



July 30, 2019

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Fixed-Quantity Unit-of-Use Blister Packaging for Certain Immediate-Release Opioid Analgesics for Treatment of Acute Pain; Establishment of a Public Docket; Request for Comment

Dear Sir/Madam:

The American Pharmacists Association (APhA) appreciates the Food and Drug Administration's request for comments ("RFC") regarding Fixed-Quantity Unit-of-Use Blister Packaging for Certain Immediate-Release Opioid Analgesics for Treatment of Acute Pain. APhA, founded in 1852 as the American Pharmaceutical Association, represents nearly 60,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, physician office practices, managed care organizations, hospice settings, and the uniformed services.

APhA supports legislative, regulatory, and private sector efforts to address our Nation's opioid epidemic as long as efforts to curb misuse are appropriately balanced with the legitimate needs of the millions of patients living with pain. According to the RFC, FDA is considering modifying the Opioid Analgesic Risk Evaluation and Mitigation Strategy (OA REMS) to require that certain solid, oral dosage forms of immediate-release (IR) opioid analgesics commonly prescribed for treatment of acute pain be made available in fixed-quantity unit-of-use blister packaging for outpatient dispensing. The RFC also indicates this change could reduce over-prescribing.

As FDA considers feedback from various stakeholders, we urge the agency to carefully consider potential unintended consequences of requiring fixed-quantity unit-of-use blister packaging for outpatient dispensing. Such consequences should be included in FDA's decision-making process, alongside the goal of reducing the amount of unused opioid analgesics. Should FDA proceed with implementing packaging or disposal-related REMS modifications, we urge the Agency to carefully coordinate efforts with a variety of stakeholders, including other government agencies (both Federal and state), pharmacists, system vendors, prescribers, and payers, among others.

1. Comment on the potential safety advantages and public health impact of broadly available, fixed-quantity unit-of-use blister packages of opioid analgesics for treatment of acute pain in adults.

Blister packages may serve various purposes. For example, they may help improve adherence, maintain quality (e.g., to prevent pills from sticking together), enhance distribution, and reduce diversion and the potential for counterfeit products.^{1,2} However, based on APhA's literature search, the strength of research supporting the role of blister packages in yielding each benefit varies. While there appears to be significant research supporting blister packages as a tool to improve adherence, less research is available regarding diversion reduction after the point of dispensing. It is also unclear whether research has been performed to determine whether fixed-quantity unit-of-use blister packages effect prescribing decisions. Given FDA's goal to address prescribing practices with blister packaging, APhA recommends FDA first study the effectiveness and intended and unintended consequences (including prescribing of alternative medications) of fixed-quantity unit-of-use blister packages on prescribing and related patient care.

APhA supports the role of the pharmacist to select appropriate drug product packaging. Pharmacists, as medication experts who work directly with patients, can help identify each patient's unique needs and recognize when these needs preclude use of fixed-quantity unit-of-use blister packages. Therefore, providing pharmacists and other health care practitioners with the ability to select customized packaging based on patient needs may improve medication safety, monitoring and adherence.

2. Comment on the specific IR opioid analgesic drug products for which it may be appropriate to require that blister packaging be made available, as well as the specific blister packaging configuration(s) it may be appropriate to require for each product or class of products, including the number of tablets or capsules to be included in the configuration(s). Specifically, please comment on the potential utility of the 5-, 10-, and 15-count configurations discussed in section.

APhA requests FDA clarify whether requiring "blister packaging be made available" means that all products with packaging as a component of the REMS will only be made available in such configurations, and whether the pharmacist would be required to dispense only packaged products. From the language in the notice, it is not clear whether FDA would envision implementing this requirement such that it would be up to the pharmacist to decide to dispense blister packaged products and/or the prescriber to require blister packaged products be dispensed. In addition, does the proposed requirement require the product from the manufacturer be provided in blister packaging or can a pharmacist package the medication themselves? APhA believes FDA needs to determine payers' perspectives regarding the additional cost for this packaging and reimbursement for these costs. Such information would help APhA consider the utility of the proposed packaging configurations.

