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Division of Dockets Management,
Department of Health and Human Services, Food and Drug Administration,
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Citizen Petition

Consumers suffering from pain, and especially from chronic pain or moderate-to-severe acute pain, require and deserve drug products that have been demonstrated to be safe and effective for their specific needs. This is true now more than ever. Alternatives to opioids that have been proven safe and effective for managing chronic pain, moderate-to-severe acute pain, and specific pain indications are in short supply. Moreover, chronic pain continues to levy a drastic economic and human toll on the United States (U.S.) population, and the U.S. healthcare system and consumers continue to wage a difficult fight against the opioid epidemic.

Over-the-counter (OTC) external analgesic drug products in patch, plaster, or poultice (PPP) dosage forms could do much to address certain gaps in pain management. However, under the U.S. Food and Drug Administration's current regulatory approach to OTC external analgesics in PPP dosage form, only a few such products have been demonstrated to be safe and effective, and generally only for limited indications.

The undersigned submits this petition under Subchapter V, Part A, of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR §§ 10.30 and 10.20 to request the Commissioner of Food and Drugs (hereinafter "the FDA" or "Agency") take the following action to ensure that OTC external analgesic drug products in patch, plaster, or poultice (PPP) dosage forms claims are limited only to those that are demonstrated, and do not include severe or acute pain.

A. Action Requested

The undersigned requests that the FDA issue the administrative order for OTC external analgesics as deemed final by section 505G of the FD&C Act, and that in the order FDA confirm and clarify for which specific indications OTC external analgesic drug products in PPP dosage forms are generally recognized as safe and effective (GRASE) (e.g., mild backpain or backache), and that the FDA further confirm and clarify in the order that submission of an application under FD&C Act section 505(b), 505(j), or potentially 505G is warranted for other indications. The labeling of OTC external analgesic drug products in PPP dosage must be limited to those specific indications and claims for which there is sufficient data demonstrating that the active ingredient and PPP dosage form combination is safe and effective.

B. Statement of Grounds

1. The United States is losing the fight against the opioid epidemic and chronic pain.

Opioids have historically been prescribed not only for moderate-to-severe acute pain and chronic pain,[1] but also at concerning levels for mild acute pain and mild chronic pain.[2] Over the years, the U.S. healthcare system's reliance on opioid pain medication has led to the current terrible epidemic of deaths and hardship from opioid addiction and overdoses. Although the U.S. government has taken several important steps to address the opioid epidemic over the past several years,[3] the epidemic continues to get worse. More Americans are dying of opioid-related drug overdoses now than ever before.[4] And in addition to this terrible human toll, chronic pain has been estimated to cost the U.S. economy over 600 hundred billion dollars per year, to afflict at least 50 million Americans, and chronic pain causes additional hardships such as increased medical bills, mental anguish, and unemployment.[5]

2. External analgesics in PPP dosage form can play an important role in addressing and managing pain, but only with incentives in place to promote development of the data necessary to demonstrate safety and effectiveness.

Preventing new addiction by fostering the development of new non-opioid analgesics is an important ongoing priority for both the U.S. healthcare system and for the FDA,[6] as opioids are often prescribed due to a lack of proven alternatives.[7] FDA just recently issued a draft guidance document encouraging the development of non-opioid analgesics to manage acute pain (FDA

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[1] See, e.g., CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016, U.S. Centers for Disease Control and Prevention (CDC), March 18, 2016 (available at https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm) (noting, for example, that an estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription") and "Prescribing Opioids for Chronic Pain," Pocket Guide, CDC (undated) (available at https://www.cdc.gov/opioids/providers/prescribing/pdf/Prescribing-Opioids-Pocket-Guide.pdf) (noting, for example, that "Opioids can provide short-term benefits for moderate to severe pain. Scientific evidence is lacking for the benefits to treat chronic pain").

[2] See, e.g., Mohamad El Moheb et al., "Pain or No Pain, We Will Give You Opioids: Relationship Between Number of Opioid Pills Prescribed and Severity of Pain after Operation in US vs Non-US Patients," Journal of the American College of Surgeons, Vol. 231, Issue 6, 2020 (finding that the number of opioid prescriptions, number of pills, and oral morphine equivalents prescribed were similar across the 4 pain severity groups (none, mild, moderate, and severe) in US patients ($p > 0.05$)) and Robin L. Toblin et al., "A population-based survey of chronic pain and its treatment with prescription drugs," PAIN, Vol. 152, Issue 6, 2011 (finding that of the 33.4% of people studied with pain who use prescription pain medication, 45.7% took opioids, including 36.7% of those with mild pain).

[3] See, e.g., "White House Releases List of Actions Taken by the Biden-Harris Administration Since January 2021 to Address Addiction and the Overdose Epidemic," Biden-Harris Administration, Press release, January 18, 2022.

