



*Advancing Quality Healthcare  
Through Over-the-Counter Medicines  
and Nutritional Supplements*

## CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

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October 15, 2003

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; Reopening of the Administrative Record and Amendment of Tentative Final Monograph

Dear Sir or Madam:

The Consumer Healthcare Products Association (CHPA) External Analgesics Task Group submits these comments in response to FDA's reopening of the administrative record for the over-the-counter (OTC) external analgesics rulemaking and the agency's proposal to amend the tentative final monograph (TFM) for external analgesics (68 FR 42324-42327, July 17, 2003). The proposed amendment would 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). FDA has reopened the administrative record for comments on the existing data in the docket and on the agency's proposed TFM amendment, and for new data and information relevant to inclusion of patch, plaster, and poultice products in the final monograph.

CHPA, founded in 1881, is the national association representing manufacturers and distributors of OTC drug products and dietary supplements. 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 this matter, and the CHPA External Analgesics Task Group welcomes the opportunity to comment on the proposed rule. These comments are not meant to supersede comments submitted by individual members of CHPA.

### **Action Requested:**

The CHPA task group requests that dosage forms different from those of creams, lotions, and ointments be permitted under the monograph for OTC external analgesic drug products. FDA's long-standing policy in the OTC Review is to determine the limits of active ingredient safety and effectiveness and to allow the marketing of many different types of products

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within those limits. The overwhelming safety and effectiveness of the OTC medications marketed today under the monograph system show that this is a wise policy.

It is also requested that FDA and industry work together to develop principles for a guidance for industry to use when developing alternate dosage forms, including patches, poultices, and plasters. This guidance would include specific recommended protocols and test methods that could be used in a product-qualification program, but it would not preclude the use of alternate methods that provide scientifically valid results. The guidance would be referenced in the final monograph for OTC external analgesics as the recommended standard for all alternate dosage forms.

Finally, the CHPA task group requests that the record be kept open for receipt of additional data. Manufacturers may need to submit data to support the development of a guidance. The task group would appreciate being able to submit these data to support alternative dosage forms.

The remainder of this submission is organized in the following sections:

- I. Executive Summary
- II. Regulatory Background
- III. Data Regarding Topical Counterirritant Patch, Plaster, and Poultice Products
- IV. Properties of Patches, Plasters, and Poultices as Vehicles for Application of Counterirritant External Analgesics
- V. Safety of Currently Marketed Products
- VI. Proposal for Testing and Development of a Guidance Document
- VII. Comments on Labeling
- VIII. Request for FDA to Work with Industry to Develop Guidance and to Keep Docket Open for Submission of Relevant Data
- IX. Summary of Requested Action

Attachment 1: Literature Search Strategy

Attachment 2: Data Regarding Topical Counterirritant Patches, Plasters, and Poultices,  
Docket 78N-0301 and Published Scientific Literature

Attachment 3: Reference Abstracts and References

Attachment 4: Untoward Effects Reported To Manufacturers

## **I. Executive Summary**

The CHPA task group requests that FDA withdraw its proposal to exclude patches, plasters, and poultices from the OTC External Analgesic Monograph. Sufficient data exist on the counterirritant active ingredients camphor, capsaicin, menthol, and methyl salicylate to support their general recognition as safe and effective for consumer use in OTC external analgesics products.

In the absence of compelling need, OTC drug products should be regulated under the OTC drug monograph system rather than individual New Drug Applications for each product. No such need for NDA approval is evident from the safety experience with marketed external analgesic products, including those in dosage forms other than lotions, creams, and ointments. FDA should not abandon a well-established, workable monograph review system in favor of a resource-intensive product-by-product review for alternative dosage forms of active ingredients that have been determined to be generally recognized as safe and effective.

In issuing the final rule on OTC external analgesics, FDA should explicitly allow alternative dosage forms that are shown to deliver monograph active ingredients in amounts that are substantially equivalent to those from lotions, creams, and ointments containing the same active ingredients in monograph concentrations. FDA has accepted that camphor, capsaicin, menthol, and methyl salicylate are generally recognized as effective (GRASE) as OTC counterirritant external analgesics. The effectiveness of the active ingredients would not be altered by their delivery in patches, plasters, or poultices.

Under its OTC Drug Review, FDA systematically classifies OTC drugs by therapeutic category and determines conditions of use (active ingredients, indications, dosage forms, dosage strengths, routes of administration, and labeling) under which products in each category would be generally recognized as safe and effective. FDA and its OTC advisory review panels have taken a flexible approach to dosage forms, and most OTC drug monographs do not specify particular dosage forms. Many OTC drug products were approved in any form suitable for oral administration, including antacids (21 CFR 331.1). Of even more relevance to approved dosage forms for OTC external analgesics are the examples in which FDA permits categories of drug products "in a form suitable for topical administration." Notably the 1983 tentative final monograph for OTC external analgesic products includes that language in its statement on the "Scope" of the rulemaking (48 FR 5867 at proposed 21 CFR 338.1). Examples of other monographs in which any dosage form suitable for topical administration is similarly permitted are those for antifungals, topical otic drug products, and skin protectants.

OTC external analgesic patch, plaster, and poultice products are safe and effective and should be regulated under the monograph in view of the information presented in this submission. Nevertheless, the CHPA task group has been working on developing a testing program, should additional data be necessary. The task group asks FDA to reference provisions for an FDA testing guidance in the external analgesic final monograph. FDA and industry should work together on these guidelines that could be used in confirming safe concentrations of counterirritant ingredients applied in patches, plasters, or poultices, or other novel dosage forms, and showing adequate dose delivery for effectiveness.

## **II. Regulatory Background**

As reflected in this comment, the CHPA task group wishes to resolve any agency concerns regarding the safety and effectiveness of OTC patch, plaster, and poultice dosage forms (hereafter in this section II referred to collectively as patch dosage forms).<sup>1</sup> However, as briefly described in this section, the administrative record does not provide an adequate basis for the exclusion of these dosage forms from the monograph. Such exclusion was asserted in the agency's *Federal Register* notice of July 17, 2003 (68 FR 42324).

Such exclusion was not proposed by the Panel's report published in the *Federal Register* of December 4, 1979 or the proposed regulations that were published with it (44 FR 69768) (ANPR). Nor was such a proposal contained in the Tentative Final Monograph published on February 8, 1983 (48 FR 5852) (TFM). The brief July 17, 2003 notice does not provide an adequate legal basis for eliminating these products from the monograph or for their summary removal from the market.

### **A. The OTC Review is Directed to Active Ingredients, Not Dosage Forms**

The orientation of the OTC Review was made clear at the outset in the agency's final rule setting the procedures for the OTC Review (37 FR 9464; May 11, 1972):

Comments stated that the Food and Drug Administration's request for the complete quantitative composition of the drug was not necessary because the review covered only the safety and efficacy of active ingredients. The Commissioner agrees with this comment and the regulations have been

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<sup>1</sup> The term "patch" as used in this document is limited to products that apply topical analgesic active ingredients to the skin by means of an adhesive matrix or cloth, fabric, or other backing. It does not refer to dosage forms intended for transdermal systemic delivery or timed release of active ingredients.

changed to require submission only of a quantitative statement of the active ingredients. (§42; page 9467)

The industry submissions which were thereafter given to the advisory panels were submitted with this understanding. Like most OTC drug monographs, the topical analgesic TFM, does not specify or exclude any particular dosage form. On the contrary, proposed section §348.1 states that external analgesic OTC products are generally recognized as safe and effective if they are “in a form suitable for topical administration” and meet the conditions of proposed Part 348 and the general conditions established in 21 CFR §330.1.<sup>2</sup>

The OTC Review was not designed as a review of alternative dosage forms, and there are no specific procedures for evaluating dosage forms. Although FDA has determined by regulation that certain dosage forms are new drugs, the agency has not done so with respect to OTC topical analgesic patch products.<sup>3</sup>

**B. The FDA Advisory Panel Did Not Propose Exclusion of Topical Analgesic Patch Products from the Monograph**

In its notice of July 17, 2003, the FDA stated that the advisory panel discussed poultices and plasters only in the context of allyl isothiocyanate (oil of mustard) (44 FR 69768, 69791). The Panel stated its concern that, used as a poultice,<sup>4</sup> the inflammatory action caused by this ingredient “may cause the inflammatory action to go beyond erythema to vesication.” The statement is specific to the ingredient being discussed and cannot be extrapolated to cover all active ingredients.

The FDA July 17 notice states:

The Panel did briefly discuss mustard plaster, National Formulary IX, but did not include a plaster dosage form in its recommended dosage for this ingredient (44 FR 69768 at 69792) (emphasis added)

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<sup>2</sup> 48 FR 5852 at 5867 (February 8, 1983).