¹ Conn, V.S., Ruppar, T.M., Chan, K.C., Dunbar-Jacob, J., Pepper, G.A. & DeGeest, S. (2015). Packaging interventions to increase medication adherence: systematic review and meta-analysis, *Curr Med Res Opin.* 31(1), 145-160.

² Inciardi, J.A., Surratt, H.L., Kurtz, S.P. & Cicero, T.J. (2007). Mechanisms for Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations, *Pain Med*, 8(2), 171-183.

As noted at the May 31 public meeting, a variety of blister packaging designs exist. For example, adherence packaging may indicate the day and/or time medications should be administered. In the question posed, it is unclear which of these designs would be most acceptable for an OA REMS. APhA requests FDA provide more information about the specific designs contemplated by the agency as this may help inform comments regarding the potential utility of the configurations most likely used in each configuration.

APhA members indicated configurations that are consistent with state limits could be helpful to pharmacists. However, benefits would not be born if these products are difficult to obtain or subject to limited distribution or high-cost. Also, variability in state limits would make implementation on a national level more difficult.

In addition, the quantity amounts are consistent with emerging recommendations for many types of surgeries.³ APhA also seeks clarification regarding how FDA intends to use evidence-based guidelines to help inform packaging. Better understanding the agency's plan would help inform our comments regarding specific information needed to be included in the configuration.

Given the risk of diversion associated with opioids and counterfeit products, APhA believes such packaging could help reduce diversion at different points in the supply chain, help patients determine whether others are misusing their prescriptions and potentially make it more difficult to produce counterfeit products. Such benefits may occur with any of the above count configurations.

3. Comment on what specific information regarding the safe and effective use of opioid analgesics would be most beneficial to include in blister packaging configurations of these products.

As noted above, APhA believes blister packaging can be helpful to patients, and pharmacists play an important role in educating patients about their medications. Should these products be provided to patients, APhA recommends the agency consider emphasizing components of labeling, such as information regarding use as needed for pain. APhA would be concerned with packaging that conveyed messaging to patients that is inconsistent with their prescription or suggestive that a patient is non-compliant if they do not use all opioids in the packaging.

In addition, APhA believes it is crucial FDA consider package design and related warnings or controls on blister packaging, in addition to the accompanying box. APhA members indicated some patients will remove the box and carry only the blister package. Therefore, FDA should consider how such packaging could be perceived by others and the patient.

Since blister packages are often used as a tool to promote adherence, APhA believes messaging, such as take "as needed" or in accordance with prescriber instructions could be

³ National Academy of Medicine, (July 2019) *Tapering Guidance for Opioids: Existing Best Practices and Evidence Standards*, slide 18, available at: <https://nam.edu/event/webinar-tapering-guidance-for-opioids-existing-best-practices-and-evidence-standards/>

emphasized to patients. Related to this, packaging and prepackaging could remind patients to dispose of the medication, even if there is some left and provided the recommended process for disposal. In addition, risks associated with the product (e.g., addiction, fatal and nonfatal overdose) would be beneficial to provide to patients.

4. When considering the relevant information needed to improve patient safety, APhA encourages FDA to identify strategies to provide pharmacists with indications or diagnosis codes on prescriptions. Such information would be relevant to pharmacists in their evaluation of the prescriptions. Often, pharmacists will receive a prescription with little context regarding the patient's condition or circumstances. Pharmacists are medication experts on care teams and receive more medication-related education and training than any other health care professional. Adding the indication or diagnosis code to the prescription will enable the pharmacist to better evaluate the appropriateness of the prescription and packaging. Comment on possible negative impacts of mandatory blister packaging, including any unintended consequences. For example, what steps could help ensure that the blister packaging contemplated here would not inadvertently lead to underprescribing for patients who need opioid analgesics to treat acute pain conditions and blister packs being inappropriately prescribed and/or dispensed to patients who may have difficulty accessing drugs contained in blister packaging?

