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February 27, 2012

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

Re: Docket No. 78N-0301: External Analgesic Drug Products for Over-the-Counter Human Use

Dear Sir or Madam:

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 42324-42324-42327, 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. The Consumer Healthcare Products Association (CHPA) External Analgesic Task Group responded to the request with a submission on October 15, 2003. CHPA submitted updated data on the safety of counterirritants administered via patches or other novel dosage forms available OTC in the United States on February 16, 2010.

CHPA is the national trade association representing the leading manufacturers and distributors of OTC medicines and dietary supplements in the United States. CHPA members account for over 90 percent of OTC drugs marketed in the United States, including many external analgesic products. Accordingly, the association has important interest in the regulatory status of external analgesic patch products.

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The following companies are current members of the CHPA External Analgesic Task Group:

Chattem, Inc.
Johnson & Johnson Consumer & Personal Products Worldwide
The Mentholatum Company
Noven Pharmaceuticals (subsidiary of Hisamitsu Pharmaceutical Co., Inc.)
Sato Pharmaceuticals Inc.
W.F. Young, Inc.

Numerous topical analgesic patch products containing TFM Category I counterirritants are currently marketed under the OTC monograph by CHPA member companies and others. Additionally, many similar private label and store-brand products are marketed OTC.

In its 2003 submission, the CHPA 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.

As the CHPA task group contended in 2003 and the FDA had accepted in the TFM, sufficient data exist on the counterirritant active ingredients camphor, capsaicin, menthol, and methyl salicylate to support their general recognition as safe and effective (GRASE) for consumer use in OTC external analgesic products. The effectiveness of the active ingredients, when appropriately formulated, would not be altered by their delivery in patches or other novel dosage matrices. FDA should expand the OTC external analgesic monograph to permit continued marketing of dosage forms different from creams, lotions, and ointments.

The CHPA task group submissions in 2003 and 2010 included compiled information from spontaneous consumer reports to companies about adverse events associated with OTC external analgesic patches, plasters, and poultices from 1998 through June 2009. That information was consistent with the general recognition that the monograph external analgesic counterirritants are safe. In this present submission, the task group provides additional, more recent safety information. The six companies on the current CHPA task group (named on page 2 of this letter) were surveyed to determine the nature of adverse events reported to them from July 2009 through April 2011 about OTC external analgesic patches marketed without NDAs. The recently compiled data are presented in the tables below and in Attachment A.

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 the reported adverse events are not medically well defined and so were grouped in this compilation into descriptive categories. 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 OTC external analgesic patches marketed without an NDA is low, particularly given the amount sold in the United States by the six companies, which was estimated for 2010 to be over 25.5 million packages and more than 262 million dosage units. The following tables present the cumulative numbers of individuals with reported adverse events as well as the cumulative numbers of reported adverse events for each of the active ingredients menthol (Table 1); capsaicin with or without menthol (Table 2); and methyl salicylate alone or in combination with menthol and camphor (Table 3). More than one effect may be reported for an individual user, and so yearly event totals are higher than the number of affected individuals. Compiled numbers for the various categories of reported adverse events are tabulated in Attachment A.

Tables 1, 2**,** and 3 also show the number of dosage units, as well as the number of package units, sold for the subject products. As can be readily seen in every case, the number of reported adverse events is extremely small given the large number of unit sales. The low frequency of adverse events is consistent with the general recognition that the monograph external analgesic counterirritants are safe.

Table 1: External Analgesic Patches With Menthol 1.25% - 16%

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**
2009 (July – Dec.)	6,544,730	22,217,838	150	5	285	13
2010	13,198,278	45,714,932	177	15	343	32
2011 (thru April)	4,463,580	14,289,743	97	3	179	5

* See Table A-1 in Attachment A for listing of adverse events.

** Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event.

Table 2: External Analgesic Patches with Capsaicin 0.025%, With or Without Menthol 5%

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**
2009 (July – Dec.)	2,262,971	2,740,103	10	0	18	0
2010	6,273,182	6,473,532	14	0	25	0
2011 (thru April)	1,696,495	1,708,547	6	0	8	0

* See Table A-2 in Attachment A for listing of adverse events.

** Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event.

Table 3: External Analgesic Patches with Methyl Salicylate at 10% alone or at 6.3% in Combination with Menthol 5.7% and Camphor 1.2%

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**
2009 (July – Dec.)	2,376,284	22,232,790	6	0	12	0
2010	6,040,288	210,129,824	20	0	38	0
2011 (thru April)	2,136,408	80,912,424	9	0	15	0

* See Table A-3 in Attachment A for listing of adverse events.

** Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event.

Given the sales volumes for OTC external analgesic patches, adverse events do not occur at a higher frequency than is expected for OTC medicines that are generally recognized as safe and effective. More information about the types of adverse events reported for OTC external analgesic patches is provided in Attachment A. All the serious adverse events tabulated in this submission were reported to FDA on MedWatch forms submitted by the companies.

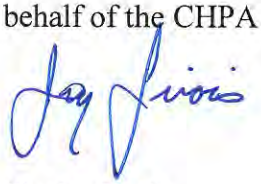
A new Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) Tracked Safety Issue (TSI) was created in August 2011 for OTC external analgesic products containing methyl salicylate, menthol, and capsaicin. This was based on reports submitted to the FDA Adverse Event Reporting System database. FDA has not identified any additional actions or responsibilities required by manufacturers or distributors of these products.

If FDA were to determine that full NDAs were required for OTC external analgesic patch products, all the same detailed information on chemistry, manufacturing, and control technology as required for a new drug would need to be submitted for all but one of the numerous products currently marketed OTC. Requiring NDAs for the numerous individual products in the category under consideration would impose a substantial financial burden on the companies as the majority of these NDAs would likely fall under so-called 505(b)(2) applications with clinical data, requiring an application fee of $1,841,500 for each individual product variant (76 Federal Register 147; 1 Aug 2011, pp. 45831-45838). Review of each of these submissions would also increase the regulatory burden on the Agency.

