CITIZEN PETITION

SALONPAS PAIN RELIEF PATCH

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DECEMBER 31, 2009
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December 31, 2009

VIA FEDEX

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

I. Actions Requested

The undersigned, Hisamitsu Pharmaceutical Co., Inc., ("Hisamitsu") submits this Citizen Petition under section 505 of the Food, Drug, and Cosmetic Act ("FDCA") and 21 CFR §10.30, among other provisions of law, to request that the Commissioner of the Food and Drug Administration refrain from approving any abbreviated new drug application ("ANDA") submitted under section 505(j) of the FDCA for a generic version of SALONPAS® Pain Relief Patch ("SPRP"), unless the ANDA contains data:

- from a placebo-controlled, non-inferiority, clinical investigation in the indicated patient population
- from a standard battery of skin safety studies to ensure the safety of the generic patch formulation
from a safety-directed pharmacokinetic study comparing the generic patch formulation to reference methyl salicylate and l-menthol ointments in order to confirm that systemic bioavailability does not exceed the allowable levels associated with maximum strength ointments as noted in the Tentative Final Monograph

generated solely with a generic product possessing a surface area (7 cm x 10 cm) identical to the SPRP, formulated to contain the same percentage of active ingredients (i.e., 10% methyl salicylate and 3% l-menthol) in the adhesive mass, and containing the same total patch amounts of active ingredients (105 mg methyl salicylate and 31.5 mg menthol), as these formulation criteria underlie the clinical safety and efficacy data submitted in support of the SPRP New Drug Application

This request is consistent with bioequivalence requirements and Food and Drug Administration ("FDA") Guidances for products intended to deliver the active moiety locally.¹

¹ 21 C.F.R. § 320.24(b)(4); Draft Guidance on Lidocaine, December 2006
II. Statement of Grounds

1. Factual Background

1.1. Overview of SALONPAS® Pain Relief Patch

On February 20, 2008, the SALONPAS® Pain Relief Patch (NDA 22-029) became the first non-prescription, topically-applied, external analgesic drug product to secure FDA-approval. To date, no other patch product containing counterirritant active ingredients has been approved. As a condition of approval, Hisamitsu was required to conduct a number of clinical and non-clinical studies confirming the safety and efficacy of the SPRP, as well as the standard chemistry, manufacturing and control determinations.

Consisting of an adhesive mass contained between a layer of light brown backing cloth and a removable plastic film, the SPRP is indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, sprains, strains, bruises and simple backache. The adhesive mass contains two external analgesic active pharmaceutical ingredients, methyl salicylate and menthol.

1.2. Introduction to FDA’s Tentative Final Monograph for External Analgesics

On December 4, 1979, FDA published an Advanced Notice of Proposed Rulemaking entitled 'External Analgesic Drug Products Monograph for Over-The-Counter Human Use; Establishment of a Monograph and Notice of Proposed Rulemaking'. This monograph included multiple active ingredients reviewed by the Expert Panel for Over-The-Counter Topical Analgesic Drug Products and found to be GRASE (Category I) for the intended indications. FDA reaffirmed these findings in 1983 with the publication of the Tentative Final Monograph (TFM), 'External Analgesic Drug Products Monograph for Over-The-Counter Human Use; Tentative Final Monograph.'

2 Fed. Reg.44, 69768-69866 (December 4, 1979)
3 Generally Recognized As Safe and Effective
4 Fed. Reg.48, 5852-5869 (February 8, 1983)
In the twenty-six years following publication of the TFM in 1983, evidence has not arisen to modify the basic findings of the GRASE classifications for topical use of these active ingredients. The TFM specifically recognized concentration ranges for methyl salicylate (10% to 60%) and l-menthol (1.25% to 16%), both as single ingredients and when combined. Certain dosage forms are specifically noted as examples in the TFM including ointments, creams and lotions and the TFM neither included nor excluded topical patch products. However, on July 17, 2003, FDA reopened the Administrative Record of the TFM and proposed a clarification of the status of external analgesic ingredients in patch, plaster and poulntice dosage forms as Category III and to exclude them from the Final Monograph.5 In the proposed rule change, FDA was explicit with its rationale relative to safety:

"FDA surveyed several standard texts that listed currently marketed topical drug products containing counterirritants and did not find any plaster or poulntice dosage forms listed therein. FDA stated (Ref. 5) that in order for poulntice and plaster dosage forms to be generally recognized as safe and effective and to develop any additional labeling that may be needed for such dosage forms, it is necessary to obtain more information, specifically:

1. The safe and effective concentration of the drug ingredient(s), especially under the occlusion of a plaster.
2. Data on percutaneous absorption under occlusion.
3. The length of contact time that it is safe to leave the poulntice or plaster on the skin; how often the plaster or poulntice needs to be changed for effective use.
4. The frequency of application that is considered safe and effective.
5. Whether or not directions and a warning are necessary regarding checking the area at specified intervals for erythema to prevent blistering, and what time intervals are recommended.
6. The age groups for whom poulntices and plasters are recommended for safe use.
7. Labeling of currently marketed products.

FDA's detailed comments are on file in the Division of Dockets Management (Ref. 5). Since that time, FDA has received a number of submissions on external analgesic counterirritant active ingredients in a plaster dosage form (Refs. 6 through 31). The submissions have included protocols and data to establish safety and effectiveness of the plaster/patch dosage forms. FDA has commented on the protocols and data, but has not found the information sufficient to support the safety and effectiveness of these dosage forms (Refs. 32 through 44). Further, FDA is not aware of sufficient data to classify any OTC external analgesic active ingredient in a patch, plaster, or poultice dosage form as Category I. Accordingly, FDA is classifying all OTC external analgesic ingredients in a patch, plaster, or poultice dosage form in Category III (more data needed).6

The administrative record was open for a period of 90 days for comments, new data and information. Included in the subsequent public responses were letters from the Consumer Healthcare Products Association and several patch manufacturers. The companies marketing non FDA-approved patches cited several small, incomplete and uncontrolled studies designed to examine the dermal irritation, sensitization or pharmacokinetic properties of their respective products. The cited studies are in no way comparable to the complete product characterization performed by Hisamitsu in support of the SALOPNPAS® Pain Relief Patch NDA and, as such, do not comply with FDA's specific mandates. To date, and to our knowledge, no other NDAs for OTC topical external analgesics have been approved. Thus, only Hisamitsu has fully evaluated and confirmed the safety and efficacy of a nonprescription, topical external analgesic product.

Hisamitsu elected to contact FDA in 2001 to discuss the requirements for an NDA. At this meeting, FDA noted concerns relating to increased skin irritation and sensitization and enhanced systemic absorption of the active ingredients with the patch products. FDA informed Hisamitsu that multiple non-clinical and clinical pharmacokinetic skin safety studies as well as Phase III studies would be needed to address these safety issues.

6 Fed. Reg. 68, 42324-42327 (July 17, 2003) at 42327 for cited references
1.3. The Active Ingredients in the SPRP Elicit Their Therapeutic Effect Locally, Not Systemically

Although FDA requested systemic bioavailability studies for the SPRP NDA to ensure safety, both active ingredients (methyl salicylate and menthol) act locally on the underlying tissue. Significant levels of salicylate are detected in dermal and subcutaneous tissues following topical application of methyl salicylate to human volunteers. Salicylate levels in tissue-dialysate samples obtained 2-3 hours following application of 20% methyl salicylate to forearm skin were ~30 fold higher than those observed in plasma. Menthol has also been shown to penetrate into skin and subcutaneous tissues following topical application.

Both methyl salicylate and menthol are classified as counterirritants; methyl salicylate is also considered a non-steroidal anti-inflammatory drug (NSAID). Analgesic and anti-inflammatory effects produced by methyl salicylate are mediated by vasodilation, resulting in increased localized blood flow and tissue temperature. Menthol, classified as a counterirritant, produces a cooling sensation through the activation of a specific thermoreceptor.

1.4. The SPRP was Approved as a Topical Product, Not a Transdermal Drug Product

SPRP is a topical patch product approved by FDA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, sprains, strains, bruises and simple backache. In the “Orange Book,” FDA classifies SPRP as an over-
the-counter topical patch rather than a transdermal patch. FDA defines topical as “administration to a particular spot on the outer surface of the body” and transdermal as “administration through the dermal layer of the skin to the systemic circulation by diffusion.” SPRP is intended to provide local pain relief to the site of application. Because topical actions of the SPRP mediate its clinical efficacy, systemic absorption data obtained in pharmacokinetic studies were utilized as evidence of safety only. A separate series of clinical studies were also conducted to determine the efficacy of the patch.

