

July 29, 2019

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Docket No. FDA-2019-P-0417: Scilex Citizen Petition requesting that FDA remove from the market and prevent further marketing of lidocaine-containing drug products in patch, plaster, poultice, or comparable delivery systems that have not been approved pursuant to a new drug application or an abbreviated new drug application submitted under 21 U.S.C. § 355

Herein, the Consumer Healthcare Products Association (CHPA), the 138-year-old trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements (chpa.org), provides feedback on the above referenced Citizen Petition from Scilex Pharmaceuticals.

Regulatory History

In 2003, the Food and Drug Administration (FDA) reopened the administrative record for the over-the-counter (OTC) external analgesics rulemaking and proposed to amend the tentative final monograph (TFM) for external analgesics (68 FR 42324-42327, July 17, 2003). FDA proposed to classify any OTC external analgesic active ingredient in a patch, plaster, or poultice dosage form as Category III (more data needed), although the active ingredients are Category I (generally recognized as safe and effective).

The agency asked for comments on the existing data in the docket (No. 78N-0301) and for new data and information relevant to inclusion of patch, plaster, and poultice products in the final monograph.

In its 2003 submission, the CHPA External Analgesic Task Group objected to FDA's proposal to reclassify all topical analgesic patch products and require them to be subject to new drug applications (NDAs). The task group's comments summarized the scientific data, including published literature, and compiled information from spontaneous consumer reports supporting the safe and effective use of topical counterirritants in patch, plaster, or poultice formulations. The CHPA task group also recommended FDA adoption of an appropriately designed program to show that products meet certain safety testing and performance standards. In its comments, the task group presented a proposed testing program, using in vitro and in vivo methods, to confirm the safe concentrations of counterirritant ingredients applied in patches or other novel dosage forms and to show adequate dose delivery for effectiveness.

The agency was asked to issue a guidance document, with example protocols and recommended conditions that testing for irritation, sensitization, and dose delivery must meet to be recognized as acceptable for confirming the safety and effectiveness of generally recognized as safe and effective active ingredients in alternative dosage forms. Unfortunately, CHPA did not receive a response to this request from the agency.

Subsequent submissions provided updated data on the safety of certain ingredients administered via patches or other novel dosage forms available OTC in the United States in February 2010 and again in February 2012. Although these submissions did not include data on lidocaine, they are supportive of the safety of the patch dosage form.

The above petition asks FDA to initiate a massive expulsion of products from the market. While the intended target is the OTC lidocaine patch, the acceptance of the petitioner's rationale would extend to all OTC analgesic patch products, anesthetics and counterirritants alike. This is essentially acknowledged by the petitioner (pg. 2, note 1); *i.e.*, the requested actions "may apply: to a "broader category" of OTC products.

The petition depends upon two propositions to support its contention that the current marketing of OTC lidocaine patch dosage products is illegal: (a) lidocaine patches, indeed all OTC analgesic patches, were originally excluded from the Tentative Final Monograph (TFM) as it was originally published on February 8, 1983 and (b) the proposed TFM amendment of July 2003 has, more explicitly, rendered such marketing illegal. Starting on page 2 and continuing throughout, the petition refers to the TFM as the "TFM, as amended." However, both the TFM itself and the 2003 proposed TFM amendment are pending proposals; *i.e.*, they do not constitute final agency action.

As to proposition (a) above, the sole significance of the TFM reference to creams, lotions, and ointments was to provide alternative statements of identity. This was done to accommodate a public comment, with no suggestion that the terms were intended to place limitations on the dosage forms allowed under the TFM:

One comment stated that there is no evidence that the term "external analgesic," the Panel's recommended statement of identity, is more informative to consumers than other terms such as "topical analgesic" or "pain relieving ointment." The comment suggested that the latter terms be allowed in addition to "external analgesic."

The agency agrees that the terms referred to by the comment would be as informative to consumers as the Panel's recommended statement of identity. Therefore, the agency is proposing the following **alternative statements of identity** in §348.50(a)(1): "The labeling identifies the product as an 'external analgesic,' 'topical analgesic,' or 'pain relieving [*insert dosage form, e.g., cream, lotion, or ointment.*]" (48 FR 5858 paragraph 20; **emphasis added**).

