DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 22 2012

Robert Barto
Mary Alice Raudenbush
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Endo Pharmaceuticals
100 Painters Drive
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Re: Docket No. FDA-2006-P-0346[1]

Dear Mr. Barto, Ms. Raudenbush, and Dr. Gerritsen van der Hoop:

This letter responds to your citizen petition received on December 18, 2006 (2006 petition), and your amendments to that petition dated August 29, 2007 (2007 amendment), and March 12, 2012 (2012 amendment), concerning the bioequivalence requirements applicable to any abbreviated new drug application (ANDA) or 505(b)(2)[2] new drug application (NDA) that references Lidoderm (lidocaine patch 5%) as its listed drug.

Your petition, as amended, presents numerous requested actions, generally reflecting your opposition to the advice given in the Agency's draft guidance on the design of bioequivalence studies for lidocaine topical patch 5% products (Draft Lidocaine Patch BE Guidance). This draft guidance recommends that bioequivalence for such products be demonstrated by measurements of lidocaine concentration in plasma (i.e., by pharmacokinetic studies), and a skin irritation/sensitization study.[3] Your petition and amendments urge the Agency instead to require comparative clinical trials in addition to pharmacokinetic studies to demonstrate bioequivalence (i.e., clinical trials that compare the safety and effectiveness of a proposed generic product with that of Lidoderm). The 20 specific requested actions included in your petition and amendments are identified and discussed in section II.C of this letter. We have carefully considered the issues raised in your petition and amendments and your comments to related FDA Docket No. FDA-

[1] This citizen petition was originally assigned docket number 2006P-0522. The number changed to FDA-2006-P-0346 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 355(b)(2).

[3] Draft Lidocaine Patch BE Guidance (May 2007), at 1, available on the Internet at http://www.fda.gov/Drugs under Guidances (Drugs).

2007-D-0369,[4] which was established to solicit public review of and comment on draft guidances for industry describing product-specific bioequivalence recommendations including the Draft Lidocaine Patch BE Guidance. Your petition is granted in part to the extent that you request and have been provided an opportunity to comment on FDA's published draft guidance on bioequivalence testing methodology for generic lidocaine topical patch 5% products. Your petition otherwise is denied, as explained in detail below.

I. BACKGROUND

A. Lidoderm

FDA approved NDA 020-612 for Lidoderm on March 19, 1999. Lidoderm is a topical patch indicated for relief of pain associated with post-herpetic neuralgia (PHN) when applied to intact skin. Each 10 centimeter (cm) x 14 cm adhesive patch contains a single active ingredient, lidocaine (700 mg). A small fraction, 3 ± 2%, of the 700 mg of lidocaine contained in a single patch, is expected to be absorbed into the skin during the 12-hour wearing time.[5] Teikoku Pharma USA, Inc., holds approved NDA 020-612 for Lidoderm.

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.[6] Lidoderm works by delivering a small dose of lidocaine, approximately 21 mg per patch, over a 12-hour period through the stratum corneum to damaged nerves, where it acts locally.

B. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), which established the ANDA approval process for generic drugs.[7] To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[8] The ANDA applicant must identify the listed drug on which it seeks to

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[4] Originally Docket No. 2007D-0168. The number changed to FDA-2007-D-0369 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[5] See CLINICAL PHARMACOLOGY Section, Lidoderm Package Insert (Lidoderm PI), at 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020612s011lbl.pdf.

[6] Id.

[7] For purposes of this response, a generic drug is a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[8] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs

rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.[9]

The ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the listed drug it references.[10] The statute, regulations, and case law give FDA significant flexibility in determining how this requirement is met. Section 505(j)(8)(B)(i) of the Act states that a generic drug is bioequivalent to the listed drug if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . .[11]

Section 505(j)(8)(C) of the Act provides that "for a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."

In 21 CFR 320.1(e), FDA defines bioequivalence (in pertinent part) as:

> ...the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the listed drug, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the listed drug. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

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are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as the Orange Book.

[9] Sections 505(j)(2)(A) and (j)(4) of the Act. See also 21 CFR 314.94(a).

[10] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.3 (defining reference listed drug); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

[11] See also 21 CFR 320.1(e) and 320.23(b).

The determination of bioequivalence for drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate, FDA may, as described in provisions of the Act and 21 CFR part 320, rely on other in vivo and/or in vitro methods to assess bioequivalence. Our regulations describe the methods in descending general order of accuracy, sensitivity, and reproducibility as follows: (1) in vivo pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) comparative clinical endpoint studies, and (4) in vitro studies.[12] In addition, consistent with section 505(j)(8)(C) of the Act, section 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

FDA has discretion to determine how the bioequivalence requirement should be met for a given product or class of products so long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion" (*Schering Corp. v. Sullivan*, 782 F.Supp. 645, 651 (D.D.C. 1992)).[13] Courts have consistently upheld FDA's implementation of the Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. at 867).

C. Section 505(b)(2) Applications

A 505(b)(2) application shares characteristics of both an ANDA and a 505(b)(1) NDA (referred to as a stand-alone NDA). Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness information as a stand-alone NDA. A 505(b)(2) application is similar to an ANDA because it may rely, in part, on FDA's finding that the listed drug it references is safe and effective as evidence in support of the proposed product's own safety and effectiveness.

However, although a drug product approved under an ANDA is generally required to duplicate an innovator product (with a few limited exceptions), a 505(b)(2) application often describes a drug with substantial differences from the listed drug it references.[14] These differences may include, for example, a different active ingredient or a new

[12] 21 CFR 320.24. While a pharmacokinetic study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream), a pharmacodynamic study measures effects associated with the delivery of the active ingredient to the site of action.

[13] See also *Fisons Corp. v. Shalala*, 860 F.Supp. 859, 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion.").

[14] Under 21 CFR 314.101(d)(9), we may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Act.

indication, dosage form, strength, formulation, or route of administration.[15] A 505(b)(2) application must support those differences with appropriate information regarding safety and effectiveness. Depending on the nature of a 505(b)(2) application, a demonstration of bioequivalence to the referenced drug may be needed.

D. Bioequivalence Guidance

Our guidance for industry on *Bioequivalence Recommendations for Specific Products* (June 2010) (BE Specific Product Guidance)[16] describes FDA's process for making available to the public FDA guidance on the design of bioequivalence studies for specific drug products. A draft of this guidance was issued for public comment in May 2007, after your original petition was submitted. Prior to establishing the product-specific bioequivalence guidance mechanism outlined in the BE Specific Product Guidance, the Agency provided recommendations on the design of bioequivalence studies for specific products on an individual basis to parties that expressly had requested such information.

Under our current process, the Agency periodically publishes notices in the *Federal Register* announcing the availability of product-specific draft, revised draft, and final bioequivalence recommendations. These notices identify a comment period for draft bioequivalence recommendations. The draft and final recommendations are available on FDA's Web site.[17]

The Agency considers comments received on product-specific bioequivalence recommendations in developing final recommendations. As with Agency guidance in general, these recommendations describe the Agency's current thinking and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following our product-specific bioequivalence recommendations have an expectation that the Agency will agree that their bioequivalence studies were properly designed.[18] However, applicants may confer with the Agency on different approaches. The Agency is not bound by recommendations made in a draft or final guidance and has the discretion to approve a product supported by bioequivalence data that meet the statutory and regulatory requirements in the absence of published product-specific bioequivalence guidance.

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[15] See 21 CFR 314.54(a); see also the draft guidance for industry on *Applications Covered by Section 505(b)(2)* (Oct. 1999), available on the Internet at http://www.fda.gov/Drugs under Guidances (Drugs). When finalized, the guidance will represent FDA's current thinking on the topic.

[16] Available on the Internet at: http://www.fda.gov/Drugs under Guidances (Drugs).

[17] Product-specific bioequivalence recommendation guidances are available on a dedicated page within our Web site, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[18] 21 CFR 10.115(d)(3) ("Although [final] guidance documents do not legally bind FDA, they represent the Agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.").

E. Draft Lidocaine Patch BE Guidance

In October 2006, FDA issued a letter setting forth the Agency's recommended methodology for demonstrating bioequivalence for a generic lidocaine patch product, under the Agency's former practice for communicating bioequivalence recommendations described above. With one minor revision,[19] the recommendations provided in our October 2006 letter were later incorporated into the Draft Lidocaine Patch BE Guidance and posted on FDA's Web Site for public comment.[20] The draft guidance recommends two studies to support a demonstration of bioequivalence for a generic lidocaine patch product:

1. Type of study: Fasting
   Design: Single-dose, in-vivo, using up to three topical patches
   Strength: 5%; 700 mg/patch
   Subjects: Normal healthy males and females, general population.

2. Type of study: Skin irritation/sensitization study
   Design: Single-dose, in-vivo (preceded by an induction phase and a rest period) Strength: 5%; 700 mg/patch
   Subjects: Normal healthy males and females, general population.

In the Draft Lidocaine Patch BE Guidance, FDA provides additional comments and guidance on these two studies.[21]

II. DISCUSSION

A. Scientific Basis for Our Recommended Approach to Establishing Bioequivalence for Lidocaine Topical Patch 5% Products

FDA has issued several product-specific recommendations that bioavailability and bioequivalence determinations for topical dermatological products applied to the skin be based on pharmacodynamic or clinical endpoint studies.[22] For topical *dermatological* drug products (i.e., drug products that treat diseases of the skin), pharmacokinetic measurements in blood, plasma, and/or urine are usually not feasible because the drug functions at upper layers of the skin, is not systemically absorbed, and is not present at measureable concentrations in these biological fluids.

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[19] A reference to the United States Pharmacopeia (USP) was omitted.

[20] The availability of our Draft Lidocaine Patch BE Guidance was announced in the *Federal Register*. *Publication of Guidances for Industry Describing Product-Specific Bioequivalence Recommendations* (72 FR 60683, 60684) (Oct. 25, 2007) (FR Lidocaine Notice) (noticing that the lidocaine guidance was posted in May 2007).

[21] Draft Lidocaine Patch BE Guidance, at 1-6.

[22] See, e.g., draft guidance on Terbinafine Hydrochloride (Aug. 2010), draft guidance on Tretinoin (Mar. 2012).

As a preliminary matter, the Agency notes that the requests in your petition are based on the erroneous premise that Lidoderm is a topical dermatological drug product (i.e., intended to treat a disease of the skin itself) for which pharmacokinetic bioequivalence studies are often not feasible due to a lack of systemic absorption. Lidoderm is a topical pain relief product, however, and not a dermatological product. As described below, Lidoderm has an active ingredient that penetrates beneath the surface of the skin, for which pharmacokinetic bioequivalence studies are feasible for several reasons.

Several characteristics of topical lidocaine distinguish the product from most other topical drug products and support the determination that bioequivalence may be demonstrated through measurements of its concentration in plasma. These factors include: (1) that lidocaine can be measured in plasma following its application to the skin; (2) that lidocaine is expected to pass through the stratum corneum to reach its site of action; (3) that capillaries are present throughout dermal tissue beneath the stratum corneum, where lidocaine acts on nerves, and lidocaine is expected to enter the bloodstream through these capillaries; and (4) that lidocaine is expected to be present in plasma at a concentration proportional to its presence at the site of action when applied topically to skin for the treatment of PHN. Based upon these considerations, discussed in detail below, we conclude that the pharmacokinetic studies and skin testing described in the Draft Lidocaine Patch BE Guidance together are the most sensitive, accurate, and reproducible method for detecting differences in bioavailability between Lidoderm and a proposed generic product (and therefore for demonstrating bioequivalence), and that comparative clinical endpoint studies, which you urge us to require, would be less sensitive, accurate, and reproducible.