[4] See "Provisional Drug Overdose Death Counts," National Center for Health Statistics, U.S. Centers for Disease Control, January 2, 2022 (available at https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm) and "Drug Overdose Deaths in the U.S. Top 100,000 Annually," National Center for Health Statistics, U.S. Centers for Disease Control, November 17, 2021 (available at https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm).

[5] See, e.g., "The Financial and Emotional Cost of Chronic Pain", the U.S. Pain Foundation, September 29, 2021 (internal citations omitted)

[6] "FDA Takes Steps Aimed at Fostering Development of Non-Addictive Alternatives to Opioids for Acute Pain Management," FDA News Release, February 9, 2022.

[7] See, e.g., Penney, Lauren S et al. "Provider and patient perspectives on opioids and alternative treatments for managing chronic pain: a qualitative study." BMC family practice vol. 17,1 164. 24 Mar. 2017 (noting that, "While prescribing opioids is increasingly viewed as at odds with best practices for chronic pain management, there remains a lack of feasible alternatives").

Guidance for Industry: "Development of Non-Opioid Analgesics for Acute Pain," February 2022), and in the guidance the FDA emphasizes the importance of conducting well-designed clinical trials to generate the data necessary to demonstrate the safety and effectiveness of non-opioid analgesics for specific indications. If entire classes of non-opioid analgesics, such as external analgesic in PPP dosage form, were declared by FDA as generally recognized as safe and effective for managing acute or chronic pain or specific pain indications, without sufficient evidence of such, it would likely severely undercut future efforts to encourage the development of data that may demonstrate the safety and effectiveness of external analgesic in PPP dosage form for managing acute, chronic, and specific pain indications. Various studies have concluded that external analgesics may be viable pain management alternatives to opioids,[8] but at the same time these studies generally acknowledge that clinical studies and data are lacking and much needed.[9]

Moreover, although OTC external analgesics in PPP dosage forms do have a role to play in the management of aches and pains, confusion as to what specific external analgesics in PPP dosage form have been demonstrated to be safe and effective for which specific indications could lead to consumer and prescriber dillusionment with these products, and in turn drive these consumers and prescribers away from opioid alternatives and back to opioids.

3. External analgesics in PPP dosage form, except for a few exceptions, have not been generally recognized as safe and effective for the management of pain, nor for chronic or moderate-to-severe acute pain in particular.

External analgesics in PPP dosage form, except for a few products that have been approved through the new drug application process, have not been generally recognized as safe and effective for the management of pain, including chronic pain and moderate-to-severe acute pain. In 2003, the FDA formally recognized there was insufficient evidence to establish PPP dosage forms for external analgesics as GRASE.[10] Today, the available data continues to support the Agency's conclusion. For example, recent studies and literature reviews have determined that:

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[8] See, e.g., Gudin JA et al., "Changes in pain and concurrent pain medication use following compounded topical analgesic treatment for chronic pain: 3- and 6-month follow-up results from the prospective, observational Optimizing Patient Experience and Response to Topical Analgesics study," J Pain Res. 2017;10:2341-2354 (noting that although there is evidence topical analgesics may be safe and effective for managing pain, "randomized controlled trials [are] needed to confirm these findings") and CE Argoff, MD, "Topical Analgesics in the Management of Acute and Chronic Pain", Mayo Clin. Proc. Vol. 88, Issue 2, p195-205, February 01, 2013 (noting that "topical analgesic therapy using NSAIDs or lidocaine has an important place in the management of acute and chronic pain conditions and warrants further study" but also noting that outside of postherpetic neuralgia and diabetic neuropathy "limited evidence is available to support the use of other topical analgesics in acute and chronic pain.")

[9] Id.

[10] External Analgesic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record and Amendment of Tentative Final Monograph, 68 Fed. Reg. 42324, July 17, 2003 (concluding, "FDA has commented on the protocols and data, but has not found the information sufficient to support the safety and effectiveness of [PPP] dosage forms. Further, FDA is not aware of sufficient data to classify any OTC external analgesic active ingredient in a patch, plaster, or poultice dosage form as Category I. Accordingly, FDA is classifying all OTC external analgesic ingredients in a patch, plaster, or poultice dosage form in Category III (more data needed)" (68 Fed. Reg. 42324, 42325)).