Regarding proposition (b) and the idea that the 2003 TFM rendered marketing of an OTC external analgesic patch illegal, this argument depends solely upon the validity of proposition (a), which we suggest above is not valid. The 2003 TFM did not offer any new rationale or support regarding the exclusion of patches from the monograph.

The 2003 proposed amendment was not promulgated as an interim final rule (IFR). It was not implemented upon being published in the Federal Register. No FDA regulatory actions have been premised on it during the 16 years which have now elapsed since its publication. The comments requested by the agency and thereafter submitted by CHPA and others on October 15, 2003 remain unanswered. Section 2 of the CHPA comment (pp.4-11) filed in Docket No. 78N-0301 is hereby incorporated by reference (see Attachment A).

From the preamble to the July 17, 2003 proposed TFM amendment - "If adequate safety and effectiveness data are not provided, FDA will not include these types of dosage forms for external

analgesic active ingredients in the FM, to be published in a future issue of the Federal Register, and any currently marketed products will no longer be able to be marketed *when the FM becomes effective*, unless they are the subject of an approved new drug application.” (*emphasis added*).

In the meantime, FDA has not contended that continued marketing of OTC analgesic patch products is subject to regulatory action as a result of this proposal. They continue to be deferred to the OTC Review and should remain so.

21 CFR 330.10(a)(10)(ii) provides:

The Commissioner shall make all decisions and issue all orders pursuant to this section solely on the basis of the administrative record, and shall not consider data or information not included as part of the administrative record.

If the data or information cited in the petition is considered to be part of the administrative record, §330.10(a)(7)(v) will apply:

New data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the Federal Register unless the Commissioner finds that good cause has been shown that warrants earlier consideration.

Amendment of TFM with respect to the status of hydrocortisone

In an analogous situation involving this same TFM, an amendment relating to the status of hydrocortisone was proposed by FDA in the Federal Register of February 27, 1990 (55 FR 6932) in response to a citizen petition. The comment period closed on April 30, 1990. FDA issued an enforcement notice implementing minor changes in response to the comments received and confirming the TFM amendment, as so modified (56 FR 43025; August 30, 1991).¹

There has been no similar order with regard to the status of patch dosage forms.

Lidocaine, the focus of the petition,² remains in Category I.

¹ Attachment 2 of the petition is a December 10, 1993 letter from FDA staff, Dr. Gilbertson, addressing an industry representative’s contention that gel dosage forms of hydrocortisone should not be declared non-monograph on the basis that they were not included in the TFM’s examples of dosage forms. Although that 1993 letter did note that gel dosage forms would be excluded from the monograph, the July 2003 TFM contained no mention of excluding gel dosage forms (see the October 15, 2003 CHPA comment on this point). Similar issues exist as to the purported exclusion of patch dosage forms on the same rationale. The opinions expressed in such correspondence do not constitute official agency action and, like FDA warning letters, are not subject to judicial review. Resolution of the issue will have to await issuance of a final monograph and will not receive extensive attention in this submission.

² As an anesthetic under proposed §348.10, the OTC lidocaine patch is not required to carry the “do not bandage tightly” label warning which is specified for counterirritant patches (proposed §348.50). The rationale for this disparate regulatory treatment was to address the possible adverse effects of occluding counterirritants on the skin. There was no similar concern in the ANPR or 1983 TFM regarding occlusion of anesthetics.

Deferral of Patch Products to OTC Review

As already stated, the products which the petition seeks to have removed from the market are deferred to the OTC Review. They are legally on the market pending the effective date of a final monograph. This has been affirmed in agency actions dating back decades.

On December 2, 1994, three years after the above referenced enforcement order concerning hydrocortisone, FDA directed a warning letter to a CHPA member stating that three of the company's OTC analgesic patch products were unapproved new drugs (*i.e.*, non-monograph) and that drug products of their composition and patch dosage form were not on the US market on or before December 4, 1975.³ The letter also stated that the company should discontinue the marketing of these products.