(1) Absorption of Lidocaine into the Bloodstream

The methodology recommended in the Draft Lidocaine Patch BE Guidance is grounded in FDA's scientific conclusion that when two lidocaine patches with the same drug concentration and the same area and time of application produce equivalent plasma concentration-time profiles, the local delivery of the drug from the formulation to the topical site of action will be equivalent. This is due to the nature of lidocaine, and in particular, the fact that a significant fraction of the lidocaine that is absorbed into the skin following application of a Lidoderm patch also is absorbed into the bloodstream. First, we note that as indicated in Lidoderm's labeling, the mean peak blood concentration of lidocaine is about 0.13 micrograms per milliliter (μg/mL) following application of Lidoderm patches at the maximum recommended dose, three patches for 12 consecutive hours in healthy volunteers.[23] Also as indicated in its labeling, at least 95% of the lidocaine present in a Lidoderm patch remains in the patch following a 12-hour application, meaning no more than 5% (or no more than approximately 35 mg from a single patch) passes into a patient's skin.[24] Approximately 3% of the lidocaine present in

[23] See CLINICAL PHARMACOLOGY section, Lidoderm PI, at 2.

[24] Id.

one patch (or 21 mg) is absorbed into the bloodstream of a healthy volunteer during the 24-hour period after initial application of the patch.[25] In sum, no more than 35 mg of the 700 mg lidocaine present in a single patch is expected to be absorbed into the skin, and roughly 60% of this amount is reflected in blood samples taken during application and for 12 hours after removal of the patch. This significant degree of systemic absorption sets lidocaine apart from most topical drugs applied to the skin and allows us to use pharmacokinetic measures to evaluate bioavailability at the site of action. How this systemic absorption of a significant portion of lidocaine that is released from the patch takes place is described in the subsections directly below.

(2) Lidocaine Passes Through the Stratum Corneum

When applied to the skin for pain relief, lidocaine penetrates the top layer of the skin, the stratum corneum, to reach its site of action on the nerve endings beneath the surface of the skin. As explained in labeling, "lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses."[26] This sets lidocaine apart from those topical drugs that do not penetrate the stratum corneum or upper layers of the skin to reach the site of action.

(3) Lidocaine is Expected to Enter the Bloodstream Through Capillaries in the Skin

Blood capillaries extend into upper layers of the dermis and are in close proximity to dermal pain receptors and nerve endings on which lidocaine acts. Therefore, the appearance of topically applied lidocaine in plasma confirms it has traveled through the stratum corneum to reach dermal capillaries proximate to the site of action, dermal pain receptors and nerve endings.

(4) Lidocaine's Presence in Plasma is Proportional to Its Presence at the Site of Action

Because capillaries are abundant beneath the surface of the skin, in proximity to lidocaine's site of action, we have the scientific expectation based on diffusional mass transport principles[27] that concentrations of lidocaine in plasma are proportional to its concentration at the site of action. The concentration gradient between lidocaine in tissue closer to the surface of the skin (higher concentration) and lidocaine in plasma (lower

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[25] Id.

[26] CLINICAL PHARMACOLOGY Section, Lidoderm PI, at 1.

[27] Diffusional mass transport is the spontaneous movement of chemical species from an area of higher concentration to an area of lower concentration. A common example is the spreading of a drop of dye in a glass of water. Movement of dye from high concentration to low concentration will eventually lead to a uniform solution. R.B. Bird, W.E. Stewart, E.N. Lightfoot, *Transport Phenomena* (Second Edition), published by J Wiley &Sons, New York 2002.

concentration) is the driving force for removal of lidocaine from the tissue.[28] The rate of uptake is directly proportional to this concentration difference. Published studies support this. Singh and Roberts reported lidocaine penetration studies conducted using isolated human epidermis that demonstrate the flux or amount of lidocaine transported from the surface layer of the skin to the lower layers is proportional to the applied concentration.[29]

The purpose of bioequivalence studies is to determine whether any formulation differences between a proposed generic product and the RLD on which it relies cause the active ingredient to reach the site of action at a different rate or extent. The pharmacokinetic studies recommended in the Draft Lidocaine Patch BE Guidance together with the recommended skin testing will reveal any differences between Lidoderm and another lidocaine topical patch product.

(5) Comparative Clinical Endpoint Trials Would Be Less Sensitive Than Pharmacokinetic Studies

In general, clinical endpoint studies are less sensitive than pharmacokinetic studies at detecting differences in formulation performance, as reflected in FDA's regulations.[30] In particular, in vivo clinical endpoint studies measure formulation differences indirectly rather than directly, include confounding variables such as different severities of disease, may have variability in the definition of the instrument used to measure efficacy (i.e. what is being used for the primary endpoint), and may have difficulty in assessing dose response (the pattern of physiological response to varied dosage). They also often require approximately 500 subjects to demonstrate bioequivalence. While sometimes appropriate, they are not here, where the nature of lidocaine permits a more precise evaluation of bioavailability through the pharmacokinetic methods and skin testing described in the Draft BE Lidocaine Patch Guidance.

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[28] Grillo, J.A.; Venitz, J., Ornato, J.P. (2001), "Prediction of lidocaine tissue concentrations following different dose regimes during cardiac arrest using a physiologically based pharmacokinetic model," *Resuscitation* **50**(3), 331-340.

[29] Singh, P. and Roberts, M.S. (1994), "Dermal and underlying tissue pharmacokinetics of lidocaine after topical application," *Journal of Pharmaceutical Sciences*, Vol. 83, No. 6, 774-782. See also Benfeldt, E., et al. (2007), "Bioequivalence of topical formulations in humans: Evaluation by dermal microdialysis sampling and dermatopharmacokinetic method," *Journal of Investigational Dermatology*, Vol. 83, No. 6, 170-178 (observed correlation between dermal microdialysis and dermatological pharmacokinetic methods supports that lidocaine transports through the skin and dermis according to diffusional mass transport).

[30] "This approach [comparative clinical endpoint trials] is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence" (21 CFR 320.24(b)(4)).

B. Petitioner's Legal, Regulatory, Scientific, and Policy Arguments

(1) Proposed Clinical Endpoint Studies in PHN Patients

You cite in your petition a published study that you assert reports lower mean peak plasma concentrations of lidocaine in patients with PHN following application of three patches for 12 hours, 0.052 μg/mL compared to 0.13 μg/mL in healthy volunteers (2006 petition, at 15-16 and Tab 1, 2007 amendment at 3, and Exhibit 4).[31] In your 2007 amendment, you argue that because damaged dermal tissue in PHN patients presents a unique and complex environment, "[p]lasma concentrations obtained downstream of this complex site of action have not been shown to correlate with changes in the rate and extent of absorption of the drug at the site of action" (2007 amendment at 3). You implicitly argue here more broadly that this potential lack of correlation between plasma concentration in PHN patients and absorption at the site of action counsels in favor of using clinical endpoint studies on patients with PHN to demonstrate bioequivalence.

We disagree with this argument on three grounds. First, the authors themselves acknowledge that their observations are of limited utility in supporting such a claim. For example, the authors observe that "[a] strict comparison of absorption between normal volunteers, patients with [acute herpes zoster], and patients with PHN is not possible" from the data generated by the study because the study was not designed with controls to capture this comparative information, and that "differences observed in absorption are confounded by differences in the site of application." As your petition acknowledges, differences in test subject age may also confound such a comparison.[32] Second, FDA's bioequivalence recommendation is not based on the proposition that plasma concentrations of lidocaine determine therapeutic effect, rather, that measurement of lidocaine in plasma from a generic lidocaine patch will indicate differences in the availability of the drug at the site of action from the RLD due to differences in formulation.

Third, on a more fundamental level, the purpose of bioequivalence testing is to determine whether any differences in formulation between a generic product and a listed drug will affect the rate and extent to which the active ingredient reaches the site of action. The use of healthy test subjects eliminates any variability in results between a generic product and Lidoderm that might be associated with varying disease states among test subjects. Even assuming that PHN may affect the absorption of lidocaine in a particular patient, you have not provided any evidence to show that observation of this potential lower absorption rate for lidocaine, if evaluated in vivo in patients, would identify *differences in formulation* that might affect bioequivalence and that would not be identified by FDA's recommended pharmacokinetic and skin testing. In other words, the article presents no

[31] Campbell et al. (May 2002) "Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster," *J. Pharm. Sci.*, Vol. 91, 1343-50.

[32] Our review of pharmacokinetic data contained in the Lidoderm NDA included this same conclusion, that "there appears to be a statistically significant difference with respect to age (p=0.0472)." Clinical Pharmacology/Biopharmaceutics Review, Appendix 2. NDA 020-612.

reason to expect that a generic product found to be bioequivalent to Lidoderm through pharmacokinetic and skin testing in healthy subjects would not be bioequivalent to Lidoderm in PHN patients. To the extent that there is lower absorption of lidocaine in PHN patients as a result of the disease (which FDA does not find has been demonstrated), FDA has no reason to believe that such effect would not be equally present for Lidoderm or a generic lidocaine patch product that has demonstrated bioequivalence through the methodology we have recommended.

(2) Replication of Analgesia without Complete Sensory Block

In the 2006 petition, you emphasize that the Lidoderm patch produces analgesia without causing a complete sensory block. This fact is reflected in Lidoderm's labeling. Specifically, under the heading "Pharmacodynamics" in the CLINICAL PHARMACOLOGY section of the labeling, it is stated:

> 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.[33]

Your petition asserts that any generic version of Lidoderm must be shown to provide an equivalent local analgesic effect without causing a complete sensory block (2006 petition at 8-14). You argue that a comparative clinical trial, rather than a pharmacokinetic study, would indicate whether a proposed generic product produces the same local analgesic effect without causing a complete sensory block, and is therefore the appropriate type of bioequivalence study. You further argue that a generic product would be misbranded if its labeling were to include an incorrect statement regarding the absence of a complete sensory block.

This argument reflects a misunderstanding of the approval process for generic drugs established under the Hatch-Waxman Amendments. To be approved, an ANDA applicant is not required to demonstrate through clinical endpoint trials that its product is safe and effective for the labeled conditions of use. Rather, it can rely on the finding of safety and effectiveness of the RLD as long as the product meets other requirements of the statute, including a demonstration that the proposed generic product is bioequivalent to the RLD.

As noted above, *bioequivalence* is defined to mean "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (21 CFR 320.1(e)). Thus, the purpose of bioequivalence testing is to determine whether any formulation differences between a generic product and the listed drug it references will affect the rate and extent to which the active ingredient reaches the site of action. When two products are pharmaceutically

[33] CLINICAL PHARMACOLOGY section, Lidoderm PI, at 1.

equivalent,[34] a demonstration of bioequivalence, together with satisfaction of the remaining requirements for approval, allows us to conclude they will have the same therapeutic effect. But the purpose of bioequivalence testing is not to measure safety or efficacy directly. Accordingly, an ANDA applicant does not have to demonstrate that its product has the same clinical effect of analgesia as Lidoderm without complete sensory block.

In a similar vein, you assert that FDA must define the dose-response relationships for analgesia without total sensory block in order to use pharmacokinetic measurements to establish bioequivalence for topical lidocaine products (2007 amendment at 23-24). In sum, you assert that pharmacokinetic studies cannot be used to demonstrate bioequivalence in the absence of data correlating applied dose, local tissue concentration, clinical effect, and plasma concentrations. We disagree with this assertion. As explained above, an applicant seeking approval of a generic drug under section 505(j) of the Act must demonstrate bioequivalence, meaning "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action. . ." (21 CFR 320.1(e)). Under the statutory scheme established by the Hatch-Waxman Amendments, ANDA applicants are not required to conduct additional studies to demonstrate a clinical effect.

You also assert that other topical pain relief drug products that contain lidocaine produce lidocaine plasma levels similar to those associated with Lidoderm but produce complete sensory block, and therefore that plasma levels do not reflect activity or availability at the site of action (2006 petition at 10-11, 2007 amendment at 6-7). The two products you cite, however, are not analogous to Lidoderm because they contain other active ingredients, in addition to lidocaine. Specifically, your petition cites two approved lidocaine products — EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) and SYNERA topical patch (lidocaine 70 mg and tetracaine 70 mg) — as suggesting that plasma concentrations of lidocaine do not reflect its rate and extent of availability at the site of action (id.). In the case of EMLA Cream, you cite the product labeling stating that peak plasma concentrations of lidocaine following its application for 3 hours or 24 hours were 0.12 μg/mL or 0.28 μg/mL, respectively.[35] You state that these plasma concentrations are comparable to those seen with Lidoderm following maximum recommended dosing

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[34] *Pharmaceutical equivalents* means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates (21 CFR 320.1(c)).