1.5. The SPRP NDA Included Pharmacokinetic Studies for Safety Assessments and Not to Predict Therapeutic Effect

In support of the NDA for the SPRP, Hisamitsu submitted results from seven pharmacokinetic trials. There were multiple safety-driven goals associated with these studies. These included determination of the systemic absorption of methyl salicylate, its pharmacologically-active metabolite (salicylic acid), and l-menthol as well as the assessment of any dermatologic-related reactions with the patch. Overall, pharmacokinetic data confirmed that the respective amounts of methyl salicylate, salicylic acid, and l-menthol absorbed systemically were extremely low and often non-detectable. Moreover, the SPRP was associated with systemic levels of methyl salicylate, salicylic acid, and l-menthol less than those obtained with application of topical formulations (e.g., ointments) included within the monograph.

Specifically, two single dose, three-treatment, crossover trials were conducted in healthy volunteers to compare the systemic absorption of methyl salicylate (FS-67-03-M) or l-menthol (FS-67-03-L) following application of the SPRP and investigational ointment

13 Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), 29th Edition
14 Route of Administration, C-DRG-00301
16 External Analgesic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph, Fed. Reg. 48 No. 27 @5868; maximum allowable limits: methyl salicylate (60%), menthol (16%); minimum allowable limits: methyl salicylate (10%), menthol 1.25%).
preparations. The ointment concentrations utilized for methyl salicylate (10% and 60%) and 1-menthol (1.25% and 16%) corresponded to the minimum and maximum allowable limits. Levels of methyl salicylate, its major metabolite, salicylic acid and 1-menthol were quantified prior to, and for 24 hours after dosing. Following application of the patch, systemic drug levels for each of the respective analytes did not exceed levels associated with the 60% methyl salicylate and 16% 1-menthol ointment preparations.

Additional studies were performed to confirm the safety and tolerability of the SPRP patch using dosing regimens exceeding the labeled indication. For example, peak blood salicylate levels associated with a single application (8 hours) of 10 patches were much less than those previously associated with salicylism.17 No serious adverse events were associated with the SPRP in any of the pharmacokinetic studies.

1.6. Approval of the SPRP NDA Required a Successful Phase III Clinical Study

FDA concluded that systemic bioavailability studies for SPRP were not valuable for the demonstration of product efficacy and required completion of a successful Phase III clinical safety and efficacy trial, comparing SPRP with matching placebo patches in patients presenting with mild to moderate aches and pains of muscles and joints. Hisamitsu conducted both pilot and pivotal Phase III trials to confirm that significantly more pain relief is associated with the SPRP compared to placebo patches in the indicated patient population. The pilot study was conducted to confirm the appropriateness of the selected primary efficacy endpoint and to assess the required patient population for the Phase III trial. Based on successful pilot data, the pivotal trial was conducted and significantly greater pain relief was observed both with the primary and secondary pain relief endpoints. The observed treatment differences dissipated when the patches were removed. The consistency of the treatment compared across the efficacy and safety endpoints provided robust affirmation that the SPRP is a safe and effective analgesic drug product for mild to moderate pain. Of note, adverse events associated with the SPRP

were similar to placebo patches and no significant safety concerns arose with the SPRP. Up to two patches per day can be used for a maximum of three days.

Hisamitsu therefore requests that all proposed generic formulations to the SPRP demonstrate safety and efficacy in placebo-controlled, non-inferiority clinical evaluations.

1.7. Any Proposed Generic Formulation of the SPRP Must Conduct a Standard Battery of Skin Safety Studies

In response to FDA concerns regarding possible skin irritation and sensitization associated with the use of a topical counterirritant patch, Hisamitsu conducted a number of skin safety studies with the SPRP. Results from these studies confirmed the safety of the SPRP for its labeled uses. Hisamitsu proposes that all generic formulations of the SPRP be required to conduct the same battery of skin safety studies in order to demonstrate that these products do not produce clinically unacceptable irritation or sensitization.

