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February 16, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, room 1061
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. FDA has projected the publication of a Final Rule on OTC external analgesic patch products for September of this year.

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.

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

**Consumer Healthcare
Products Association**
900 19th Street, NW, Suite 700
Washington, DC 20006
T 202.429.9260 F 202.223.6835
www.chpa-info.org

Chattem, Inc.

Johnson & Johnson Consumer & Personal Products Worldwide

The Mentholatum Company

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. Those products include:

Absorbine Jr.® Back Patch (5% menthol; 22 x 10 cm)

Absorbine Jr.® Ultra Strength Pain Patch (6.5% menthol; 14 x 10 cm)

ActivOn Ultra Strength Back & Body Medicated Patch (5% menthol, 0.025% histamine dihydrochloride; 9.8 x 14 cm)

Icy Hot® Arm, Neck, Leg Patch (5% menthol; 8 x 12 cm)

Icy Hot® Back Patch (5% menthol; 10 x 20 cm)

Icy Hot® PM Patch (5% menthol, 0.025% capsaicin; 8 x 12 cm)

Icy Hot® XL Back Patch (5% menthol; 14 x 25 cm)

Original Strength Bengay® Pain Relieving Patch (menthol 1.4%; 10 x 14 cm)

Original Strength Bengay® Pain Relieving Patch (menthol 1.4%; 10 x 20 cm)

Salonsip® Aqua-Patch (1.25% menthol; 10 x 14 cm)

Salonpas® Gel-Patch (0.025% capsaicin, 1.25% menthol; 10 x 14 cm)

Salonpas® Hot Capsicum Patch (0.025% capsaicin; 13 x 18 cm)

Salonpas® Pain Relieving Patch (5.7% menthol, 6.3% methyl salicylate, 1.2% camphor; 4.2 x 6.5 cm)

Salonpas® Pain Relieving Patch (5.7% menthol, 6.3% methyl salicylate, 1.2% camphor; 8.4 x 13 cm)

Satogesic (0.5% *dl*-camphor, 0.4% I-menthol, 0.8% methyl salicylate; 10 x 7 cm)

Satogesic (0.5% *dl*-camphor, 0.4% I-menthol, 0.8% methyl salicylate; 13 x 8 cm)

Sato Hap (0.5% *dl*-camphor, 0.4% I-menthol, 0.8% methyl salicylate; 10 x 7 cm)

Sato Hap (0.5% *dl*-camphor, 0.4% I-menthol, 0.8% methyl salicylate; 13 x 8 cm)

Satogesic Hot Gel Pad (0.04% capsicum oleoresin, containing capsaicin 0.025%:
13 x 8 cm)

Satogesic Hot Pad (0.04% capsicum oleoresin, containing capsaicin 0.025%: 10 x
7 cm)

Tiger Balm Pain Relieving Patch (80 mg camphor, 24 mg menthol, 16 mg
capsicum extract per patch)

Ultra Strength Bengay® Pain Relieving Patch (5% menthol; 10 x 14 cm)

Ultra Strength Bengay® Pain Relieving Patch (5% menthol; 10 x 20 cm)

WellPatch® Arthritis (10% methyl salicylate; 6.5 x 10 cm)

WellPatch® Arthritis (10% methyl salicylate; 10 x 14 cm)

WellPatch® Backache (5% menthol; 10 x 20 cm)

WellPatch® Capsaicin (0.025% capsaicin; 12 x 18 cm)

WellPatch® Pain (5% menthol; 8 x 12 cm)

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 that support 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 submission in 2003 included compiled information from spontaneous consumer reports to companies about adverse events associated with OTC external analgesic patches, plasters, and poultices from 1998 through August 2003. 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 five 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 about OTC external analgesic patches from 2003 through June 2009. (None are currently marketing OTC external analgesic plasters or poultices.) The recently compiled data are presented in the tables below and in an attachment.

Most of the reports included below come from consumer complaints made by telephone, e-mail, or letter, and were grouped in this compilation into descriptive categories. While consumer reported complaints do not necessarily establish causality, they do provide useful information about the nature of events to support the safety of the products.

The number of reported adverse events associated with use of OTC external analgesic patches is low, particularly given the number of dosage units, estimated to be nearly 11.6 million packages with over 52 million dosage units in 2008, for example, sold by the five companies. The following tables present 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 combined 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 reported products. As can be readily seen in every case, the ratio of reported adverse events to unit sales is extremely small. The relatively low frequency of adverse events is consistent with the general recognition that the monograph external analgesic counterirritants are safe.

Given the sales volumes for OTC external analgesic patches, adverse events do not occur at a higher frequency than is expected for OTC medicines. 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.