[35] See Table 1, "Absorption of Lidocaine and Prilocaine from EMLA Cream: Normal Volunteers (N=16)," CLINICAL PHARMACOLOGY section of EMLA Package Insert, at 4, available at Drugs@FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019941s018lbl.pdf.

in healthy volunteers (0.13 μg/mL), and yet EMLA Cream is labeled as capable of producing a complete sensory block, while Lidoderm is not. Similarly, in the case of the SYNERA topical patch, you suggest that mean peak plasma lidocaine concentrations of just 0.0017 μg/mL may be associated with blocked sensation to the treated skin. These comparisons are inapposite, however, because both the EMLA and SYNERA products contain a second active ingredient, prilocaine or tetracaine, in combination with lidocaine. The observed complete sensory block may be due to synergistic or additive effects of the two ingredients, and thus cannot be selectively attributed to lidocaine alone. More fundamentally, this information does not support your position that any given plasma concentration of lidocaine by itself is associated with the possibility of complete sensory block in treated skin.

In the absence of evidence, your assertion that a generic lidocaine topical patch 5% product may satisfy our draft bioequivalence guidance and yet produce a complete sensory block is speculative and unavailing.

(3) Portfolio Approach to Bioequivalence Testing for Topical Products

In your 2007 amendment, you indicate that FDA employees at 2003 and 2004 meetings of our Advisory Committee for Pharmaceutical Science (ACPS)[36] referenced a "portfolio approach" to establishing bioequivalence for topical products, whereby a collection of tests taken in combination would be sufficient to demonstrate bioequivalence. You assert that FDA should take such an approach, and that the value of pharmacokinetic studies in such an approach is "limited to systemic exposure safety concerns rather than local bioequivalence" (2007 amendment at 21). Upon review of this position and the statements referenced therein, nothing in this discussion persuades FDA that that we should change our recommended pharmacokinetic and skin testing studies to demonstrate bioequivalence for topical lidocaine products.

First, statements made by an FDA employee, either orally or in writing, are informal communications representing the judgment of the individual at the time. Such statements do not qualify as advisory opinions, do not necessarily represent the formal position of FDA, and do not bind or otherwise obligate or commit the Agency to the views expressed (21 CFR 10.85(k)).[37] Accordingly, even if FDA employees had indicated that the Agency should use the portfolio approach discussed at the meeting for all topical products (which they did not, as discussed below), such statements would not bind the Agency in determining the appropriate bioequivalence method for a particular product.

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[36] Now called the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology.

[37] Courts have rejected efforts to cite statements made by FDA employees regarding bioequivalence to demonstrate the Agency's official position on the issue. *Serono Labs., Inc. v. Shalala*, 158 F.3d at 1321 (rejecting reference to documents that revealed pre-decisional disagreement among FDA chemists as to whether an active ingredient in an ANDA product was the same in RLD); *Fisons Corp. v. Shalala*, 860 F. Supp. at 867-68 (rejecting citation to prior public statements made by Agency employees about how generic impurities would be considered in an ANDA review as evidence of an Agency policy or practice of waiving a bioequivalence requirement, citing subsections 10.65(a) and 10.85(k)).

Second, some of the statements by Agency employees you cite in this context to challenge our bioequivalence recommendation for lidocaine patch products in fact support the recommendation. For example, you assert that some of the statements from FDA staff indicate that the Agency has "stepped back" from general acceptance of dermatopharmacokinetic (DPK) testing in bioequivalence determinations for topical products and that rather than trying to develop a single universally applicable method, we are focusing on a "mechanistic understanding of the topical drug absorption process" (2007 amendment at 19-20). These statements are consistent with our approach in developing the bioequivalence recommendation for generic lidocaine patches, in which we have examined the particular nature of Lidoderm as topical pain relief product for which pharmacokinetic measure does reflect availability of lidocaine at the site of action at the nerves, as described in detail above.

You also refer to a statement made by FDA's Dr. Jonathan Wilkin at the 2003 ACPS meeting. According to the transcript you reference, his statement was: "I think Dr. Hussain mentioned that *there can be* a portfolio approach" (emphasis added).[38] Dr. Hussain later stated:

> But *I think* what we will be doing is moving towards a portfolio approach on looking at a combination test, different test, and sort of trying to construct that portfolio that either a combination of tests will cover all aspects or if you will have a test which will be different for different indications. So *I think* that is the concept we want to move forward with.[39] (Emphasis added.)

Even if these and other statements you reference were binding on the Agency, which they are not, they were carefully qualified, and do not reasonably imply that a portfolio approach requires multiple types of bioequivalence studies for every topical drug product.

Third, you assert that pharmacokinetic studies were generally omitted from discussions about the portfolio approach, suggesting they should therefore have no role in bioequivalence determinations for topical lidocaine patch products. In fact, pharmacokinetic studies likely would not come up in discussions of a portfolio approach because many topical dermatological drugs cannot be quantified in pharmacokinetic studies. In contrast, lidocaine is significantly absorbed and easily quantified in plasma.[40]

Because of the specific properties of Lidoderm, we have determined that pharmacokinetic studies on patches of the same size, together with skin irritation, sensitization, and

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[38] ACPS Oct. 22, 2003 meeting transcript at 252.

[39] Id. at 277.

[40] This is consistent with the statement you cite by FDA's Dr. Robert Lionberger in which you describe that he "suggested it may be possible to demonstrate bioequivalence through plasma concentration profiles where 'you knew that plasma concentration actually reflects the delivery at the site of action'" (2007 amendment at 20 (quoting 2007 ACPS Meeting Transcript)).

adhesion data, would be the most appropriate method. Other tests mentioned in your petition would not be useful in this case for the following reasons:

- Diffusion cell tests are not needed because pharmacokinetic studies can quantify the amount of drug that crosses the skin;
- Rheology tests are not needed because the patch does not spread;
- DPK is not appropriate because lidocaine's site of action is not the stratum corneum; and
- Microdialysis could be an alternative to pharmacokinetic sampling for this drug, but would not offer a more sensitive, accurate, and reproducible method than that recommended in the Draft Lidocaine Patch BE Guidance, and is not needed in addition to pharmacokinetic testing.

(4) Measurement of Residual Lidocaine in Used Patches

In your petition (2007 amendment at 26), you question the following recommendation in our Draft Lidocaine Patch BE Guidance:

> In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. The amount of adhesive residue from each patch left on the skin should be analyzed and included in the calculation.[41]

You state that the amount of lidocaine in a used patch relative to levels of lidocaine at the site of action differs "by orders of magnitude." You also state that clinical experience with Lidoderm suggests there is no adhesive residue associated with its use and that there is no evidence of correlation between residual drug in the patch and blood levels, local concentration at the site of action, or clinical effect of lidocaine from the Lidoderm patch, and therefore the apparent dose delivered should not be used to support a demonstration of bioequivalence.

FDA recommends evaluation of the apparent dose delivered to demonstrate that there is no significant difference in the apparent dose delivered between Lidoderm and a proposed generic product. This value is obtained in part by determining how much lidocaine remains in used patches, notwithstanding that most of the lidocaine present remains in the patch. Whether or not Lidoderm leaves behind any adhesive residue on patients' skin, we recommend that generic applicants evaluate this characteristic in their proposed generic products.

In this discussion, you further question our recommended skin irritation, sensitization, and adhesion testing, asserting that such testing normally is "performed principally for safety considerations rather than as a mechanism of assessing local delivery" (2007

[41] In other words, the amount of lidocaine present in any adhesive residue left on the surface of the skin should not be counted as part of the delivered dose.

amendment at 27).[42] The recommended skin testing is necessary to demonstrate bioequivalence, and is appropriately rigorous, as discussed below in our responses to the second and third requested actions in your 2012 amendment. That such testing may also be conducted to evaluate the safety of a product does not preclude FDA from recommending use of such testing in support of bioequivalence.

(5) Potential Impact of Excipients on the Rate and Extent of Absorption

In your 2007 amendment, you point out that formulation differences can affect the rate and extent to which active ingredients in topical products are absorbed (2007 amendment at 24). You further assert that "excipient-associated changes may not be reflected in integrated downstream sampling of systemic lidocaine in blood" (id.). You suggest FDA lacks scientific data in this area to support our reliance on pharmacokinetic studies to demonstrate bioequivalence for topical lidocaine products.

We agree that inactive ingredient formulation differences can affect the rate and extent to which an active ingredient reaches the site of action. Indeed, this is why bioequivalence testing is needed to support the approval of generic products. However, we disagree with your view that this creates a special challenge in the case of topical lidocaine products. For the reasons explained in section II.A above, we are confident that measurements of lidocaine in plasma can be used to assess any differences in the rate and extent to which it reaches the site of action in PHN patients. Your petition does not persuade us otherwise, and does not include data showing that formulation differences in topical lidocaine patch products may affect the rate and extent to which lidocaine is delivered to the site of action in a way that would not be revealed in the pharmacokinetic testing we have recommended.

(6) Cmax and AUC as Indicators of Bioequivalence for Topical Drugs

You assert that maximum plasma concentration (Cmax) and total area under the plasma concentration-time curve (AUC) are not reliable indicators of bioequivalence for topical drug products such as Lidoderm (2007 amendment at 24-25). To support this, you state that Lidoderm relies on a slow onset of clinical effect, and pharmacokinetic measurements are "unsuitable for this type of drug where clinical effect is tied directly to absorption rate" (id.).

With respect to certain types of products, including multiphasic products with multiple delivery mechanisms, FDA has recommended partial AUC studies as part of the bioequivalence analysis.[43] However, for an active ingredient such as lidocaine with a simple, well characterized pharmacokinetic profile, AUC and Cmax (along with Tmax)

[42] You also assert that asserting that the recommended irritation, sensitization, and adhesion testing is inadequate to ensure bioequivalence (2012 amendment, at 16-24.

[43] By "multiphasic" we mean a product that delivers active ingredient(s) in more than one phase, such as an immediate-release phase and an extended-release phase. See, for example, our guidance on bioequivalence testing for oral, extended-release zolpidem tablets (October 2011).

are sufficient to compare two pharmacokinetic profiles and ensure that the rate is the same. There is no evidence that partial AUC would be more appropriate to evaluate the bioequivalence of generic lidocaine patch products.

(7) Anatomical Placement of Patches in Testing

You state that our Draft Lidocaine Patch BE Guidance includes no recommendations regarding the anatomical placement of patches (2012 amendment at 23-24). You argue that multiple sites should be tested to ensure adhesion is consistent regardless of anatomical placement. You further argue that application of lidocaine patches to different anatomical sites may disrupt skin architecture differently and exacerbate differences in drug absorption.

You have not persuaded us that our recommended test methods are inadequate in this respect. We recognize that PHN may occur anywhere on the body, and that the Lidoderm labeling instructs patients to apply Lidoderm patches "to intact skin to cover the most painful area" using up to three patches for up to 12 hours in a 24-hour period.[44] The recommended skin testing directs 21 days of continuous patch application at the same anatomical site. In a crossover pharmacokinetic study, both the test patch and the reference patch are expected to be applied to the same site to provide a comparison of formulation performance. As we have stated previously, the purpose of bioequivalence testing is to detect differences in formulation that may affect availability at the site of action. It is not to test comparative effectiveness between the generic and the RLD in each and every possible scenario of use. We have determined that the recommended skin testing is sufficient to reveal any differences in adhesion or skin irritation that could lead to differences in bioavailability.

