



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-1845]

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 Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the establishment of a docket to solicit public comment on a potential modification to 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. This could reduce the amount of unused opioid analgesics, thereby reducing opportunities for misuse, abuse, inappropriate access, and overdose, and possibly reducing the development of new opioid addiction.

DATES: Submit either electronic or written comments by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before

[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL*

***REGISTER*]**. The <https://www.regulations.gov> electronic filing system will accept comments

until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2019-N-1845 for “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 Comments.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover

sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public docket, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6260, Silver Spring, MD 20993, 301-796-3522, Patrick.Raulerson@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In 2017, opioid-involved overdoses killed more than 47,000 people, with more than a third of those deaths involving prescription opioids (Ref. 1). The volume of prescription opioid analgesics dispensed has decreased from a peak in 2012 and continues to trend downward. However, opioid analgesics continue to be prescribed at a high rate--an estimated 196 million retail prescriptions, resulting in an estimated 13 billion units (e.g., tablets or capsules) dispensed in 2017 from U.S. outpatient retail pharmacies (Ref. 2). Approximately 89 percent of people who report misuse or abuse of prescription opioid pain relievers state they obtained their most

recently used drugs from their own prescriptions or from a friend or relative (Ref. 3). In addition, many people who begin with misuse or abuse of prescription opioids transition to illicit substances (Refs. 4 to 7).

Accordingly, FDA's efforts to address the opioid crisis will continue to include a focus on encouraging rational, "right-size" prescribing of opioid analgesics. This includes efforts aimed at reducing both the number of people unnecessarily exposed to opioid analgesics (either through legitimate prescriptions or due to inappropriate access) and encouraging healthcare providers to prescribe amounts that better reflect the quantity expected to meet the needs of the patient with acute pain. At the same time, we must help ensure appropriate access to opioid analgesics to address the medical needs of patients experiencing acute pain severe enough to require opioid analgesic treatment.

The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act), signed into law on October 24, 2018, provides FDA several new authorities to address the opioid crisis. The new law allows FDA to require certain packaging and disposal systems under a REMS for opioids and other drugs that pose a serious risk of abuse or overdose if, among other things, FDA determines that such packaging or disposal system may mitigate such risks (see section 505-1(e)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1(e)(4))). The purpose of this notice is to seek public comment on application of this new authority, including the potential application of this authority to require under the OA REMS that certain solid oral dosage forms of IR opioid analgesics commonly used to treat acute pain be made available in fixed-quantity unit-of-use blister packaging for outpatient dispensing.

FDA recognizes that the fixed-quantity unit-of-use blister packaging requirement the Agency is considering as part of the OA REMS is just one possible application of FDA's new authorities related to packaging and disposal. We are considering, and invite comment on, other potential mandates, including mail-back pouches or other safe disposal options. Furthermore, we actively encourage drug manufacturers and others to innovate in this space. We are aware of many promising packaging and disposal technologies that could have a positive impact on reducing misuse, abuse, inappropriate access, accidental poisoning, or overdose, or could otherwise facilitate the safe and appropriate use of prescription opioid analgesics. We believe that the potential packaging requirement outlined here could be a significant and readily achievable step towards improving the safe use of opioids, one that could be supplemented in the future by other safety-enhancing measures.

FDA is establishing this docket to solicit input from stakeholders on all aspects of this potential requirement under the OA REMS, including comments on specific questions posed in section III.

II. Fixed-Quantity Unit-of-Use Blister Packaging for Certain IR Opioid Analgesics for Treatment of Acute Pain

In this section, we describe data suggesting that many patients who are prescribed an opioid analgesic to treat acute pain use substantially fewer units of the drug than they receive, resulting in millions of excess opioid analgesic tablets and capsules dispensed every year. We then describe a potential requirement, as part of the OA REMS, that fixed-quantity unit-of-use blister packs for certain IR opioid analgesics be made available to be dispensed in the outpatient setting. We discuss how these proposed new packaging configurations could encourage more appropriate prescribing, reducing the amount of unused opioid analgesics available for misuse,

abuse, inappropriate access, and accidental poisoning or overdose. We also discuss other potential safety benefits associated with blister packs.

A. Actual Opioid Use Compared to Prescribed Amounts for Common Surgical Procedures and Other Conditions that Cause Acute Pain

FDA has reviewed published studies that compared the amount of opioid analgesics patients received to treat their acute pain with their reported actual use after several common surgical procedures. Most of these studies focused on opioid-naïve adults. *Opioid-naïve* is defined in various ways across the studies; one common definition is a patient who filled no opioid analgesic prescriptions in the prior 12 months. We also analyzed patterns of additional fills after an initial opioid analgesic prescription fill for acute pain in post-surgical and primary care settings. We define an *additional fill* as a second prescription fill for an opioid analgesic in a short period after the first fill.

In the post-surgical setting, following several common minimally or less-invasive surgical procedures,¹ most opioid-naïve adults who used an opioid analgesic appeared to use only 1 to 3 days' worth, or 15 or fewer, opioid analgesic tablets or capsules despite receiving prescriptions exceeding the number they used (Refs. 8 to 11). Patients reported that they usually retain these unused tablets or capsules and store them in unsecure locations (Ref. 8), providing opportunities for later misuse, abuse, inappropriate access, and accidental poisoning or overdose.

For example, after a less-invasive cholecystectomy, the median number of opioid analgesic tablets prescribed to treat pain was 18, even though 75 percent of patients used 9 or

¹ These surgical procedures included dermatologic surgery, carotid endarterectomy, inguinal/femoral hernia repair, breast lumpectomy, partial mastectomy, parathyroidectomy, thyroidectomy, vaginal or laparoscopic hysterectomy, laparoscopic cholecystectomy, laparoscopic colectomy, laparoscopic appendectomy, small-bowel resection/enterolysis, minimally-invasive prostatectomy, knee arthroscopic meniscectomy, tooth extraction, bunionectomy, carpal tunnel release, ovarian cancer cytoreduction, breast lumpectomy, and arteriovenous fistula creation.

fewer tablets (each tablet equivalent to an oxycodone 5 milligram (mg) dose). Of the 75 percent of patients who used 9 or fewer tablets, 35 percent reported using no opioids (Ref. 10). In an FDA analysis of surgical procedures in opioid-naïve adults, our model estimated that less than 20 percent of patients undergoing laparoscopic cholecystectomy might need an additional fill if they were given a 1-day supply of an opioid analgesic, but the median days actually supplied to patients was 4, with a median of 30 tablets per prescription filled (Ref. 11).

The unused tablets from each opioid analgesic prescription for a common surgical procedure such as cholecystectomy--there were an estimated 950,000 cholecystectomies in community hospitals in the United States in 2014 (Ref. 12)--contribute significantly to the number of unused tablets available for misuse, abuse, inappropriate access, and accidental poisonings or overdose. In our analyses of opioid analgesic prescription fills after surgical procedures and published studies in which patients were asked about their opioid analgesic use after surgical procedures, we also found that about 30 percent of patients either never filled their prescriptions or filled them but did not actually consume any of the tablets or capsules following several types of minimally or less-invasive surgical procedures (e.g., laparoscopic cholecystectomy, laparoscopic hysterectomy, laparoscopic appendectomy) (Refs. 10 and 13).

We observed a similar pattern of prescribing more than patients appeared to use for several other common non-surgical acute pain conditions in the primary care setting. For example, for headaches, muscular strains and sprains, and certain forms of acute back pain, in our modeling of additional fill patterns, most patients could be expected to only need an opioid analgesic for up to 3 days, but they often received enough doses to treat pain for a significantly longer period (Ref. 14).

B. Proposal: 5-, 10-, and 15-Count Blister Packages of Certain IR Opioid and IR Opioid/Acetaminophen Products

As discussed above, we have found that for many common, minimally or less-invasive surgical procedures and some common acute pain conditions treated in the primary care setting for which opioid analgesics are prescribed, we expect most opioid-naïve adult patients to use significantly fewer tablets or capsules than the average prescription has historically provided. Most of these patients appeared to use an opioid for 1 to 3 days and used 15 or fewer tablets or capsules when they used an opioid analgesic to treat their pain.

Accordingly, we anticipate that if 5-, 10-, and 15-count blister package configurations of certain IR opioid analgesics commonly used for treatment of acute pain were made available, one or more of these options could be expected to meet the needs of most opioid-naïve adults who require opioid therapy following many common minimally or less-invasive procedures and other acute pain conditions for which opioid analgesics are prescribed. We further anticipate that utilization of these fixed-quantity unit-of use blister package configurations would substantially reduce the quantity of opioid analgesics dispensed per prescription compared to the status quo. Table 1 below compares the morphine milligram equivalent (MME) of 5-, 10-, and 15-count packaging of seven commonly prescribed opioid analgesic products to the mean MME and mean number of tablets per “new-to-therapy start prescriptions” (NTS Rx) dispensed in 2017. This table illustrates the potential for utilization of fixed-quantity unit-of-use blister packages to substantially reduce the amount of opioid analgesics prescribed for opioid-naïve patients receiving prescriptions for seven commonly prescribed products.

Table 1.--5-, 10-, and 15-Count Packages by MME Content/Package Compared to Mean MME and Mean Tablets per NTS Rx[±] Dispensed in 2017

	MME per Package			2017 NTS Rx	
	5-Count (1 days*)	10-Count (2 days*)	15-Count (3 days*)	Mean MME/ NTS Rx	Mean Tabs/ NTS Rx
Oral Tablets					
Hydrocodone 5 mg/APAP 325 mg	25	50	75	108	22
Tramadol 50 mg	25	50	75	180	36
Oxycodone 5 mg/APAP 325 mg	37.5	75	112.5	199	27
Codeine 30 mg/APAP 300 mg	22.5	45	67.5	96	21
Hydrocodone 7.5 mg/APAP 325 mg	37.5	75	112.5	192	26
Hydrocodone 10 mg/APAP 325 mg	50	100	150	393	39
Oxycodone 5 mg	37.5	75	112.5	261	35

²New to Therapy Start Prescriptions (NTS Rx): Nationally estimated number of first opioid analgesic prescriptions dispensed to patients with no opioid analgesic dispensed in previous 12 months. Source: IQVIA, National Prescription Audit New To Brand (NPA NTB), year 2017. Extracted January 2019.

*Days' supply does not correlate well with the number of units to package, estimated days supply based on around-the-clock dosing of 1-2 tablets every 4-6 hours PRN.

MME Estimates based on CMS's Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors. Accessed at <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf>.

Our analyses revealed that the number of days for which opioids are prescribed or used does not correlate well with a specific number of tablets or capsules per day, as what is considered an appropriate amount of an opioid analgesic for a day's worth of treatment varies across procedures and patients. This type of variation is reflected in the labeling of IR opioid analgesics, which describes the need to individualize dosing regimens based on patient treatment goals. Accordingly, we are considering requiring that applicants or application holders make available 5-, 10-, and 15-count blister pack configurations without prespecifying that any of these given configurations constitutes an appropriate amount of opioid analgesic for a specified duration, such as a specific number of days of treatment. Rather, we anticipate that prescribers would use their expertise and consult appropriate prescribing guidelines to determine which, if any, of the newly available blister packages is appropriate for their patients on a case-by-case basis.

We note that several existing prescribing guidelines recommend outpatient days of treatment or quantity of tablets or capsules for common minimally or less-invasive surgical

procedures or acute pain conditions treated in primary care and emergency department settings that are in line with our proposal for 5-, 10-, and 15-count packages of certain IR opioid analgesics (Refs. 15 to 21). Additionally, section 3002 of the SUPPORT Act requires FDA to develop evidence-based opioid analgesic prescribing guidelines for the indication-specific treatment of acute pain only for the relevant therapeutic areas where such guidelines do not exist. These guidelines, once available, should help to encourage more appropriate, “right-sized” opioid analgesic prescribing. We anticipate that these prescribing guidelines, as well as prescribing guidelines developed by others, would provide appropriate recommendations regarding the use of blister pack configurations made available pursuant to an OA REMS packaging requirement, facilitating prescriber understanding and uptake of such product packaging configurations.

C. New Packaging/Disposal REMS Element

Section 3032 of the SUPPORT Act amends FDA’s REMS authority. Specifically, as a part of a REMS, FDA may now require that a drug for which there is a serious risk of an adverse event occurring from abuse or overdose be made available for dispensing to certain patients in unit-dose packaging, packaging that provides a set duration, or another packaging system that FDA determines may mitigate such serious risk (21 U.S.C. 355-1(e)(4)). FDA may also require that such drugs be dispensed to certain patients with a safe disposal packaging or safe disposal system for purposes of rendering drugs non-retrievable if FDA determines that such safe disposal packaging or system may mitigate a serious risk of an adverse event occurring from abuse or overdose of the drug and is sufficiently available (see section 505-1(e)(4) of the FD&C Act).

A packaging or disposal requirement under this provision is applicable to prescription drugs that are the subject of applications approved under section 505(b) of the FD&C Act (21

U.S.C. 355(b)) or section 351 of the Public Health Service Act (42 U.S.C. 242), as well as drugs that are the subject of abbreviated new drug applications (ANDAs) approved under section 505(j) of the FD&C Act if a packaging or disposal requirement is required for the applicable listed drug (see section 505(i)(1)(B) of the FD&C Act). The law provides that FDA will permit packaging systems and safe disposal packaging or safe disposal systems for drugs that are the subject of ANDAs that are different from those required for the applicable listed drugs (see section 505(i)(2)(B) of the FD&C Act). FDA must take into consideration the burden on patients' access to the drug and the burden on the healthcare delivery system that would be associated with any such packaging or disposal requirement and must consult with other relevant Federal Agencies with authorities over drug disposal packaging in certain circumstances (see section 505-1(e)(4) of the FD&C Act).

FDA is contemplating using this new authority to require fixed-quantity unit-of-use blister packaging for certain IR opioid analgesics under the OA REMS, as described in this notice. For purposes of soliciting comments, FDA is considering the following general process for any packaging requirement under the OA REMS.

First, for already-approved opioid analgesic products, FDA would notify the application holders by letter that the Agency is requiring a modification to the OA REMS to include a packaging requirement. The notification letter would set forth details of the required modification, including the specific products subject to the new requirement, the number of blister packaging configurations required for each product and the number of units in each, key information regarding safe and effective use of opioid analgesics to be printed on the blister packaging, and other data and information needed for FDA to review and approve new blister package configurations (e.g., stability data).

Second, the application holders subject to the OA REMS would submit a proposed REMS modification within 120 days or such other reasonable time as FDA specifies. FDA anticipates that the proposed OA REMS modification would include all necessary specifications and timeframes for the blister packages. FDA would expect for the notification letters, the proposed REMS modifications, and the REMS approval to be sufficiently general that they are uniform across all affected application holders and products, to the extent possible.

Third, the application holders of products that are subject to the blister packaging requirement would individually submit a prior approval supplement (PAS) to their respective applications to obtain approval of the new packaging configurations.

For new drug applications (NDAs) or ANDAs for opioid analgesics that have not yet been approved, FDA anticipates that it would work with applicants at an appropriate stage in the application process to discuss blister packaging configurations that should be included as a part of the application to comply with the REMS.

FDA is also considering whether a staggered blister packaging requirement, a conditional requirement, or both would be appropriate. First, we are considering whether it may be appropriate to first require blister packages be made available for the most commonly prescribed IR opioid analgesics for treatment of acute pain, and then to require the blister packages be made available for other, less commonly prescribed products. In table 2, FDA has identified four opioid analgesics, alone or in combination with acetaminophen, formulated as seven specific drugs at specific strengths, that together account for almost 90 percent of all NTS Rx.²

² These data reflect recent dispensing patterns and should not be interpreted as appropriate starting doses for opioid-naïve patients. The data may include patients who are not, in fact, opioid-naïve because they received opioids not captured in the database (e.g., inpatient or emergency room prescribing).

Table 2.--Nationally Estimated Number of First Opioid Analgesic Prescriptions Dispensed to Patients with No Opioid Analgesic Prescription Dispensed in Previous 12 Months from U.S. Outpatient Retail Pharmacies

Oral Solid Formulations	Prescriptions Dispensed as "New to Opioid Analgesic Patients" Year 2017			
	NTS Rx*	%	Tab	%
Total New to Opioids Prescriptions	34.4M	100%	937M	100%
Hydrocodone 5 mg/APAP 325 mg	11.2M	32%	242M	26%
Tramadol 50 mg	5.8M	17%	208M	22%
Oxycodone 5 mg/APAP 325 mg	4.7M	14%	126M	13%
Codeine 30 mg/APAP 300 mg	4.6M	13%	98M	10%
Hydrocodone 7.5 mg/APAP 325 mg	2.7M	8%	69M	7%
Hydrocodone 10 mg/APAP 325 mg	1.4M	4%	55M	6%
Oxycodone 5 mg	1.3M	4%	46M	5%
All Others	2.7M	8%	92M	10%

Source: IQVIA, National Prescription Audit New to Brand (NPA NTB), year 2017. Extracted January 2019.

*New-to-Therapy Start Prescriptions (NTS Rx): Nationally estimated number of first opioid analgesic prescriptions dispensed to patients with no opioid analgesic dispensed in previous 12 months.

Starting with these products could help expedite the availability of blister packs for products in a way that could have the greatest public health impact, based on current prescribing patterns.

We are continuing to consider the potential public health consequences of requiring these specific products to be made available in fixed-quantity unit-of-use blister packages, and, if so, in what specific configurations, including the precise number of units to be included in each configuration. We are also continuing to consider for which other products, in addition to those identified in table 2, it could be appropriate to mandate blister packaging, and, if so, in what specific configurations. We recognize that the products in table 2 do not represent the lowest available strengths available for opioid analgesics. For example, although hydrocodone 2.5 mg/325 mg acetaminophen combination products are available, they accounted for less than 0.1 percent of total prescriptions dispensed to patients with no previous opioid analgesic prescription dispensed in the prior 12-month period. Additionally, we note that the proposed

fixed-quantity unit-of-use blister packages containing hydrocodone 10 mg would have a substantially higher MME than the other products on this list in the same quantities.

Furthermore, we are considering whether it may be appropriate to impose only a conditional mandate on approved but discontinued products, whereby the application holders of such products would only need to seek approval to produce blister package configurations of those products if they decide to reintroduce them to the market. This would reduce the burden on both application holders and FDA associated with the production and evaluation of blister package configurations for products that may not ever be marketed.

Finally, we are considering what measures may be appropriate to help ensure that blister packaging required as part of the OA REMS is sufficiently available in the market. How could the REMS be designed to set bright-line and evenhanded standards for the availability of blister packages and facilitate the Agency's ability to monitor compliance? For example, should FDA consider requiring that a certain fraction of marketed product be in blister package configurations to encourage the broader use of these products, or that the application holder continually has product available for sale in the required blister package configurations? Should FDA consider requiring that application holders periodically report on the production and uptake of their blister package configurations?

D. Safety-Enhancing Benefits of Fixed-Quantity Blister Packaging for Opioid Analgesics for Treatment of Acute Pain

The availability of fixed-quantity unit-of-use blister packages for certain IR opioid analgesics dispensed in the outpatient setting could help encourage and facilitate more rational “right-size” opioid analgesic prescribing by providing a range of convenient options to prescribers that corresponds well with the expected needs of many opioid-naïve patients with

acute pain. The availability of such product configurations could help “nudge” prescribers to more carefully consider prescribing an amount of opioid analgesics better matched to the patient’s needs. We anticipate that opioid prescribing guidelines, including those required to be developed under the SUPPORT Act, will provide appropriate recommendations regarding the use of any available blister packaging configurations. Furthermore, assuming these configurations are on their drug formularies, prescribers could readily select one of these configurations in computer physician order entry systems. Of course, prescribers will continue to exercise their clinical judgement to prescribe opioid analgesics in the quantity appropriate for a given patient; the blister packaging configurations contemplated in this notice would not be required to be the only packaging option available for these products.

In short, FDA anticipates that the widespread availability of fixed-quantity unit-of-use blister packaging could play a significant role in reducing overprescribing that leads to unused opioid analgesics without impairing access to opioid analgesics for patients who need them. Unused opioid medication is often retained and stored in unsecure locations (Ref. 8) where it can be accessed for prescription opioid analgesic misuse and abuse. Reducing the amount of unused opioid analgesics reduces opportunities for misuse, abuse, inappropriate access, or overdose, and could reduce the development of new addiction.

In addition, blister packaging could help reduce the incidence of accidental childhood poisoning. FDA expects that, for blister packaging that may be required under the OA REMS, each tablet or capsule would be individually protected with child-resistant packaging,³ making it harder for a child to be exposed to a toxic or lethal dose compared to a child-resistant pill bottle

³ All drugs consisting in whole or in part of a controlled substance in a dosage form intended for oral administration must be in child-resistant packaging (see 16 CFR 1700.14(a)(4), 16 CFR 1700.15; see generally 15 U.S.C. 1471-76, 16 CFR part 1700).

in the event that the child-resistant packaging is defeated. That is, even if a child accesses one of the tablets or capsules (for example, from a broken seal on a blister pack well), the remaining tablets or capsules would remain sealed. Furthermore, blister packaging offers passive protection with no further intervention required from an adult to keep the packaging child resistant. In contrast, when an adult opens a child-resistant pill bottle, he or she must take an additional step to close the cap properly to prevent a child from accessing the contents.

Blister packaging can also be designed to include additional information regarding the safe and appropriate use of the drug. If this information were printed on the blister packaging itself, it could not be easily separated from the drug nor could it be easily discarded. As such, blister packaging presents an opportunity to educate patients each time the drug is administered, potentially improving patient understanding of and compliance with key information regarding appropriate dosing, storage, disposal, or other important information regarding the safe and appropriate use of opioid analgesics. FDA is continuing to consider what information concerning the safe and appropriate use of opioid analgesics would be beneficial to include on blister packaging.

Furthermore, blister packaging may make it easier for a patient or caregiver to identify whether a third party, such as a member of the household or a visitor, has inappropriately accessed the opioid medication. While such packaging would not thwart a determined attempt to access the drug, the patient or caregiver is more likely to be alerted to inappropriate access of opioids contained in a blister pack compared to opioids contained in a standard pill bottle. Additionally, the fact that monitoring for inappropriate access may be easier with certain blister packaging (compared to a standard pill bottle) may serve as a partial deterrent to inappropriate access.

III. Request for Comments

FDA is soliciting comment from stakeholders regarding the potential blister packaging requirement described in this notice. In addition to any other aspects of or issues raised by the potential mandate stakeholders may care to comment upon, FDA is interested in comments on the following topics:

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.
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 II.B.
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.
4. 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?

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?
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?
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?
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?

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.

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

*1. Scholl, L., Seth, P., Kariisa, M., et al., "Drug And Opioid-Involved Overdose Deaths-United States, 2013-2017." *Morbidity and Mortality Weekly Report (MMWR)*, vol. 67, pp. 67:1419-1427, 2019 (available at <http://dx.doi.org/10.15585/mmwr.mm675152e1>).

*2. Mundkur, M., "Background and Rationale for the Development of Opioid-Sparing and Opioid-Replacement Drugs." Anesthetic and Analgesic Drug Products Advisory Committee Meeting. Presented on November 15, 2018. Available at : <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM626666.pdf>. Accessed April 1, 2019.

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