Duke | Robert J. Margolis, MD Center for Health Policy

Exploring Packaging, Storage, and Disposal Solutions to Enhance Opioid Safety

Duke-Margolis Center for Health Policy Conference Center
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Event Summary

In light of widespread opioid-related overdose deaths, the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration (FDA) are committed to using the tools at their disposal to prevent the misuse and abuse of prescription opioid drug products (opioids). The opioid epidemic is a national problem that extends across all classes of opioids. Of the 52,404 drug-related overdose deaths in the United States in 2015, over 33,000 involved opioids—more than any other year on record.[i] Despite recent declines in opioid prescriptions, the number of opioids prescribed per person was more than three times higher in 2015 than in 1999.[ii] Over this time, deaths related to prescription opioids more than quadrupled.[iii] In light of these statistics, FDA has committed to take steps to help reduce the impact of opioid abuse on the American public. FDA Commissioner Scott Gottlieb declared addressing the opioid epidemic as his "highest initial priority."[iv] In 2016, FDA released its "Opioids Action Plan" which committed to: consulting with its advisory committees before approving any new drug application for an opioid that does not have abuse-deterrent properties and when abuse-deterrent formulations raise novel issues; improving safety labeling; updating the Risk Evaluation and Mitigation Strategies (REMS) Program for opioids; strengthening requirements for post-market studies; encouraging the development of abuse deterrent formulations of opioid analgesic products; and supporting the improvement of addiction and pain treatment.[v]

As part of FDA's overall initiative to improve the safe use of opioids, the Agency has undertaken an effort to examine potential or proposed solutions for opioid packaging, storage, and disposal (collectively "solutions") that may enhance the safe use of legally-prescribed opioids and ensure appropriate access to therapies for patients living with acute or chronic pain. Currently, there is relatively little evidence available on how these solutions may affect opioid misuse, abuse, and inappropriate access. Further discussion on analytical approaches to testing the efficacy of such solutions is needed, as well as further discussion of how these options may be implemented across multiple care and pharmacy settings.

To support the Agency's ongoing work, the Duke University, Robert J. Margolis, MD, Center for Health Policy convened an expert workshop entitled, "Exploring Packaging, Storage, and Disposal Solutions to Enhance Opioid Safety." This workshop was convened through a cooperative agreement with FDA,[1] and examined key issues, including:

- The potential role of packaging, storage, and disposal in addressing opioid abuse and misuse or inappropriate access
- The current landscape of existing solutions that may prevent or deter abuse and misuse or inappropriate access to prescription opioids

[1] Funding for this workshop was made possible by the Food and Drug Administration through grant 5U13FD001597. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.

- Approaches to evaluating the impact of these solutions on deterring misuse and abuse or inappropriate access of prescription opioids
- Considerations for integrating the use of solutions into healthcare and pharmacy systems.

This multi-stakeholder workshop included experts from healthcare systems, academia, industry, government, and patient advocates. Moving forward, FDA intends to evaluate the information gathered from this workshop and seek additional public input to gain further stakeholder perspectives.

Potential Roles for Packaging Solutions

Several participants emphasized the need to understand the functions of drug packaging, theories of patient-packaging interaction, and injury prevention principles before considering the potential role of packaging in enhancing the safe use of opioids. Traditionally, the principal function of drug packaging is to protect and preserve active pharmaceutical ingredients from external contamination. This helps to maintain the quality and safety of the packaged drug product throughout its shelf life. Packaging also protects drug products from environmental influences such as heat, light, the presence or absence of moisture, and elements that may render the drug less effective. Other major functions of drug packaging include containment, convenience, marketing, and communication of important information for consumers.

While the primary goal of drug packaging is to facilitate patient access to medication, packaging can also include safety features to deter inappropriate access (e.g. prevent child access or reduce the likelihood of accidental exposure). Participants noted that designing solutions to prevent misuse, abuse, or inappropriate access for people intent on accessing a drug is extremely difficult. Most of the experts were skeptical that packaging solutions, even those employing specific technologies to deter or prevent abuse, would thwart a determined abuser, and suggested focusing on achievable goals, such as reducing accidental household exposure in young children, serving as a deterrent to teenagers in the home of patients, and equipping healthcare providers with tools to monitor patient adherence with prescribed frequency and dosage of opioids. Participants also suggested that packaging technologies can ultimately facilitate proper dosing, becoming a resource patients want to use.

Identifying Target Populations and Behaviors

Observing the many different behaviors that fall under the umbrella of “abuse,” “misuse,” and “inappropriate access,” the group noted the need to identify specific populations and behaviors or “factors that enable abuse” that may be best addressed by packaging. Given the complexity of these factors, participants urged that solutions be focused on interventions that can produce the biggest “bang for the buck.” There was general agreement among participants that a more focused approach improves the chances of sustainable impact on public health. Locking cap technologies, for example, might be effective in supporting safe storage for households with young children that might be at risk for accidental exposure or those with young adults that might be at risk for non-medical use of opioids found in the household. According to the 2015 National Survey on Drug Use and Health (NSDUH), over half (53.7 percent) of people who misused a pain reliever in the past year obtained the drug for free from friends or family.[vi]

Experts suggested that building current knowledge of patterns of abuse, misuse, and addiction, while targeting specific populations with appropriate interventions at critical intervention points might produce the largest effect. Specifically, many participants focused on approaches aimed at the patient or third-party who would be physically interacting with or manipulating these solutions at the point of

administration. For example, some participants mentioned that preventing accidental exposure in children between the ages of zero and five years could be a potential intervention due to the propensity of young children to accidentally ingest prescription opioids. Another suggestion was to focus on interventions in households with older children since there is some evidence that parents may be less likely to properly secure their prescription opioids compared to parents with younger children. Patients who do not adhere to their prescribed regimen due to intentional non-adherence or forgetfulness and or patients with established risk factors for opioid abuse and dependence, may also be populations that could benefit from packaging solutions with a built-in monitoring component. Table 1 (below) describes targeted interventions that participants indicated held the most promise for reducing misuse or abuse prescribed opioid medication.

TABLE 1: Packaging, Storage, and Disposal Interventions Targeted by Population and Goal

Target Population	Intervention or Behaviors Targeted	Intervention Goal	Packaging, Storage or Disposal Mechanism
Households with Young Children	Improve medication storage and disposal	• Reduce accidental child exposures	• Locking technologies • Disposal pouches • Child-resistant blister packs
Households with Older Children	Improve safe storage practices and deter inappropriate access	• Reduce accidental exposures • Reduce inappropriate access and misuse or abuse	• Locking technologies • Calendarized blister packs • Disposal pouches
Adult Patients	Adherence Support for patients at risk of unintentional non-adherence or misuse	• Improve adherence with prescribed dosage • Reduce forgetfulness, unintentional non-adherence, or dose escalation	• Calendarized blister packs • Dispensing technologies
	Monitoring for patients at risk of intentional abuse	• Deter abuse • Improve ability of provider to detect and intervene in cases of misuse or abuse	• RFID-enabled monitoring • Dispensing technologies

Preventing Accidental Exposures

In discussing efforts to prevent accidental exposures in young children (or in some cases elderly populations), participants noted that relatively low-cost solutions such as locking caps or blister packs could be the "low hanging fruit" in preventing accidental exposure. Injury prevention experts cited the success of the Poison Prevention Packaging Act (PPPA) as an example of how passive packaging safety

interventions had a meaningful impact on public health by reducing oral prescription medicine-related death for children under five years by 45 percent.[vii]

Supporting Adherence

Participants also saw the potential for safety-enhanced packaging solutions to enhance safe use by facilitating adherence with prescribed regimens and providing opportunities for healthcare providers to monitor and intervene in cases of misuse or abuse. Several participants noted available evidence that blister packaging positively affects medication adherence[viii] [ix], and further noted that emerging technologies such as radio frequency identification (RFID)-enabled devices might facilitate better provider monitoring of patients at risk of developing opioid use disorders. For example, RFID-enabled devices might allow providers to limit access to prescription medications, send reminders, or observe data generated by these technologies that might help support pain management. Some participants also noted that secure technologies that limit access or monitor dosage could have specific promise in methadone maintenance or other medication-assisted treatment settings supervised by a medical professional.

Design Principles for Packaging Solutions

A Lehigh University descriptive study on packaging and storage options used for prescription opioids found a range of solutions in varying stages of development with the potential to address abuse and misuse. Participants discussed several of the strategies and technologies featured in the study including disposal technologies to render substances inert, tamper-proof packaging, locking caps, biometric gatekeepers, microchips in tablets, monitoring technologies to track when doses were taken, and electronically limiting access until a dose is due. The study asserted that solutions such as locking caps, tamper-resistant packaging, and pill dispensers could be effective in deterring accidental exposure in children and misuse by seniors but have a limited capacity to effectively prevent intentional abuse.[x] Based on this study, the discussion at the workshop primarily focused on four types of solutions currently in use: blister packs, locking caps, automatic dispensers, and disposal pouches.

While some of these options are commonly used for pharmaceutical and over-the-counter medications (e.g., calendarized, tamperproof and child-resistant blister packaging), little is known about their efficacy in reducing abuse or misuse of prescription opioids. There is also limited information about the effectiveness of other solutions that are in limited distribution and/or are undergoing pilot testing including locking caps, disposal pouches, and automatic dispensers.

Changing Patient Behaviors

Although patient education or engagement campaigns may help change public behavior, experts emphasized that the effectiveness of safety interventions is improved when the interventions are carefully designed to reflect existing patient behavior patterns and require less behavioral change. Several participants stressed the need to build on accepted injury prevention principles and knowledge of patient behavior and values in the development of future solutions. Highlighting successful public health and safety interventions like reductions in traffic fatalities through increased seatbelt usage, one participant shared that interventions are most successful when they are passive, acceptable to patients, feasible to distribute, sustainable over the long term, targeted, timely, and cost-efficient. Patients are more likely to resist interventions that alter their daily life. It is therefore critical to develop solutions that are largely passive and automatic.

Similarly, developers of packaging solutions may also need to consider typical patient behavior with regard to storing and disposing of prescription opioids. Studies on prescription drug take-back programs routinely show that only small amounts of what is disposed of is made up of controlled substances.[xi] Experts with experience with patients conjectured that patients are often hesitant to dispose of leftover pills that might be needed in the future because of the time and energy to obtain, and perceived value of, prescription opioids. Thus, efforts to promote safe storage and disposal should take these behaviors into account. For instance, patients may be more receptive to secure storage over disposal options, or additional "pull incentives" such as small cash or prize rewards may help bolster the success of disposal efforts.

Additionally, participants noted that there are many factors unrelated to packaging that may contribute to the potential effectiveness of any specific intervention. One expert noted that there are more than one hundred individual factors related to medication adherence, and only some of them can be meaningfully addressed by safety-enhanced packaging. These packaging solutions should therefore be seen as one of the many kinds of tools that may contribute to reducing opioid misuse and abuse. Additionally, participants stressed that limitations should be considered and that there is no "one-size fits all" solution. As such, different solutions will need to be targeted at different populations, while still being flexible and iterative.

Evaluating Packaging Solutions

In evaluating packaging solutions, many participants emphasized that the desired outcome of the intervention should drive the design of a given packaging product's evaluation. Because the current landscape of packaging, storage, and disposal solutions includes a variety of technologies and goals, the data required to evaluate each may be different depending on the targeted population, context of use, and intended effect. The discussion covered the types of data and evaluation that may be helpful in assessing the efficacy and impact of packaging solutions in both a pre-market and post-market settings. Many participants found pre-market human factors and efficacy testing to be relatively straightforward given an already-developed knowledge base that industry has built around drug safety packaging. Solutions already implemented in other contexts, such blister packaging, were thought to require much less robust clinical testing than more technologically intricate solutions like automatic drug dispensers or RFID enabled enclosures. However, beyond clinical data, experts noted that post-market or "real world" impacts of such solutions on misuse and abuse behaviors are much more difficult to quantify.

Pre-market Evaluation Approaches

In discussing possible approaches to pre-market evaluation, presenters reflecting industry and academic packaging perspectives shared common methods to understand human and packaging interaction and how to evaluate the usability of packaging solutions. One of the presentations laid out three components of evaluations that could be used to determine whether packaging enhances the safe use of opioids. First, clinical evaluations should be conducted to assess the structure, durability, reliability and functionality of the packaging itself. Testing protocols for child resistance and usability required under the PPPA were cited as examples. Secondly, testing may also focus on cognitive usability considerations and human-packaging interactions, including comprehension and practicality. By focusing on these human factors and the cycle through which patients interact with packaging (including perceiving, processing, encoding, comprehending, and ultimately executing based on information conveyed through the packaging), it is possible to understand where in the cycle of interaction, and at what step(s), failures can occur. Other potential clinical and human factors criteria included testing to assess device durability, reliability and/or consistency in performance, contribution to undue burden on

the patient, and positive interaction with elderly and arthritic patients. Participants also highlighted the need to evaluate products for cognitive usability factors such as the ability of patients to understand a product's label design, blister layout, and opening instructions. Lastly, testing might also substantiate the impact on a patients, including whether the packaging results in a functional improvement in behavior and results in additional value for the consumer, although these impacts are much more difficult to substantiate.

Post-market and Real-World Evaluations

Many participants agreed that clinical trials offer only limited insight into how these products may perform in real world settings or their potential to support the broader public health effort. For example, the stigmatized and sometimes illicit nature of opioid misuse and abuse is one of the factors that has hindered efforts to obtain reliable data to assess the impact of opioid analgesic formulations labeled with abuse deterrent properties, known as "ADFs." Challenges in assessing post-marketing effectiveness of ADFs with respect to the existing methodology and data systems available were discussed subsequent to the Duke-Margolis packaging solutions meeting in an FDA public workshop on July 10-11, 2017.[2] During this workshop, experts participated in a scientific discussion about ways to address the challenges by modifying existing data systems and by designing new data collection efforts to assess the effectiveness of ADFs. Evaluation of opioid product packaging solutions within existing data systems is an additional major challenge to those discussed at the public meeting on assessing ADF opioids.

Similarly, participants in the Duke-Margolis workshop noted that clinical trials typically study the benefit for populations for whom medication is prescribed. The intent of packaging interventions may be aimed at broader populations and include family members or the general public. In light of such challenges, participants focused on establishing potential methods for understanding the individual behavioral effect of such interventions along with their potential public health outcomes.

Participants continued to emphasize that aligning solutions with target populations (e.g. non-adherent patients, high risk populations) and behaviors (e.g. intentional vs. unintentional misuse) can provide for the most meaningful measure of a solution's effectiveness. For these evaluations, small pilot studies in partnership with community groups, advocacy organizations, or health systems may help demonstrate a positive effect on behavioral change as well as an actual reduction of misuse, abuse, inappropriate access and accidental ingestion. Some participants suggested that a household could be a unit of analysis to track the effectiveness of technologies against inappropriate access. Others advocated for a more population-based approach—possibly using a cohort format for a geographical region—noting the relatively small percentage of abuse relative to widespread utilization requires a broader approach to understand the desired societal outcomes. Potential outcomes or criteria for success could include changes in adoption of the intervention (e.g. utilization of safety-enhanced packaging) as well as opioid-related deaths, ER visits, and/or opioid use disorder incidence in targeted populations. Poison control data may also reflect the effect of these solutions through fewer calls with regard to a certain age range, or a reduction in certain types of recorded opioid exposures, particularly those relating to childhood poisonings. However, participants noted the potential difficulty in measuring these outcomes or relating them directly to packaging.

[2] Meeting materials and recorded discussions are available at https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm

Participants acknowledged that information on the efficacy and cost-effectiveness of safety-enhancing solutions is relatively limited and requires further study. There was also a strong sentiment among many in the group that the urgency of the opioid crisis requires a swift, multifaceted response. While some participants urged caution until more data are developed, others raised the success of past injury prevention interventions and noted that we should "not let the perfect be the enemy of the good." Instead, the efforts to reduce health-related consequences of prescription opioids are best served by developing a flexible and iterative approach that incorporates packaging as one of many possible tools in a "toolbox."

Integrating Packaging Solutions into Patient Care and the Healthcare System

Beyond issues of efficacy, participants also engaged in a robust discussion around the implications of integrating packaging, storage, and disposal solutions into the broader healthcare system. Many felt that there was potential for packaging to be a mitigation tool against opioid abuse, misuse and accidental ingestion. However, it is necessary to consider potential unintended consequences, including barriers to access, cost, and integration into pharmacy and clinical practice. For example, participants cautioned that developers should be careful that packaging does not cause undue burden on elderly or chronic pain patients. More complex technologies such as RFID, fingerprinting, and lockouts may inadvertently prevent or delay patients from being able to open packaging to take needed medication and may be more costly for the patient due to out-of-pocket expenditures. Some experts also cautioned that efforts to add security measures may "stigmatize" the use of opioids and reduce access to necessary therapies for pain patients.

Participants voiced a number of concerns related to cost, specifically who would bear the costs for safety-enhanced packaging. Participants raised concern that more sophisticated technologies may have a considerable effect on the cost, and therefore access, as payers may be reluctant to support widespread use without sufficient cost effectiveness data. Although substance abuse prevention initiatives have broadly been shown to be cost effective—with every dollar invested in prevention efforts resulting in as much as ten dollars of savings in downstream treatment costs[xii]—there are little data to substantiate potential cost savings resulting from implementation of preventative packaging solutions. While these concerns were universal across all payers, public payers serving large populations, such as the Department of Defense and U.S. Veterans Affairs, would face particularly acute budget impacts related to increased costs for prescription opioids. Some participants noted the wide variety of opioid-related interventions already taking place across health systems, including efforts to reduce prescriptions and increase take-back activities. Given budgetary pressures and limited bandwidth of providers, some participants noted that costly interventions such as packaging should require further proof of social benefit before costs are assumed by payers, patients, and the broader public.

Participants also noted the potential reluctance of patients and providers to voluntarily take on extra costs that more sophisticated packaging, storage and disposal of opioids may impose because patients and providers often feel that they aren't "part of the problem." Behavioral economics approaches will be required to understand economic needs, the roles of doctors and pharmacists, as well as how to make these solutions patient-accessible. Participants also noted that physician acceptance and pharmacy workflow were important considerations for health system integration. Pharmacists are a major line of defense against illegitimate use of prescription opioids, and any "high-tech" solution should support electronic prescribing. Continuing medical education will likely be needed to effectively prepare physicians for safe dose escalation and dose tapering.

Throughout the day, participants representing various perspectives raised the issue of other efforts occurring on a federal, state, health system, or community level to reduce health-related consequences of opioid abuse and misuse. These interventions included prescriber education, prescription drug monitoring programs, prescribing guidelines, safe storage and take-back initiatives, and public education campaigns. While participants sometimes voiced disagreements on where resources might most meaningfully be used, others noted the capacity for packaging solutions to leverage or bolster these other efforts. For instance, automatic or timed dispensers may assist providers with monitoring patients at risk for developing substance use disorders, or disposal pouches can provide a way for patients to conveniently dispose of medications that may be at risk of inappropriate access. In this way, packaging, storage, and disposal solutions should be viewed as part of a more comprehensive approach to opioid abuse.

Key Lessons and Possible Next Steps

Overall, participants agreed that even though packaging, storage, or disposal solutions are not a single solution to stopping the opioid epidemic, they could be useful in helping to mitigate risks abuse and misuse of prescribed opioids while maintaining access to necessary pain treatment. Many participants suggested targeting interventions to a specific subpopulation or behavior along the spectrum of abuse as a starting point. Packaging, storage, and disposal solutions may have a greater effect on some factors that enable misuse or abuse, such as incorrect dosing or accidental exposure, than intentional abuse. Building on injury prevention principles, a combination of passive protections, such as abuse deterrent drug formulations, and safety enhanced packaging, storage and disposal solutions, may significantly help to improve the safe use of prescribed opioids.

Promising technologies are available at present, but there is a need for additional information to address how to analyze a solution's effectiveness. Participants offered a wide variety of clinical, human factors, and post-market outcomes that may be used as criteria for assessing a solution's effect on individual behavior and wider public health outcomes. Overall, there were differing perspectives on levels of data that may be required to justify wider development and implementation, but all participants noted the inherent difficulties in data collection around patterns of opioid use and behavior and the additional layer of difficulty that collecting information on specific packaging presents.

Many experts raised the need to integrate packaging solutions into existing efforts to reduce inappropriate prescribing as well as other efforts to reduce the supply of prescription drugs that might be vulnerable to misuse. Participants noted that low-tech policy solutions such as changing prescriber practices, partial fills and refills, among others, should be combined with high-tech engineering and packaging solutions to achieve maximum effect. Participants reinforced throughout the day the need for interdisciplinary stakeholder collaboration. To establish effective and minimally burdensome technology solutions, protocols, and regulatory practices, stakeholders (e.g., prescribers, patients and their advocacy groups, regulatory bodies, pharmaceutical and medical device manufacturers and federal and state governments) must align with one another. Many participant comments focused on the preventative potential of packaging interventions, suggesting both the solutions and behavioral interventions are easier to achieve before a patient begins misusing prescribed opioids or develops an opioid-related substance use disorder. Although it was noted that packaging could help reduce the abuse of prescription opioids, other participants strongly felt that such efforts must be coupled with meaningful efforts to expand the availability of substance use disorder treatments to truly reduce the societal impact of prescription opioid abuse.

Although the assembled experts displayed a wide range of opinions, overall, many thought that packaging, storage, and disposal solutions may be an appealing tool to mitigate the harmful impact of prescription opioid misuse, abuse, and inappropriate access. To maximize the likelihood of a positive impact, experts thought that solutions should be passive, cost effective, supported by payers, and appealing to patients, providers, and pharmacists alike, without imposing excess burden. Furthermore, the current public health crisis stemming from burden of the opioid epidemic requires deliberate speed in the iterative process of development and testing of tools such as packaging solutions that can meaningfully reduce the risk of misuse and abuse of prescription opioids.

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