(8) Regulatory and Legal Issues

a. Measurement of Bioavailability at the Site of Action

You argue that bioequivalence must be determined through measurements directly *at the site of drug action* (2006 petition at 6 and 16), citing 21 CFR 320.1(e). You state that the site of action for Lidoderm is the location where the patch is applied. On this basis, you argue that bioequivalence must be *measured* at the site of action rather than through plasma concentrations. This reflects a misreading of our statute and regulations. Nothing in the Act, in our regulations, or in Agency guidance suggests that bioequivalence must be determined through measurements made directly at the site of drug action. Rather, as section 320.23(a)(1), another regulation you cite in support of your position, provides, "[f]or drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements *intended to reflect* the rate and extent to which the active ingredient or active moiety becomes available at the site of action" (emphasis added). As described above, FDA has determined that, due to the specific characteristics of the lidocaine patch, plasma concentration of lidocaine reflects the rate

[44] See Dosage and Administration, Lidoderm PI, at 6-7.

and extent to which lidocaine becomes available at the site of action, dermal pain receptors and nerve endings.

b. Applicability of Section 505(j)(8)(C) of the Act

Your petition cites section 505(j)(8)(C) of the Act, which states:

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

You contend that this provision requires that bioequivalence testing for a lidocaine topical patch product be capable of detecting a significant difference between Lidoderm and a proposed generic product in safety and therapeutic effect (2006 petition at 13-14). You further contend that plasma concentrations of lidocaine cannot demonstrate whether a proposed generic product will produce local analgesia without complete sensory block, and therefore pharmacokinetic studies may not be used in place of comparative clinical endpoint studies to show bioequivalence.

We disagree with this analysis for several reasons. Section 505(j)(8)(C) states that the Secretary *may*, not *must*, establish alternative methods, meaning methods other than the standard pharmacokinetic studies, to demonstrate bioequivalence for drugs not intended to be absorbed into the bloodstream. This provision reinforces FDA's discretion to determine the appropriate bioequivalence method on a product-by-product basis, and FDA does not interpret it to be a bar to the bioequivalence methodology recommended in the Draft Lidocaine Patch BE Guidance.[45] In the case of lidocaine topical patch products, the Agency recommends standard pharmacokinetic testing to assess bioequivalence. Therefore, the statement in section 505(j)(8)(C) regarding alternative test methods is not applicable to pharmacokinetic bioequivalence testing for lidocaine topical patch products. Furthermore, regardless of whether section 505(j)(8)(C) were applicable here, it is our scientific judgment that the Agency's recommended pharmacokinetic testing and skin testing is more capable than clinical endpoint studies of detecting any differences between Lidoderm and a proposed generic product in the rate and extent to which the active ingredient becomes available at the site of action. Because the drug's safety and therapeutic effect depends on skin irritation potential and the rate and extent to which the active ingredient reaches the site of action, our recommended studies will detect any significant difference in safety and therapeutic effect between Lidoderm and a proposed generic product.

c. Effect of 21 CFR 320.24(b)(4)

Your petition quotes portions of section 320.24(b)(4) of our regulations as follows:

[45] See section I.B above and note 84 for a discussion of FDA's broad authority to determine bioequivalence data necessary to support an ANDA.

> Furthermore, section 320.24(b)(4) provides for the use of "appropriately designed comparative clinical trials for the purposes of demonstrating bioequivalence . . . of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes. . . ."

(2006 petition at 16-17)

You argue that Lidoderm falls squarely into the category of product contemplated by this provision and that any generic applicant must follow its requirements. We do not agree.

Section 320.24(b) identifies five general methods that are acceptable for determining bioavailability or bioequivalence and additionally allows for any other approach deemed adequate by FDA. We agree that section 320.24(b)(4) describes the use of comparative clinical trials to assess bioequivalence for topical skin preparations, but this regulation cannot be read as *requiring* the use of comparative clinical trials for such products. The regulation states that comparative clinical trials *may*, not *must*, be acceptable for testing bioequivalence of locally acting products, and provides topical skin preparations as an example of a general category for which comparative clinical trials may be appropriate. It does not set forth the exclusive means of demonstrating bioequivalence for topical products. Such an interpretation would be directly inconsistent with subsection 320.24(b)(6), which provides that in addition to the delineated categories, FDA may use "[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence." Moreover, section 320.24(b)(4) expressly states that comparative clinical trials are the least accurate, sensitive, and reproducible for demonstrating bioequivalence. In the context of orally administered drugs, we have stated in guidance that "we recommend that the use of comparative clinical trials as an approach to demonstrate BE generally be considered insensitive and be avoided where possible."[46] The same principle applies here. If pharmacokinetic studies are capable of measuring the rate and extent of drug delivery to the site of action, as they are in the context of our Draft Lidocaine Patch BE Guidance, they are preferred over comparative clinical trials.

d. Notice and Comment

You argue that FDA's recommendation of pharmacokinetic studies to demonstrate bioequivalence for a lidocaine patch constituted a substantive change in our interpretation of the regulations that required notice and comment rulemaking (2007 amendment at 30-31). In support of that argument, you state that FDA previously identified bioequivalence studies with clinical endpoints as the bioequivalence approach most generally applicable to non-solution topical dermatological products. This argument is based on the flawed premise that Lidoderm is a dermatological product. As explained in section II.A, above, lidocaine is a topical pain relief product; although lidocaine is applied to the skin, it is

[46] Guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (March 2003), available on the Agency's Web site under Guidances (Drugs).

expected to pass through the stratum corneum to reach its site of action on the nerves. It is not a dermatological product as you suggest.

In sum, FDA rejects your argument that FDA has changed its recommendations on bioequivalence testing for lidocaine patches. FDA has not previously recommended comparative clinical endpoint studies for these products, and the Agency's determination that bioequivalence may be demonstrated by pharmacokinetic studies is not inconsistent with prior FDA recommendations.[47]

e. Explanation of Scientific Support for Bioequivalence Recommendations

Citing section 706(2) of the Administrative Procedure Act, you maintain that the Agency has not satisfactorily explained or supported with substantial evidence its recommended method for bioequivalence testing of lidocaine topical patch products, and therefore that the Agency must withdraw the draft guidance (2007 amendment at 27-28). Again, this argument misconstrues the nature of our bioequivalence recommendations. FDA's regulations expressly provide that "[g]uidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA."[48] As courts have upheld, FDA's guidance documents are not final Agency actions the publication of which is subject to review under the standards set forth in the Administrative Procedure Act.[49]

f. Timing of FDA's Response to the Petition

You also argue that FDA's failure to provide a substantive response to your petition at the time of your 2012 amendment was unreasonable and in violation of the law, citing section 706(1) of the Administrative Procedure Act (2012 amendment, at 43-44). In this argument you refer to the enactment of section 505(q) of the Act as "useful context" for considering what qualifies as reasonableness in the length of time it takes for the Agency to respond to petitions (id.). You are correct that your petition, filed in 2006, prior to the

[47] We are not addressing your claim that a change in a bioequivalence recommendation would constitute a substantive change in interpretation that would require notice and comment rulemaking. FDA expressly has rejected this position in other petition responses. See Letter fr. J. Woodcock to T. Doyle, ViroPharma, Inc., at 63-64 (April 9, 2012) (detailing FDA's position that guidance documents are by their nature not definitive interpretations of the bioequivalence regulations the amendment of which requires notice-and-comment rulemaking).

[48] 21 CFR 10.115(d)(1).

[49] *In re Flonase Antitrust Litig.*, 795 F. Supp. 2d 300, 303 (E.D. Pa. 2011) ("[e]ven a final [FDA] guidance, however, does not 'create or confer any rights for or on any person and does not operate to bind FDA or the public'"); *BBK Tobacco & Foods, LLP v. FDA*, 672 F. Supp. 2d 969, 975 (D. Ariz. 2005) ([i]t is clear that the guidance documents, which represent only the FDA's 'current thinking,' do not constitute the final administrative word"). *See generally, Nat'l Ass'n of Home Builders v. Norton*, 415 F.3d 8, 14 (D.C. Cir. 2005) (concluding EPA "recommended" protocols that do not impose legal obligations are not final Agency actions).

enactment of section 505(q), does not fall into this category and is therefore not subject to the 180-day deadline of section 505(q).

As for the timeliness of this response, FDA notes that you amended your petition twice, once in August 2007 and most recently in March 2012. In particular, your March 2012 amendment was extensive, with 14 new requested actions. Your petition and each amendment raised a significant number of scientific, regulatory, and legal arguments that the Agency carefully considered prior to approving an ANDA for a lidocaine patch, which it is doing today. You are receiving this substantive response to your petition and amendments approximately 5 months after the submission of your last amendment.

(9) Prior Statements of FDA and FDA representatives on Bioequivalence for Topical Products

Throughout your submissions, you cite numerous statements from FDA staff regarding bioequivalence testing for topical products (e.g., 2006 petition at 18-21, 2007 amendment at 8-21). Your petition presents these statements as inconsistent with the bioequivalence methodology set forth in the Draft Lidocaine Patch BE Guidance.

As a preliminary matter, as noted above in section II.B.3, statements made by an FDA employee, either orally or in writing, are informal communications representing the judgment of the individual at the time.

The statements you cite do not support your assertion that FDA employees "consistently" have rejected the use of pharmacokinetic data to demonstrate bioequivalence for a lidocaine patch product. For example, Dr. Robert Lionberger, a chemist in FDA's Office of Generic Drugs, is quoted from a presentation at a 2004 Advisory Committee for Pharmaceutical Science saying "[t]he current state of topical bioequivalence is that . . . for almost all locally acting dermatological products clinical trials are necessary to determine bioequivalence" (2006 petition at 19). Dr. Lionberger's statement on its face was qualified as pertaining to *almost all* locally acting *dermatological* products. This statement explicitly pertains only to dermatological products (i.e., drugs that treat diseases of the skin) and, in any event, did not purport to relate to "all" locally acting dermatological products. As explained above, dermatological drugs more often do not penetrate the stratum corneum and are not expected to be absorbed into the bloodstream. Lidocaine is a pain relief product; it is intended to penetrate the stratum corneum, and it is absorbed into the bloodstream to a significant degree.

In your 2007 amendment, you refer to statements made by Dr. Dale Conner of our Office of Generic Drugs at March 2003 meeting of FDA's Advisory Committee for Pharmaceutical Science (2007 amendment at 8 and 18). You allege that FDA's 2003 decision to approve generic versions of EMLA cream, supported by pharmacokinetic bioequivalence data, was contradicted in Dr. Conner's discussion at this meeting. However, you overlook Dr. Conner's introductory statement:

> First, we have to clearly say what we're talking about here because for those who don't deal with dermatologic products or deal with the skin all the time, there is

> sometimes confusion. What we're dealing with in this discussion is products applied locally to the skin *to treat diseases of the skin.* (Emphasis added.)[50]

As we have clarified throughout this response, topical dermatological products (i.e., drugs that treat diseases of the skin) often act in the stratum corneum or upper layers of the skin and are not systemically absorbed to the extent that topically applied lidocaine is. Dr. Conner's remarks were carefully qualified as applying to these products, and hence it is not surprising that he did not discuss or distinguish the generic EMLA products, which are topical anesthetics with a site of action beneath the stratum corneum.