- "Although patches offer advantages over oral analgesic medications, drawbacks to the use of topical analgesics exist, including local irritation or skin sensitization; interindividual variability of skin properties that can affect absorption (e.g., adult vs pediatric patients); limited availability of medications that can be delivered via this route of administration; inappropriateness of the topical route of administration for patients with decreased peripheral blood flow (e.g., Shock); and cost."[11]
- OTC lidocaine patches produce the highest lidocaine and metabolite, monoethylglycinexylidide (MEGX), levels compared to prescription lidocaine patches.[12]
- The concentration of lidocaine, the formulation of the drug, and the individual patient all have significant effects on serum levels of lidocaine, and OTC topical anesthetics should be used under the supervision of a healthcare professional to avoid adverse toxic effects and, in rare cases, death.[13]
- "There is a general lack of data regarding the safety, effectiveness, and pharmacokinetics of OTC lidocaine preparations."[14]
- "There is a paucity of studies evaluating menthol patches."[15]
- "Some transdermal products contain metallic backings, which can lead to excessive burns and local tissue damage if the patch is not removed prior to undergoing an MRI scan."[16]
- "There are very limited published clinical data on the use of [methyl salicylate] in conjunction with menthol [in topical patch dosage form]."[17]
- Medicated patches may retain up to 95% of the initial total amount of drug, even after the duration of use has passed, which can and has posed a risk to curious, unattended children.[18]
- The safety and efficacy of external analgesic drug products in a PPP dosage form can vary significantly based on the active ingredient, active ingredient concentration, and the design and composition of the PPP.[19]

The data currently available does not and cannot support scientifically sound bases for a meaningful OTC standard for external analgesics in PPP dosage form for moderate-to-severe acute pain and chronic pain. As FDA has recognized,[20] the CARES Act does not change the

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[11] Lisi D., "OTC Transdermal Analgesic Patches in Pain Management," US Pharm. 2019; 44(3):15-21.
[12] Oni G, Brown S, Kenkel J., "Comparison of five commonly-available lidocaine-containing topical anesthetics and their effect on serum levels of lidocaine and its metabolite monoethylglycinexylidide (MEGX),": Aesthetic Surgery J. 2012; 32(4):495-503.
[13] Id.
[14] Gudin J. & Nalamachu S. "Utility of lidocaine as a topical analgesic and improvements in patch delivery systems," Postgraduate Medicine, 2020; 132:1, 28-36.
[15] Lisi D., "OTC Transdermal Analgesic Patches in Pain Management," US Pharm. 2019; 44(3):15-21.
[16] Id.
[17] Lisi D., "OTC Transdermal Analgesic Patches in Pain Management," US Pharm. 2019; 44(3):15-21.
[18] Pastore MN, Kalia YN, Horstmann M, et al. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015; 172:2179-2209.
[19] See, e.g., Nalamachu S., Gudin J., "Characteristics of Analgesic Patch Formulations," J Pain Res. 2020; 13:2343-2354. Published 2020 Sep 22 (finding that, "Patches that are bioequivalent may deliver the same amount of drug, but can differ substantially in design, adhesive used, and properties such as the amount of drug in the patch and the amount of residue" and "attributes of these patch systems, that derive from their design and composition, affect the delivery of drug, and their efficacy and safety.")
[20] See, e.g., FDA Proposed Order POTC000008, "Amending Over-the-Counter (OTC) Monograph M020: Sunscreen drug products for OTC Human Use," at p. 4.

legal and scientific standards for assessing whether a drug is GRASE.[21] Data supporting a finding of GRASE must still include well-controlled clinical studies corroborated by other reliable data.[22] Further, the tentative final monograph (TFM) for external analgesics does not provide any meaningful basis to establish specific standards for PPP dosage forms, as the TFM provides only that the TFM does not apply to external analgesic active ingredients in a PPP dosage form, with few additional specific findings.

For all these reasons, this petition requests that the FDA issue the administrative order for OTC external analgesics as deemed final by section 505G of the FD&C Act, and that in the order the FDA confirm and clarify for which specific indications OTC external analgesic drug products in PPP dosage forms are GRASE (e.g., mild backpain or backache), and that the FDA further confirm and clarify in the order that submission of an application under FD&C Act section 505(b), 505(j), or potentially 505G is warranted for other indications. OTC external analgesics in PPP dosage form can serve an important purpose in the treatment of more mild aches and pain. However, the stakes are higher, and evidence of safety and effectiveness more lacking, when it comes to treating chronic pain (including mild chronic pain) and moderate-to-severe acute pain. In such cases in particular, strong and reliable evidence of safety and effectiveness must be required.

The sooner the FDA clarifies the specific indications for which external analgesics, particularly those in PPP dosage form, can be marketed without submission and approval of a new or abbreviated new drug application or submission an OTC drug administrative order request and FDA issuance of such order, all of which must be supported by well-controlled clinical studies corroborated by other reliable data and evidence of safety and effectiveness, the sooner the U.S. healthcare system and U.S. consumers may have additional non-opioid alternatives in their arsenal for safely and effectively managing pain in the U.S.

C. Environmental Impact

Petitioner claims a categorical exclusion under 21 CFR 25.30.

D. Economic Impact Statement

Petitioner will, upon request by the Commissioner, submit economic impact information.

[21] See FDCA 505G(k)(1) (providing that unless specified otherwise in the Cares Act, nothing in FDCA section 505G supersedes regulations establishing general requirements for nonprescription drugs, including in 21 CFR Part 330).
[22] See 21 CFR 330.10(a)(4) (Standards for safety, effectiveness, and labeling).

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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