In the present submission, the task group provides updated data on the safety of counterirritants administered via patches or other novel dosage forms. Companies distributing OTC counterirritant patch products regulated according to a tentative final monograph are seeking FDA input on whether changes in the regulatory status for OTC external analgesic products are anticipated, whether FDA requires additional data to support the safety and efficacy of the products, what test protocols the agency suggests and what FDA’s proposed timeframes are.

I can be reached by telephone at 202-429-3535 or by e-mail, jsirois@chpa-info.org, whenever FDA feedback is available.

On behalf of the CHPA External Analgesic Task Group,



Jay Sirois, Ph.D.
Director, Regulatory & Scientific Affairs

cc: Charles Ganley, M.D., Director, Office of Drug Evaluation IV
Scott Furness, Ph.D., Director, Division of Nonprescription Regulation Development

Attachment A

Adverse Events Reported to Manufacturers
Of OTC External Analgesic Patch Products
July 2009 through April 2011

Table A-1

External Analgesic Patches with Menthol 1.25% - 16%
Adverse Events Reported to Manufacturers

Active Ingredient(s)	Description of Adverse Event*	Number of Reported Adverse Events		
		2009 (July-Dec.)	**2010**	**2011** (thru April)
Menthol 1.25% - 16%	Serious**	13	32	5
	Local irritation or contact dermatitis	91	121	69
	Erythema or blistering	98	115	69
	Delayed bruising or pain	7	19	6
	Other***	89	88	35

*More than one adverse event may be reported for each affected individual; actual effect sometimes difficult to ascertain from consumer reports

**Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event; see note on next page for list of reported serious events

***Such effects as application site burns, skin disorder, urticaria, pruritus, rash, swelling, burning sensation, blistering, discomfort, feeling cold, paresthesia, hypersensitivity, feeling abnormal, dyspnea, nasal discomfort, eye irritation, malaise, headache, nausea, pyrexia, scarring, lack of therapeutic effect, accidental exposure, incorrect usage process, incorrect drug, incorrect dose or duration, use during pregnancy or lactation, expired product used, product quality issues

Note to Table A-1

External Analgesic Patches with Menthol 1.25% - 16%

Listing of Serious Adverse Events Reported to Manufacturers July 2009 through April 2011

2009 [5 individuals]

- Application site pain; application site burn and infection
- Application site burn with blistering and erythema; pain and discomfort
- Application site burn
- Swollen lip, face feeling "hard" after off-label use for toothache
- Application site burn; oozing and scarring

2010 [15 individuals]

- Skin removal, bleeding at adhesive application site
- Skin burns
- Body-wide hives, rash, swollen lips; emergency department treatment
- Skin removal leaving large wound/scar
- Rash, blisters
- Third-degree burns at application site; urgent-care clinic treatment
- Blistering at application site
- Difficulty removing patch; skin removal
- Allergic reaction; lips and eyes swollen shut; treatment in hospital ICU
- Burn, irritation at application site; subsequent infection and loss of toes
- Incorrect application of expired patch over external analgesic ointment; physician-diagnosed second-degree chemical burn
- Application site pain; physician-diagnosed second-degree burn; scarring and fibrosis
- Application site burn, chemical injury, skin exfoliation, pain; wound infection and necrosis; impaired work ability
- Application site pruritus, pain, chemical injury (burn); lack of therapeutic effect, product quality issue
- Physician-diagnosed second-degree burn; stress, pain, and suffering

2011 [3 individuals]

- Skin removal, bleeding at application site; emergency room treatment
- Difficulty removing patch; "descquamation" [*sic*]
- Application site burn; expired drug incorrectly used under a heater

Table A-2

External Analgesic Patches with Capsaicin 0.025%, with or Without Menthol 5%

Adverse Events Reported to Manufacturers

Active Ingredient(s)	Description of Adverse Event*	Number of Reported Adverse Events		
		2009 (July-Dec.)	**2010**	**2011** (thru April)
<u>Capsaicin</u> 0.025% with or without menthol 5%	Serious**	0	0	0
	Local irritation or contact dermatitis	7	16	6
	Erythema or blistering	4	6	2
	Delayed bruising or pain	0	1	0
	Other***	7	2	0

*More than one adverse event may be reported for each affected individual; actual effect sometimes difficult to ascertain from consumer reports

**Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event

***Such effects as dizziness, increased blood pressure, tremor, nausea, fatigue, lack of therapeutic effect, herpes zoster, chemical injury, second-degree burn

Table A-3

External Analgesic Patches with Methyl Salicylate at 10% alone or at 6.3% in Combination with Menthol 5.7% and Camphor 1.2%

Adverse Events Reported to Manufacturers

Active Ingredient(s)	Description of Adverse Event*	Number of Reported Adverse Events		
		2009 (July-Dec.)	**2010**	**2011** (thru April)
Methyl Salicylate at 10% alone or at 6.3% in combination with menthol 5.7% and camphor 1.2%	Serious**	0	0	0
	Local irritation or contact dermatitis	8	21	11
	Erythema or blistering	3	8	0
	Delayed bruising or pain	0	0	1
	Other***	1	9	3

*More than one adverse event may be reported for each affected individual; actual effect sometimes difficult to ascertain from consumer reports

**Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event

***Such effects as application site exfoliation, first-degree burns, muscle spasm, joint swelling, hypertension, hypoesthesia, sensation of "heaviness," eye disorder, dizziness, herpes zoster