Your 2012 amendment also quotes our 2009 response to a citizen petition submitted by Hill Dermaceuticals, Inc. regarding a topical dermatological product called Derma-Smoothe (Docket No. FDA-2004-P-0215) (2012 amendment at 8).[51] Specifically, you quote our statement that when a product "acts locally and is not intended to be systemically absorbed, bioequivalence must be measured by another method," meaning a method other than pharmacokinetic studies. This citation is inapposite. First, the product at issue in that case was a locally acting dermatological product, not an anesthetic with a site of action beneath the stratum corneum. Moreover, even with respect to dermatological products, that statement was not precise. More specifically, bioequivalence is *most often* measured by another method when a drug acts locally and is not intended to be systemically absorbed. FDA has significant flexibility in determining how the bioequivalence requirement is met on a product-by-product basis. Notably, FDA has recommended pharmacokinetic data in conjunction with other testing, as it has here, to evaluate bioequivalence of other locally acting products.[52]

In addition, contrary to your representations in the petition and its amendments, the Agency's views on bioequivalence testing for topical lidocaine products have remained constant since 2003. In 2003, we approved three ANDAs for generic topical cream products that relied on pharmacokinetic studies to show bioequivalence to EMLA Cream (lidocaine 2.5%, and prilocaine 2.5%).[53] Since the time of our October 5, 2006, Dear Applicant letter, the Agency has publicly recommended pharmacokinetic studies to establish bioequivalence for lidocaine topical patch 5% products. The Agency's continuing examination of bioequivalence methods for topical dermatological products does not undermine this position. Notably, your petition includes no claims or evidence suggesting that generic versions of EMLA Cream do not match the safety and

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[50] Dale Conner, remarks at March 12, 2003, meeting of FDA's Advisory Committee for Pharmaceutical Science, Transcript at 167.

[51] Letter fr. J. Woodcock to J. Roth, Hill Dermaceuticals, Inc. (Mar. 25, 2009) (regarding appropriate bioequivalence methodology for generic fluocinolone acetonide 0.01% topical oil).

[52] See, e.g., Aug. 20, 2010 Letter fr. FDA to I.Hara, Warner Chilcott Co. LLC. at 11 (Mesalamine CP Response) (concluding comparative clinical endpoint studies "less sensitive, accurate, and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product).

[53] See ANDA approval history for lidocaine and prilocaine topical cream 2.5%/2.5%, available on FDA's Web site at Drugs@FDA.

effectiveness of the RLD, to which they were deemed bioequivalent on the basis of pharmacokinetic data. Nor does your reference to the studies required for approval of a topical patch dosage form of EMLA cream support your position (2007 amendment at 18-19). For that supplement, FDA found that pharmacokinetic studies showed comparable blood levels of the two active ingredients delivered by the two dosage forms (patch and cream), but determined that clinical studies were required to show efficacy of the patch.[54] There, FDA was reviewing different formulations in different dosage forms to assess differences in lidocaine release characteristics and absorption of the two different products. Those considerations differed from what FDA is considering here — the bioavailability of two lidocaine patches with the same drug concentration, time of application, and identical areas of application. Finally, the fact that the European Medicines Agency required comparative clinical endpoint studies for approval of generic EMLA products, and the resulting "scientific isolation" of FDA's recommendation for use of pharmacokinetic and skin testing, do not counsel in favor of FDA's requiring comparative clinical trials where the Agency has determined, in its scientific expertise and within our own regulatory framework, that such trials are not the most sensitive, accurate, and reproducible (see 2012 amendment at 14-16).

In sum, for the lidocaine patch, we have determined, for the scientific reasons set forth above, that the pharmacokinetic and skin tests recommended in the Draft Lidocaine Patch BE Guidance are appropriate. This conclusion is not inconsistent with historical, general statements made by FDA employees about a class or classes of products.

(10) Substantive Criticism of Our Draft BE Guidance

You criticize the Agency's recommended use of single-dose pharmacokinetic testing to demonstrate bioequivalence. Specifically, you argue that single-dose 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" (2012 amendment at 21). You also state that "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" (id. at 18).

Instances in which multiple-dose studies can be useful to determine the bioavailability of a drug product are identified in 21 CFR 320.27(a)(3). In general, however, it is recognized that single-dose pharmacokinetic studies are preferred for bioequivalence determinations as they are more sensitive at detecting differences in formulation performance.[55]

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[54] See approval package for EMLA Anesthetic Disc, NDA 20-962, available through the Drugs@FDA searchable database on our Web site.

[55] See, e.g., FDA's guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*, at 8 (March 2003) ("this guidance generally recommends single-dose pharmacokinetic studies for both immediate- and modified-release drug products to demonstrate BE because they are *generally* more sensitive in assessing release of the drug substance from the drug product into the systemic circulation") (emphasis in original).

Your statement quoted above that "OGD assumes blood levels seen after a single use will accurately represent blood levels seen under [repeated daily use]" also reflects your misunderstanding of bioequivalence testing. As stated above, an ANDA applicant does not need to submit data demonstrating the bioavailability of the active ingredient in the generic lidocaine patch over the indicated course of use. The point of bioequivalence testing is to detect whether differences in formulation between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action. Lidoderm is not a product that falls within the circumstances set out in section 320.27(a)(3), and you have not submitted any evidence that a multi-dose study would be better in detecting such differences than the bioequivalence methods we have recommended.

C. Requested Actions

Actions Requested in 2006 Petition

In your original 2006 petition, you asked that FDA amend its October 5, 2006, Dear Applicant letter to include two additional requirements: (1) that an applicant seeking to demonstrate its product's bioequivalence to Lidoderm be required to conduct comparative clinical studies, and (2) that an applicant relying on Lidoderm as its RLD be required to show its product produces the same local analgesic effect without producing a complete sensory block.

We are denying these two requested actions. For the reasons discussed above, we have determined that pharmacokinetic studies along with skin tests are appropriate for evaluating whether a lidocaine topical patch 5% product is bioequivalent to Lidoderm. Pharmacokinetic and skin testing is expected to be more accurate, sensitive, and reproducible than comparative clinical endpoint studies for this purpose. If an ANDA applicant has demonstrated bioequivalence to the RLD and has met the other approval requirements set forth in section 505(j) of the Act, the Agency will approve the application. An ANDA applicant is not required to demonstrate independently the safety or effectiveness of its product.

Actions Requested in 2007 Amendment

In your 2007 amendment, you asked FDA to take four actions; the requested actions, and our response to each request, are set forth in items 1 through 4 below.

1. Withdraw the lidocaine topical patch, 5%, bioequivalence recommendations contained in the October 2006 controlled correspondence from FDA's Office of Generic Drugs.

You make this request on the basis of your assertion that FDA's bioequivalence recommendations for a lidocaine patch "lack scientific validity, conflict with statutory provisions and regulations regarding bioequivalence, and violate administrative law"

(2007 amendment at 1).[56] For the reasons set forth in this petition response, FDA's lidocaine patch bioequivalence recommendation is scientifically valid, is consistent with the Act and FDA regulations, and does not violate administrative law. We therefore are denying this request.

2. Convene a joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Advisory Committee for Pharmaceutical Science (now called the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology) to discuss development of appropriate method(s) for demonstrating bioequivalence for drug products with patch dosage forms and local routes of administration.

We are denying this requested action. As explained above, we have determined that pharmacokinetic studies together with skin testing can reliably be used to evaluate bioequivalence for lidocaine topical patch 5% products. Although FDA acknowledges the fundamentally important role that advisory committees play in the regulatory approval process, FDA is not limited to accepting only data endorsed by an advisory committee. As recognized in our regulations, FDA has discretion in deciding whether to refer a matter to an advisory committee.[57] We have determined that bioequivalence testing methodology for lidocaine topical patches is not sufficiently controversial or of such significant public interest that it would be highly beneficial for FDA to obtain the advice of an advisory committee. Nor do we find that this subject requires special expertise that an advisory committee could provide.[58] Accordingly FDA declines your request.

3. Decline to approve or stay the approval of any ANDA or 505(b)(2) application referencing Lidoderm that does not contain studies with clinical safety and efficacy endpoints that demonstrate bioequivalence to Lidoderm.

We are denying this request consistent with our determination, explained above, that pharmacokinetic studies along with skin testing are more accurate, sensitive, and reproducible than comparative clinical endpoint studies for demonstrating the bioequivalence of lidocaine topical patch 5% products.

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[56] FDA interprets this requested action to applying to the Draft Lidocaine Patch BE Guidance as well as the October 2006 letter that first set forth FDA's recommendation for the appropriate bioequivalence method for generic lidocaine patch products.

[57] 21 CFR 14.5(b). By contrast, the Act requires FDA to refer matters to advisory committees in certain circumstances. See, e.g., sections 505A(i)(2)(A), 513(c), and 520(l)(2) of the Act.

[58] For a general discussion of factors we consider in deciding whether to refer a matter to an advisory committee, see our draft guidance for the public and FDA staff on *Convening Advisory Committee Meetings* (August 2008), available on FDA's Web site under Advisory Committee Guidance Documents. When finalized, this guidance will represent FDA's current thinking on this topic.

4. If the Agency contemplates an alternative to bioequivalence studies with clinical endpoints for Lidoderm, only develop such method through a valid public process, with input from FDA advisory committees, including the Dermatologic and Ophthalmic Drugs Advisory Committee and the Advisory Committee for Pharmaceutical Science (now called the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology).

To the extent this request calls for notice of and an opportunity to comment on bioequivalence guidance for a lidocaine patch product that does not recommend comparative clinical trials, this request already has been granted. FDA posted the Draft Lidocaine Patch BE Guidance on its Web site in May 2007. In addition, FDA provided public notice of this guidance in the *Federal Register*.[59] Public comments were requested by January 23, 2008. Endo submitted comments dated November 2, 2007, which we have reviewed and considered.

For the reasons stated in responding to your second 2007 requested action above, we also deny your request that FDA seek input from advisory committees regarding bioequivalence testing for lidocaine topical patch 5% products.

Actions Requested in 2012 Amendment

In your 2012 amendment, you asked FDA to take fourteen actions; the requested actions, and our response to each request, are set forth in items 1 through 14 below.

1. Not review or approve any generic lidocaine patch 5% product 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 analgesia and absence of complete sensory block have been conducted; 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 Lidoderm and the proposed generic product.

This request proposes two significant data requirements: (1) a clinical study that correlates pharmacokinetic measurements (e.g., concentrations of lidocaine in plasma) with a pharmacodynamic endpoint (analgesia without complete sensory block), and (2) a repeated-dose pharmacokinetic study, of indefinite duration, in which you specify three things that would be measured: "drug absorption, rate and extent of drug delivery at the site of action, and rate and extent of delivery to the blood."

[59] FR Lidocaine Notice at 60683. (See note 20.)

We are denying this request as inconsistent with our determination, explained above, that bioequivalence testing for lidocaine topical patch 5% products should be evaluated through pharmacokinetic and skin testing as set out in the Draft Lidocaine Patch BE Guidance, and as inconsistent with the statutory requirements for approval of an ANDA. An ANDA applicant is required to demonstrate bioequivalence to Lidoderm, meaning "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[60] It is the Agency's scientific judgment, for the reasons explained above, that pharmacokinetic testing is the most sensitive, accurate, and reproducible method for testing lidocaine topical patch 5% products for bioequivalence to Lidoderm. Accordingly, it would not be appropriate for the Agency to require additional studies from ANDA applicants, aimed at demonstrating, as you propose, a correlation between pharmacokinetic measurements and pharmacodynamic effects when such data are not necessary to demonstrate bioequivalence.[61]

Your petition also urges us to require repeated-dose pharmacokinetic testing. The Draft Lidocaine Patch BE Guidance recommends a single-dose study in which patches are applied to healthy volunteers over a 12-hour period. We recommend inclusion of a 24-hour sampling time after application of the patch, which provides for measurement during 12 hours the patch is on, and for 12 hours after the patch is removed. Your petition argues that a repeated-dose study would be more appropriate to evaluate any differences in absorption of lidocaine caused by skin stripping or skin irritation associated with long-term use of the patch. As discussed above, single-dose pharmacokinetic studies are generally preferred as they are more sensitive at detecting differences in formulation performance. Multiple-dose studies lead to baseline concentrations of the active ingredient in plasma that may mask differences in the rate and extent of systemic absorption. For this reason, we recommend a single-dose pharmacokinetic study, along with a separate evaluation of skin irritation.