<sup>3</sup> Cf. 21 CFR §310.502

<sup>4</sup> In the July 17, 2003 Federal Register notice, the agency describes a poultice as “a soft, moist mass about the consistency of cooked cereal, spread between layers of muslin, gauze or towels and applied hot to a given area in order to create moist local heat or counterirritation.” Based on present information, no such products are currently on the market. It is also observed that the backing material described, i.e., muslin, gauze or towels, would not provide an occlusive barrier.

This is true, but no negative inferences can be drawn from that fact. The Panel similarly made no mention of creams, lotions, ointments or any other dosage form. Consistent with the overall approach of the OTC Review, mentioned above, the Panel's recommended dosages for this and the other active ingredients, were limited to percentage concentration of active ingredient, maximum application, etc., without specific reference to any particular dosage form. The proposed regulations contained in the Panel's report (proposed Part 348) did not exclude patch dosage forms.

The Panel's recommendations were not directed to exclusion of patch products but to assurance of safety through adequate packaging, labeling, and application. This approach is reflected in the Panel's conclusions regarding allyl isothiocyanate:

[A]lthough the actual number of adverse effects attributed to the external use of mustard preparations is relatively low, care should be taken to assure that safety is maintained through adequate packaging, labeling and application (ANPR, 44 FR 69791)

In its July 17, 2003 notice, FDA contends that the above statement had reference only to a specific ointment dosage form. No such limitation is evident in the Panel's choice of language, however, and the context indicates that this conclusion reflected the Panel's overall evaluation of the total marketing history of this ingredient. The circumstance that the Panel had previously made a reference to OTC Volume 060051 cannot be interpreted as qualifying the Panel's general conclusion.<sup>5</sup>

The Panel did include other comments expressing concern over the general subject of occlusion of counterirritants on the skin. The Panel did not, however, provide any definition of how it was using the term "occlusion." The literal meaning of this term, total impermeability, however, would make it inapplicable to most, if not all, patch products currently on the market.

The Panel recommended the warning "Do not bandage." The implications of this proposed warning, and the single comment it provoked, will be discussed in the next section.

**C. The Tentative Final Monograph Did Not Propose Exclusion of Patch, Plaster, or Poultice Dosage Forms**

The TFM made changes in the proposed Part 348 regulations included with the Panel's report. It has been suggested that the exclusion of patch products from the monograph can be

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<sup>5</sup> OTC Volume 060051 was identified as Ref. 8 in the Panel's report (44 FR 69791) and as Ref. 2 in the FDA notice of July 17, 2003. The placement of the reference in the Panel report does not indicate that it was being relied upon for the general statement quoted above.

inferred from the TFM's proposed §348.50(a)(1), relating to the labeling statement of identity. That section provides three alternatives: "external analgesic," "topical analgesic," or "pain relieving (insert dosage form, *e.g.*, cream, lotion, or ointment)."

As to the third alternative, "pain relieving \_\_\_", it is noted that the three named dosage forms are presented only as illustrative examples. This is clear from the choice of the well understood abbreviation "*e.g.*," (*exempli gratia*), meaning "for the purpose of example," or "for instance." Far from limiting topical analgesic products to the three dosage forms given in the third alternative statement of identity, the proposal states the opposite; *i.e.*, that these three dosage forms are not exclusive. The same dosage forms are in fact listed as examples in labeling regulations for other OTC drug categories with no implication that any dosage forms not listed as examples are thereby excluded from coverage.<sup>6</sup>

The dosage forms not mentioned as examples include salves, balms, liniments, sprays, and gels, among others. The listing of the three examples cannot fairly be interpreted as a proposal to exclude all non-mentioned dosage forms. The agency has, nevertheless, claimed that gels are excluded.<sup>7</sup> On the other hand, it has indicated the acceptability of another non-listed dosage form, *i.e.*, sprays.<sup>8</sup>

The absence of any proposed exclusion of patch products in the ANPR was consistent with the fact that the agency subsequently received only one related comment. This was not directed to a perceived proposal to exclude patch products. Rather it was directed to the possible confusion that would arise from the proposed "do not bandage" warning in the case of the commenter's counterirritant product. In use, the product was intended to be placed under a wrapping of plastic and tape.

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<sup>6</sup> See 21 CFR 346.50(a) statement of identity for anorectal OTC drug products; see also §358.750 (labeling of OTC drugs for the control of dandruff, seborrheic dermatitis, or psoriasis). With regard to the topical analgesic ANPR and TFM, had the Panel or the agency intended to propose exclusion of all dosage forms not listed as examples in the statement of identity section, a more appropriate means to convey this intention to interested parties would have been use of another well-known abbreviation, "*i.e.*" (Latin: *Id est*), meaning "that is", or "in other words." Better yet, of course, would have been a clear statement of the proposal.

<sup>7</sup> Letter of 10/1/96 from D. Bowen, MD to D. Manelli ( D.78N-0301 Comment No. LET 69; 68 FR 42324; 7/17/03, Ref. 39): "Gel dosage forms (vehicles) are also not included in the TFM. Gels are vehicles that enhance penetration." Despite this stated conclusion, the agency's July 17 notice did not in fact amend the TFM to exclude gels.

<sup>8</sup> *Id.*

The comment was filed by Cramer Products, Inc. (D. 78N-0301, C00015). It noted concern that the proposed "do not bandage" warning was inconsistent with the usage of its product. The comment read, in pertinent part, as follows:

I take exception to the proposed warning for counterirritants: "Do not bandage." Our milder counterirritant products contain from 10% to 15% Methyl Salicylate, in combination with Oleoresin Capsicum, in a lanolin-petrolatum base. In normal use these products are often covered either to protect clothing or to increase the stimulation of cutaneous receptors. The latter is especially true for the temporary relief of such common athletic complaints as lower back pain, a charley horse or shin splints. Please see enclosed articles which appeared in *The First Aider*, a Cramer publication. One additional reference to the analgesic balm pack may be found in *Modern Principles of Athletic Training* [footnote reference omitted]. I hope that the committee will give a great deal of thought to my comments and will consider an alternative warning statement such as "Bandage with caution" for inclusion in the labeling of OTC counterirritants.

The comment was accompanied by an article illustrating the commenter's topical analgesic being applied to the skin, then covered over with the company's Cramerol® plastic backed cellulose padding, followed by use of a 4- or 6-inch wide elastic wrap to hold the pack in place.

The agency responded to this comment as follows:

31. One comment objected to the Panel's recommended warning in §348.50(c)(2)(ii) for counterirritants: "Do not bandage." The comment argued that it is common practice in athletic training procedures to cover injuries after applying counterirritants either to protect clothing or to increase the stimulation of cutaneous receptors. The comment suggested that a warning such as "Bandage with caution" be substituted for the Panel's warning.

The agency agrees with the comment that it is desirable to protect clothing from stains by covering the application site, but believes that such covering should not be tightly applied. The agency is not aware of any evidence that the risk of adverse reactions to counterirritants increases when the application site is lightly covered, but is aware that under tight bandaging or occlusive dressing there is an increased risk of irritation, redness, or blistering. The Panel did not provide specific reasons for recommending the warning "Do not bandage" for counterirritants. However, counterirritants are, as the name itself implies, irritating and occlusion by tight bandaging may increase their absorption through the skin. Therefore, it is proposed in this tentative final monograph that the Panel's recommended warning "Do not bandage" be revised to "Do not bandage tightly." The agency believes that this



warning is more helpful to consumers because it provides more specific information and is therefore clearer than the warnings proposed by the comment. (TFM, page 5864).(emphasis added)

It may be observed that, even in response to this comment, the agency did not state that the monograph actually excluded all patch products, regardless of whether they were truly occlusive and did not explain the intended meaning of the phrase “occlusion by tight bandaging” or the term “lightly covered.” Moreover, the intelligibility of the specified warning to consumers may be debated since, without further explanation, “tightly” can be read as referring to occlusion or constriction.

A citizens petition was filed in an attempt to correct what was regarded as a potential source of confusion caused by the “do not bandage tightly” warning as applied to a patch product. The purpose of the petition was not to amend the monograph to add dosage forms, as stated in the July 17 notice. The purpose was “to preclude misinterpretation of the TFM as excluding medicated analgesic plaster and poultice products. Both plasters and poultices are traditional dosage forms for OTC analgesics, are included in the OTC Review, and were before the panel’ (Petition, pp. 1-2; D.78N-0301 CP 6, 68 FR 42324; 7/17/03, Ref. 1).<sup>9</sup>

#### **D. The Notice of July 17, 2003 Is Insufficient as a Proposal**

The July 17, 2003 notice states that FDA is amending the monograph to place all external analgesic ingredients in a patch, plaster, or poultice dosage form in Category III and will add the following language at the end of the currently proposed language: “The active ingredients of the product consist of any of the following within the established concentration for each ingredient, but not for use in a patch, plaster, or poultice dosage form.”