1.8. Clinical Studies Performed in Support of a Generic SPRP Should Utilize Patches with an Identical Surface Area and Total Amount of Active Ingredient

Drug products intended for transdermal application result in measurable systemic drug levels which then mediate the clinical efficacy and systemic safety. As such, generic versions of transdermal patches receiving FDA approval have relied upon results from the standard battery of pharmacokinetic studies, as well as skin sensitization studies for local toxicity determinations. These products are designed to deliver a defined amount systemically (usually per hour or per day). For these reasons, generic transdermal

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18 FDA APPROVAL PACKAGE FOR ANDA 75-182 (estradiol); FDA APPROVAL PACKAGE FOR ANDA 89-884 (nitroglycerin); and FDA APPROVAL PACKAGE FOR ANDA 76-258 (fentanyl)
patches are not required to be the same physical size as their reference listed drug product.\textsuperscript{19}

However, this is not the case for generic formulations of locally-acting topical products. For topical patches, including the SPRP, active ingredients are listed on a percentage basis (3% menthol; 10% methyl salicylate).\textsuperscript{20} Given the pharmacologic nature of counterirritant ingredients, linkage to the safety data associated with the SPRP requires that the generic formulation have the same size, contain the same percentage of active ingredient in the adhesive mass and have the same total amounts of active ingredients per patch.\textsuperscript{21} Patches larger than 7 cm × 10 cm (the size of the SPRP) and containing 10% methyl salicylate and 3% l-menthol, would provide more overall active ingredients and data obtained with such a formulation could not be linked to the SPRP NDA safety databases. Only patches with the same total (mg) amounts of active pharmaceutical ingredients can be linked to the nonclinical and clinical trials conducted by Hisamitsu.

In conclusion, Hisamitsu conducted a large number of clinical and nonclinical studies to ensure the safety of SPRP. Not all studies will be required for the proposed generic formulations. However, in order for the generic products to rely upon the totality of the safety data associated with the SPRP, it will be necessary for these patches to be the same size and contain the same percentage of active ingredient as contained in the SPRP.

\textsuperscript{19} Prescribing Information for Climara vs. estradiol (Mylan Pharmaceutical); Nitro-Dur vs. nitroglycerin (Mylan Pharmaceutical). In each case, the generic prescribing information notes a different size patch compared to the reference listed drug.
\textsuperscript{20} OFFICE OF GENERIC DRUGS, FDA, APPROVED DRUGS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (29th ed. 2009)
\textsuperscript{21} FDA Draft Guidance on Lidocaine, December 2006
2. Establishing Bioequivalence of Topical Products

The active ingredients in the SPRP (methyl salicylate and l-menthol) exert their therapeutic effect locally via counterirritant actions. Although systemic levels of methyl salicylate (as well as its metabolite, salicylic acid) and l-menthol are measurable following patch application, these do not correlate with the onset of pain relief. Thus, bioequivalence between any proposed generic and the SPRP should be determined based upon the “most accurate, sensitive, and reproducible approach available”. A number of statements (provided below) made by FDA officials reveals that the most appropriate means of determining bioequivalence between topical products is via performance of a clinical trial. As such, also provided below are several examples illustrating instances in which FDA required a clinical endpoint bioequivalence study for approval of a topical (or locally-acting) generic product. Recent Draft Guidances released by FDA have also noted the appropriateness of performing a clinical endpoint study when attempting to demonstrate bioequivalence between two locally-acting drugs. Thus, Hisamitsu believes that the provided evidence reveals the necessity for performance of a clinical trial with an efficacy endpoint to establish bioequivalence between any proposed generic product and the SPRP.

2.1. Overview of Statutory and Regulatory Framework

Regulations issued subsequent to the Drug Amendments of 1962 contained a requirement for all new drug applications to submit bioavailability data. However, in cases where bioavailability was considered “self evident or not necessary for the product to achieve any of its intended purposes” FDA was permitted to waive in vivo bioequivalence requirements for new topical products. Demonstration of in vivo bioequivalence between topical products could also be waived if FDA believed that an in vitro test was acceptable. Thus, prior to the passage of the Hatch/Waxman Act in 1984, in vivo bioequivalence requirements were typically waived for new topical products and results from in vitro tests were used to demonstrate therapeutic equivalence.