Our recommended skin irritation study includes a 21-day induction phase, during which patches are worn continuously, 24 hours per day, and changed three times each week. This induction phase is followed by a 2-week rest period and a 48-hour challenge application to test for sensitization and irritation. These test conditions significantly exaggerate the labeled conditions of use, notably the 12-hours-on, 12-hours-off, use pattern. The Agency consistently recommends a 21-day induction phase as part of skin irritation and sensitization testing of topical and transdermal patches (see footnote 64 for examples). We have determined that such a study will be adequately sensitive to detect

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[60] 21 CFR 320.1(e).

[61] Your 2012 amendment references two poster presentations by Patrick Noonan et al., commenting on our Draft Lidocaine BE Guidance. You assert that these presentations highlight many open issues and data insufficiencies. As presented in this section of our response letter, we are not persuaded that any additional data are needed to support reliance on pharmacokinetic studies to demonstrate bioequivalence for a lidocaine topical patch product.

significant differences in skin stripping or irritation associated with the patch that would lead to significant differences in absorption of lidocaine (i.e., a lack of bioequivalence).

When reviewing an ANDA or a 505(b)(2) application for a product claimed to be bioequivalent to Lidoderm, the Agency would be interested in the possibility that differences in skin irritation or skin stripping would lead, over time, to differences in bioavailability. Our recommended skin irritation study was designed with this in mind and is adequate to evaluate this possibility.

In this requested action, and in several others, your petition asks us not to *review* or approve an ANDA or 505(b)(2) application seeking to demonstrate bioequivalence to Lidoderm unless the studies described above are provided (see requested actions 1-5, 7, and 11 in 2012 amendment). With respect to your request that FDA decline to review such an application, we note that our regulations set forth criteria for the receipt and initial review of NDAs and ANDAs to determine whether they may be filed or received and placed into review.[62] These regulations provide the bases on which FDA *may* or will refuse to receive or file an application. We may, for example, refuse to receive or file an application if "it is incomplete because it does not *on its face* contain information required under section 505(b), section 505(j), or section 507 of the Act and 314.50 or 314.94."[63] As described in this response, FDA has determined that none of the bases on which you seek FDA's refusal to file or receive are meritorious, and therefore we decline to refuse to file or receive an application for lidocaine patch on those grounds.

2. 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 certain in-use wear characteristics.

We are denying this request. The Draft Lidocaine Patch BE Guidance allows for adhesion to be evaluated during the 21-day irritation/sensitization study, as part of the pharmacokinetic study, or as a stand-alone study. Whether or not a separate adhesion study is undertaken, we recommend that adhesion data be collected during the irritation/sensitization study to document that patch adhesion is adequate for the induction of any skin irritation or sensitization. The draft guidance states that "to support product approval, the test product must adhere *at least as well as* the reference product."

You state that a generic patch that is more adherent than Lidoderm may strip more skin cells from the area of application. Because the patch must be repeatedly applied to the same location, the area where PHN pain occurs, you state this could lead to increased skin permeability at the site of application, and therefore a lack of bioequivalence between a more adherent patch and Lidoderm (2012 amendment, at 17-19).

We have determined that the testing recommended in our draft guidance is adequate to identify any differences in bioavailability that may be caused by different adhesion/skin

[62] 21 CFR 314.101.

[63] 21 CFR 314.101(d)(3) (emphasis added).

stripping properties. Patch adhesion testing for generic products is ordinarily aimed at ensuring adequate patch adhesion. Any significant increase in patch adhesion and associated skin stripping would be revealed in the irritation/sensitization study we recommend. The Draft Lidocaine Patch BE Guidance recommends that the skin irritation/sensitization study be conducted as a blinded comparison between a proposed generic product and Lidoderm. This study involves 21 days of continuous patch application, with new patches applied three times weekly. This exaggerates the labeled conditions of use, in that the patches will be in contact with skin continuously for 21 days, rather than 12 hours on and 12 hours off. During this 21-day period, nine patches will be applied and removed.

You further argue that skin irritation and sensitization potential must be evaluated under "conditions of maximal stress," as this phrase was used in our withdrawn draft guidance on Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (2012 amendment at 21). This phrase, "conditions of maximal stress," reflects our recommendation that skin irritation and sensitization studies look for signs of irritation or sensitization in skin that has been "stressed" by repeated or long-term application of the test patch. Our standard and long-standing recommendation in this regard is that patches be applied for a 21-day induction phase followed by a challenge phase.[64] The exaggerated conditions of use, 21 days of continuous application, recommended in the Draft Lidocaine Patch BE Guidance, reasonably qualify as conditions of maximal stress. A significant difference in skin stripping between Lidoderm and the test patch would be revealed in the skin irritation scoring. You have not presented data showing that our recommended testing would fail to reveal differences in skin irritation or sensitization potential that could lead to differences in bioavailability.

Your petition cites studies suggesting that intentional skin stripping can lead to increased absorption of topically applied drugs (2012 amendment at 18). This information does not persuade us that a small difference in unintentional skin stripping between Lidoderm and a proposed generic version of Lidoderm could go undetected in our recommended skin irritation testing while leading to significant differences in permeability affecting bioequivalence over time.

Your petition also cites experience with fentanyl transdermal patches in which skin irritation may have led to increased absorption of the active ingredient. Fentanyl patches differ significantly from Lidoderm patches in several respects. Fentanyl patches are

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[64] See, for example, our bioequivalence guidances for:
Rotigotine transdermal film (2012 draft),
Clonidine transdermal film (2009 draft),
Diclofenac Epolamine topical patch (2012 draft),
Estradiol transdermal film (2010 draft),
Ethinyl Estradiol transdermal film (2009 draft),
Granisetron extended release transdermal film (2012 draft),
Methylphenidate extended release transdermal film (2010 draft),
Selegiline extended release transdermal film (2011 final), and
Scopolamine extended release transdermal film (2011 final).

designed to provide systemic absorption of the active ingredient, and they are applied continuously, with each patch replaced after 72 hours, for patients who require around-the-clock opioid administration for pain relief. This differs significantly from the 12-hours-on, 12-hours-off use pattern for Lidoderm patches. Thus, the potential for skin irritation is much different between these products. In further support of your position, you cite standard labeling for transdermal patches recommending against repeated patch application to the same skin site, as a routine precaution. In the case of transdermal patches, skin deposition of the active ingredient (i.e., formation of a reservoir of active ingredient in upper layers of the skin, from which systemic absorption takes place) is often known to occur[65] and is a factor in this recommendation that the application site be rotated. Application of each patch to different skin location is recommended to reduce the possibility that an excessive amount of active ingredient will accumulate in one location, leading to excessive systemic absorption. You have not provided any evidence that lidocaine patch products present this same risk of active ingredient accumulation. The recommendation in transdermal patch labeling regarding patch site rotation does not support your claim that our recommended test methods for topical lidocaine patch products are inadequate.

You also state that "OGD's test ignores the potential for repeated patch application to the same anatomical site to decrease adhesion of subsequently applied patches" (2012 amendment at 19). This statement overlooks that we ask for adhesion data to be collected during the course of the 21-day irritation/sensitization study, in which patches are worn continuously in the same location and replaced with a new patch 3 times each week. Any material differences caused by such under-adhesion would be detected in this study.

Your petition states that "any generic lidocaine patch should have similar adhesive properties when cut into smaller pieces in order to be equivalent to Lidoderm" (2012 amendment at 23). However, you do not provide evidence as to why our recommendations regarding this property of Lidoderm are inadequate. As the labeling states, the patch can be cut, and our Chemistry, Manufacturing, and Controls (CMC) review of each ANDA will include evaluation of the design characteristics of a generic patch related to how the patch can be cut. Our recommended irritation study uses cut patches to ensure that the adhesive performance of cut patches is acceptable. FDA has determined that these review elements together are sufficient to capture any "cutting-related" differences that can affect bioequivalence.

3. 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 certain in-use wear characteristics.

We are denying this request. You set forth in your petition that, because PHN can be a chronic condition, the adhesiveness, or "tack" of the Lidoderm patch is sufficiently gentle so the patch does not irritate skin sites where it is repeatedly applied (2012 amendment at 16-17). You assert that a generic lidocaine patch should have similar characteristics to be

[65] See, for example, Margetts and Sawyer, "Transdermal drug delivery: principles and opioid therapy," *Continuing Education in Anaesthesia, Critical Care & Pain*, Vol. 7, No. 5, 171-176 (2007).

considered "equivalent to" Lidoderm (id.). As discussed in our response to your first 2012 requested action above, FDA has determined any significant increase in skin irritation caused by a proposed generic product (in excess of what may be caused by Lidoderm) would be detected in the skin irritation testing we recommend in the Draft Lidocaine Patch BE Guidance. To note, you assert that FDA has withdrawn its draft guidance for industry on *Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products* originally issued in 1999, and state that the recommendations for skin irritation, sensitization, and adhesion testing in our draft guidance on bioequivalence testing for lidocaine topical patch 5% products are largely based on this withdrawn guidance. You infer that any skin testing that is similar to that described in the withdrawn guidance was infirm. Draft guidance may be withdrawn or not finalized for a variety of reasons, however. It is not correct to assume that our withdrawal of the draft guidance relating to transdermal products indicates that the Agency has rejected all the scientific concepts contained therein. As noted above, it remains our standard advice that skin irritation studies for topical and transdermal patch products include a 21-day induction phase, as reflected in our product specific bioequivalence guidances.

4. Not review or approve any generic lidocaine topical patch 5% product unless it passes the performance tests identified in requests 2 and 3 above.

Consistent with our denial of requests 2 and 3, this request is denied.

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

We are denying this request. In your 2012 amendment, you state that pharmacokinetic testing has never been validated as a bioequivalence method for locally acting topical drugs (2012 amendment, at 7). You also argue that additional research would be needed to assess and validate the use of pharmacokinetic testing to establish bioequivalence for locally acting topical drugs generally and lidocaine topical patch 5% products in particular (id., at 11-14).

As a preliminary matter, it is important to recognize that FDA has not determined that pharmacokinetic testing can be used to establish bioequivalence for locally acting topical drugs generally. We have made this determination with respect to lidocaine topical patch 5% products for the reasons discussed above, relating to the specific properties of lidocaine.

Your petition points out that we — and others — have recognized the need to validate alternative and novel approaches to bioequivalence testing. Thus, you assert, "one would assume that [the Draft Lidocaine Patch BE Guidance] was based on hard scientific data validating the [pharmacokinetic] method pursuant to the standards FDA itself enunciated in the context of the DPK [dermatopharmacokinetic] experience" (2012 amendment at

13). You also cite a scientific approach the Agency took to evaluate the newer bioequivalence testing methodology for topical dermatological corticosteroid products, specifically pharmacodynamic studies using a vasoconstrictor assay, or skin blanching (2012 amendment at 11).

We disagree that validation studies are needed before the Agency can rely on pharmacokinetic testing to show bioequivalence for lidocaine topical patch 5% products. Pharmacokinetic testing is the standard methodology by which bioequivalence determinations are made, and thousands of products have been approved based on bioequivalence data from pharmacokinetic studies. Thus, it is not necessary here to require validation or investigation of the conduct of a pharmacokinetic study in ways that might be used for a more novel methodology like skin blanching. Moreover, our recommended use of pharmacokinetic testing to establish bioequivalence for lidocaine topical patch products is consistent with our 2003 approval of three generic versions of EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) based on pharmacokinetic bioequivalence studies. More generally, as mentioned above, lidocaine is not the only locally acting drug for which we have accepted pharmacokinetic studies to establish bioequivalence. For example, FDA has recommended pharmacokinetic testing to demonstrate bioequivalence for mesalamine products, which act locally in the GI tract,[66] and in our draft bioequivalence guidance for balsalazide disodium capsule/oral products.[67] Like topically applied lidocaine, these products are believed to act locally with incidental systemic absorption, but have characteristics that make pharmacokinetic measurements indicative of availability at the site of action. Your petition has not provided evidence that this approach is unreliable.