As indicated in the previous sections, neither the Panel report (ANPR) nor the TFM proposed the relegation of all patch products to Category III. As discussed in the next section, the July 17, 2003 notice does not meet the requirements of the Administrative Procedure Act.

#### **E. The Current Administrative Record Does Not Support the Exclusion of Patch Products**

In order to provide a legally sufficient basis for the indicated exclusion from the monograph of all patch dosage forms, the agency must provide a clear rationale for the proposed action so that interested parties can have a reasonable opportunity to comment. The FDA can rely on its own expertise outside of the rulemaking record, but failure to inform interested parties of relevant scientific information precludes informed comment. “To suppress meaningful

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<sup>9</sup> The petition was subsequently withdrawn.

comment by failure to disclose the basic data relied upon is akin to rejecting comment altogether.” *United States v. Nova Scotia Food Products Corp.* 568 F.2d 240 (2d Cir. 1977).

As stated by the District of Columbia Circuit:

[T]here must be an exchange of views, information, and criticism between interested persons and the agency . . . . Consequently, the notice required by the APA, or information subsequently supplied to the public, must disclose in detail the thinking that has animated the form of a proposed rule and the data upon which that rule is based. *Home Box Office v. FCC*, 567 F.2d 9, 35-36 (D.C. Cir. 1977)

As noted earlier, the proposed total exclusion of patch dosage forms transcends the Panel recommendations and the TFM and is not supported elsewhere in the administrative record. A rule “must be explained, not merely explainable,” *Environmental Defense Fund v. EPA*, 465 2d 528, 539 (D.C. Cir. 1972).

Explanations are needed. In the TFM, responding to one comment (see above)<sup>10</sup>, FDA stated that it “agrees . . . that it is desirable to protect clothing from stains by covering the application site, but believes that such covering should not be tightly applied.” No definition was provided to indicate what the agency might intend by “tightly applied.” The further reference to “tight bandaging or occlusive dressing” does not define these alternative terms and does not address currently marketed non-occlusive patch products. The subject is further clouded by FDA’s acknowledgment that it is “not aware of any evidence that the risk of adverse reactions to counterirritants increases when the application site is lightly covered.”

Furthermore, the July 17 amendment of the TFM to exclude “patch, plaster, or poultice” dosage forms, provides no definition of patch or plaster.<sup>11</sup> Such definitions, and the underlying rationale, are required for effective comment.<sup>12</sup> A rationale is also required to explain the fact that the notice does not purport to exclude gels from the monograph despite prior agency statements that this dosage form (also undefined) is excluded (see note 7, *supra*). Finally, the Panel’s original failure to provide any specific reasons for the proposed “do not bandage” warning, an omission noted by FDA (see above), makes it all the more important for the agency to reassess and carefully articulate its approach to the regulation of these products.

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<sup>10</sup> Response to comment No. C00015, quoted in text.

<sup>11</sup> As noted, a definition of the poultice dosage form is provided by the July 17 notice (see note 4, *supra*); the definition, however, appears irrelevant to currently marketed products.

<sup>12</sup> This is particularly true with regard to the analysis of economic impact.

In the past, FDA has acknowledged its responsibility in this regard. In a 1975 memorandum to the Bureau of Veterinary Medicine, the then General Counsel stated:

“It is a basic principle of administrative law that, to withstand court challenge, an agency’s decision must be fully explained in terms of the governing legal standards for such decisions. An unexplained decision that can subsequently be explained as comporting with those standards is subject to judicial reversal. A decision that is not sustainable on the explanation contemporaneously provided, even though sustainable on some other ground, is subject to judicial reversal. And, similarly, a decision couched simply as an assertion that statutory standards are met is subject to judicial reversal.” *Memorandum to Bureau of Veterinary Medicine* (November 19, 1975)

A comprehensive explanation of the proposed rule is needed to permit “searching judicial scrutiny of how and why the regulations were actually adopted,” *Amoco Oil C. v. EPA*, 501 F.2d 722, 739 (D.C. Cir. 1974). In the absence of any rationale supporting the unqualified exclusion of all patch dosage forms, the rule amounts to an “ipse dixit”; Cf. *Associated Industries of New York State, Inc. v. United States*, 487 F.2d 342, 352 (2d Cir. 1973), *cert. den.* 416 U.S. 921 (1974). We believe that, lacking an adequate rationale, the courts would set aside the action. *Portland Cement Ass’n v. Ruckelshaus*, 46 F.2d 375, 393, n.67 (D.C. Cir. 1973), *cert. den.* 417 U.S. 921 (1974) (scientific methodology supporting the regulation not disclosed in time for comment), *Mobil Oil Corp. v. FTC*, 483 F.2d 1238 (D.C. Cir. 1873) (crucial evidence supporting rule not disclosed).

Accordingly, CHPA is requesting the Agency reconsider the record and withdraw the July 17th proposed amendment to the TFM or provide adequate explanation for the exclusion or patch, poultice, and plaster dosage forms from this monograph.

### **III. Data Regarding Topical Counterirritant Patch, Plasters, and Poultice Products**

#### **A. Data Reviewed**

This section presents a summary of the available scientific data and published literature that support the safe and effective use of topical counterirritants in patch, plaster or poultice formulations. This information was obtained using two sources. The first source was references reviewed by the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Advisory Panel Report of December 4, 1979, 44 FR 69768) and referenced in 68 FR 42324-42327 (Docket 78N-0301). The second source of information was obtained using an updated literature search of scientific databases to supplement the existing docket information and to ensure inclusion of all relevant published scientific literature in this summary (see Attachment 1, Literature Search Strategy).

To index and capture the totality of the data that are currently available regarding topical counterirritant products, a table was constructed: Data Regarding Topical Counterirritant Patches, Plasters, and Poultices, Docket 78N-0301 and Published Scientific Literature (Attachment 2). Attachment 2 organizes the data according to the following subject areas of interest: Data regarding safety, efficacy, percutaneous absorption, frequency of application, labeling, marketing experience, and age groups. As this table indicates, Docket 78N-0301 contains a variety of documents related to topical analgesic and counterirritant products containing menthol, methyl salicylate, capsaicin, and camphor. Listed are document number, the product, sponsor, ingredients studied; the study type; and the nature of the information presented. The table does not include a full description of study results, a discussion of findings, or correspondence between Sponsor and FDA relating to the study, as these materials are already included in the docket. The table is designed to illustrate the number of studies in each topic area, and the location in Docket 78N-0301.

Attachment 2 also refers to additional data from the published literature that was not previously submitted to the docket (search strategy described in Attachment 1). These data were identified by searching five of the major scientific databases, representing citations from the 1960's to present, for English language publications providing relevant human data for patch, plaster or poultice formulations of topical counterirritants; i.e., the dosage forms of capsaicin, menthol, methyl salicylate, and camphor tentatively classified as Category III (68 FR 42324). General areas covered by the search terms included safety/toxicity, efficacy, and dermal absorption. Literature for other delivery formulations of these counterirritants was not sought as FDA has concluded these dosage forms are generally recognized as safe and effective (GRASE). A second additional literature search was conducted to identify any animal literature that provided relevant quantitative information for topical counterirritants administered under occlusive conditions.

The literature search identified eight publications that supplement the docket information previously reviewed by the Panel. With one exception, this literature was published after the time of the Panel's deliberation. The studies have been included in the table in Attachment 2, within the appropriate topic area. Additional details are provided in reference abstracts that serve as cover sheets to each hard copy reference (reference abstracts and references are provided in Attachment 3).

These additional data, which are summarized below, substantially augment the scientific considerations of the Advisory Panel with regard to the safe and effective use of counterirritant topical formulations in patch, plaster or poultice delivery formulations. These data constitute a reasonable scientific basis for FDA to expand the list of GRASE topical products to also include delivery via patch, plaster or poultice formulations. The data are discussed below, in accordance with the topic areas of interest.

## **B. Safety and Efficacy**

Four articles (Keitel et al. 2001, Kim et al. 2002, Munce 2003, Horn and Enge 1982) present data that support the safe and/or effective use of capsaicin in patch or plaster formulation. Two studies were controlled and blinded, and two were not. All were from the relatively recent literature.

In the two placebo-controlled blinded studies, capsaicin plaster effectively decreased lower back pain (Keitel et al. 2001) or post-operative nausea and vomiting (Kim et al. 2002) vs. placebo. Both efficacy responses were highly statistically significant vs. placebo. In both studies, the patches were well tolerated. Side effects of active-drug patches (Keitel et al. 2001) were limited to warmth, itching and skin irritation reactions consistent with capsaicin use in other delivery formulations.

In one of the non-blinded and uncontrolled studies, capsaicin patch induced the desired local skin blood flow change (increased vascular conductance, related to stimulation of capsaicin-sensitive primary afferent sensory nerves) without any reported adverse effects (Munce and Kenney 2003). In the other unblinded but controlled study, capsaicin plaster and UV light exposure were each utilized to generate local cutaneous erythema. Capsaicin generated the desired experimental mild erythema without affecting systemic inflammatory modulators, whereas UV-induced erythema was associated with changes in catecholamine modulators (Horn and Enge 1982).

Additional studies support the safety of plaster, patch or poultice delivery of topical methyl salicylate, camphor or menthol. In Maruta et al. (1977), six repeated applications of methyl salicylate plaster in healthy volunteers were accomplished with no reported adverse effects and specifically no abnormalities in liver function tests. Chiyotani et al. (1994) conducted a four-week treatment study of asthmatics with poultice containing a mixture of menthol, methyl salicylate, camphor, and scopolia extract (scopolamine and hyoscyamine), which was accomplished without reported adverse effects. In the latter study, the quantity of delivered menthol (0.7 g/100 g) was sufficient to produce clinical improvement in peak expiratory flow.

A single study (Valdez et al. 1999) provided evidence of safety of a mixed menthol/methyl salicylate/camphor patch. In this comparative study of the dermal absorption of the three counterirritants, application of the patches for 8 hours had no adverse effects.

These literature citations demonstrating the safe and effective use of topical methyl salicylate, camphor or menthol in plaster, patch or poultice delivery formulations are in general agreement with results presented in several references from Docket 78N-0301. Docket references CP8 and RPT4 (corresponding to 69 FR 42324 references 7 and 10) present evidence of good tolerability with the exception of mild irritation reactions using a combination of these three counterirritants in Sato Mediplaster. Docket reference CP13

(corresponding to 69 FR 42324 reference 8) shows similar good tolerability with these ingredients in Salonpas-E<sup>®</sup> patches. Docket reference CP13 (corresponding to 69 FR 42324 reference 18) demonstrates both good tolerability without irritation or sensitization, and efficacy in treating muscle strain, using Pain Patch (Mentholatum) menthol.

The studies of Munce and Kenney (2003), Maruta et al. (1977), Valdez et al. (1999), Chiyotani et al. (1994), and Kim et al. (2002) provide evidence of efficacy and/or good tolerability of counterirritants applied as patches, plasters or poultices was demonstrated in Caucasian, African American, Hispanic, Japanese and Korean subjects. No evidence of any racial differences in efficacy or tolerability was produced.

The safety and efficacy data summarized above demonstrate the following:

- Various topical administrations of capsaicin, methyl salicylate, camphor, or menthol, in patch, plaster or poultice formulations, were well tolerated in a variety of racial groups.
- Observed side effects to these various preparations were limited to cutaneous irritation as are characteristic of Category I (GRAS) formulations (e.g., creams, lotions, ointments) of these counterirritants.
- Capsaicin in patch or plaster formulations had demonstrable efficacy in pain indications.
- Poultice containing menthol, methyl salicylate, camphor and scopolia extract had demonstrable efficacy in an asthma indication.

### **C. Dermal Absorption**

With regard to dermal absorption, two human studies and one animal preclinical study provide quantitative data on percutaneous absorption of capsaicin, menthol, methyl salicylate, and camphor from patches or plasters. In Maruta et al. (1977), absorption of methyl salicylate from ten plaster patches on the back (350 mg total) was measured during a single 12-hour application or multiple 12-hour applications (6 consecutive applications with 12-hour rest periods in-between). Peak serum concentrations of salicylic acid (4 µg/ml) and total salicylate (12.5 µg/ml) were measured at 8 to 12 hours after a single plaster application; drug was undetectable by 48 hours. With multiple applications, serum levels were reported as either trace or non-detectable. In Valdez (1999), 8-hour exposures to patches containing camphor (46.8 mg), menthol (37.4 mg) and methyl salicylate (74.9 mg) generated peak drug levels of 41 ng/ml, 32 ng/ml and 29 mg/ml, respectively. Peak levels were detected at between 1.5 and 3.5 hours, and serum half-lives ranged from 3.02 to 5.61 hours. For perspective, toxic doses of salicylate are seen at serum concentrations greater than 150,000 ng/ml to 500,000 ng/ml.<sup>13</sup> Furthermore, the salicylate levels achieved in Valdez et al. (1999) and Maruta et al. (1977) are similar to or considerably below the peak concentration of

methyl salicylate that is delivered from the Salonpas-E<sup>®</sup> Patch (1.3 µg/ml) as described in Docket reference SUP8 (corresponding to 69 FR 42324 reference 8).

A non-clinical rat study (Wu 1997) provided comparative absorption data based on skin concentrations for delivery of capsaicin via plaster vs. rubber or Gelva (acrylic-based) patches. Capsaicin, in concentrations ranging from 1.87 to 3.52 µg/cm<sup>2</sup> on 1×5 cm<sup>2</sup> patches or plaster, generated a skin concentration of approximately 10 ng/cm<sup>2</sup> from plaster vs. a wide range of concentrations, from undetectable to greater than 120 ng/cm<sup>2</sup>, when delivered via rubber or Gelva.

The dermal absorption data summarized above demonstrate the following:

- Patch administrations of menthol, methyl salicylate, or camphor (range 37 to 75 mg/patch) resulted in very low serum concentrations (ng/ml range) and short half-lives.
- Plaster application of methyl salicylate (350 mg) resulted in low µg/ml serum concentrations of salicylic acid and total salicylates.
- All dermal absorption data indicate that patch and plaster formulations of counterirritants generate non-toxic serum concentrations.
- A rodent study demonstrated variability of absorbed skin concentrations of capsaicin dependent upon delivery vehicle.

#### **D. Length of Safe Contact Time**

Three studies provide long-term tolerability information. Long-term application of 11 mg capsaicin in plaster as 4 to 12 hour exposures for 21 days (Keitel et al. 2001) was well tolerated with demonstration of mostly mild, anticipated adverse effects of skin irritation. Adverse events, noted in 20% of capsaicin treated subjects vs. 12% of placebo, spontaneously resolved. Methyl salicylate 350 mg in plaster, applied for 12-hour periods over 6 days, also was well tolerated and was demonstrated to have no adverse effects on hepatic function (Maruta et al. 1977). Finally, menthol of unknown concentration in poultice was without apparent side effects when applied over a 4-week period in a study of bronchial asthma (Chiyotani et al. 1994).

The data from prolonged plaster and poultice exposure with regard to length of contact time summarized above demonstrate the following:

- Capsaicin plaster and methyl salicylate plaster are well tolerated when administered as 4 to 12 hour exposures for 21 days and as 12-hour exposures for 6 days, respectively.
- Poultice containing a mixture of menthol, methyl salicylate, camphor, and scopolia extract was well tolerated over 4 weeks administration.

### **E. Frequency of Application**

Two studies have examined the safety and efficacy of capsaicin plaster (Keitel et al. 2001) or methyl salicylate plaster (Maruta et al. 1977) according to application schedules of once daily for up to 21 and 6 days, respectively. In Keitel et al. (2001), patients were allowed to choose application periods of between 4 and 12 hours based on tolerability, whereas in Maruta et al. (1977) all subjects had daily applications of 12 hours. This schedule of once-daily application with intervening rest periods was shown to be effective in lower back pain (Keitel et al. 2001), and was well tolerated in both studies. Although in Keitel et al. (2001) tolerability was not differentially discussed with regard to application period, there was 90% total compliance overall indicating that daily application schedules with a range of allowed application times is clinically satisfactory. In Maruta et al. (1977), 12-hour application of methyl salicylate plaster showed peak serum concentrations at 8 to 12 hours and undetectable blood levels by 48 hours. These pharmacologic data support a choice of once-daily applications, for up to 12 hour duration, as were shown safe and effective in Keitel et al. (2001). The results are furthermore consistent with the conclusions of Docket reference C109 (corresponding to 69 FR 42324 reference 6), that J & J Back Plaster (capsaicin) provides effective warmth for at least 4 hours, and consistent with the pharmacokinetic conclusions using Salonpas-E<sup>®</sup> in Docket Reference SUP8 (corresponding to 69 FR 42324 reference 8) that changing to new patches every 8 to 12 hours is safe and effective.

The cited clinical efficacy and tolerability data, supported by pharmacokinetic findings, demonstrate the following:

- Once-daily application of plaster formulations of capsaicin or methyl salicylate, for durations of between 4 and 12 hours, is safe and effective.

### **F. Age Differences**

With regard to age groups in which patches, poultices, and plasters can be safely utilized, the published literature spans exposures to young adults and to the elderly (up to 80 years). Clinically and statistically significant efficacy and good safety/tolerability with 21-day repeated exposure to capsaicin plaster were described within a study population ranging from 18 to 75 years (Keitel et al. 2001). No age-related differences were noted. Munce (2003) compared acute capsaicin exposure on bandages over a 4-log concentration range (0.001% to 10%) in a young cohort (18 to 30 years), middle-aged cohort (40 to 55 years), and a more elderly group (65 to 80 years). Cutaneous vascular conductance and vasodilation (erythema) was less pronounced in older skin (approximately 50% of the maximum response of young skin), consistent with an attenuated response of the capsaicin-sensitive primary afferent cutaneous sensory nerves in the elderly.



The data evaluating potential age-related differences in responses to topical counterirritants in patches, poultices and plasters demonstrate the following:

- Up to 21-day exposure of capsaicin plaster is well tolerated in patients spanning young adults to the elderly.
- Older skin has an attenuated vascular response to capsaicin patches compared to younger skin.

### **G. Summary of the Findings**

It is important to consider all data in aggregate to derive a weight-of-the-evidence conclusion regarding what is known about the safety and efficacy, and use characteristics of these products. To obtain a complete and comprehensive assessment, company-specific unpublished data should also be considered for a complete analysis.

While it is beyond the scope of this review to provide a comprehensive analysis of all results, the following can be concluded from the present review:

- A variety of plaster, patch, or poultice formulations of capsaicin, methyl salicylate, menthol, or camphor have been shown effective for local treatment of pain, as well as other indications, including prevention of nausea and vomiting and improvement of respiratory function in asthmatics.
- These formulations have been well tolerated, with only expected cutaneous irritation reactions being observed with prolonged exposures.
- These formulations have demonstrated similar tolerability among adult patients of a wide age range and among the major racial groups.
- Dermal absorption from patches or plasters results in low blood levels of the delivered counterirritants with relatively rapid clearances.
- The cited literature, which is predominantly more recent than the items previously submitted to the docket, are in general agreement with the comparable docket items, and do not raise any new safety or efficacy issues.

In conclusion, literature describing the use of plaster, patch, or poultice formulations of capsaicin, methyl salicylate, menthol, or camphor indicate that these formulations are qualitatively similar to other topical formulations with respect to efficacy and safety. Literature conclusions supplement the existing evidence previously submitted to the docket of safety and effectiveness of these products. Although head-to-head comparison between formulations would be needed to determine relative clinical benefits, the existing literature clearly supports the safe and effective use of patch, plaster and poultice formulations, and raises no new toxicity concerns in comparison with the other formulations tentatively considered generally safe and effective.

## H. References<sup>13</sup>

Chiyotani, A., Tamaoki, J., Sakai, N. et al. 1994. [Effect of menthol on peak expiratory flow in patients with bronchial asthma.] *Jap. J. Chest Dis.* 53(11):256-259. (Japanese language article, abstract in English)

Horn, M. and Enge, B. 1982. Influence of UV and capsaicin-induced erythema as well as of acetylsalicylate acid on the urinary excretion of vanil-mandelic acid and homovanillic acid in man. *Agents Action Supplements* 10:173-183.

Keitel, W., Frerick, H., Schmidt, U., Kuhlmann, M., and Bredehorst, A. 2001. Capsicum pain plaster in chronic non-specific low back pain. *Arzenimittel-Forschung (Germany)* 11:896-903.

Kim, K., Koo, M., Jeon, J., Park, H., and Seug, I. 2002. Capsicum plaster at the Korean hand acupuncture point reduces postoperative nausea and vomiting after abdominal hysterectomy. *Anesth. Analg.* 95:1103-1107.

Maruta, H., Minami, K., Yamagata, T., and Noda, K. 1977. Percutaneous absorption of methyl salicylate from medicated plaster in mice and humans. *Krume Med. J. (Japan)* 24(3):131-137.

Munce, T. and Kenney, W. 2003. Age specific skin blood flow responses to acute capsaicin. *J. Gerontol. Biol. Sci.* 58B(4):304-310.

Valdez, J., Martin, D., and Mayersohn, M. 1999. Sensitive and selective gas chromatography methods for the quantitative of camphor, menthol, methyl salicylate from human plasma. *J. Chromatog. B.* 729:163-171.

Wu, P., Fang, J., Huang B., and Tsai, H. 1997. Development of evaluation of transdermal patches of nonivamide and sodium nonivamide acetate. *Pharmazie* 52:135-138.

## IV. Properties of Patches, Plasters, and Poultices as Vehicles for Application of Counterirritant External Analgesics

Counterirritant external analgesic active ingredients are dispersed in a vehicle and applied to the skin to elicit an effect within the epidermis and dermis. The vehicle is simply a means to externally apply the active drug. In the TFM, three examples of vehicles are given:

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<sup>13</sup> References are located in Attachment 3

“(…cream, lotion, or ointment).” FDA’s Center for Drug Evaluation and Research (CDER) Data Standards Manual agrees with the U.S. Pharmacopeia (USP) definition of ointments as “semi-solid preparations intended for external application to the skin or mucous membranes.” USP goes further to recognize four classes of ointments bases: hydrocarbon bases, absorption bases, water-removable bases and water-soluble bases (USP 26, 2402). The choice of base depends upon many factors, each providing a range of characteristics.

Patch, plaster, and poultice dosage forms have been used as vehicles to apply topical active ingredients. Patch dosage forms can be described as a soft, flexible pad intended to be applied directly to the skin. The pad consists of a medicated layer on a porous backing. The medicated layer is covered with a protective film that is removed prior to application of the pad to the skin. The medicated layer is composed of suitable materials to deliver the drug, in a base that provides the adhesion. The base is typically a water-based polymer semi-solid preparation or an organic-based polymer semi-solid preparation. The backing is typically a non-woven polyester, non-woven polyolefin, porous polyurethane or similar suitable porous backing.

The medicated layer and porous backing together form a topical vehicle that, while physically covering the skin, allows vapors to transfer across the seeming physical barrier. Based on a CDER definition, topical patches can be described as non-occlusive because there is diffusion of gases and water vapor through the structure.<sup>14</sup> In recognition of the physical barrier, the patches can also be described as semi-occlusive. For the purpose of this document, semi-occlusion will be defined as permeable to gases and liquids.

The medicated layer of the patch directly contacts the skin; upon application it conforms to the contour of the body surface. The medicated layer contains a uniformly distributed measured dose of an external analgesic ingredient as described in the TFM. The medicated layer in contact with the skin allows the active ingredient to work locally, similar to a cream, lotion, or ointment vehicle.

The patch dosage form allows consumers a convenient means of applying a topical medication. When applying the external analgesic patch to the skin, there is little or no residue on the hands and the site of application has no surface oiliness or mess. This form provides the consumer dose control greater than that of a cream, lotion or ointment as each discreet pad provides a fixed quantity of active. The patch can be removed by the consumer if desired.

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<sup>14</sup>In the CDER FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness, non-occlusive is defined as allowing gases and water vapor to diffuse through the structure and occlusive is defined as impermeable to gases and liquids.

## V. Safety of Currently Marketed Products

Compiled information from spontaneous consumer reports is consistent with the general recognition that the monograph external analgesic counterirritants are safe. The CHPA External Analgesic Task Group conducted a survey to determine the nature of adverse experiences or untoward events that had been reported to companies about OTC external analgesic patches, plasters, and poultices from 1998 through August 2003. The compiled data are presented in the tables below and in Attachment 4.

Seven companies completed the survey. They represent most of the U.S. market share for the products. In 2002, for example, the seven companies sold nearly 11.5 million packages of OTC external analgesic patches or plasters with close to 150 million dosage units.

As is generally true for consumer healthcare products, most of the reports come from informal consumer complaints made by telephone or letter, and so the information is imprecise and incomplete. Consequently the reported untoward effects 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 untoward effects associated with use of OTC external analgesic patch, plaster, and poultice products is low, particularly given the number of dosage units sold. The following tables present the cumulative numbers of individuals with reported untoward effects for each of the active ingredients capsaicin (Table 1), menthol (Table 2), and methyl salicylate (Table 3) and the combination of those counterirritant ingredients (Table 4). These tables 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 untoward effects to unit sales is extremely small. All but two of the reported experiences, affecting 305 individuals, were "nonserious" as defined by FDA's MedWatch classification. In two of the instances, one in 1998 and one in 2000, the person was admitted to a hospital for treatment. On that basis, these instances would be classified as "serious" under the MedWatch definitions. The recorded information for those two experiences, reported for a combination product, is provided in Attachment 4.

Compiled numbers for the various categories of reported untoward effects are tabulated in Attachment 4. Each consumer report may include more than one effect, and so yearly effect totals are higher than the numbers of affected individuals reported for each year.

**Table 3: Methyl Salicylate 10%**

Year	Number of Package Units Sold at Retail	Number of Dosage Units Sold at Retail	Number of Individuals with Reported Untoward Effect*	
			Nonserious	Serious <sup>16</sup>
1998	--	--	--	--
1999	--	--	--	--
2000	--	--	--	--
2001	--	--	--	--
2002	327,636	1,965,816	5	0
2003 (thru Aug.)	314,952	1,889,712	2	0

\*See Table 4-3 in Attachment 4 for listing of untoward effects.

-- Product(s) not reported as sold before 2002.

**Table 4: Combinations of Methyl Salicylate 0.8% - 6.2%,  
 Menthol 0.4% - 5.7%, and Camphor 0.5% - 1.2%**

Year	Number of Package Units Sold at Retail	Number of Dosage Units Sold at Retail	Number of Individuals with Reported Untoward Effect*	
			Nonserious	Serious <sup>16</sup>
1998	2,953,938	76,051,522	2	1
1999	3,325,298	76,970,704	4	0
2000	3,791,396	101,162,278	5	1
2001	4,680,807	135,240,173	16	0
2002	4,151,175	124,522,232	8	0
2003 (thru Aug.)	3,264,755	99,110,679	1	0

\*See Table 4-4 in Attachment 4 for listing of untoward effects.

<sup>16</sup> 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.

## **VI. Proposal for Testing and Development of a Guidance Document**

FDA is seeking additional data to support the safety and effectiveness of counterirritant external analgesics in dosage forms other than creams, lotions, and ointments. The agency has posed questions specifically about safe dermal contact and systemic absorption resulting from use of alternative dosage forms. FDA is also looking for information that would be useful in supporting appropriate labeling for such products to be used safely and effectively by consumers who obtain them over the counter.

The CHPA task group recommends that FDA adopt an appropriately designed program to show that products meet certain safety testing and performance standards. The program would include testing to show:

- Dermal safety
- Percutaneous absorption (upper limit of dose delivery)
- Delivery of active ingredient to the skin (lower limit of dose delivery)

FDA has precedents for requiring final formulation testing in monographs for OTC drug products. Examples are:

- Aspirin and acetaminophen would be required under the Tentative Final Monograph for OTC internal analgesics to meet in vitro disintegration and dissolution performance standards that are set in the relevant United States Pharmacopeial (USP) monograph (53 FR 46260).
- Under the OTC monograph for oral care products, fluoride-containing dentifrices must meet standards for releasable fluoride, limits for specific gravity and pH, and biological testing standards as developed under a USP monograph and reference standard program (45 FR 20677-20681 and 53 FR 22434).
- The OTC monograph for ophthalmics requires demonstration of an acceptably low irritancy potential (53 FR 7087-7088).
- The final monograph for OTC antacids includes specifications for products to meet USP acid neutralizing capacity test standards, which were originally developed by an FDA OTC review panel. The final monograph subsequently referred to in vitro test procedures as the standard for surrogate OTC antacid bioactivity (61 FR 4822).

On a number of occasions in the OTC Review rulemaking FDA has addressed the need for performance standards for products containing monograph ingredients and has expressed both the rationale and the biologic and in vitro testing criteria, as needed, to support its

decision to utilize the monograph system as a cost- and resource-efficient mechanism of drug regulation.

In the TFM for OTC antimicrobial drug products, for example, FDA clearly stated its intention to utilize the OTC monographs in a flexible and dynamic way in justifying its requiring certain additional testing of products with approved monograph ingredients, as follows:

“The Commissioner will not require every company to test and will ordinarily not require testing of the active ingredient, vehicle, and total product. However, within the broad and varied field of OTC drugs there may possibly be circumstances in which review and testing of individual products is the only way to determine whether the statutory and regulatory criteria are met. While this may result in more extensive testing for a very few classes of OTC products than was envisioned at the beginning of the OTC drug review, the requirements applicable to those products will be nowhere near as extensive and detailed as the new drug application (NDA) requirements. For certain product classes in this monograph, where issues of skin sensitivity and irritation are of importance, data will have to be submitted on active ingredients, vehicles, and/or total products. Those ingredients or product classes will be delineated in appropriate testing guidelines.” (43 FR 1211)

FDA has identified several concerns about whether external analgesic active ingredients in patch, plaster, or poultice dosage forms should remain in the OTC Review subject to Final Monograph standards or be placed under individual New Drug Applications. These issues pertain to:

- Safe concentrations of counterirritant ingredients applied in patches, plasters, or poultices
- Extent of percutaneous absorption of counterirritant ingredients
- Safe frequency and duration of applications
- Labeling information for patch, plaster, and poultice products

The safety and effectiveness concerns about specific dosage forms can be addressed through a specified testing program conducted according to a guidance that should be developed and referenced in the Final Monograph for OTC external analgesics.

In the case of alternative dosage forms for OTC counterirritant external analgesics, the agency should consider developing a guidance document for specific test methods and endpoints, which it could reference in the Final Monograph for OTC external analgesics. The guidance approach allows the agency to take in account scientific advances and different testing methods on a contemporary basis rather than needing to rely on the resource-intensive and cumbersome notice-and-comment rulemaking approach to incorporating new methodology in OTC monographs.

FDA has used this approach and incorporated greater flexibility most recently in the Final Monograph for Antiperspirant Drug Products (68 FR 34273, June 9, 2003). Section 350.60 states, "An antiperspirant in finished dosage form may vary in degree of effectiveness because of minor variations in formulation. To assure the effectiveness of an antiperspirant, the Food and Drug Administration is providing guidelines that manufacturers may use in testing for effectiveness." The guidelines further state, "[t]hese guidelines do not preclude the use of alternate methods that provide scientifically valid results, subject to FDA approval."

FDA has set another precedent for such a guidance approach in the tamper-evident packaging (TEP) guidance for OTC drugs (Compliance Policy Guide 7132a.17). The TEP regulation (21 CFR 211.132) establishes the performance standard. The guidance identifies examples of technologies currently capable of meeting the standard while also providing that manufacturers are free to use any technology that satisfies the performance standard.

The CHPA task group asks that FDA issue a guidance document recommending the conditions that testing for irritation, sensitization, and dose delivery must meet to be recognized as acceptable for establishing the safety and effectiveness of generally recognized as safe and effective active ingredients in alternative dosage forms. While such guidance could include examples of specific protocols, it should also allow for enough flexibility to allow for scientific advancement.

The CHPA task group proposes a testing program and development of a guidance document. This proposal is designed to generate data and develop an industry guidance to address the dermal and systemic safety of patch, plaster, and poultice products and the dose delivered to the skin (effectiveness), and to support potential changes in labeling.

To provide additional assurance of dermal safety, studies would be performed once in an identified standard delivery system to encompass counterirritant active ingredients and combinations thereof used in any patch, plaster, or poultice product. These tests would establish maximum concentration limits for all alternate dosage forms, below which no additional irritation and sensitization testing would be required. If possible the irritation and sensitization components could be combined into one study following related current FDA guidance documents.

#### **A. Initial Testing Proposal**

In order to demonstrate that the monograph topical counterirritant active ingredients and combinations thereof are safe and provide an adequate dose when applied under semi-occlusive conditions, the CHPA task group proposes the following testing program:



1. **Corroboration of Dermal Safety:** These studies will provide assurance that the monograph active ingredients can be applied to the skin under semi-occlusive conditions without producing sensitization and damaging irritation. The studies will be based on well established and accepted protocol designs as outlined in FDA guidance documents.
  - a. **Irritation:** Within the monograph concentrations for active ingredients, identify what level of active ingredient does not produce significant irritation when tested using an industry standard semi-occlusive patch application against accepted standard positive and negative controls. Similarly, demonstrate what levels of active ingredients in combinations do not produce significant irritation when tested under semi-occlusion.
  - b. **Sensitization:** Based upon the maximum tolerated concentration established in the irritation study described above, evaluate the active ingredients for sensitization when patched under a semi-occlusive standard following the modified Draize protocol. Combinations would be tested separately to demonstrate they do not produce sensitization under similar conditions.
  
2. **Systemic Exposure:** This component of the testing program is based on FDA's published conclusions that monograph category I ingredients are safe when a specified dose is delivered to the skin. Accordingly, safety is defined as dose delivered that is less than or equal to that delivered when the maximum monograph concentration of the same ingredient or combination is applied in the form of a cream, lotion, or ointment. In addition, the FDA has commented that occlusive application of test article tends to enhance the dermal permeability of many test materials. To address these concerns about less than fully occlusive dosage forms<sup>17</sup>, the CHPA task group proposes in vivo pharmacokinetic studies designed to determine the level that the systemic exposure to active ingredients under semi-occlusion is less than or equal to the systemic exposure observed for the maximum monograph active levels when applied in a cream, lotion, or ointment. The maximum levels tested in this exposure analysis would be based on the results of the irritation and sensitization testing described in section A.1.

In addition, in vitro percutaneous absorption studies would be performed on each counterirritant active in parallel to the in vivo studies to develop a validated in vitro assay with a correlation between in vivo and in vitro assays.

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<sup>17</sup>As noted previously, 100% occlusive dosage forms are not currently marketed.

If a correlation for systemic exposure were established, the in vitro assay would be used in the future to determine systemic exposure for products that need to be tested as described in section B.2.

3. **Dose Delivery:** This component of the testing program is based on the FDA's published conclusions that the monograph Category I ingredients are effective when an adequate dose is delivered to the affected site. Accordingly, effectiveness for patch, plaster, and poultice products is defined as the dose delivered at the site of action that is equal to or greater than the dose delivered for the same ingredient or combination at the monograph minimum levels when delivered in the form of a cream, lotion, or ointment. In addition, FDA expressed concern that these dosage forms may retard delivery of effective monograph levels of active ingredients. To address this issue, the CHPA Task Group proposes in vitro percutaneous absorption assays to demonstrate that the concentration of active ingredient at the target site (e.g., stratum corneum) for patch, plaster, and poultice products is equal to or greater than the minimum monograph concentrations for active ingredients in creams, lotions, and ointments. The in vitro methods used will be developed using the FDA guidance on this topic (Bronaugh method). This same assay would be used for new products that need to be tested as described in section B.3.

For a schematic presentation of the Initial Testing Proposal see Figure 1

#### **B. Proposed Qualification Procedure for Industry After Levels Are Established in Section A**

For new dosage forms and for products that may contain labeled concentrations of active ingredients above or below the concentrations established in section A and deliver an amount of active ingredient equivalent to that attained at the site of action by a cream, lotion, or ointment, the CHPA task group is recommending the creation of a qualification procedure to demonstrate product-specific safety and dose delivery.

This qualification procedure is a two-stage standard. All new dosage forms and products that contain labeled concentrations of active ingredients above or below the levels established in Section A would be required to demonstrate dermal safety by completing Part 1. Then, depending on whether the dosage form or product has labeled concentrations above or below the established standard, either Part 2 or Part 3 would be completed. Part 3 would be done for products with active ingredients within levels established in section A.

1. Dermal Safety:

Perform irritation testing and sensitization testing for all new dosage forms and for products containing a labeled concentration of active above or below the concentrations established in Section A as described:

- a. Demonstrate that the product does not produce significant irritations under an appropriate cumulative irritation protocol.
- b. Demonstrate that the product does not cause sensitization when patched, following a modified Draize protocol.

**AND EITHER**

2. For High Labeled Concentrations Maximum Exposure:

- If the product has labeled concentrations of active ingredient(s) higher than the levels established in section A, a study demonstrating that the exposure to the active ingredient in the test product was equal to or less than the exposure for the monograph concentration in a cream, lotion, or ointment is conducted. The systemic exposure to the active ingredient could be demonstrated using in vitro techniques provided that correlation between the in vivo method and the in vitro method is validated.

**OR**

3. For Products with Concentrations within Levels Established in Section A or Low Labeled Concentrations: Minimum Dose:

- If the product has labeled concentrations of active ingredient(s) within the levels established in Section A or the product had lower than the monograph concentrations (i.e. sub-monograph), a study demonstrating that the dose delivered to the skin was equal to or greater than the dose delivered from a cream, lotion, or ointment containing active ingredient at the monograph minimum level would be conducted. This analysis would be based on results from a validated in vitro model.

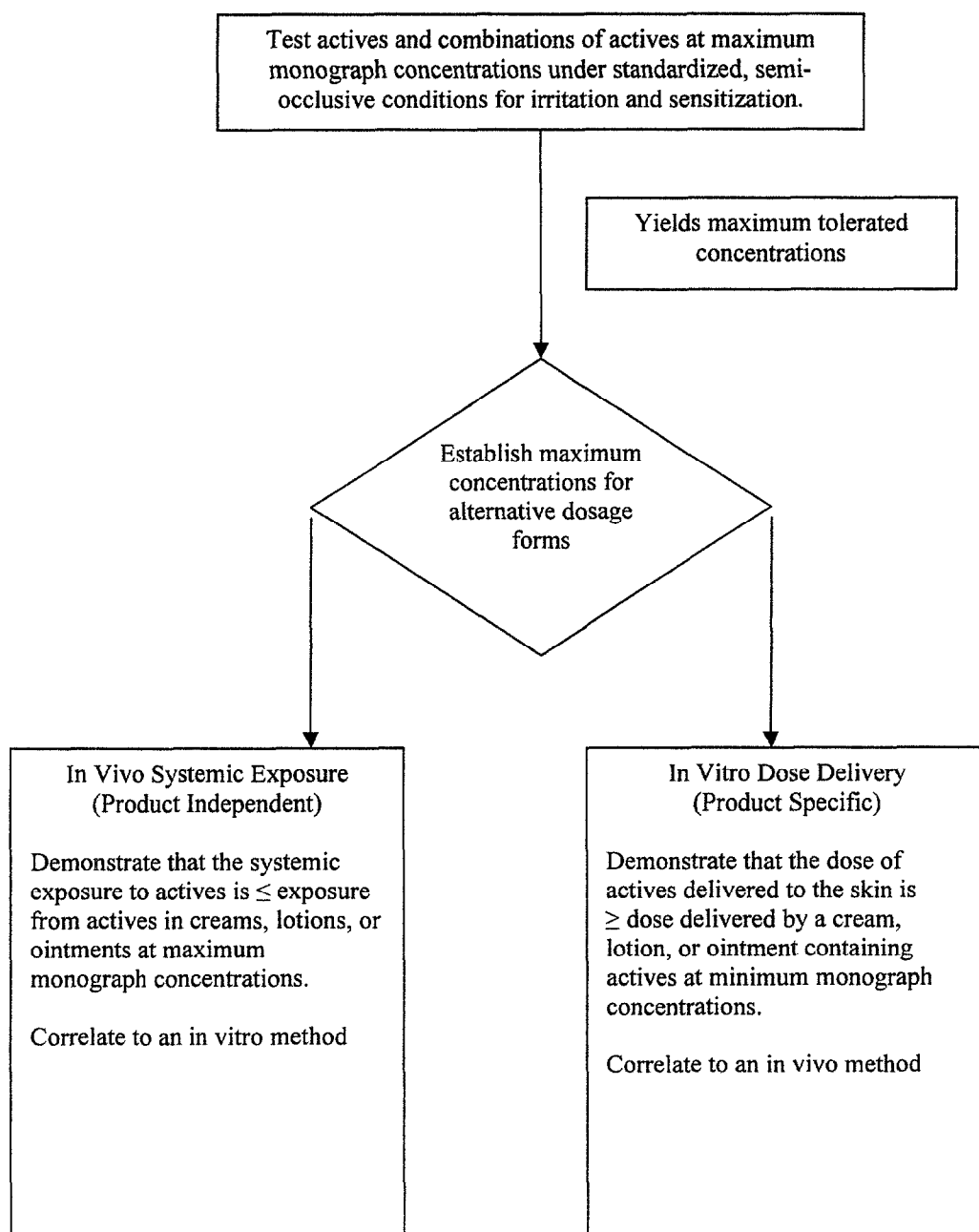
For a schematic representation of the proposed qualification procedure see Figure 2.