APhA foresees several potential negative impacts of mandatory blister packaging. For example, mandatory blister packaging could detract from patient care, increase costs, create administrative burden in aligning prescriptions with package quantities, and create issues where coverage, corporate policy or state law differ in the amount of opioids that can be prescribed or dispensed. APhA's concerns are discussed in more detail below.

Patient Care

APhA believes it is crucial FDA carefully considers how such packaging will impact patient care. APhA is concerned FDA may be taking a one-size fits all approach when considering the number of different tablets or capsules to be included in the configurations. APhA appreciates the agency's attention to different prescribing guidelines but notes that even prescribing guidelines provide for clinical judgment and patient-specific factors that could impact the amount prescribed and treatment plan.⁴ For example, Table 1 in the RFC indicates a 5-count of tramadol 50mg would constitute a 1-day supply. However, it is not clear what patient factors were considered and whether these supplies would be perceived as being safe for all patient populations. Practitioners seeking to align their prescribing decisions with packaging may decide to underprescribe which could increase follow-up visits or overprescribing which runs counter to the purpose of the policy. In both circumstances, care is not personalized to the patient. APhA seeks clarity regarding what options will be available to health care practitioners when providing care to patients, including permitting dispensing of IR opioid prescriptions in

⁴ See Centers for Disease Control and Prevention, CDC Guidelines for Prescribing Opioids for Chronic Pain – United States, 2016, stating, “The lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8)... Some experts thought that because some types of acute pain might require more than 3 days of opioid treatment, it would be appropriate to recommend a range of ≤3–5 days or ≤3–7 days when opioids are needed.”

traditional packaging when patients needs vary from the quantities in fixed quantity blister packages.

Patient Access

APhA reiterates our concerns that blister packaging may not be appropriate for all patients and emphasizes the need to consider different access needs. Currently, as a service, some pharmacies create adherence packaging to help their patients. Under a mandatory packaging policy, a pharmacy could dispense products knowing that a patient will have trouble accessing the medication because of the packaging yet no alternative, or more user-friendly option would be available.

While FDA does not typically include cost in its decision-making process, APhA encourages the agency to consider how the likely increased costs of blister packages could impact patient access to medications. For example, with more controls and policies in place to monitor opioids, some APhA members have reported an increase in patients opting to pay out of pocket for their prescriptions. Anticipated cost increases can pose patient access issues, in addition to costing the health care system more when payers do cover these products. Formulary placement may also be impacted, which would also have patient access implications.

In addition, Federal and state laws, including those related to prescribing limits and emergency prescriptions, could result in quantities prescribed or dispensed that vary from packaging requirements under the OA REMS program. This could create patient access issues if the amount in the blister package varies from legal requirements or is not covered by payers.

Administrative Burden

One foreseeable issue is how pharmacists will respond to prescriptions that are inconsistent with the packaged configurations. APhA is aware that legislative and/or regulatory changes are needed to permit pharmacists to modify prescribed quantities to correspond with the amount available in a blister package. Communicating with the prescriber could be time-consuming, creating additional burden on pharmacists and prescribers, and also potentially increase costs from transaction fees should prescribers utilize electronic prescriptions.

While federal law has been passed regarding partial fills, state laws are variable regarding implementation and several states have not updated their laws or regulations to address partial fills. The Drug Enforcement Administration (DEA) has not updated regulations regarding partial fills which adds to the confusion regarding a pharmacists' responsibilities in the event of a partial fill.⁵ Therefore, FDA should not assume a pharmacist can independently reduce the amount of a prescription such that it is consistent with a blister package quantity.