22 21 C.F.R. § 320.24, Types of evidence to measure bioavailability or establish bioequivalence
23 21 C.F.R. § 320.22(b) (1977).
Following passage of the Hatch/Waxman Act all generic products were required to submit information demonstrating in vivo bioequivalence to the RLD.\textsuperscript{25} "[S]ection 505(j)(2)(A)(iv) of the act requires that the applicant provide information to show that its drug product is bioequivalent to the listed drug referred to by the applicant. Thus, there is no statutory provision for deferral of the requirement. Therefore, in those situations where methodology for in vivo testing is not available, the applicant is required to develop adequate methodology for such testing, or to carry out clinical studies to assess therapeutic equivalence, unless the agency determines that in vitro methods can be used to demonstrate bioequivalence."\textsuperscript{26}

Sponsors seeking approval of a generic drug must submit information demonstrating that the product is the same as the reference listed drug (RLD) with respect to active ingredient, dosage form and strength, route of administration, and product labeling.\textsuperscript{27} A generic product is considered bioequivalent to the RLD when "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 conditions in either a single dose or multiple doses".\textsuperscript{28}

Bioequivalence between generic and innovator products must be demonstrated using evidence obtained by the "most accurate, sensitive, and reproducible approach available".\textsuperscript{29} Pharmacokinetic analyses examining plasma concentrations of the drug or a metabolite following a single dose administration are typically used for products which elicit their therapeutic effect via a systemic action. Alternative methods which are "scientifically valid" and "expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect" are allowed to establish bioequivalence for locally-acting drugs, including those administered topically.\textsuperscript{30} This

\begin{footnotesize}
\begin{itemize}
  \item \textsuperscript{25} 21 U.S.C. § 355(j)(2)(A)(iv)
  \item \textsuperscript{26} Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872-942.
  \item \textsuperscript{27} 21 U.S.C. § 355(j)(2)(A)
  \item \textsuperscript{28} 21 U.S.C. § 355(j)(8)(B)(i)
  \item \textsuperscript{29} 21 C.F.R. § 320.24(a)
  \item \textsuperscript{30} 21 U.S.C. § 355(j)(8)(C); OFFICE OF GENERIC DRUGS, FDA, APPROVED DRUGS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (29th ed. 2009)
\end{itemize}
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includes the performance of a clinical trial, an approach “considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes.”

2.2. FDA Officials Have Repeatedly Noted That Comparative Clinical Trials are the Most Appropriate Method to Determine Bioequivalence Between Topical Products

Efforts to develop adequate methods for determining the bioequivalence of topical drug products has proven to be difficult, a fact repeatedly acknowledged by FDA. Despite significant effort aimed at establishing adequate bioequivalence methodology for topical products, FDA has not implemented such a method. The following examples demonstrate FDA acknowledgement of the necessity for clinical bioequivalence trials when comparing topical products.

➢ In 1993, FDA officials published a book which discussed then current methods for demonstrating bioequivalence, stating that pharmacokinetic, pharmacodynamics and in vitro testing were not suitable for the demonstration of bioequivalence between topical products. Because of that, “comparative clinical studies between the generic and pioneer products are now required by the FDA to document bioequivalence.”

➢ In 1997, Roger Williams, Deputy Director of CDER, noted that with topical products “you don’t get a useful measurement of bioavailability/bioequivalence by looking at the blood level.”

31 21 C.F.R. § 320.24(b)(4)
32 Bioequivalence of Topical Dermatological Drug Products, in TOPICAL DRUG BIOAVAILABILITY, BIOEQUIVALENCE, AND PENETRATION (Shah and Maibach, eds. 1993).
33 Roger Williams, M.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science (ACPS) (May 7, 1997)
One year later, Dr. Williams noted that "[t]he real important thing [for topical products] is equivalent safety and efficacy which really should be shown in comparative clinical trials."\textsuperscript{34}

At a 1998 Dermatologic and Ophthalmic Drugs Advisory Committee Meeting, Vinod P. Shah, Ph.D. stated that the Office of Generic Drugs "require[s] the clinical efficacy studies for the bioequivalency determinations of dermatological products other than glucocorticoids."\textsuperscript{35}

In a 2001 publication\textsuperscript{36}, Dr. Shah wrote that "Comparative clinical trials, to document bioequivalence between generic and innovator products, are now required by the FDA for most post-1962 nonsolution topical formulations, except corticosteroids ... they are considered 'gold standards'.'"

In 2003, FDA's Deputy Director of the Office of Pharmaceutical Science noted that FDA has "struggled for the last 12 years trying to develop a method for assessing the bioequivalence to drugs applied to the skin and we have not been successful in trying to move the decision forward in a consensus way."

