regulations, guidance documents, and the

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[128] 21 C.F.R. § 320.24(a).

[129] 21 C.F.R. § 320.1(f).

[130] Moreover, by permitting differing BE showings, FDA also increases the risks of bio*in*equivalence among generic versions of the same product, i.e., while each generic may have "demonstrated" BE to Lidoderm, generic approvals based on different BE methods are likely to result in the various different generic lidocaine products being less bioequivalent and hence less interchangeable with one another.

recommendations they include, are not intended to be binding on the public or FDA or to require a particular BE approach.[131]

Second, the plain language of both the relevant statute and FDA's own regulations provide that bioequivalence requirements must be published in the Orange Book. Guidance documents, however, are not published in the Orange Book.

Nonetheless, at least one generic applicant (Watson) has stated that its lidocaine patch ANDA relies on the BE method described in OGD's draft BE guidance for lidocaine patch generics.[132] By specifying that FDA must publish BE requirements, however, Congress ruled out the possibility that BE guidance documents could take the place of those requirements. Therefore, Watson's ANDA (and any other ANDA relying on the 2007 Draft Lidocaine Guidance for approval of a generic copy of Lidoderm) is not approvable. If it approved such an ANDA, FDA would violate the FDCA by failing to appropriately publish BE testing requirements per 21 U.S.C § 355(j)(7)(A)(i) and 21 C.F.R. § 320.24, and FDA's action would be "arbitrary, capricious... or otherwise not in accordance with law."[133] Congress has spoken on the issue of whether and in what manner BE testing requirements are to be published, thus FDA can expect no deference to either its reliance on guidance documents for setting forth BE testing requirements for generic copies of Lidoderm or any approvals based on following such guidance documents.[134]

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[131] 21 C.F.R. § 10.115(d). Guidance documents make this explicit. *See e.g., 2007 Draft Lidocaine Guidance* at 1 ("This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternate approach if the approach satisfies the requirements of the applicable statutes and regulations.").

[132] The CEO of Watson Laboratories, Inc. has stated that "FDA modified Lidoderm guidance, and [Watson] followed the new guidance." *See* THOMSON REUTERS STREETEVENTS, Final Transcript: WPI - Q2 Watson Pharmaceuticals Inc [sic] Earnings Conference Call, Statement by Watson President and CEO, p. 16 (Jul. 26. 2011) [hereinafter, *Watson Transcript*]. *Exhibit 25*. Watson has also claimed that Endo's "citizen petition . . . has already been answered by the FDA." *Id.* Watson's CEO explains that FDA's purported answer to Endo's petition is "why [Watson is] so confident" about the prospects for approval of its application for a generic copy of Lidoderm. *Id.* Endo is unaware of any modification to FDA's 2007 Draft Lidocaine Guidance or FDA's answer to this petition. The only available Lidoderm guidance is in draft form and provides for pharmacokinetic demonstration of BE. Endo has explained in this and previous filings to this petition why PK is not a valid BE method for generic copies of Lidoderm and thus FDA should require generic lidocaine patch applicants to conduct clinical endpoint BE studies.

[133] 5 U.S.C. § 706(2)(A). FDA approval of ANDAs based on non-binding guidance instead of statutorily mandated BE requirements would be "final agency action" not in accordance with law and set aside. *See* 5 U.S.C. §§ 704, 706(2)(A). In a similar case, *American Lands v. Norton*, 242 F. Supp. 2d at 18-19, the court held that a Fish and Wildlife Service guidance was facially invalid because, in using it as a basis for making decisions, it allowed the Secretary of the Interior to avoid her "non-discretionary obligations mandated" by statute. Similarly, FDA's reliance on guidance documents allows it to avoid the statutory mandate that it publish BE requirements. In *American Lands*, the court set aside the Secretary's actions taken pursuant to the invalid guidance and ordered her to act in accordance with the statutory mandate. Generic lidocaine patch 5% approvals based on OGD's draft guidance—or any other method not published in the Orange Book as a BE requirement—would similarly be unlawful and set aside.

[134] *See Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984) (noting that no deference is afforded to an agency when "Congress has directly spoken to the precise question at issue");

VII. FDA Selective Disclosure of Its Response to Endo's Petition, if it Occurred, Was Contrary to Law

A. Selective Disclosure of BE Methods Would Violate the Administrative Procedure Act

Agency actions that treat similarly situated persons differently violate the Administrative Procedure Act's (APA) prohibition against arbitrary and capricious conduct.[135] Here, the facts suggest FDA has provided information selectively to one party to the detriment of another.

In this petition Endo has requested that FDA, *inter alia*, require lidocaine patch 5% ANDA applicants to conduct clinical endpoint studies to demonstrate bioequivalence to Lidoderm. However, to the best of Endo's knowledge, Watson did not submit the results of such studies with its ANDA.[136] Yet Watson has publicly asserted that "the [Endo] citizen petition in this case has already been answered by the FDA," and that it is "confident" about its approval prospects based on "the status of our FDA application [ ] and how it's moving through the process."[137] Despite Watson's claim that Endo's petition has been answered, Endo itself has received no response from FDA. The petition docket is also devoid of any FDA answer to Endo's petition.

Any FDA communication to Watson, however, that FDA will accept a BE showing based on the PK method in its 2007 Draft Lidocaine Guidance would also be a communication that FDA will not grant Endo's petition, at least insofar as the petition requests FDA to require clinical endpoint studies for lidocaine patch generics. If this has occurred, then FDA has treated similarly situated parties differently by selectively disclosing material information to, and thereby conferred a material informational advantage on, Watson to the detriment of Endo and other interested parties, e.g., other ANDA applicants. This would be arbitrary and capricious FDA action under the APA.

B. FDA's GDUFA Pledge to Tell Generic Applicants How it Will Address Issues Raised in Citizen Petitions Indicates FDA Willingness to Selectively Disclose to Generic Applicants

Also arbitrary and capricious would be FDA's August 2011 pledge to the generic drug industry that FDA "will strive to address issues raised in citizen petitions [like Endo's

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Household Credit Servs., Inc. v. Pfennig, 541 U.S. 232, 239 (2004) (noting that *Chevron* requires agencies to give effect to the unambiguously expressed intent of Congress).

[135] 5 USC § 706(2)(A); *see Transactive Corp. v. U.S.*, 91 F.3d 232, 237(D.C. Cir. 1996)(A long line of precedent establishes that agency action is arbitrary when an agency offers insufficient reasons for treating similar situations differently); *see also Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997)("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA" (quoting *Allergan v. Shalala*, 6 Food and Drug Rep. 389, 391(D.D.C. 1994))).

[136] Watson has asserted that it followed FDA guidance in submitting its ANDA, and there is no published guidance for lidocaine topical patches that recommends clinical endpoint studies. *Watson Transcript* at 16.

[137] *Id.*

here] in complete response letters where possible."[138] FDA made this pledge in a meeting with certain generic drug companies regarding possible legislation known as the Generic Drug User Fee Act, or GDUFA. As part of GDUFA, generic drug companies and FDA are seeking to apply the "complete response letter" practice used for new drug applications to generic applications as well.[139]

In the GDUFA negotiations, generic companies raised the issue of:

> the interaction between complete response letters and citizen petitions, particularly with regard to citizen petitions submitted prior to legislation in 2007 establishing response timelines under Section 505(q) of the Federal Food, Drug and Cosmetic Act (FDCA); this was noted to be a small number of petitions existing at the agency.[140]

The instant petition falls within this category because it was submitted prior to the 2007 legislation. For such petitions "FDA indicated that it will strive to address issues raised in citizen petitions in complete response letters where possible".[141]

If FDA's pledge to address citizen petition issues in complete response letters to generic applicants means such applicants learn of FDA's resolution of such issues before the petitioner or the general public, then FDA has promised to commit arbitrary and capricious acts. FDA's answers to issues raised in citizen petitions can have significant and immediate implications for regulated industry. Tipping generic companies about how FDA will answer a petition privileges those companies with information unknown to the general public.

Consequently, Endo requests herein that FDA not address issues raised in this citizen petition in a complete response letter to any generic applicant unless prior to issuing such a letter the Agency has answered this petition in full.

C. OGD Selective Disclosure Would Violate FDA's Regulations

FDA selective disclosure to Watson would also violate FDA's regulations regarding standards of conduct and conflicts of interest.[142] Selectively dispensing material information to one recipient when such information is sought by and valuable to other interested parties would "discriminate unfairly by the dispensing of special favors or privileges...whether for remuneration or not" in violation of 21 C.F.R. § 19.6(5).

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[138] GDUF Negotiation Sessions, FDA-Industry Generic Drug User Fee (GDUF) Negotiations Meeting Minutes, p. 2 (Aug. 18, 2011) http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM270798.pdf [hereinafter, *GDUF Negotiation Minutes*].
[139] *GDUFA Letter* at 6.
[140] *GDUF Negotiation Minutes* at 2.
[141] *Id.*
[142] 21 C.F.R. Part 19.

D. FDA Selective Disclosure Would Violate the Good Guidance Law and Implementing Regulations

In addition to asserting that FDA has responded to Endo's citizen petition, Watson's CEO has claimed that "FDA modified Lidoderm guidance, and [Watson] followed the new guidance."[143] If FDA has indeed modified its 2007 Draft Lidocaine Guidance, in communicating this information first to Watson (who made the information public in an investor conference call) instead of through a guidance document, FDA has violated the FDCA and its own regulations.

The FDCA requires FDA to observe certain good guidance practices (hereinafter, "GGP").[144] FDA has implemented this provision with regulations codified at 21 C.F.R. § 10.115. An agency must adhere to its own regulations; failure to do so is fatal to the "deviant" action.[145] The GGP regulations provide that FDA:

> [M]ay not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time. These GGP's must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are *first* communicated to a broad public audience.[146]

Endo is unaware of any modification to OGD's 2007 Draft Lidocaine Guidance, last issued in May 2007. A search on FDA's website only turns up the May 2007 guidance; no other, more recent guidance documents are returned in the search.[147] Thus, to the extent that the May 2007 Draft Lidocaine Guidance no longer reflects FDA's current thinking on the subject, FDA has violated its own regulations by failing to publicly issue amended guidance. This failure would be "fatal" to any attempt by FDA to rely on the "modified Lidoderm guidance" of which Watson's CEO speaks, and thus to Watson's ANDA.[148]

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[143] *Watson Transcript* at 16.

[144] 21 U.S.C. § 371(h).

[145] *See Oregon v. FCC*, 102 F.3d 583, 585 (D.C. Cir. 1996) ("it is a well-settled rule that an agency's failure to follow its own regulations is fatal to the deviant action" (quoting *Way of Life Television Network, Inc. v. FCC*, 193 U.S. App. D.C. 202, 593 F.2d 1356, 1359 (D.C. Cir. 1979))).

[146] 21 C.F.R. § 10.115(e) (emphasis added).

[147] Using the search function on FDA's website www.fda.gov as of March 9, 2012.

[148] Selective disclosure, in addition to violating the law, also contributes to inefficient resolution of disputes regarding standards for ANDA approvals. Here, had FDA also informed Endo and the general public at the same time FDA supposedly informed Watson of its "modified" approach, then any disagreements Endo or others may have had could have been raised well before now and FDA could have addressed them. But this did not occur, with the result being that if FDA were now to approve generic products based on the modified approach, FDA would have played favorites among regulated companies, hid the fact of final agency action in order to benefit Endo's competitors, and dramatically raised the probability of last-minute litigation.

VIII. FDA's Failure to Provide a Substantive Response to Endo's Petition, to Date, is Unreasonable and in Violation of Law

Federal agencies, such as FDA, may not unreasonably delay agency actions that they are obligated to undertake.[149] Agency action is "unreasonably delayed" where the agency's timeline for taking the action is not "governed by a rule of reason."[150] And "where Congress has provided a timetable or other indication of the speed with which it expects the agency to proceed in the enabling statute, that statutory scheme may supply content for this rule of reason."[151]

Notably, Congress has recently provided an express indication as to the speed with which it expects FDA to provide a final response to citizen petitions. Specifically, in 2007, Congress enacted legislation that directs FDA to respond to citizen petitions within 180 days.[152] While Endo's petition is not itself subject to the 505(q) provision or its deadlines, the timetable contained therein provides useful context (and a reference point) for considering the reasonableness of the length of time that FDA has taken to respond.[153]

Endo filed this petition in December 2006. Yet, as discussed above, FDA has yet to provide a final, substantive response.[154] Thus, Endo's petition has been pending with the agency for *over 5 years*—more than *ten times* the amount of time that Congress believes is appropriate for responding to such filings. Separate and apart from Congress's stated intent on this subject, there is simply no legitimate reason why FDA could not have made a fully informed decision on Endo's petition in the 5 years that it has ostensibly been under review.[155]

Indeed, a five-year delay by FDA in responding to a citizen petition is so egregious that at least one court has said that a delay of that length "alone raises questions about the good faith of the FDA."[156] And any delay of agency action "that is the result of bad

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[149] *See* 5 U.S.C. § 706(1) (authorizing a court to "compel agency action unlawfully withheld or unreasonably delayed").

[150] *In re Core Commc'ns, Inc.*, 531 F.3d 849, 855 (D.C. Cir. 2008).

[151] *Id.* at 855.

[152] *See* Food and Drug Administration Amendments Act of 2007 (FDAA), Pub. L. No. 110-85, § 914(a), 121 Stat. 922 (2007) (codified at 21 U.S.C. § 355(q)(1)(F)) (amending Sec. 505 of the FDCA by adding Sec. 505(q) governing Citizen Petitions).

[153] Applications filed prior to the law's effective date are governed by FDA's pre-existing regulations, which give the agency 180 days to respond to a citizen petition but permit that response to be a "tentative response" that explains why a final decision has not yet been issued. *See* 21 C.F.R. § 10.30(e)(2). Nonetheless, even in those situations where a tentative response initially is appropriate, the regulations contemplate that a final response will ultimately be provided. *See* 21 C.F.R. § 10.30(e)(2).

[154] As discussed *supra*, the agency provided a tentative, non-substantive response in June 2007. *See Axelrad Letter*.

[155] Endo's petition discusses general bioequivalence requirements applicable to all lidocaine 5% topical patch ANDAs and requests, *inter alia*, that FDA take certain procedural actions as it develops such requirements. Reaching a decision on these issues did not require FDA to wait for, or consider, specific ANDAs. Nonetheless, it should be noted that at least one lidocaine 5% topical patch ANDA was filed over two years ago.

[156] *Tummino v. Von Eschenbach*, 427 F. Supp. 2d 212, 232 (E.D.N.Y. 2006).

faith—that is, a delay for improper reasons—is a delay that is per se unreasonable."[157] An example of an improper basis for delay would be where such a delay was, in essence, "a calculated 'filibuster' designed to avoid making a decision subject to judicial review."[158]

Here, FDA's 5-plus year delay is unreasonable in any event. And it is particularly troubling and prejudicial to Endo because it appears that FDA has, in fact, reached determinations regarding the issues raised in Endo's petition (and perhaps shared those determinations with others). By not sharing such conclusions with Endo through a formal response to its petition, FDA has unfairly precluded Endo from providing informed input regarding FDA's determinations and improperly shielded its decision-making process from public scrutiny and perhaps judicial review.

CONCLUSION

In previous filings to this petition, Endo has outlined the many uncertainties associated with using pharmacokinetics as a bioequivalence method for generic applicants seeking to copy Lidoderm (lidocaine patch 5%). In this amendment Endo further addresses some of the many additional issues that presently preclude the approval of generic lidocaine patch 5% products. For all of the reasons cited in its various filings, Endo respectfully reiterates its requests that FDA take the actions Endo has requested in this petition and its amendments.

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.

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[157] *Id.* at 231.
[158] *Id.* at 232.

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.

Sincerely,

Robert Barto

Robert Barto
Vice President, Regulatory Affairs
on behalf of Endo