Table 1: External Analgesic Patches with Menthol 1.4% - 16%

Year	Number of Package Units Sold at Retail	Number of Dosage Units Sold at Retail	Number of Reported Adverse Events*	
			Nonserious	Serious**
2003	>3,685,400	>18,350,000	84	0
2004	>6,730,500	>31,690,000	317	6
2005	11,815,244	55,549,427	284	6
2006	10,791,206	51,819,438	192	8
2007	10,871,791	52,258,088	169	9
2008	9,598,435	45,606,797	225	15
2009 (thru June)	5,593,024	27,337,440	78	6

>: indicates available data were incomplete and, consequently, estimates given are substantially lower than actual sales

* See Table A-1 in the 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 Reported Adverse Events*	
			Nonserious	Serious**
2003	4,176	20,880	0	0
2004	3,252	16,260	0	0
2005	2,914	14,570	0	0
2006	424,101	2,120,505	6	0
2007	123,348	616,740	2	0
2008	1,802,032	4,859,951	14	1
2009 (thru June)	1,098,621	2,308,893	6	0

* See Table A-2 in the 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 10% alone or at 8% in Combination with Menthol 0.4% and Camphor 0.5%

Year	Number of Package Units Sold at Retail	Number of Dosage Units Sold at Retail	Number of Reported Adverse Events*	
			Nonserious	Serious**
2003	>30,000	>150,000	2	0
2004	>11,000	>56,000	5	0
2005	273,072	1,630,720	9	0
2006	337,949	2,017,259	3	0
2007	246,520	1,472,004	2	0
2008	190,543	1,651,842	1	0
2009 (thru June)	74,118	228,227	0	0

>: indicates available data were incomplete and, consequently, estimates given are substantially lower than actual sales

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

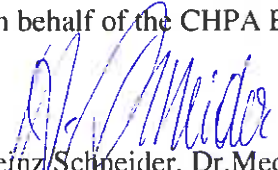
** Serious events, as defined for FDA's MedWatch classification, include death, life-threatening occurrence, hospitalization, disability, congenital anomaly, or condition that required intervention to prevent permanent impairment or damage, or other important medical event.

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 each of the numerous products previously listed on pages 2 and 3. Requiring NDAs for the numerous individual products in the category under consideration would impose a substantial burden on FDA and industry. Officials in FDA's Center for Drug Evaluation and Research (CDER) would need to review the submitted information, and preapproval inspections would have to be conducted, many of them in manufacturing facilities outside of the United States. The median approval time for a standard NDA reported by CDER for 2008 was 13.1 months. The submission of NDAs would also place a significant financial burden on the companies. Presumably the majority of these NDAs would fall under so-called 505(b)(2) applications with clinical data, which under the 2010 PDUFA would require a fee of \$1,405,500 for each individual product variant.

Although in 2003 the CHPA External Analgesic Task Group requested a meeting with FDA to engage in an in-depth scientific dialogue on the proposed testing program and the related agency guidance, no feedback has been received from FDA. In the present submission the task group provides updated data on the safety of counterirritants administered via patches or other novel dosage forms. We are looking to FDA to advise companies who distribute such OTC products specifically about whether the agency is seeking additional data to support the safety and efficacy of the products. It is important that companies hear from FDA what additional data might be sought regarding OTC external analgesic products and what test protocols the agency suggests, whether the products are regulated according to a final monograph or under an approved NDA. It is also important for companies to know what the timeframes would be for any change FDA might make in the regulatory status for OTC external analgesic products.

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

On behalf of the CHPA External Analgesic Task Group,


Heinz Schneider, Dr.Med.
Vice President, Science and Medical Affairs

cc: Charles Ganley, M.D., Director Office of Nonprescription Products (ONP)
Scott Furness, Ph.D., Director Division of Nonprescription Regulation Development, ONP
Matthew Holman, Ph.D., Deputy Director Division of Nonprescription Regulation Development, ONP

Attachment A

**Adverse Events Reported to Manufacturers
Of OTC External Analgesic Patch Products
January 2003 through June 2009**

Table A-1

Adverse Events Reported to Manufacturers of OTC Menthol Patches

Active Ingredient	Description of Adverse Event*	Number of Reported Adverse Events						
		2003	2004	2005	2006	2007	2008	2009 (thru June)
Menthol 1.4% - 16%	Serious**	0	6	6	8	9	15	6
	Local irritation or contact dermatitis	36	128	130	79	74	111	28
	Erythema or blistering	15	65	76	48	41	61	21
	Delayed bruising or pain	11	22	21	30	27	28	17
	Other***	22	102	57	35	27	25	12

*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 the required intervention to prevent permanent impairment or damage, or other important medical event; **see note on next two pages for listing of reported serious events

***Such effects as application site feeling cold or numb; application site warmth; burning sensation; thermal burns at application site; urticaria; application site discoloration, inflammation, erosion, discharge, ulceration, scabbing

Note to Table A-1

**Listing of Serious Adverse Events Reported to OTC Menthol Patch
Manufacturers**

January 2003 through June 2009

2003 [none]

2004 [6 serious adverse events]