In March 2003, OGD employee Dale Conner noted that pharmacokinetic studies were not suitable for topical products and that "we really need to measure a PD [pharmacodynamics endpoint] or a clinical response to determine what's really happening, how that drug from that product is available to the site of activity within the skin."\textsuperscript{38}

\textsuperscript{34} Roger L. Williams, M.D., (ACPS transcript October 23, 1998).
\textsuperscript{35} Vinod P. Shah, Ph.D., Remarks at Dermatologic and Ophthalmic Drugs Advisory Committee Meeting, March 19, 1998
\textsuperscript{37} Ajaz S. Hussain, Ph.D., Remarks at ACPS Meeting, March 12, 2003.
\textsuperscript{38} Dale Conner, Pharm. D., Remarks at the ACPS Meeting, March 12, 2003
In April 2004, Robert A. Lionberger, Ph.D., noted that "[t]he current state of topical bioequivalence is that ... for almost all locally acting dermatological products clinical trials are necessary to demonstrate bioequivalence".39

A May 2007 report by OGD entitled 'Critical Path Opportunities for Generic Drugs' notes that for topical products other than corticosteroids "clinical studies are recommended to establish bioequivalence because no alternative methods have been developed." 40 This document also notes that topically-applied products can produce measurable systemic drug levels; however, the relationship of these levels to those delivered locally is "still unknown".

In a Draft Guidance released in 199841, FDA proposed using an approach termed dermatopharmacokinetics to assess bioequivalence between topical drug products. Briefly, this method measures drug levels in the stratum corneum, the outer-most layer of the epidermis, by a process termed skin-stripping. FDA withdrew this Draft Guidance in May 200242, based on numerous comments concerning the adequacy and reproducibility of the method.

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39 Robert A. Lionberger, Ph.D. Presentation titled Topical Bioequivalence Update; April 14, 2004 Advisory Committee for Pharmaceutical Science, ACPS
40 CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS; May 1, 2007
42 Fed. Reg. 67, 35122-35123; May 17, 2002
2.3. Examples of Generic Topical Products Approved by FDA for Which Clinical Endpoint Trials Were Required for the Demonstration of Bioequivalence

Generic topical/locally acting products have been approved by FDA based on bioequivalence studies with clinical endpoints. The following examples illustrate the necessity of clinical studies in order to confirm bioequivalence between a generic product and its Reference Listed Drug.

2.3.1. Ketoconazole Shampoo

FDA recommends performance of a randomized, double-blind, placebo controlled, parallel design bioequivalence study with a clinical endpoint for manufacturers seeking to market a generic form of ketoconazole shampoo, 2%. As part of the requirements for approval of a generic ketoconazole shampoo, Atrix Laboratories conducted a clinical endpoint bioequivalence study comparing their product to the reference listed drug.

2.3.2. Efudex

Efudex (5-fluorouracil) is a locally-acting product approved for the topical treatment of multiple actinic (or solar) keratoses as well as superficial basal cell carcinomas. In their response to a December 2004 Citizen Petition, FDA noted that “decisions regarding the bioequivalence of two potentially equivalent 5-FU [5-fluorouracil] formulations are to be based on evidence of comparative efficacy and safety in clinical trials.” On April 11, 2008, Spear Pharmaceutical received FDA approval of an ANDA for 5-fluorouracil based on a 318 patient clinical bioequivalence study.

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43 Draft Guidance on Ketoconazole Shampoo (Recommended July 2008), Individual Product Bioequivalence Recommendations
44 Approval Package for ANDA 76-942 (Ketoconazole Shampoo, 2%; April 11, 2005)
45 FDA response to Valeant Citizen Petition (FDA-2004-P-0557) dated April 11, 2008
46 Spear Pharmaceutical Inc., ANDA (77-524) for Fluorouracil Cream 5%, April 11, 2008
2.3.3. Sucralfate

As discussed in the Medical Officer Reviews for two generic sucralfate oral tablet approvals (ANDA #’s 70-848 and 74-415), generic manufacturers were required to perform clinical bioequivalence studies.  