In responses provided on January 23 and 30, 1995, the CHPA member company documented the presence of two of the three challenged products in the US market, beginning well prior to the 1975 date, and contended that such products were deferred to the OTC Review. FDA acknowledged the adequacy of the company's marketing history documentation, confirming that they are deferred to the OTC Review:

[W]e have determined that it is in the Agency's interest to defer further regulatory action against these products to the Final Monograph for OTC external analgesic drug products under the OTC Drug Review. You should be aware that this does not represent a determination that such drugs are generally recognized as safe and effective and not misbranded; such a determination will await the publication in the Federal Register of the aforesaid Final Monograph. (Letter from B. Williams, Director Div. of Drug Labeling Compliance; April 4, 1995).

The FDA regulatory decision to defer OTC patch analgesic products to the OTC Review was not limited to the two products⁴ as to which pre-1975 US marketing was documented. It was extended to all analgesic patch products incorporating the same conditions. This regulatory policy has now been in effect continuously for 24 years and applies to both counterirritant and anesthetic patches for pain relief.

The regulatory policy for drugs subject to the OTC Review was reaffirmed in June of 2006 (three years after the publication of the proposed TFM amendment) when FDA issued a revised Compliance Policy Guide (CPG 400.100)⁵ summarizing its regulatory policy regarding the status of non-NDA'd drug products: This included the following:

[G]enerally products subject to an ongoing ... OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which a final monograph is not yet in place) may remain on the market during the pendency of that proceeding.

When this CPG was revised and re-issued in September of 2011⁶ the policy was again affirmed.

“OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies.” (Page 6, footnote7).

³ The reference date specified in the regulations is May 11, 1972. FDA staff elected to use the later (1975) date for convenience as an exercise of administrative discretion. The point is not material to the issues under discussion in this comment since Hisamitsu was able to document that US marketing of its Salonpas OTC patch products began in the 1950's.

⁴ Marketed by Hisamitsu

⁵ Marketing Unapproved Drugs - Compliance Policy Guide - Marketed New Drugs Without Approved NDAs or ANDAs, June 2006.

⁶ Guidance for FDA Staff and Industry, Marketing Unapproved Drugs - Compliance Policy Guide, September 2011; available at <https://www.fda.gov/media/71004/download>

The continued OTC Review status of lidocaine patch products can be further confirmed by referring to 21 CFR 310.545 which lists those OTC drug conditions - including active ingredients and dosage forms - excluded from further consideration under the OTC Review. Products or dosage forms which have ceased to be reviewed are listed in this section. Products incorporating these conditions are considered to be new drugs and subject to regulatory action if they do not have an approved NDA.⁷ The petition notes that lidocaine has been excluded from further consideration under the OTC Review for use in oral healthcare products (Petition, p. 5, note13). This is true, but is irrelevant to the action which the petition requests since neither the external analgesic use of lidocaine or a patch dosage form is included in §310.545.

FDA has confirmed that *[N]onmonograph status for the indications included in this final rule has no bearing on the ingredients' inclusion in other OTC drug monographs covering other uses.*⁸ Neither lidocaine, as an external analgesic, nor the patch dosage form is among the discontinued conditions listed in §310.545.

Inactive ingredients

The petition, page 26, et seq., expresses concern regarding the inactive ingredients being used in lidocaine patches. The regulatory requirement for inactive ingredients in OTC drug products⁹ reads as follows:

(e) The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 721 of the act and subchapter A of this chapter. 21 CFR 330.1(e).

The expressed concern is based on the use of inactives which are not included in the FDA Inactive Ingredient database. Petition Attachment 7 identifies inactive ingredients currently used in lidocaine patches and characterizes those which are not also on the Inactive Ingredient database as “novel.” This misconceives the nature and purpose of the database. The database is limited to inactives which have previously been reviewed in NDA or ANDA applications. The circumstance that an inactive is not listed on the database does not indicate noncompliance with §330.1(e). Such ingredients cannot be characterized as “novel.” The purpose of the database is described as follows on the FDA website¹⁰:

What is the purpose of the Inactive Ingredient Database?