⁵ See 21 CFR §1306.13 Partial Filling of Prescriptions, *stating* (a) The partial filling of a prescription for a controlled substance listed in Schedule II is permissible if the pharmacist is unable to supply the full quantity called for in a written or emergency oral prescription and he makes a notation of the quantity supplied on the face of the written prescription, written record of the emergency oral prescription, or in the electronic prescription record. The remaining portion of the prescription may be filled within 72 hours of the first partial filling; however, if the remaining portion is not or cannot be filled within the 72-hour period, the pharmacist shall notify the prescribing individual practitioner. No further quantity may be supplied beyond 72 hours without a new prescription.

According to a DEA presentation where the partial fill provisions of the Comprehensive Addiction and Recovery Act of 2016 (P.L. 114-198) were discussed, CARA provides “Additional Options for Patient/Practitioner if state law permits.”⁶ In addition, states or corporate policies may demand 3-day or 7-day limits, which are not adequately contemplated in the RFC. Consequently, APhA encourages FDA to work with DEA and states to identify strategies to reduce burdens on health care practitioners that would result from prescription quantities inconsistent with packaging amounts and to clarify requirements related to partial fills.

Technology

As FDA is likely aware, different standards and systems exist to help pharmacy and prescriber operations run effectively. Standards and software systems, such as those related to electronic prescribing, electronic prior authorization and billing, and pharmacy and medical records, may need to be updated to reflect new packaging options. Such updates take time and coordination among many different stakeholders. Therefore, FDA may need to consider this when imposing requirements on application holders.

Pharmacy Inventory

As FDA is likely aware, DEA and states impose certain requirements regarding a pharmacy’s inventory. Blister packaging of products will increase the amount of space needed to store such products and may make certain products stand out should the pharmacy conceal them by dispersal throughout their stock of noncontrolled substances.⁷ Such changes may make it more difficult for pharmacies to comply with certain DEA and/or state requirements.

(b) A prescription for a Schedule II controlled substance written for a patient in a Long Term Care Facility (LTCF) or for a patient with a medical diagnosis documenting a terminal illness may be filled in partial quantities to include individual dosage units. If there is any question whether a patient may be classified as having a terminal illness, the pharmacist must contact the practitioner prior to partially filling the prescription. Both the pharmacist and the prescribing practitioner have a corresponding responsibility to assure that the controlled substance is for a terminally ill patient. The pharmacist must record on the prescription whether the patient is "terminally ill" or an "LTCF patient." A prescription that is partially filled and does not contain the notation "terminally ill" or "LTCF patient" shall be deemed to have been filled in violation of the Act. For each partial filling, the dispensing pharmacist shall record on the back of the prescription (or on another appropriate record, uniformly maintained, and readily retrievable) the date of the partial filling, quantity dispensed, remaining quantity authorized to be dispensed, and the identification of the dispensing pharmacist. The total quantity of Schedule II controlled substances dispensed in all partial fillings must not exceed the total quantity prescribed. Schedule II prescriptions for patients in a LTCF or patients with a medical diagnosis documenting a terminal illness shall be valid for a period not to exceed 60 days from the issue date unless sooner terminated by the discontinuance of medication.

(c) Information pertaining to current Schedule II prescriptions for patients in a LTCF or for patients with a medical diagnosis documenting a terminal illness may be maintained in a computerized system if this system has the capability to permit:

(1) Output (display or printout) of the original prescription number, date of issue, identification of prescribing individual practitioner, identification of patient, address of the LTCF or address of the hospital or residence of the patient, identification of medication authorized (to include dosage, form, strength and quantity), listing of the partial fillings that have been dispensed under each prescription and the information required in [Sec. 1306.13\(b\)](#).

(2) Immediate (real time) updating of the prescription record each time a partial filling of the prescription is conducted.

(3) Retrieval of partially filled Schedule II prescription information is the same as required by Sec. [1306.22\(b\)\(4\)](#) and (5) for Schedule III and IV prescription refill information.

