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Re: Docket No. FDA-2022-P-0896

May 2, 2023

Dear Ms. Taylor:

This letter responds to your citizen petition (Petition), which the Food and Drug Administration (FDA or we) received on May 24, 2022. The Petition requests that:

> the FDA issue the administrative order for [over the counter (OTC)] external analgesics as deemed final by section 505G of the [Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. 355h)], and that in the order FDA confirm and clarify for which specific indications OTC external analgesic drug products in [patch, plaster, or poultice (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), [21 U.S.C. 355] or potentially 505G [of the FD&C Act] 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 (Petition at 1).[1]

In support of the requests, the Petition explains how external analgesics in PPP dosage forms can play an important role in addressing and managing pain and therefore may also help address the opioid epidemic, but only with incentives in place to promote development of the data necessary to demonstrate safety and effectiveness (Petition pp. 2-3). The Petition goes on to discuss that external analgesics in PPP dosage forms, except for a few exceptions, have not been GRASE and effective for the management of pain, nor for chronic or moderate-to-severe acute pain in particular (Petition pp. 3-4).

The Petition concludes that "the sooner the FDA clarifies the specific indications for which external analgesics, particularly those in PPP dosage forms, can be marketed without submission and approval of a new or abbreviated new drug application or submission [of] 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" (Petition p. 5).

[1] Petition at 1

We have carefully considered your Petition. However, for the reasons described below, we are not taking the requested actions at this time.

I. BACKGROUND

Your request is, in part, for FDA to "issue" the external analgesic final order as deemed by section 505G of the FD&C Act and to specify in that order "for which indications OTC external analgesic drug products in PPP dosage form[s] are generally recognized as safe and effective (GRASE)" (Petition p. 1). However, this request cannot be granted by FDA because it is inconsistent with the provisions of section 505G of the FD&C Act governing deemed final orders.

The Coronavirus Aid Relief and Economic Security (CARES Act)[2] added section 505G of the FD&C Act, which revised the framework for the regulation of OTC monograph drug products. Among other things, section 505G of the FD&C Act provides as a baseline status that, as of the date of enactment of the CARES Act, drugs that satisfy requirements described in section 505G(a)(1) or (2) are deemed to be GRASE under section 201(p)(1) of the FD&C Act (21 U.S.C. 321), not a new drug under section 201(p) of the FD&C Act, and not subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353). Complementary to the requirements described in section 505G(a)(1) and (2) of the FD&C Act, Congress, under section 505G(b)(8) of the FD&C Act, set the content of the initial OTC monograph final orders by providing that a final monograph or tentative final monograph that establishes conditions of use for a drug described in section 505G(a)(1) or (2) of the FD&C Act and that represents the most recently issued version of the conditions of use, including as modified, in whole or in part, by any proposed or final rule, is deemed to be a final order. Accordingly, Congress, not FDA has determined the content of the deemed final orders, including the deemed final order for external analgesics. FDA therefore does not have discretion in determining which conditions of use, including dosage forms and indications, are included as GRASE in the external analgesic deemed final order.

We note that although Congress established the content of the deemed final orders, FDA is making available the final orders as deemed by section 505G(b)(8) of the FD&C Act, including the external analgesic deemed final order. These deemed final orders are available on FDA's website at https://dps.fda.gov/omuf/monographsearch.[3] Please refer to the posted OTC external analgesic deemed final order, OTC000033,[4] for information on the conditions of use under

[2] On March 27, 2020, the CARES Act was signed into law. The CARES Act includes provisions that govern the way certain OTC drugs are regulated in the United States. In particular, the CARES Act added section 505G to the FD&C Act, which reforms and modernizes the OTC drug review process that was established in 1972. Under the OTC drug review, OTC drug monographs (also referred to as OTC monographs) for different therapeutic categories are established. OTC drugs are GRASE if they meet the conditions of an OTC monograph, including the specified active ingredients, uses (indications), dosage forms, routes of administration, labeling, and testing, along with other applicable requirements.

[3] 86 FR 52474 (September 21, 2021) available at https://www.govinfo.gov/content/pkg/FR-2021-09-21/pdf/2021-20393.pdf.

[4] OTC000033 available at https://www.accessdata.fda.gov/scripts/cder/omuf/index.cfm.

which OTC external analgesic drug products have been found to be GRASE in accordance with sections 505G(a)(1) and (b)(8) of the FD&C Act. The conditions of use in the deemed final order include the ingredients, dosage forms, and indications for which of these products are GRASE. Conditions of use for external analgesic drug products in PPP dosage forms were not included in OTC000033 because products in PPP dosage forms were not in category I in the most recently issued tentative final monograph setting forth the conditions of use for external analgesic drug products marketed under the OTC monograph prior to the enactment of the CARES Act.

II. DISCUSSION

In addition to the deemed final orders, section 505G(a)(3)(A) of the FD&C Act permits OTC drugs that were categorized in category III for safety and effectiveness under a tentative final monograph (and thus excluded from a deemed final order) to be legally marketed. Under the OTC drug review in place prior to the passage of the CARES Act, category III included those conditions that had insufficient data for FDA to propose whether they were GRASE. As noted in the Background section of the External Analgesic Deemed Final Order (see OTC000033), "in the Federal Register of July 17, 2003 (68 FR 42324), FDA amended the tentative final monograph to clarify the status of PPP dosage forms for OTC external analgesic drug products. FDA classified all OTC external analgesic ingredients in a PPP dosage form as Category III (more data needed)." Therefore, OTC external analgesic drug products that are marketed in PPP dosage forms and conform with the provisions of section 505G(a)(3)(A) of the FD&C Act may currently be legally marketed without an approved application, despite not being GRASE.

We understand the Petition to also request that FDA clarify "that submission of an application under sections 505(b) or 505(j) [of the FD&C Act, or submission of an OTC monograph order request under section 505G(b)(5) of the FD&C Act] is warranted for other indications" (Petition p. 2). As noted above, OTC external analgesic drug products in PPP dosage forms may currently be legally marketed under section 505G(a)(3)(A) of the FD&C Act, even though they are not included in the external analgesics deemed final order. In order to categorically amend the conditions under which OTC external analgesic drug products in PPP dosage forms are legally marketed under the OTC monograph (e.g., to narrow or expand permissible indications for use), FDA would need to proceed via the order process described in section 505G(b)(1) of the FD&C Act. Alternatively, requestors seeking to modify the conditions of marketing with respect to OTC external analgesics may submit a request under section 505G(b)(5)(B) of the FD&C Act to initiate administrative order proceedings. Individuals wishing to market external analgesic drug products in PPP dosage forms not under the OTC monograph may also submit an application for approval of a new drug under section 505 of the FD&C Act and FDA's regulations at part 314 (21 CFR part 314).

III. CONCLUSION

Based on the reasons above, we are denying the Petition. However, we recognize the need for safe and effective nonopioid alternatives for chronic pain or moderate-to-severe acute pain and welcome discussion with those seeking to begin drug development programs with respect to OTC external analgesic drug products in PPP dosage forms.

Sincerely,

Douglas C. Throckmorton S

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Director
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