⁷ 21 CFR 310.545 lists active ingredients and dosage forms (conditions) which FDA has already determined to be non-GRASE and which will not receive further consideration under the OTC Review; e.g. §310.545(a)(3) (“Opium, powdered; Opium tincture”). Any drug product incorporating those conditions will require an approved NDA to enter the market.

⁸ 55 *Fed Reg* @46915, Nov. 7, 1990, Status of Certain Over-the-Counter Drug Category II and III Active Ingredients, Final Rule

⁹ Section 502(e) of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Modernization Act of 1997, requires the listing of the established name of each inactive ingredient on the outside container of the retail package. Prior to the 1997 Act, CHPA (then the Proprietary Association) had adopted a voluntary program to identify inactive ingredients on OTC drug product labels on an alphabetical basis. This voluntary program was made obsolete by the 1997 FDA Modernization Act.

¹⁰ <https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredient-search-approved-drug-products-frequently-asked-questions>

The Inactive Ingredient Database provides information on inactive ingredients present in FDA-approved drug products. This information can be used by industry as an aid in developing drug products. For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product. For example, if a particular inactive ingredient has been approved in a certain dosage form at a certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product.

The petitioner notes (p. 25) that it has been advised by agency staff that not all inactives in the IIG database are suitable for use in OTC products. However, a CHPA member has been advised by agency staff that failure of an ingredient to appear on the database is *not* an indication that it is unsuitable for OTC use. Regardless, inactive ingredients not present in the IIG database and used in lidocaine patch products could be replaced, if necessary, without declaring the products to be new drugs and forcing them from the market pending NDA approval.

Review of Actions Requested by Petitioner

The Petitioner requests that FDA take five specific actions. Responses to each of these requests are provided below.

1. *Initiate all administrative and judicial actions necessary to remove from the market, and to prevent the further marketing of, lidocaine-containing drug products in patch, plaster, poultice, or comparable delivery systems that have not been approved pursuant to a new drug application (“NDA”) or an abbreviated new drug application (“ANDA”) submitted under 21 U.S.C. § 355 and implementing regulations*

Comment: As FDA’s OTC Drug Review regulations and CPG 440.100 make clear, OTC drug products marketed in accordance with the OTC Drug Review are legally on the market until the effective date of a final OTC monograph.

In appropriate circumstances, FDA can and has acted to remove OTC drug products from the market prior to the effective date of a final monograph if they are toxic or subject to abuse or misuse. See 37 FR 20160 (Sept. 27, 1972) (codified at 21 CFR 250.250 (hexachlorophene)); 40 FR 50527 (Oct. 30, 1975) (codified at 21 CFR 510.502) (certain halogenated salicylanilides)); 41 FR 26842 (June 29, 1976) (codified at 21 CFR 310.513 (chloroform)); 42 FR 41374 (Aug. 16, 1977) (codified at 21 CFR 310.510 (zirconium-containing aerosols)); 45 FR 43400 (June 27, 1980) (codified at 21 CFR 310.525 (sweet spirits of nitre)); 47 FR 41716 (Sept. 21, 1982) (codified at 21 CFR 310.526 (camphorated oil)); 50 FR 25171 (June 17, 1985) (codified at 21 CFR 310.529) (orally administered insect repellants)); 50 FR 46587 (Nov. 8, 1985) (codified at 21 CFR 310.533) (anticholinergics)); and 51 FR 26114 (July 16, 1986) (codified at 21 CFR 310.534) (oral wound healing agents)).

FDA also can and has acted to remove classes of OTC drug products from the market. See 44 FR 36378 (June 22, 1979) (codified at 21 CFR 310.519) (daytime sedatives)); 48 FR 52513 (Nov. 18, 1983) (caffeine/phenylpropanolamine/ephedrine or pseudoephedrine combination products)); 53 FR 31270 (Aug. 17, 1988) (codified at 21 CFR 310.540) (stomach acidifiers)); 54 FR 28780 (July 7, 1989) (codified at 21 CFR 310.528 (aphrodisiacs)); 54 FR 28772 (July 9, 1989) (hair growth/hair loss products)); 55 FR 6930 (Feb. 27, 1990) (codified at 21 CFR 310.532) (products intended for use in the treatment of benign prostatic hypertrophy)).