6. Confirm that any ANDA or 505(b)(2) application seeking to demonstrate bioequivalence to Lidoderm will not be reviewable or approvable unless it contains either a summary report or a complete report of all bioavailability and bioequivalence studies conducted during development of the drug product, including bioavailability and bioequivalence studies on all experimental formulations that are pharmaceutically equivalent to the formulation intended to be marketed.

Section 314.94(a)(7) of our regulations requires ANDA applicants to submit all bioequivalence studies conducted on a drug product formulation for which approval is sought.[68] When this regulation was promulgated, the Agency explained that "data from additional BE studies may be important in our determination of whether the proposed formulation is bioequivalent to the reference listed drug (RLD), and are relevant to our

[66] Aug. 20, 2010 Letter fr. FDA to I.Hara, Warner Chilcott Co. LLC, at 11 (concluding comparative clinical endpoint studies "less sensitive, accurate, and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product).

[67] Draft guidance on Balsalazide Disodium (Jan. 2008), available on the Internet at http://www.fda.gov/Drugs under Guidances (Drugs).

[68] 21 CFR 314.94(a)(7).

evaluation of ANDAs in general."[69] Any ANDA applicant that filed its ANDA after July 15, 2009, is subject to this regulation.[70] FDA issued final guidance in May 2011 intended to assist ANDA applicants in complying with the requirements of this regulation.[71]

The regulation requires submission of: (1) a complete study report for the bioequivalence study upon which the applicant relies for approval; and (2) either a complete or summary report for all other bioequivalence studies conducted on the "same drug product formulation."[72] The "same drug product formulation" is defined in § 320.1(g) to mean:

> The formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the agency's determination of bioequivalence.[73]

FDA amended subsection 320.1 to include this definition when it promulgated section 314.94(a)(7).[74]

With respect to your concern that applicants may not submit all studies that fall within the scope of § 314.94(a)(7) (2012 amendment at 27-28), FDA concludes, as discussed in the preamble to the final rule,[75] that there are sufficient mechanisms in place to enforce compliance with section 314.94(a)(7), including authority to inspect a clinical site, a bioanalytical site, or the sponsor. We also conduct inspections of manufacturing facilities evaluating compliance with current good manufacturing practices (cGMPs) before approval, which may include review of pharmaceutical development records. You also request on these grounds that FDA refuse to file or receive an application that does not comply with section 314.94(a)(7) (2012 amendment at 4).

As reflected in our discussion of your first 2012 requested action above, related to the regulatory bases on which FDA may or must refuse to file an application, if an applicant's failure to submit summary or complete reports of all bioequivalence and bioavailability studies is apparent on the face of an application, we may refuse to receive or file it for that reason. However, we will not categorically grant your requested action;

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[69] *Requirements for Submission of Bioequivalence Data; Final Rule*, 74 FR 2849, 2849 (Jan. 16, 2009) (Failed BE Studies Final Rule).

[70] Id., at 2858.

[71] Guidance for Industry on *Submission of Summary Bioequivalence Data for ANDAs* (May 2011), available on the Internet at http://www.fda.gov/Drugs under Guidances (Drugs).

[72] 21 CFR 314.94(a)(7).

[73] 21 CFR 320.1(g).

[74] Failed BE Studies Final Rule, at 2850.

[75] Failed BE Studies Final Rule at 2856 (discussing enforcement mechanisms).

refusal to file based on failure to submit studies generally would be contrary to section 314.101 if such failure is not apparent on the face of the application.

7. Not review or approve any lidocaine patch 5% ANDA or 505(b)(2) application as bioequivalent to Lidoderm unless FDA has verified that all bioavailability and bioequivalence studies identified in the sixth requested action have been submitted to FDA. You specifically request that such verification activities include (a) asking each applicant to submit the identified studies, including complete pharmacokinetic profiles for each study subject, along with names and contact information for all third parties associated with the studies; (b) contacting any third parties FDA believes may have been associated with the identified studies and asking them to provide summaries of all such studies; and (c) reviewing all studies conducted by Cetero Research on lidocaine patch 5% products or experimental pharmaceutical equivalents thereof, given what you [FDA] characterize as Cetero's particular expertise in patch products and FDA's recent concerns regarding data integrity of bioanalytical studies conducted by Cetero between April 2005 and August 31, 2009.

In responding to your sixth requested action above, we explained that applicants for a lidocaine patch are subject to the requirements of section 314.94(a)(7), and we described in general terms our inspection program connected with NDAs and ANDAs. With this requested action, you are asking us to conduct a very detailed and targeted investigation into bioavailability and bioequivalence studies undertaken by certain applicants. In the absence of cause, which your petition does not provide, we will not subject any application to additional scrutiny at the request of a petitioner.

Your request that we specifically review "all studies conducted by Cetero Research on any lidocaine patch 5% product or experimental pharmaceutical equivalent thereof . . . between April 2005 and August 31, 2009" is not fully explained or supported. As you indicate, in July 2011, FDA notified pharmaceutical manufacturers that bioanalytical studies conducted at Cetero between April 2005 and June 2010 in support of marketing applications may need to be repeated or confirmed.[76] We agree that any ANDA applicant must submit all bioequivalence studies conducted on the same drug product formulation for which approval is sought, and this would include any such studies conducted by Cetero Research at any time. If an applicant is relying on studies conducted by Cetero Research during the stated 2005-2009 time frame, those studies would need to be repeated or audited as we have specified. Any bioequivalence studies conducted by Cetero that are not relied upon to support approval would be reviewed in the same way we review such studies generally. During the review of such studies, if we determine the summary results indicate that a review of the full study report is needed, FDA would perform an evaluation of the integrity of the data in the full study report. We will determine on a case-by-case basis whether any Cetero studies not relied upon for

[76] See Notification to Pharmaceutical Companies: Acceptance of third-party data integrity audit for Cetero studies conducted from March 1, 2008, to August 31, 2009. Available on FDA's Web site at http://www.fda.gov/Drugs/DrugSafety/ucm265559.htm.

approval require special scrutiny or confirmation. We therefore deny your request to make wholesale determinations about all lidocaine patch product ANDAs or 505(b)(2) applications that contain data from Cetero.

8. If FDA concludes that a generic lidocaine patch 5% product should be approvable despite the existence of any failed bioavailability or bioequivalence studies, obtain the concurrence of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) with FDA's approval decision before it is issued.

We decline this request at this time, as we do not anticipate that such an approval decision would warrant consideration by one or more advisory committees, consistent with our draft guidance for the public and FDA staff on *Convening Advisory Committee Meetings* discussed above in our response to your second 2007 requested action.

You further request that we obtain the concurrence of two advisory committees — not merely seek their advice — before issuing certain approvals. As the advisory committee regulations explicitly state, "[t]he Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee."[77] FDA is not bound by an advisory committee recommendation and is empowered to act even in the absence of an advisory committee vote.

For these reasons, we are denying this request.

9. Develop and publish an analysis of the information submitted on failed bioavailability and bioequivalence studies 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.

You ask the Agency to study and publish a report on failed bioequivalence studies for patch products, focusing on the types of formulation differences that appear to affect bioequivalence. We are denying this request on several grounds. First, granting such a request likely would be inconsistent with our regulations governing disclosure of data and information contained in drug approval applications and not in keeping with the Agency's priorities. Patch formulations that an applicant studies during product development but later modifies — to satisfy the bioequivalence requirement or for any other reason — are not publicly disclosed by the Agency. Second, we do not know that information available to the Agency in failed bioequivalence studies for patch products allows for any conclusions concerning formulation differences that affect bioequivalence. Even if we were able to draw conclusions in this area, they may apply only to one active ingredient or one type of topical product. Finally, it is not clear that such a study would help further the Agency's public health mission. Applicants seeking approval of ANDAs

[77] 21 CFR 14.5(b).

and 505(b)(2) applications for products claimed to be bioequivalent to a listed drug must demonstrate bioequivalence to our satisfaction through appropriately designed studies. We will continue to rely on bioequivalence studies, not general assessments concerning formulation differences, to establish bioequivalence. For all of these reasons, this request is denied.

10. 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 topical patch 5% products to Lidoderm.

This request is denied, consistent with our determination that validation studies are not needed before the Agency can rely on pharmacokinetic testing to show bioequivalence for lidocaine topical patch 5% products. Pharmacokinetic testing is the standard methodology by which bioequivalence determinations are made, and we have accepted pharmacokinetic studies since 2003 to show bioequivalence for topical lidocaine products.

11. 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 proposed generic product is demonstrated to meet such requirements.

We are denying this request. In your petition, you contend that FDA is legally required to publish in the Orange Book whether in vitro and/or in vivo testing is required for generic copies of an approved drug at the time that drug is first approved, and has failed to do so in the case of Lidoderm (2012 amendment, pp 35-39). This contention is unavailing.

Section 505(j)(7)(A)(i) provides that "the Secretary shall publish and make available to the public" three sets of information: "(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c). . .; (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published." The Orange Book lists approved drugs together with the approval date and the application number at the time the NDA is approved or shortly thereafter. As provided in our bioequivalence regulations, the Agency fulfills the third prong of this statutory directive by including on the list of approved products a "therapeutic equivalence" code for each product once another product that is pharmaceutically equivalent to the listed product is approved.[78] These therapeutic equivalence codes indicate the type of bioequivalence data FDA required

[78] 21 CFR 320.24(a). *Abbreviated New Drug Application Regulations, Proposed Rule,* 54 FR 28872, 28911 ("FDA satisfies [the section 505(j)(7)(A)(i)(III)] requirement through the use of therapeutic equivalence codes" in the Orange Book).

before approving the therapeutically equivalent product(s), and inform any subsequent ANDA applicants about the type of data FDA required in approving that first pharmaceutically equivalent product.

You assert that FDA must publish information regarding bioequivalence requirements within 30 days of an NDA approval (2012 amendment at 35). Specifically, you contend that subsection 505(j)(7)(A)(ii), which requires that the Orange Book be updated to include a drug approved under section 505(c) or 505(j) within 30 days of approval, also requires publication of the type of bioequivalence data FDA will require within 30 days of NDA approval. This interpretation is inconsistent with other provisions of section 505(j), however. For example, section 505(j)(3)(b) requires the Agency to meet with an ANDA applicant to agree on the design and size of bioequivalence studies needed for approval if an applicant submits a reasonable written request for such a meeting. Under your view, the bioequivalence method would have been determined and published when FDA first approves and lists the RLD, and there would be no reason for such meetings with the ANDA applicant.

As a practical matter, your position is infeasible, as it would require the Agency to expend enormous resources to generate and evaluate the scientific data required to determine bioequivalence requirements, data the Act requires ANDA applicants to provide in the ANDA. There is no evidence that Congress intended to place such a burden on the Agency through subsection 505(j)(7)(A)(i).[79] In addition, none of the courts that have considered FDA's compliance with section 505(j)(7)(A)(i)(III) have construed the statute in the manner you suggest or otherwise have found any legal deficiency in FDA's practice of listing bioequivalence data requirements for a listed drug at the time a pharmaceutically equivalent drug is approved.[80]

You make several related assertions that are unavailing. First, you assert that FDA violated section 505(j)(7)(A)(i) by failing to publish bioequivalence requirements for lidocaine patches within 30 days of approving Lidoderm in 1999. For the reasons set

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[79] The legislative history of section 505(j)(3)(b) supports this point. In the Report from the House of Representatives, members noted that "[t]his section is intended by the Committee to provide for a predictable and dependable structure through which the FDA and sponsors of applications for marketing of new products can communicate effectively regarding requirements that must be met to secure marketing clearance or approval. The Committee believes that meetings between the appropriate FDA experts and their industry counterparts may provide the avenue to successful communication that may result in agreements that can expedite a manufacturers understanding of what information, data, or investigations may be needed for any particular product." H. Rep. 105-310, at 72 (1997). Were FDA already to have determined the type of data required for any ANDA at the time of RLD listing, such discussion of the requirements for approval would not be necessary.