2.4. Other Examples of FDA Recommendations for Clinical Endpoint Bioequivalence Studies for Locally-Acting Drugs

2.4.1. Vancomycin

Vancomycin is indicated for the treatment of severe bacterial infections of the gastrointestinal tract. Vancomycin acts locally on the gastrointestinal tract and systemic drug levels are typically low following oral dosing. Until recently, FDA had considered in vivo clinical trials a requirement for approval of a generic version of the reference listed drug (Vancocin). An Advisory Committee Meeting was convened in June 2009 to discuss an in vitro dissolution test proposed as a replacement for clinical endpoint determination of bioequivalence for generic versions of vancomycin. It was noted that the “proposal to waive in vivo bioequivalence testing for generic oral Vancomycin capsule products … does not appear to be supported by sufficient evidence or the public health interest.”

47 ANDA 70-848 and ANDA 74-415
48 Clostridium difficile and enterocolitis caused by Staphylococcus aureus; See Vancocin® HCl labeling information.
49 Briefing Information for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology regarding the Proposed Bioequivalence Method for Oral Vancomycin Capsules, June 30, 2009 (p. iii)
50 Draft Guidance on Vancomycin Hydrochloride, December 2008
51 Briefing Information for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology regarding the Proposed Bioequivalence Method for Oral Vancomycin Capsules, June 30, 2009 (p. 43)
2.4.2. Nasal Inhalers

In FDA’s guidance for nasal inhalers, the Agency has noted that clinical studies or bioequivalence studies with clinical or pharmacodynamic endpoints are recommended to establish bioequivalence:

“Locally acting drugs are intended to produce their effects upon delivery to nasal sites of action without relying on systemic absorption. Although systemic absorption may contribute to clinical efficacy for certain corticosteroids and antihistamines, the consequences of systemic absorption (e.g., hypothalamic-pituitary-adrenal (HPA) axis suppression by corticosteroids) are generally undesirable. In the absence of validated in vitro methodology for characterizing drug PSD for suspension products and when measurable plasma levels can be obtained, this guidance recommends PK studies to measure systemic exposure BA or to establish systemic exposure BE (see Section VII). For suspension products that do not produce sufficient plasma concentrations to allow assessment of systemic exposure, clinical studies or BE studies with a pharmacodynamic or clinical endpoint are recommended to measure systemic absorption BA and establish systemic absorption BE.”

2.4.3. Mesalamine Suppositories

In the FDA draft bioequivalence guidance for generic mesalamine suppositories, FDA’s Office of Generic Drugs recommends three studies: 1) an in vitro dissolution study; 2) a single bioequivalence study with pharmacokinetic endpoints; and 3) a single bioequivalence study with clinical endpoints in the treatment of active ulcerative proctitis to establish bioequivalence of a generic mesalamine suppository.

52 Draft Guidance For Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003
53 Draft Guidance on Mesalamine (Recommended Feb 2006; May 2007), Individual Product Bioequivalence Recommendations

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2.4.4. Adapalene

Adapalene is a topical product used to treat acne. FDA recently released a Draft Guidance on Adapalene\textsuperscript{54} noting that the recommended method for demonstrating bioequivalence is a randomized, double-blind, parallel, placebo-controlled, in vivo study.

3. Conclusion

For the reasons outlined above, Hisamitsu respectfully requests that the Commissioner of the Food and Drug Administration refrain from approving any ANDA submitted under section 505(j) of the FDCA for a generic version of SALONPAS\textsuperscript{®} Pain Relief Patch, unless the ANDA contains data: (1) from a non-inferiority comparative study with clinical endpoints in the indicated patient population; (2) from skin safety studies to ensure the safety of the generic patch formulation; (3) from a pharmacokinetic study comparing the generic patch formulation to reference ointments; and (4) utilizing a product which has the same surface area (7 cm x 10 cm) and the same total amounts of active ingredients, \textit{i.e.}, methyl salicylate (105 mg) and \textit{l}-menthol (31.5 mg).

\textsuperscript{54} Draft Guidance on Adapalene, November 2009
III. Environmental Impact

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31. Hisamitsu is not aware of any extraordinary circumstances that would necessitate an environmental impact statement.

IV. Economic Impact

As provided in 21 CFR 10.30(b), information on the economic impact of this proposal will be submitted upon request of the Commissioner of the Food and Drug Administration.

V. Certification

Hisamitsu certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Kenichi Furuta
General Manager
International Development Department
Hisamitsu Pharmaceutical Co., Inc.
APPENDIX – References
Cited Literature Exhibits:


