CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

February 19, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**Re: Docket No. FDA-2019-D-4447: Transdermal and Topical Delivery Systems - Product Development and Quality Considerations, Guidance for Industry**

On behalf of the Consumer Healthcare Products Association (CHPA)[1], enclosed herein are comments on "Transdermal and Topical Delivery Systems - Product Development and Quality Considerations", published as a draft FDA guidance (November 2019). CHPA and our member companies marketing external analgesic ingredients in patch dosage form have an interest, experience and expertise in this area and appreciate this opportunity to comment. We first provide general comments (Section A) on the lack of applicability of testing conditions described in the current guidance to over-the-counter (OTC) external analgesic patch products containing ingredients generally recognized as safe and effective (GRASE) by the agency in a 1983 Tentative Final Monograph. Subsequent comments address specific points contained within the draft guidance (Section B).

## A. General Comments

In the current draft guidance, the agency has outlined a significant set of testing procedures/conditions, previously applicable only to application products,[2] for external analgesic patch products currently marketed under the OTC monograph construct. As such, the agency notes that "*The general principles in this guidance can also be applied to nonapplication drug products; for example, over-the-counter drugs* [sic] *products marketed under the monograph regulatory construct (see 21 CFR part 330).*" Patch dosage forms containing these ingredients have a long history of safe use as supported by adverse event data previously provided to the agency by CHPA in 2003, 2010, and 2012.[3] Requiring manufacturers marketing an external analgesic patch containing GRASE ingredients to test their respective products to specifications described under Section IV (Information To Be Submitted In An Application; Sections A and C) would impose significant resource burdens and costs on manufacturers and provide no incremental benefit in terms of safety.

As such, we request that FDA waive these specific testing requirements for external analgesic patch products containing Category I ingredients, or failing that, to separately address specific testing

[1] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. Every dollar spent by consumers on OTC medicines saves the U.S. healthcare system more than $7, contributing a total of $146 billion in savings each year. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

[2] The first paragraph of the guidance document notes that the document covers "*…pharmaceutical development and quality information to include in new drug applications (NDAs) and abbreviated new drug applications (ANDAs).*"

[3] Adverse Events Reported to Manufacturers of OTC External Analgesic Patch Products – 1998 through August 2003; January 2003 through June 2009; July 2009 through April 2011 (documents submitted by CHPA to FDA Docket No. 78N-0301).

conditions the agency considers necessary for recognition of topical patch products containing Category I external analgesic ingredients under the OTC monograph in a separate guidance.

Members of the CHPA External Analgesic Task Group previously submitted[4] a detailed set of comments requesting that the agency work with industry to develop *"…principles for a guidance for industry to use when developing alternate dosage forms, including patches…"*. Contained within this submission was a proposal for testing and development of a guidance document which would address dermal safety (irritation/sensitization), systemic exposure and dose delivery. We remain committed to this approach and look forward to discussing with the agency an approach which would address any concerns that the agency may have and allow for the recognition of the patch dosage form as GRASE without imposing conditions required for application products.

**B. Comments addressing specific aspects of the draft guidance**

Should the agency decide that the current guidance applies to OTC monograph patch products, CHPA requests that consideration be given to each of the individual points listed below.

- Page 1, Line 19 (footnote #4): "*The general principles in this guidance can also be applied to nonapplication drug products; for example, over-the-counter drugs products marketed under the monograph regulatory construct (see 21 CFR part 330).*"

The agency's use of the term "*general principles*" in this case is vague (*e.g.*, it is unclear whether this statement refers to specific tests or to all tests described in the guidance) and, as such, this sentence should be clarified, or removed.

- Page 2, Line 37 (footnote #5): "*Topically administered liquid and semi-solid drug products without a carrier device (e.g., gels, creams, lotions, foams, ointments, or sprays) are not considered to be TDS and are not covered by this guidance, even though they can be formulated to provide local, or in some cases, transdermal delivery of the drug.*"

External analgesic topical patches containing only GRASE ingredients have local effects and are not the same as the products discussed in the guidance. As such, CHPA requests that OTC external analgesic topical patches be considered similar to other suitable topical dosage forms (e.g., cream, lotion, or ointment) and thus not subject to the conditions contained in this guidance.

- Page 3, lines 61-86 (Regulatory Status): *"Transdermal and topical delivery systems are combination products as defined by 21 CFR part 3, and must comply with 21 CFR part 4 subpart A (Current Good Manufacturing Practice Requirements for Combination Products). Within 21 CFR part 4, there is description of how requirements from 21 CFR parts 210 and 211 (drug CGMPs) and 21 CFR part 820 (device Quality System regulation) apply to combination products."*

Topical OTC external analgesic patches should not be considered combination products as defined in 21 CFR3.2(e). These patch products consist of active drug ingredient(s) delivered to the skin by means of an adhesive base on a porous cloth, non-woven polyester or other suitable backing and are not adequately described by any of the four categories encompassing "combination product", including

[4] FDA 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; October 15, 2003



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i. A product comprised of two or more regulated components,[5] i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

ii. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

iii. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

iv. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Further, FDA has identified nine different types of combination product,[6] including two categories that encompass "transdermal systems"; however, none of the identified categories describe the specifications of a topical patch designed to deliver active ingredients locally.

- Page 5, lines 135-140: "*Selection of a drug substance should be justified based on the physicochemical and biological properties of the drug substance that can influence the performance of the TDS product and its manufacturability*."

This is not applicable to OTC topical matrix patches which already use well established drug actives suited to topical delivery.

- Page 7, lines 188-201: "*Transdermal and topical systems that are clear, translucent, or colored to match human skin tones can make it difficult to find the TDS on the patient, and have led to medication administration errors when patients or caregivers fail to remove old systems and apply more than one system at a time. Clear or translucent TDS may also be difficult to find if they detach prematurely from a patient, thereby increasing the potential for secondary or accidental exposure of the drug to a health care provider, caregiver, or child. Therefore, we recommend the backing membrane be printed with ink that has adequate contrast and remains visible for the duration of system wear and after disposal*."

This aspect of the guidance should not be applicable to OTC monograph ingredients delivered in a topical patch dosage form. Product labeling for OTC external analgesic patches provides directions for safe use and the safety record for this dosage form over decades of use is excellent.

[5] The medicated base and porous backing together form a topical vehicle that enables the medication to be in contact with the skin allowing the active to work locally similar to a cream or ointment. The porous backing alone is not a regulated device as described in this combination.

[6] https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types



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- Pages 8-24, Section IV. "**INFORMATION TO BE SUBMITTED IN AN APPLICATION**."

CHPA requests that the agency clarify this section by inserting a footnote stating that this information is only related to applications and not applicable to OTC monograph products. Should this footnote not be added, we request that the agency address the following:

i. Pages 11-12, lines 354-379: "*Consistent with FDA guidance for industry Residual Drug in Transdermal and Related Drug Delivery Systems (August 2011), scientific justification sufficient to support the amount of residual drug in a TDS should be included in the pharmaceutical development section of the application*."

The Final Guidance document noted by the agency in this instance (Residual Drug in Transdermal and Related Drug Delivery, August 2011) notes on lines 31-33, "*This guidance is applicable to investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental new drug applications (sNDAs) for TDDS, TMDS, and topical patch products*." CHPA believes the same clause should be included in the current draft guidance as the contents are not related to OTC monograph products.

ii. Pages 12-13, lines 381-422 (In Vitro Permeation Testing):

CHPA requests that specific aspects of this testing not apply to OTC monograph products, including range of skin thickness, results from skin barrier integrity testing, trans-epidermal water loss (TEWL), and use of an antimicrobial agent. Preliminary results from a study comparing skin permeation of active ingredients resulting from topical patch application versus that obtained with an ointment revealed no significant difference between these dosage forms. The testing described in this portion of the guidance should not be required for external analgesic topical OTC patches containing monographed GRASE ingredients designed to produce local effects.

iii. Pages 13-15, lines 424-499 (Extractable and Leachable Testing):

CHPA requests that the agency address whether an adequately conducted post stability testing program could address the conditions provided in this section of the guidance.

iv. Pages 22-23, lines 822-870 (In vitro Drug Release):

This section is not applicable to OTC patches which are well established, locally acting topical drugs. Validated analytical methods demonstrate availability and stability of active pharmaceutical ingredients in gel matrices.



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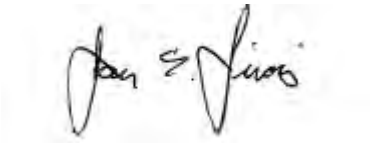
CHPA and our member companies appreciate the opportunity to comment on this process. Should you have any questions, please do not hesitate to contact me.

Regards,



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