[80] See, e.g., *Schering Corp. v. FDA,* 51 F.3d at 398 (citing section 505(j)(7)(A)(i)(III) as evidence of Congressional intent to provide FDA discretion to determine appropriate bioequivalence methodology through the course of the ANDA approval process); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (citing section 505(j)(7)(A)(i)(III) in support of holding that FDA has authority to change bioequivalence recommendation to accept in vitro data rather than formerly recommended in vivo and in vitro data).

forth above, this assertion is incorrect. Consistent with the Act and 21 CFR 320.24(a), FDA will publish in the Orange Book whether the Agency requires in vivo studies, in vitro studies, or both, when it approves any lidocaine patch ANDA. Your claim that FDA has unreasonably delayed publishing the type of bioequivalence data it will require for a generic lidocaine patch in violation of the Administrative Procedure Act (2012 amendment, at 37) is unavailing for the same reason.

Second, you assert that FDA's "failure" to publish bioequivalence requirements within 30 days "undermines" the transparency of bioequivalence method development by FDA (2012 amendment, at 37). On the contrary, FDA has several forums in which it makes public and solicits public comment in its bioequivalence thinking. For example, FDA's current process of issuing product-specific bioequivalence recommendations in guidances in draft form, one fundamental purpose of which is to provide public notice of an opportunity to comment on recommended bioequivalence methodologies, is much more transparent and open to public comment than the system you propose, which would require FDA to publish what the Agency will require for generic applicants less than a month after the RLD has been approved, essentially foreclosing meaningful public participation.[81] At all times FDA encourages potential generic applicants for products for which a bioequivalence recommendation has not been published to confer with the Agency on appropriate bioequivalence methodologies.

Third, you argue that FDA has not met the "high standard" of developing bioequivalence requirements (2012 amendment, at 37). You cite the requirement in section 320.24(a) that an applicant use the most accurate, sensitive, and reproducible method of demonstrating bioequivalence, and maintain that FDA has abdicated its statutory duty of identifying the best bioequivalence approach for generic copies of Lidoderm by not definitely determining the bioequivalence requirement back in 1999 when Lidoderm first was approved. This is incorrect. As part of the review process for each ANDA, FDA ensures that the requirements of section 320.24(a) are met, and, as the Act requires, will not approve any ANDA that fails to demonstrate bioequivalence.

Fourth, you assert that FDA cannot approve an ANDA until FDA has published bioequivalence requirements. This argument conflicts directly with two provisions of the Act. FDA decides whether to approve an ANDA based on the Agency's evaluation of the scientific information provided in the application, under the requirements of the Act and regulations, and in reliance upon the Agency's scientific experience and judgment. If the applicant complies with all applicable statutory requirements, the statute directs the Agency to approve the application regardless of whether the Agency has published applicable bioequivalence requirements.[82] The Agency's delay or denial of an ANDA's approval based on a failure to publish bioequivalence requirements in the Orange Book

[81] As of the date of this response, over 995 draft or final product-specific guidances are available on the Agency's Web site. See Bioequivalence Recommendations for Specific Products, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[82] Section 505(j)(4) of the Act.

would be inconsistent with this provision of the Act. In addition, as courts have uniformly endorsed, the Act gives FDA broad discretion to determine how bioequivalence must be demonstrated for a generic product.[83]

Fifth, you assert that the requirement to publish the bioequivalence methodology information mandates uniformity and thus precludes FDA from approving ANDAs referencing the same RLD that use different methodologies to demonstrate bioequivalence (2012 amendment at 38). This assertion is unavailing. Section 320.24(a) provides that "[t]he selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product." This regulation requires applicants to "conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section." Limiting FDA to accepting one type of bioequivalence study for all ANDAs referencing the same RLD could result in ANDA approvals that are directly inconsistent with this regulatory directive.

For example, regulatory science has made significant advances with respect to the type of data available to demonstrate bioequivalence for a variety of products for which comparative clinical endpoint studies were once recommended.[84] Your interpretation effectively would limit FDA to accepting only those bioequivalence data available at the time the RLD was listed in the Orange Book. It thus would preclude FDA from accepting innovative data, notwithstanding the fact that such data were more sensitive, accurate, and reproducible under the latest scientific developments, which practice courts have endorsed.[85] In addition, FDA has exercised, and courts have upheld, the Agency's

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[83] The Third Circuit, in upholding FDA's "method to determine bioequivalence on a case-by-case basis depending on the drug under consideration for approval pursuant to an ANDA," concluded after detailed review of the legislative history and Agency rulemaking that "there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for the purposes of ANDA approval." *Schering Corp. v. FDA*, 51 F.3d at 399. See also *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 217 ("the expressed desire of Congress, through the 1984 amendments, was that FDA retain its historically wide discretion in defining showings of bioequivalence") (internal citation and quotation omitted); *Fisons Corp v. Shalala*, 860 F. Supp. at 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion"); *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 19 (D.D.C. 2009) (the "high degree of deference" given to FDA's scientific determinations "has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic").

[84] Aug. 20, 2010 Letter fr. FDA to I.Hara, Warner Chilcott Co. LLC, at 11 (concluding comparative clinical endpoint studies "less sensitive, accurate, and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product); See generally, guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000).

[85] *ViroPharma, Inc. v. Hamburg*, No. 12-0584, 2012 U.S. Dist. LEXIS 56128, at *58 (D.D.C. April 23, 2012) (upholding FDA's authority to accept in vitro data in support of demonstrating bioequivalence in lieu of prior recommendation to submit in vivo data from clinical endpoint studies); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218.

discretion to accept different bioequivalence methodologies for different ANDAs that reference the same RLD depending on differences between the products. For example, FDA has determined under section 320.24(a) that certain products that have qualitatively (Q1) and quantitatively (Q2) the same inactive ingredients as the RLD can be supported by in vitro data to demonstrate bioequivalence, but that comparative clinical trials may be the most sensitive, accurate, and reproducible for certain products that do not share the same inactive ingredient profile as the RLD.[86] Finally, to the extent that information available at the time the RLD is approved only supports use of in vivo data, such a requirement also runs counter to the important public health policy recognized in FDA's bioequivalence regulations that no unnecessary human research should be done, should FDA subsequently determine that other in vivo, or in vitro data are the most accurate, sensitive, and reproducible.[87]

In sum, FDA's interpretation of the requirement of section 505(j)(7)(A)(i) is reasonable, gives effect to (and does not abrogate) other provisions of section 505(j), does not impose on the Agency the onerous burden of determining bioequivalence requirements at the time of RLD approval without input from generic applicants, and furthers the significant public health policies of encouraging innovation and reducing unnecessary human testing. Your interpretation is not consistent with any of these outcomes.

12. Confirm that since the filing of this petition in December 2006, no FDA employee had 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.

The action you request here is for FDA to respond directly to a factual inquiry concerning communications between the Agency and generic lidocaine topical patch applicants. This is not a proper use of the citizen petition process. As stated in our regulations, "[a]n interested person may petition the Commissioner to issue, amend, or revoke a regulation

[86] See April 9, 2012, Letter fr. FDA to T. Doyle, at 20-21 (affirming in vivo clinical endpoint studies are required for non-Q1/Q2 generic vancomycin hydrochloride capsules unless applicant can demonstrate formulation differences do not affect safety or effectiveness of product). See also Dec. 8, 2010, Letter fr. FDA to J. Jonas, Shire Development Inc., at 6-7 (denying request to require clinical efficacy studies to demonstrate bioequivalence for locally acting lanthuanum carbonate oral chewable tablets, concluding that "comparative in vivo trials would be less sensitive, accurate or reproducible than [pharmacodynamics] or properly designed and conducted in vitro dissolution and binding studies with respect to the capability to detect product differences"); draft guidance on Acarbose, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM170242.pdf.

[87] 21 CFR 320.25(a). See also 21 CFR 320.30(a) ("[t]he Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a bioavailability or bioequivalence study submit the proposed protocol for the study to FDA for review prior to the initiation of the study").

or order, or to take or refrain from taking any other form of administrative action."[88] The petition process cannot be used to compel the Agency to respond to this type of factual inquiry. Accordingly, this request is denied.

Implicit in this request is your contention that FDA cannot communicate with ANDA applicants about a subject raised in a citizen petition until the Agency answers the petition. In a related vein, your 2012 amendment challenges FDA's authority to use "complete response" letters to address issues raised in citizen petitions concerning ANDA approval requirements (2012 amendment at 40-41).[89] You quote a statement appearing in the minutes of a negotiation meeting between FDA and representatives of the generic drug industry concerning user fees, and argue that it would be inappropriate for the Agency to indicate in a complete response letter how we intend to resolve a matter raised in a citizen petition.

FDA notes that it necessarily communicates with applicants on a range of issues that could relate to an issue raised in your petition. For example, the Draft Lidocaine Patch BE Guidance invites applicants to submit complete study protocols for our review before initiating the studies. The existence of your citizen petition urging us to adopt a different approach to these bioequivalence studies does not preclude us from reviewing protocols or having discussions with applicants regarding their applications. Likewise, the existence of your citizen petition cannot be used to preclude FDA's communications with an ANDA applicant about a deficiency in an application for a lidocaine patch product.

If we were to adopt your position, petitioners effectively could prevent communication regarding and the approval of ANDAs and 505(b)(2) applications indefinitely by submitting serial petitions or petitions for reconsideration. This is directly inconsistent with the Act. The law does not allow FDA to refuse to approve an ANDA because we have not responded to a petition. Section 505(j)(4) of the Act states that we shall approve an ANDA unless FDA identifies a deficiency expressly delineated in the Act.[90] Our regulations include parallel provisions in section 314.127 concerning refusal to approve an abbreviated application. Neither section 505(j) nor 21 CFR 314.127 permits us to refuse to approve an ANDA for the reason proposed in this requested action. In addition, your position is directly inconsistent with the important policy that the citizen petition process not be used to prevent approvals of ANDAs that meet the requirements of the Act and FDA's regulations, a policy embodied in section 505(q) of the Act itself.[91]

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[88] 21 CFR 10.25(a).

[89] A complete response letter communicates to an applicant that our initial review of a drug application is complete, but we cannot approve the application in its present form. Section 314.110 of our regulations governs complete response letters. The Agency does not disclose CR letters publicly.

[90] Section 505(j)(4)(F) of the Act. This subsection does not include the pendency of a citizen petition as a basis for refusing to approve an ANDA.

[91] Section 505(q) provides that "[t]he Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request" except under certain delineated circumstances.

Therefore, we decline your request "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" (2012 amendment at 41).

13. 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 reviewing any applications, relying on any bioequivalence method other than the method described in the draft guidance or clinical endpoint bioequivalence studies.

Again, with this request you are asking FDA to respond to a factual inquiry concerning communications with applicants, which we decline to do, consistent with our response to the 12th requested action, above.

Furthermore, this request reflects a misunderstanding of the nonbinding nature of FDA guidance. As indicated in our good guidance practice regulations, and as stated in each guidance, FDA guidance, when finalized, represents the Agency's current thinking. It does not, however, create or confer any rights and does not operate to bind FDA or the public. An applicant is free to suggest an approach different from one recommended in guidance and explain how it satisfies relevant statutory and regulatory requirements.

Finally, your 2012 amendment suggests that FDA may have provided an applicant with modified guidance on bioequivalence testing for lidocaine topical patch 5% products (2012 petition at 42). FDA has not amended the Draft Lidocaine BE Guidance, and a general statement by a representative of an applicant, without more, does not indicate that FDA is selectively providing "modified guidance" to individual applicants.

14. Not approve a 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 the petition.

We are denying this request.

As stated above in our response to the 12th requested action from your 2012 amendment, we decline this request on the ground that a petition does not and cannot be used to prevent review or approval of an ANDA.

III. Conclusion

For the foregoing reasons, FDA has determined that the recommendations in our draft guidance regarding bioequivalence studies for lidocaine topical patch 5% products are scientifically sound. FDA has clear legal authority to approve ANDAs and 505(b)(2)

applications that include pharmacokinetic studies demonstrating bioequivalence in accordance with our draft guidance.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research