- Hands swelling and painful itchy blotches on hands of consumer who used menthol patches on shoulder; emergency room treatment and diagnosis of angioedema
- Full-body rash with welts, feeling of throat closure; treatment at hospital
- Grand mal seizure and drooling in consumer with history of epilepsy
- Several hospitalizations for back pain or respiratory distress in consumer with history of back surgery and extensive use of OTC external analgesic products
- Itchy rash and welts on body; hospital treatment with intravenous steroid
- Asthma attack in consumer with history of asthma who reported menthol scent aggravated his asthma

2005 [6 serious adverse events]

- Allergic-type reaction (burns and sores), possible cellulitis, scarring in consumer reported to be diabetic
- Second-degree burn; woozy feeling
- Blistering, pain, and burn-like injury at application site; scarring
- Difficulty breathing and vomiting after used menthol patch was “lost somewhere” in the home; emergency room treatment
- Ruptured intervertebral disc
- Second-degree burns diagnosed by physician; pain and scabbing

2006 [8 serious adverse events]

- Full-body red itchy rash, shortness of breath, swelling and numbness of lips; emergency room treatment
- Burning, blistering, and skin removal at application site; physician diagnosis of third degree burns reported by affected consumer
- Burning, blistering, and pain at application site; feeling of feverishness
- Wheezing and difficulty breathing; anaphylactic shock diagnosed by paramedics
- Sweating, fever, hallucinations
- Reddening, itchiness, and swelling of hands and face (including mouth, eyes, ears), feeling of throat closure
- Painful burn-like skin injury (“chemical burn”) at application site
- Swelling of face, lips, and throat; hives

Note to Table A-1 (continued)

2007 [9 serious adverse events]

- Irritation, darkening, blistering, pain, and chemical burn at application site
- Reddening, itching, purple discoloration, pain, and burn-like injury at application site
- Shortness of breath and pulmonary thrombosis (about 3 weeks after quadruple bypass surgery); hospitalization
- Reddening, itchiness, and blistering at application site on back; swelling of leg; diagnosis of contact dermatitis; emergency room treatment
- Reddening, itchiness, and burning at application site; burn-like injury with darkened skin
- Burn-like skin injury at application site, discomfort
- Itchiness, blistering, and burn-like injury at application site
- Burning of the eyes reported to be caused by product's scent
- Irregular heartbeats

2008 [15 serious adverse events]

- Breathing difficulty; unknown outcome
- Allergic-type reaction; emergency room treatment
- Burning sensation and skin discoloration at application site; blistering and burn-like skin injury
- Rash, roughening, and burn-like injury at application site
- Full-body itchiness and welting, and swelling of feet
- Burn at application site
- Skin removed (abrasion), scarring
- Reddening, itching, blistering, and burn-like skin injury
- Reddening and blistering at application site
- Reddening, welting, and burn-like skin injury at application site
- Headache and elevated blood pressure reading without diagnosis of hypertension
- Skin removed ("excoriation"), pain, insomnia
- Blistering at application site; hospital diagnosis of second-degree burns; scabbing
- Irritation and burn-like skin injury at application site
- Reddening and burn-like skin injury at application site

2009 [6 serious adverse events]

- Blistering and burn-like skin injury that became cellulitic and was slow to heal
- Irritation and burn-like skin injury that became infected in consumer reported to be diabetic; several toes amputated
- Application site discomfort (chemical burn) from product described as "too warm"
- Reddening, blistering, and "welting" at application site
- Burning (second degree burns), reddening, blistering, pain, scabbing; physician diagnosis of possible allergic reaction and shingles; scarring
- Burn-like skin injury at application site

Table A-2

Adverse Events Reported to Manufacturers of OTC Capsaicin Patches

Active Ingredient	Description of Adverse Event*	Number of Reported Adverse Events						
		2003	2004	2005	2006	2007	2008	2009 (thru June)
Capsaicin 0.025% with or without menthol 5%	Serious**	0	0	0	0	0	1	0
	Local irritation or contact dermatitis	0	0	0	3	0	7	0
	Erythema or blistering	0	0	0	3	2	6	3
	Delayed bruising or pain	0	0	0	0	0	0	1
	Other	0	0	0	0	0	1***	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 the required intervention to prevent permanent impairment or damage, or other important medical event; **one serious event reported (in 2008)—allergic-like reaction for which consumer sought medical treatment

***Burning sensation

Table A-3

Adverse Events Reported to Manufacturers of OTC Methyl Salicylate Patches

Active Ingredient	Description of Adverse Event*	Number of Reported Adverse Events						
		2003	2004	2005	2006	2007	2008	2009 (thru June)
<u>Methyl Salicylate</u> 10% alone or at 8% in combination with Menthol 0.4% and Camphor 0.5%	Serious**	0	0	0	0	0	0	0
	Local irritation or contact dermatitis	0	0	3	1	0	1	0
	Erythema or blistering	1	4	6	1	2	0	0
	Delayed bruising or pain	0	0	0	0	0	0	0
	Other***	1	1	0	1	0	0	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 the required intervention to prevent permanent impairment or damage, or other important medical event

***2003—"nervousness"; 2004—increased blood count; 2006—"skin eaten away"