See also 21 CFR 310.545, discussed above, regarding ingredients and dosage forms which FDA has eliminated from further consideration under the OTC Review.

2. *Strictly apply the provisions of 21 U.S.C. § 355, 21 C.F.R. Part 330, and related regulatory decisions, which do not allow the marketing or distribution of lidocaine-containing patch dosage form drug products that were introduced into United States (“U.S.”) commerce after the OTC drug review was initiated on May 11, 1972*

Comment: Petitioner seems to be maintaining that the “continuing stream” of lidocaine and perhaps other analgesic patch products that come onto the OTC market necessarily violate OTC Drug Review regulations. Perhaps the most fundamental underpinning of the OTC Drug Review, namely, that it is a review of *conditions* under which OTC drugs can legally be marketed without a new drug application (NDA). It is not a review of *products*.

21 CFR 330.14 defines the word “condition”:

(2) Condition means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use, except as excluded in paragraph (b)(2) of this section [which pertains to OTC drugs theretofore marketed only in foreign countries].

The Review does not prohibit or limit new OTC drug *products* from coming onto the market after May 11, 1972 (the date of publication of the final regulations governing the OTC Drug Review). It requires only that those products be marketed in accordance with the *conditions* set forth in and under the Review, among which are that the product contain ingredients in dosage forms at dosage strengths and with labeling that were on the market before the OTC Drug Review began in May 1972.

The first sentence in footnote 2 of the petitioner’s request (p. 2) is consistent with this:

21 C.F.R. Sec. 330.13(e) (establishing that conditions for marketing ingredients recommended for OTC use under the OTC Drug Review “appl[y] only to conditions under consideration as part of the OTC Drug Review initiated on May 11, 1972, and evaluated under the [expert panel review and monograph development] procedures set forth in Sec. 330.10.”

The second sentence of petitioner’s note 2 (at 2) appears to be where the petitioner’s understanding of the OTC Drug Review falters. Petitioner states:

Separate regulations apply to OTC drugs initially marketed in the U.S. after the OTC drug review began in 1972. Id. (cross-referencing 21 CFR Sec. 330.14) (emphasis added).

21 CFR 330.14 describes circumstances under which a “post-May 11, 1972” OTC drug product *that theretofore had been marketed only overseas* can come under the OTC Drug Review. (Hence the detailed discussion of “material extent/material time”).

However, 21 CFR 330.14 leaves untouched the status of “post-May 11, 1972” OTC drug products whose “conditions” (active ingredients, dosage forms, etc.) already come under the Review. These might include, for example, “new” (*i.e.*, post-1972) aspirins labeled for pain relief that contain aspirin at levels marketed before the Review. Also, with respect to the December 2, 1994 FDA warning letter, described above, its resolution permitted the continued marketing of the product¹¹ which had entered the US market after the 1975 date.

CHPA members believe this position comports with FDA Compliance Guide 440.100, meaning that patches may remain on the market at least until FDA finalizes the External Analgesic monograph.

3. *Finalize the Tentative Final Monograph for External Analgesic Drug Products for Over-the-Counter Human use, as amended (the “TFM” or “External Analgesics TFM”), which expressly excludes lidocaine-containing products in patch dosage forms from its scope because of concerns about the safety and efficacy of these products*

Comment: CHPA members acknowledge that the language of the 2003 proposed amendment is explicit. Any enforcement actions regarding this amendment will constitute final agency action which will permit judicial review. It is hoped that, prior to such time, the ongoing review will lead to appropriate clarification as to the issue raised.

¹¹ Marketed by Hisamitsu

4. *Publish an immediately applicable enforcement policy guidance document that will apply until the final OTC External Analgesics Monograph is codified, and that affirms that lidocaine-containing drug products marketed in nonprescription patch dosage forms (“OTC lidocaine patches”) and that are marketed without approved NDAs or ANDAs do not conform to the terms of the External Analgesics TFM, are outside the scope of any enforcement discretion that may exist pursuant to Compliance Policy Guide 450.200 or other relevant statements of enforcement discretion, and may be the subject of immediate enforcement action without further notice*

Comment: Here, the petitioner is evidently asking for immediate regulatory action which is to take effect prior to the effective date of the Final Monograph. The requested action would be in contravention of the long-standing regulatory procedures codified in 21 CFR Part 330.

5. *Initiate and regularly review drug listing and other marketplace information to identify lidocaine-containing products in patch dosage forms and take appropriate administrative and judicial action to ensure their compliance with the Federal Food, Drug, and Cosmetic Act, implementing regulations, and findings pursuant to this petition.*

Comment: In the context of this petition, CHPA takes no position on the need or the wisdom of the surveillance effort being urged by the petitioner.

Adverse events with topical lidocaine patches

The Petitioner has cited a number of adverse events associated with the use of topical products claiming that these demonstrate a “safety issue” associated with this dosage form. While FDA Public Health Advisories in 2007 and 2009 did note the potential for serious and life-threatening side effects following the improper use of topical anesthetics (including lidocaine), these cases involved improper use of the product (*e.g.*, wrapping the area in plastic wrap following application). A 2018 safety announcement from FDA covered reports of methemoglobinemia associated with oral over-the-counter benzocaine products used for teething and mouth pain and prescription local anesthetics (including lidocaine).

The Petitioner points out that there are reports in the literature associating the use of lidocaine (5% transdermal patch) with methemoglobinemia. However, a closer examination of these reports reveals in one case that the subject used a 5% patch chronically and was given 100 mg of lidocaine (IV) prior to surgery.¹² In a response to this case report, it was noted that the exposure to lidocaine from the IV may have been considerably higher than that from the 5% patch.¹³

Another case report of methemoglobinemia cited by the Petitioner¹⁴ involved an 83-year old patient with significant comorbidity (impaired renal function) administered a 5% patch near the surgical incision. The Petitioner also cites a review¹⁵ of methemoglobinemia cases associated with a combination lidocaine-prilocaine cream (EMLA). A total of 13 cases were found, 11 of which were in children/infants ≤ 8 years. See also Gay and Amaral, 2018.¹⁶

As such, a search of the literature revealed no reports of methemoglobinemia associated with OTC lidocaine patches in the literature. One article does note cases of methemoglobinemia with lidocaine, but these are in subjects undergoing a medical procedure such as TEE, EGD, ERCP, bronchoscopy, and NGT placement.¹⁷ Indeed, one author has stated the following “If lidocaine does cause methemoglobinemia, it must be quite rare, given the paucity of reports and the huge clinical exposure”.¹⁸ Consistent with these findings, an analysis of CHPA member internal company adverse event for lidocaine patches revealed a very low rate of adverse events (only 2 serious adverse events during the 2016-2019 period).

Further, conditions which may increase the absorption of lidocaine are addressed in the product labeling for OTC lidocaine patch products. As it is known that increased temperature can enhance drug absorption^{19,20} the product labeling says do not use with a heating pad or local heat. Further, users are instructed to not bandage tightly following application of the product.

¹² Weingarten *et al.*, 2012 Methemoglobinemia in the setting of chronic transdermal lidocaine patch use, *Pain Med* 13(7):976-977

¹³ Wieman MS *et al.*, 2013 Response to Weingarten, “Methemoglobinemia in the setting of chronic transdermal lidocaine patch use,” *Pain Medicine* 2012

¹⁴ Acevedo FA *et al.*, 2018 Rare cause of delirium and hypoxemia after coronary bypass surgery: transdermal lidocaine patch-associated methemoglobinemia, *Int J Legal Med* 132(3):767-769.

¹⁵ Shamriz O Methemoglobinemia induced by lidocaine-prilocaine cream *Isr Med Assoc J* 16(4):250-254

¹⁶ Gay HC and Amaral AP Acquired methemoglobinemia associated with topical lidocaine administration: a case report, *Drug Saf Case Rep* 5(1):15

¹⁷ Chowdhary S *et al.*, 2013 Risk of Topical Anesthetic-Induced Methemoglobinemia, *JAMA Int Med* 173(9): 771-776.

¹⁸ Guay J 2009 Methemoglobinemia related to local anesthetics: a summary of 242 episodes, *Anesth Analg* 108(3):837-845

¹⁹ Thomas S *et al.*, 2018 In vitro and in vivo evaluation of two lidocaine topical delivery systems with or without the influence of transient heat, *AAPS PharmSci360*, Washington DC Nov 4-7, *abstract*

²⁰ Wood DG, Brown MB and Jones SA 2012 Understanding heat facilitated drug transport across human epidermis, *Eur J Pharm Biopharm* 81(3):642-649.

Use of a topical patch product may help certain populations avoid adverse events associated with systemic exposure following oral administration.²¹

In a double-blind placebo-controlled trial,²² authors compared an OTC lidocaine patch (lidocaine 3.6% combined with menthol 1.25%) to a prescription lidocaine patch (5%) and placebo. The OTC patch was found to be equivalent to the prescription patch in terms of efficacy, adverse events and quality of life assessments. These authors also noted that the average blood level of lidocaine following use of the lidocaine patch (over 72 h) was 0.2 µg/mL, a value well below the reported toxic level of lidocaine (5µg/mL)²³

The authors of this study also note that “[d]ecreased cost and resource utilization could benefit patients and payers”, a finding consistent with recent research estimating that every dollar spent on OTC products instead of prescription saves the US healthcare system approximately \$7.20 amounting to an annual savings of approximately \$146 billion dollars.²⁴

Adverse events associated with OTC lidocaine patches reported to CHPA member companies

In 2003, the FDA reopened the administrative record for the OTC external analgesics rulemaking, proposing to amend the TFM.²⁵ FDA proposed to classify any OTC external analgesic active ingredient in a patch, plaster, or poultice dosage form as Category III (more data needed), although the active ingredients are Category I (generally recognized as safe and effective). The agency asked for comments on the existing data in the docket (No. 78N-0301) and for new data and information relevant to inclusion of patch, plaster, and poultice products in the final monograph.

The CHPA External Analgesic Task Group responded to the request with a detailed submission (including information on the low observed rate of adverse events) in October 2003. Updated data on the safety of counterirritants administered via patches or other novel dosage forms available OTC in the United States was submitted by CHPA in February 2010 and again in February 2012.

The current analysis is restricted to OTC patch products containing lidocaine (4%). The period covered for this analysis is 2016-2019 and represents information available from two CHPA member companies. As is generally true for consumer healthcare products, most of the reports come from informal consumer complaints made by telephone, e-mail, or letter, and so the information is imprecise and incomplete. Consequently, reported adverse events are often not medically well-defined. While such data cannot be used to calculate precise rates of occurrence, or to establish causality related to use of OTC products, they do provide useful information about product safety.

The number of reported adverse events associated with use of marketed lidocaine-containing OTC external analgesic patches is low, particularly given the amount sold in the United States, which was estimated for 2018 to be over 18 million packages and more than 88 million dosage units. Table 1 presents the cumulative numbers of individuals with reported adverse events as well as the cumulative numbers of reported adverse events (non-serious and serious) for lidocaine. Calculation of the rate of

²¹ CDC Guidance - Module 2: Treating Chronic Pain without Opioids (2016)

²² Castro E and Dent DA 2017 A comparison of transdermal over-the counter lidocaine 3.6% menthol 1.25%, Rx lidocaine 5% and placebo for back pain and arthritis, *Pain Management* 7(6):489-498.

²³ US National Library of Medicine. Medline Plus Therapeutic Drug Levels (2016), www.nlm.nih.gov/medlineplus/ency

²⁴ Consumer Healthcare Products Association, Value of OTC Medicines to the U.S. Healthcare System, 2019; available at <https://www.iriworldwide.com/en-US/Insights/Publications/Value-of-OTC-Medicines>

²⁵ 68 *Fed. Reg.* 42324-42327, July 17, 2003

adverse events (both serious and nonserious) per 1 million dosage units provides further evidence of the safety of OTC lidocaine patches.

As can be readily seen for both nonserious and serious adverse events, both the number of individuals reporting an event, as well as the number of events is extremely small given the large number of unit sales. The low rate of reported serious adverse events is particularly evident, as only two individuals have reported a serious adverse event despite more than 40 million being sold during the 2016-2019 period. The low frequency of adverse events is consistent with the general recognition that lidocaine containing OTC patch products are safe.

Table 1: External Analgesic Patches with Lidocaine 4%

Year	Number of Package Units Sold at Retail	Number of Dosage Units Sold at Retail	Number of Individuals with Reported Adverse Event		Number of Reported Adverse Events	
			Nonserious	Serious*	Nonserious	Serious
2016	1,964,305	10,172,006	97	1	118	1
<i>rate</i> [#]			9.54	0.1		
2017	15,281,872	72,276,193	244	1	365	1
<i>rate</i>			3.16	0.01		
2018	18,675,477	88,663,356	160	0	296	0
<i>rate</i>			1.80	0		
2019	5,075,877	26,587,035	64	0	104	0
<i>rate</i>			2.41	0		

*Serious events are those that result in one of the following: death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, a congenital anomaly or birth defect, or requires, based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome described above.

[#] Expressed as rate of nonserious and serious adverse events per million dosage units sold at retail

Throughout the petition, a number of references are cited^{26,27,28,29} which discuss “transdermal delivery”. Based on a review of the literature and expert bodies it is clear that there is a meaningful distinction between transdermal and topical dosage forms. Differences between the topical lidocaine patch products marketed by CHPA members and transdermal patch dosage forms are addressed by the USP in General Chapters <3>³⁰ and <1151>³¹ and have been for a long time. Transdermal drug delivery systems are designed to deliver drugs “through the skin to the systemic circulation” while drugs intended to exert their effects topically (such as the patch products under consideration) are commonly applied to the skin “embedded in glue [adhesive] on a cloth or plastic backing.” Although the USP refers to these products as “plasters or tapes,” the categorization clearly encompasses the patch/pad form.

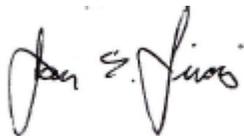
Should FDA determine that full NDAs would be required for lidocaine-containing OTC external analgesic patch products, detailed information on chemistry, manufacturing, and control technology as required for a new drug would need to be submitted by each company marketing an OTC lidocaine patch. Review of each of these submissions would also increase the regulatory burden on the Agency.

Conclusion

The petition should be denied. The regulatory actions requested by the petition would inflate the cost and decrease the availability of a large segment of the external analgesic market without commensurate benefit to the public. Any significant data or information having a material bearing on the suitability of lidocaine patch products for OTC use should be considered within the context of the OTC Review. Any threat to the public health by, for example, use of unsuitable inactive ingredients should promptly be addressed under existing agency authority. Consideration of the petition and supporting information should be conducted pursuant to 21 CFR 330.10(a)(7)(v) as stated above.

CHPA and our member companies appreciate the opportunity to comment on this process. Should you have any questions, please do not hesitate to contact me.

Regards,



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²⁶ Paudel KS *et al.*, 2010 Challenges and opportunities in dermal/transdermal delivery, *Ther Deliv* 1(1):109-131

²⁷ Kandavilli S *et al.*, 2002, Polymers in transdermal drug delivery systems, *Pharm Tech* 26(5):62-80

²⁸ Strasinger C *et al.*, 2016 Navigating sticky areas in transdermal product development, *J Control Release* 233:1-9

²⁹ Choi SH *et al.*, 2018 Generic drug device combination products: regulatory and scientific considerations, *In J Pharm* 544(2):443-454

³⁰ USP Topical and Transdermal Drug Products: Product Quality Tests

³¹ USP Pharmaceutical Dosage Forms