⁶ See Drug Enforcement Administration, (Dec. 2017). *Dispensing Controlled Substances for Narcotic Drug Treatment*, available at: https://www.deadiversion.usdoj.gov/mtgs/drug_chemical/2017/miller3.pdf, last accessed: July 24, 2019.

⁷ 21 CFR 1301.75 (b) “(b) Controlled substances listed in Schedules II, III, IV, and V shall be stored in a securely locked, substantially constructed cabinet. However, pharmacies and institutional practitioners may disperse such substances throughout the stock of noncontrolled substances in such a manner as to obstruct the theft or diversion of the controlled substances.”

In addition, APhA notes ordering and stocking multiple fixed-quantity packaging could be burdensome for pharmacies, especially since there are already extra requirements for procuring and storing opioids already. In addition, it could be difficult for pharmacies to predict demands for products in each packaging configuration. With lower reimbursement and the desire to stock minimal levels of opioids and turnover stock quickly, such packaging could make it difficult for pharmacies to meet patient needs and provide care.

Generics

Another potential challenge is considering how generic products will be approved should such packaging requirements be included in REMS. APhA requests clarity from FDA regarding this issue.

Safety Alerts

APhA notes several payers, including Medicare, have implemented different types of safety alerts depending on a patient's opioid prescription(s). Fixed-quantity packaging may result in an influx of alerts, especially where prescribers opt for a higher quantity.

5. Comment on the potential challenges, including technical and logistical challenges, with the potential blister packaging requirement. What factors could impact application holders' ability to produce blister packaging of the type described in this notice?

Although not related to an application holder, pharmacists may encounter challenges obtaining products should application holders face challenges in producing blister packaging. Packaging that is excessively costly or available through a small subset of distributors would also pose a challenge for pharmacies in obtaining such products.

Different quantities of products in packages could be challenging since it is anticipated the pharmacist would not be able to dispense an amount different than that in the blister packaged saleable unit and the pharmacist would not be able to modify the quantity dispensed. A framework where products were blister packaged but the pharmacist could modify the quantity dispensed or package products in store could pose fewer logistical and technical challenges. Determining whether such blister packaging would broadly affect application holders' ability to comply would be relevant before imposing such a requirement to prevent patient access issues should cost or packaging infrastructure limitations impact manufacturing.

6. How much time would be needed for application holders to submit prior approval supplements for blister packaging that would satisfy the proposed REMS requirements discussed in section II.C? How much time would be needed for an application holder to develop REMS-compliant packaging and manufacture sufficient quantities to perform the stability and other product quality testing necessary to support the approval of a PAS, and how much time would be needed to perform such testing? How much time after approval

of a PAS would be needed for an application holder to manufacture and make the product commercially available?

APhA recommends FDA pilot test the effectiveness of different potential iterations of REMS requirements before considering different application holders' submissions. In addition, APhA notes the above mentioned potential consequences and challenges that should also be considered before products are made commercially available. APhA also strongly recommends FDA engage impacted stakeholders throughout the testing and implementation process.

7. Comment on the idea of implementing a blister packaging mandate in a staggered fashion, targeting the products most commonly prescribed to treat acute pain first, as well as the idea of imposing a conditional mandate for discontinued products. Are there other ways the Agency could consider staggering implementation of this requirement to minimize burden on manufacturers and other stakeholders, while maximizing the public health benefit?

APhA recommends FDA pilot test the effectiveness of different potential iterations of REMS requirements before considering different application holders' submissions and potential implementation structures. Information learned from pilot tests could help determine the role blister packaging has on patients, pharmacists and prescribers, among other stakeholders. It is unclear how implementing blister packaging in a staggered fashion would impact patient access or care since patients', healthcare practitioners' and other stakeholders' responses to these products in blister packages has not been tested.

A staggered roll out could impact prescribing decisions but could also have implications on formulary placement or coverage.