# Figure 1

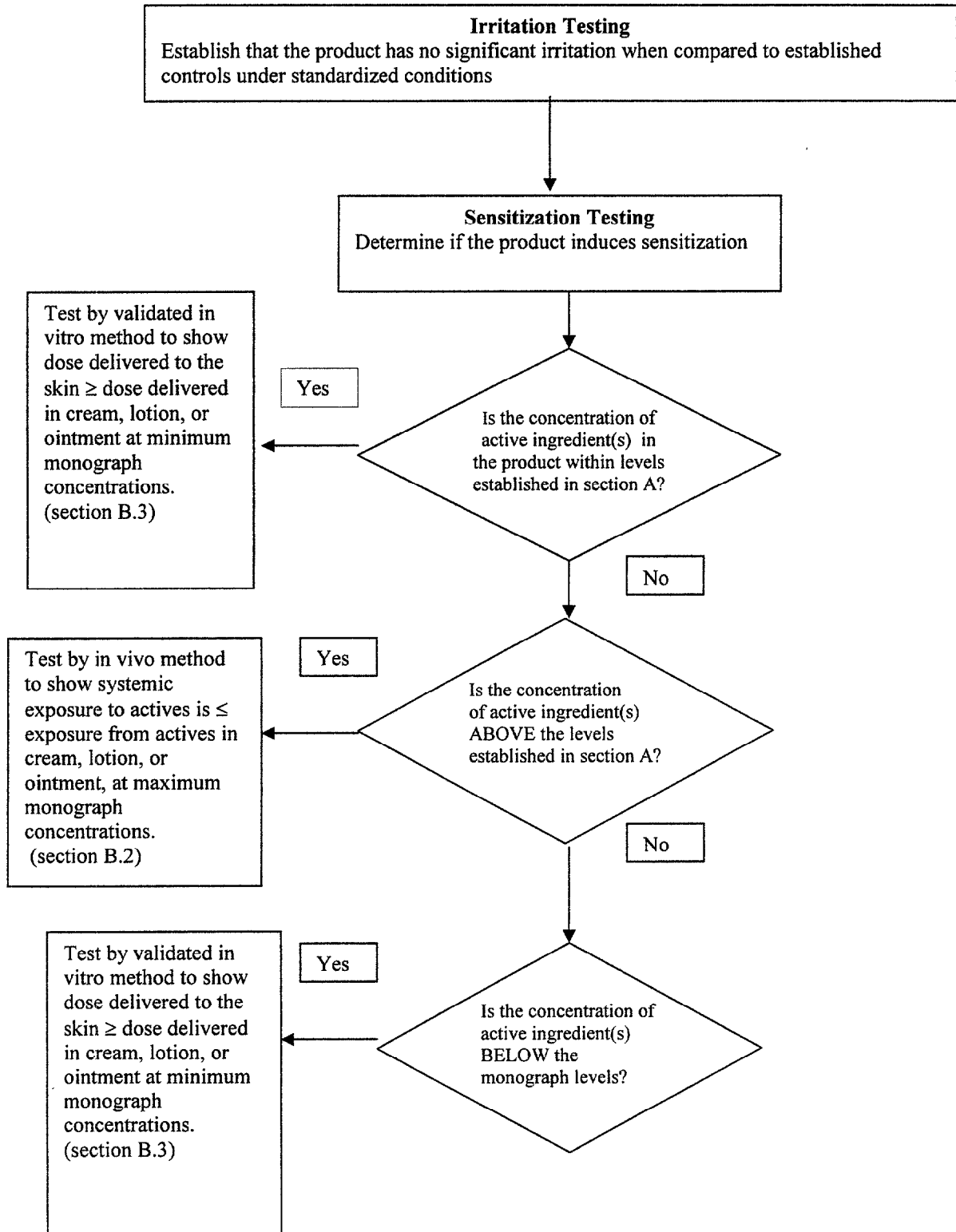
## Establishing Systemic Exposure and Dose Delivery Relative to Irritation and Sensitization Potential

**Irritation Testing** (Product Independent)  
Purpose: To establish the maximum concentration of actives or combinations of actives when applied under standardized, semi-occlusive conditions.

**Sensitization Testing** (Product Independent)  
Purpose: To determine if the maximum tolerated concentrations of actives or combinations of actives induce sensitization.



**Figure 2**  
**To Qualify New Products or Dosage Forms**



## VII. Comments on Labeling

CHPA has particular interest in matters regarding labeling improvements that assist consumers to use OTC drug products correctly. CHPA members have been working for many years to make their product labels more consumer-friendly and worked cooperatively with FDA in the development of the 1999 OTC labeling rule.

Clear, complete labeling is important for the consumer to be able to use the products safely and effectively. It plays a valuable role in helping the consumer understand both the benefits and risks associated with OTC medicines, and to avoid unnecessary adverse events.

Adequate labeling is designed to ensure proper usage so that the benefits outweigh any risks. With that in mind, the CHPA task group has recommendations for enhancing labeling for such alternative dosage forms as patches, plasters, and poultices using counterirritant external analgesic active ingredients.

An example Drug Facts label is shown on the next page. The CHPA task group is recommending adding labeling that is consistent with 21 CFR 369.20 Counterirritants and Rubefacients, and Salicylates: Methyl Salicylate (Wintergreen Oil):

### **Ask a doctor before use**

- if redness is present
- on children under 12 years with arthritis-like conditions [*if product is offered for use in arthritis*]

### **When using this product**

- avoid contact with eyes or mucous membranes
- do not apply to wounds or to irritated or damaged skin

### **Stop use and ask a doctor if**

- rash or excessive irritation develops

Two other changes are suggested, which are not in 21 CFR 369:

### **When using this product**

- do not cover with any additional wrap
- do not use with a heating pad or external heat

## Proposed Drug Facts for Patch, Plaster, Poultice Dosage Forms

<b>Drug Facts</b>	
<b>Active ingredient</b>	<b>Purpose</b>
Ingredient x % .....	External analgesic
Ingredient x % .....	[alternate] Topical analgesic
<b>Uses</b> temporarily relieves minor aches and pains of muscles and joints associated with ■ simple backache    ■ arthritis    ■ strains    ■ sprains    ■ bruises	
<b>Warnings</b> For external use only	
<b>Ask a doctor before use</b> ■ if redness is present ■ on children under 12 years with arthritis-like conditions	
<b>When using this product</b> ■ avoid contact with eyes or mucous membranes ■ do not apply to wounds or to irritated or damaged skin ■ do not cover with any additional wrap ■ do not use with a heating pad or external heat	
<b>Stop use and ask a doctor if</b> ■ rash or excessive irritation develops ■ condition worsens ■ symptoms persist for more than 7 days ■ symptoms clear up and occur again within a few days	
<b>Keep out of reach of children.</b> If swallowed, get medical help or contact a Poison Control Center right away.	
<b>Directions</b> ■ adults and children 2 years and over: apply to affected area not more than 3 to 4 times daily ■ children under 2 years: ask a doctor ■ [product specific application directions]	
<b>Other information</b> [as applicable]	
<b>Inactive ingredients</b>	
<b>Questions or comments?</b> [optional]	

We recommend revising the current warning "Do not bandage tightly." Because some of these products could be in a bandage form, consumers may understand the warning more clearly by cautioning against covering with any *additional* wrap. The intent of the warning is to maintain the semi-occlusive nature of these products.

There is no warning currently relating to the use of heat with these ingredients. For safe use, external heat should not be applied.

The directions for use of these products will vary depending on product-specific application. The CHPA task group believes that patch, plaster, and poultice products are within the scope of the TFM. Reported consumer usage would appear to be indicative that a change to create dosage-form-specific labeling directions in the monograph is not necessary. The task group recognizes, however, that the proposed testing program may address some of FDA's labeling concerns. If data suggest the need for specific labeling changes, the task group will work with FDA on new labeling directions.

#### **VIII. Request for FDA to Work with Industry to Develop a Guidance and to Keep the Docket Open for Submission of Relevant Data**

The CHPA External Analgesics Task Group asks that FDA withdraw its proposal to exclude patches, poultices, and plasters from the monograph for OTC external analgesics. Existing data are sufficient to support general recognition that OTC counterirritants are safe and effective in alternate dosage forms, but FDA has requested additional information. In this submission, the task group proposes a testing program and development of a guidance document.

The task group requests a meeting with FDA to engage in an in-depth scientific dialogue on the proposed guidance for testing. The proposed testing program raises certain specific practical issues that product manufacturers must resolve and will want to discuss directly with FDA. FDA should remain open to receiving example protocols and other information and data that would be useful in setting up the guidance for the required testing.

The task group also requests that the docket be kept open for submission of the testing results necessary to develop a guidance. It is important for manufacturers of OTC external analgesic products to be assured that data resulting from the proposed testing will be used by the agency to support continued marketing of the products under the provisions of the OTC final monograph for external analgesics. The industry's proposed testing program will provide additional data in support of the outstanding safety of camphor, capsaicin, menthol, and methyl salicylate topically applied in such dosage forms as patches, plasters, and poultices.



**IX. Summary of Requested Action**

The CHPA task group contends that dosage forms different from creams, lotions, and ointments are within the scope of the tentative final monograph for OTC external analgesic drug products. These products are safe and effective as supported by the additional information in this submission, and the task group requests that patch, plaster, and poultice dosage forms be permitted under the monograph.

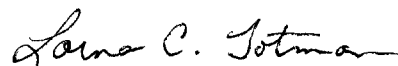
The task group also requests that FDA work with industry to create a guidance that will help define an acceptable pathway for the development of new OTC products or dosage forms, thus helping to assure safe and effective choices for consumers. This guidance would become the recommended standard in the external analgesic final monograph. A meeting is requested with FDA to engage in an in-depth scientific dialogue on the proposed guidance.

Additionally, the task group would like FDA to consider the comments and suggested labeling for patch, poultice, and plaster products, and that the labeling for those dosage forms remain consistent with the proposed monograph labeling for creams, lotions, and ointments.

Finally, the CHPA task group requests that the docket remain open while the guidance is being created, and to accept data that may be generated to support the marketing of alternative dosage forms.

We appreciate FDA's consideration of our requests and would be pleased to provide further information or clarification as needed.

On behalf of the CHPA Analgesic Task Group,



Lorna C. Totman, Ph.D., DABT  
Senior Director of Scientific Affairs and Toxicology