8. Comment on how the OA REMS modification could be designed and implemented to help ensure that required blister packaging is sufficiently available. Comment on the impact of any opioid analgesic blister packaging requirement on other stakeholders, including prescribers, payers, and pharmacies. What steps could be taken to help encourage uptake and mitigate any adverse impacts associated with such a mandate?

APhA urges FDA to gain information from users and to pilot blister packaging before implementing changes more broadly. APhA believes this is an important step that could be taken to help mitigate adverse impacts associated with such a mandate.

As noted above, should FDA proceed with making blister packaging available as part of the OA REMS, the program must be made flexible as not to force prescribing and/or dispensing decisions or quantities. APhA recommends FDA also consider the impact variable blister packages has on pharmacies' inventory and subsequent patient access issues.

Also noted above, APhA reiterates the need for FDA to carefully and thoughtfully coordinate efforts with DEA and states, especially those who have imposed restrictions related to opioids. Significant work at all levels (e.g., Federal, state, employers, payers) has been done and is in progress to address the opioid epidemic by improving prescribing and dispensing practices. State and Federal laws have changed which our members are working to learn and comply with

to serve their patients most effectively. It is important FDA is sensitive to these changes and the broader healthcare environment as it seeks to implement this new policy.

9. As noted, FDA recognizes that the approach described in this notice is only one possible use of the Agency's REMS authority concerning packaging. Comment on other possible uses of this authority.

APhA believes FDA could test different types of packaging as it considers the scope of its authority. There are many different packaging options available, including different points when packaging may occur. Products can be packaged and depending on the goals, different packaging configurations may be utilized. APhA encourages FDA to identify different packaging designs and engage in user testing and pilots to better understand real-world implications. Also, APhA notes the important role pharmacies play in packaging, particularly to improve adherence and address patient-specific needs.

10. Other potential mandates

In the RFC, FDA indicates it is considering other potential mandates, including mail-back pouches or other safe disposal options. APhA strongly supports safe disposal of opioids to prevent diversion and appreciates FDA's efforts to update resources it provides to clarify patients could consider flushing certain products if a drug take-back location is not readily available. Like FDA, APhA is aware of many different disposal options, some of which include ongoing disposal programs (e.g., pharmacy take-back receptacles).

APhA encourages pharmacists to expand patient access to secure, convenient, and ecologically responsible drug disposal options, however, ongoing costs can make it difficult for pharmacies to provide this option to patients at no cost. While recently enacted Federal legislation provides some funding to support such disposal options, broader and more consistent funding could help increase availability of disposal options within different health care facilities, such as pharmacies.

Alternatively, requiring pharmacies to regularly stock specific disposal options for certain products could pose storage issues, and it is unclear who would bear the cost of providing such products. A policy that would prevent a medication from being dispensed absent a certain disposal option could have negative implications for patient access if the pharmacy is unable to provide the disposal option at the time of dispensing. APhA would be concerned with any disposal mandate that shifts costs to pharmacies and could impede patient access to medications.

Lastly, APhA encourages FDA to gather information regarding patient use of different disposal options to determine their effectiveness in limiting availability of unused medications before mandating specific requirements. For example, it may be helpful to learn whether patients utilize mail-back envelopes. To the extent possible, should certain disposal options be included in a REMS program, APhA encourages FDA to identify strategies to determine their effectiveness in decreasing the amount of unused opioids available within households.

Thank you for the opportunity to provide comments in response to the RFC. APhA believes it is imperative that a proper balance be maintained in delivering appropriate pain

management for the millions of patients with legitimate needs for opioids while taking steps to minimize and prevent misuse and abuse. As you move forward, please do not hesitate to use APhA as resource. If you have any questions or require additional information, please contact Jenna Ventresca, Director, Health Policy, at jventresca@aphanet.org or by phone at (202) 558-2727.

Sincerely,

A handwritten signature in black ink that reads "Thomas E. Menighan". The signature is fluid and cursive, with "Thomas E." on the first line and "Menighan" on the second line.

Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO