formulation

Abuse-deterrent formulation technologies: Opportunities and limitations

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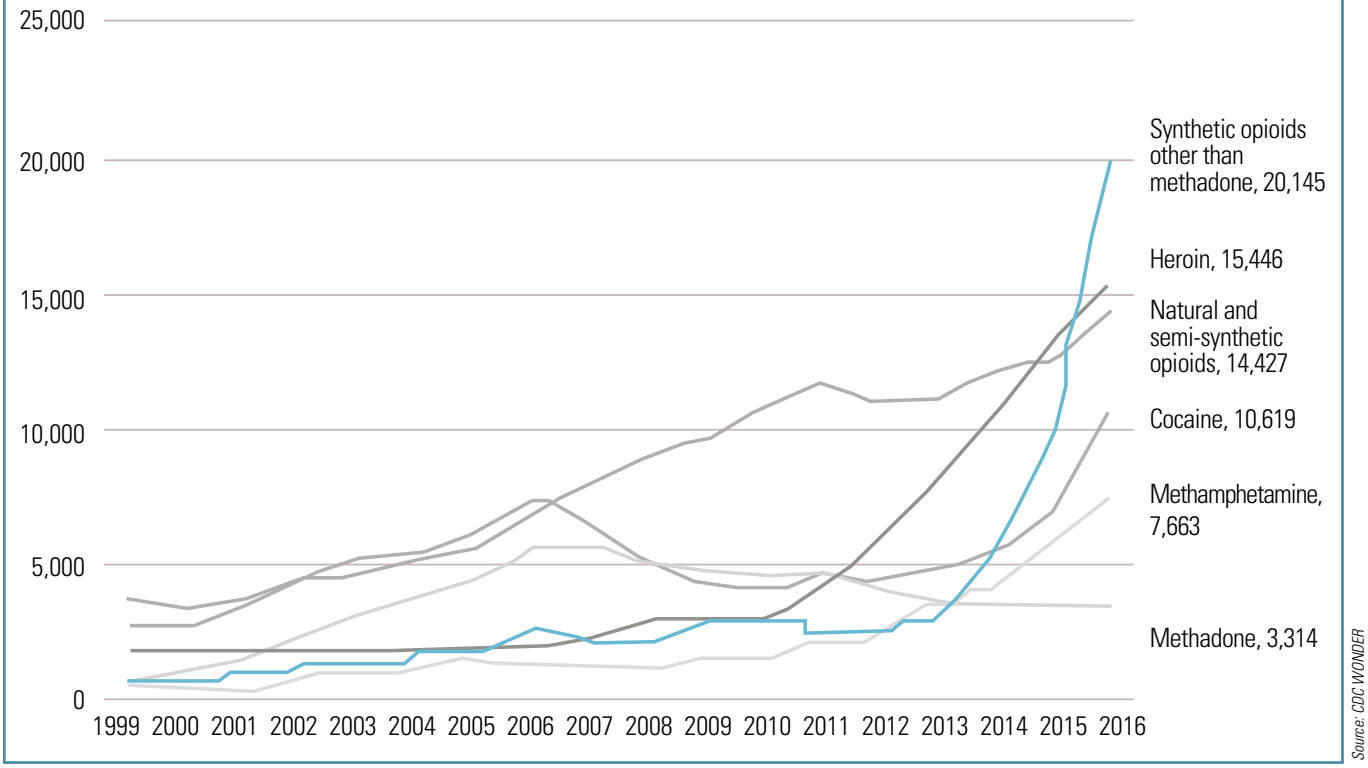
Too many Americans are misusing or abusing prescription opioids. This article summarizes recent FDA initiatives in this area and assesses the technologies manufacturers have adopted to curb abuse. It concludes with a description of how the author's company developed a capsule-based, abuse-deterrent formulation of levorphanol.

Abuse of opioid painkillers in the US is a major problem contributing to an escalating drug overdose epidemic. According to the US Department of Health & Human Services, 12.5 million people misused prescription opioids in 2015, with 2.1 million misusing them for the first time. As a consequence, 33,091 people died from overdosing on opioids, and more than 22,000 of these cases involved prescription opioids. A 2016 study estimated that in 2013, the economic burden of

Figure 1

Drugs involved in US overdose deaths, 2006 to 2016



prescription opioid overdose, misuse, and addiction cost $78.5 billion [1].

Since 1999, the volume of drug products prescribed and sold in the USA has nearly quadrupled, and the rate of overdose deaths and of admissions to treat substance-abuse disorders related to prescription pain relievers have increased in parallel [2].

Due to the need to curtail opioid abuse, drug delivery technology companies and contract development and manufacturing organizations (CDMOs) have developed technologies that can deter abuse. The US FDA states that "The agency recognizes that abuse-deterrent opioids are not abuse-proof but are a step toward products that will help reduce abuse" [3]. Abuse-deterrent formulations (ADFs) make manipulation for abuse by routes such as snorting (insufflation), injection, or dose dumping more difficult and/or less rewarding. Yet these technologies must also allow the product to deliver the prescribed, effective pain-relieving dosage when taken by patients through the correct route of administration. Abuse deterrence, promoted through new FDA regulations and guidelines, has shaped how manufacturers address painkiller development and production, especially for controlled-release dosage forms. These products are most often abused in order to immediately obtain their drug loads, which are larger than those of immediate-release (IR) products. The FDA has been encouraging the development of abuse-resistant formats for both IR and extended-release (ER) forms of opioids, and promoting labeling that identifies the abuse-deterrent technologies used in the drug formulation in order to further deter abuse.

While the focus of these technologies remains on opioid-related products, there is also now some consideration for other drug products at increased risk for abuse.

The science of abuse deterrence is relatively new, and the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the developing nature of the field, the FDA continues to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse.

Pharmaceutical companies, drug delivery companies, and CDMOs are evaluating the evolving regulatory environment and developing ADF technologies that better address the abuse of opioid painkillers. This article examines how the pharmaceutical industry, and CDMOs in particular, are working with the FDA to design, develop, and produce drug products that are more abuse-resistant; establish guidelines on labeling; and promote the safe and proper use of such products.

Understanding the FDA regulatory actions

The FDA's "Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling," issued in April 2015, provides a framework for the development of ADF testing, though it principally addressed ER products. Draft guidelines introduced in March 2016 and finalized in November 2017—"General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products, Guidance for Industry"—establish more

systematic testing to support the development of generic ADF products in "Category 1 studies." These are included in the first step of a four-step route to approval of ADF formulations:

Category 1 studies: Lab-based in vitro manipulation and extraction studies

Category 2 studies: Pharmacokinetics

Category 3 studies: Clinical evaluation of the potential for abuse, and

Category 4 studies: Post-market studies to determine the effectiveness and impact of the product.

However, with the realization that 90 percent of all opioid pain medication prescribed in the USA are IR formulations, the FDA has taken steps to evaluate how best to prevent their misuse. As noted above, most of the currently approved opioids with labels describing abuse-deterrent properties are ER products. But IR products can also be readily abused through injection or snorting and are often a gateway for abusers to migrate to ER products.

In a more recent response to the current opioid crisis, the FDA has developed a comprehensive action plan to take concrete steps toward reducing the impact of opioid misuse and abuse. The establishment in May 2017 of the Opioid Policy Steering Committee demonstrated that the FDA continues to expand its efforts to confront the opioid addiction crisis. This has led to the update of the Risk Evaluation and Mitigation Strategy (REMS) program—currently applied to ER opioids—to apply to IR products. The FDA is also developing changes to IR opioid labeling, including adding warnings and safety information similar to the 2013 update for ER forms. The key components of the plan:

1. Expand the use of advisory committees to review an opioid product that does not have abuse-deterrent properties and get expert advice on pediatric opioid labeling.

2. Develop warnings and safety information for IR opioid labeling that incorporate elements similar to those found on ER/long-acting opioid analgesics to provide better information to physicians about the risks and how to prescribe safely.

3. Strengthen post-market requirements to generate better evidence of the serious risks of misuse and abuse associated with long-term use of opioids, identify predictors of opioid addiction, and raise other important issues, such as "whether these products result in a real-world, meaningful decrease in the frequency and patterns of opioid misuse and abuse" [4].

4. Update the REMS program to increase the number of prescribers who receive training in pain management and safe prescribing of opioid drugs in order to decrease inappropriate opioid prescribing.

5. Expand access to ADFs to discourage abuse. As noted above, the FDA's final Guidance in November 2017 included its recommendations for the approval standards for generic ADFs to spur innovation and generic ADF product development.

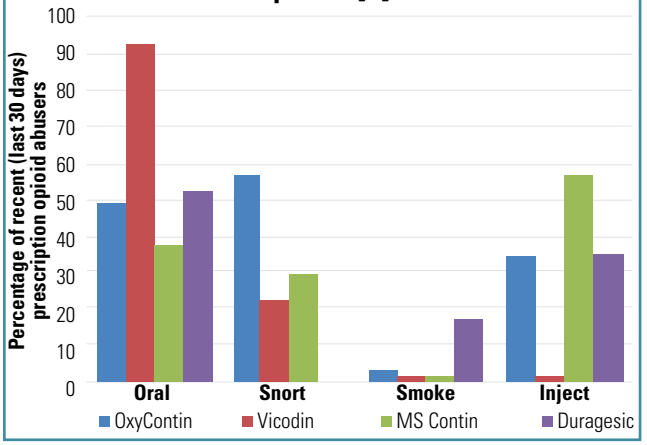
6. Support better treatment, including approval of naloxone as an OTC treatment of opioid overdoses, safer prescribing and use of opioids and, ultimately, new classes of pain medicines without the same risks as opioids.

7. Reassess the risk-benefit approval framework for opioid use by formal incorporation of the broader public health impact of opioid abuse into approval decisions.

8. Police approved products. In June 2017, the FDA requested that Endo Pharmaceuticals remove its Opana ER product from the market due to risks related to its abuse following the product's reformulation. This is the first time the Agency has taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse.

Figure 2

Routes of administration for various prescription opioids [1]



Advancing ADF technology

Abusers often manipulate opioid products to take them by different routes of administration or to defeat a product's ER properties and gain immediate access to the drug load. Most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. None of these technologies, however, has proved successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must, in the end, deliver the opioid to the patient, there will likely always be some abuse of these products.

Each manufacturer of opioid products has its own licensed or proprietary technology for deterring abuse. Some ADFs consist of tablets with a hardened surface that is difficult to crush. Others turn the crushed medicine into a gooey substance that is difficult to inject. Another approach is to combine the opioid with naloxone or naltrexone—drugs that block the effects of the opioid in the body (opioid antagonists)—so that they are activated when the opioid is crushed. It is also possible to take advantage of the bioavailability differences between the opioid and the antagonist. That

Figure 3

Category 1 testing of an ADF

a. Capsule is ground with water as a dispersion aid.

b. Attempt to expel the formulation through various sizes of needles

means the antagonist is poorly absorbed when administered through the correct route but is more highly available when abused through alternative routes. Similarly, inactive pro-drugs that require intestinal activation can be used, preventing abuse through other administration routes.

Additional approaches that provide enhanced deterrence are in development. However, it is important to appreciate that the required abuse-deterrent properties designed into a product are based on the specific mechanism(s) of potential abuse for that particular product. This can be related to dose dumping for ER products or even differences in bioavailability when administered by different routes. For example, as illustrated in Figure 2, Oxycontin (oxycodone) is commonly abused through oral, nasal, and injection routes but not through smoking [5]. Vicodin (hydrocodone bitartrate and acetaminophen) is predominately abused only orally, with a small number of abusers snorting it. Rarely is it injected or smoked. Fully understanding the abuse profile of a product is critical because by deterring one route of abuse, the product must not simply shift the abuser to an alternative abuse route that entails greater risks for the abuser. Switching an abuser from snorting to injection, for example, increases risk through exposure to HIV and other blood-borne diseases.

Figure 4

ADF Abusolve prototype formulation ground using a domestic coffee grinder and passed through sieve [6]

Various controlled IR and ER drug products, such as opioids and morphine derivatives, antidepressants, and stimulants are at risk for abuse by melting or solubilizing the product and directly injecting, crushing, or snorting. For ER products, abusers simply chew or chemically extract the active compound and swallow the solution, making it instantly available for absorption.

The roles of excipients

Capsugel, now a Lonza company, has developed ADFs that allow encapsulated products to meet the target IR and ER profile while deterring the potential abuser from manipulating the drug substance in order to abuse the product through alternative routes of administration. This technology is built on Lonza's decades of experience in designing, developing, and manufacturing liquid-filled hard capsule (LFHC) products. LFHC technology provides a foundation to ADFs by using liquid and thermo-softening excipients that provide an immediate barrier to injection or to extracting a powder for insufflation. Of course, the excipients must be chosen to optimize deterrence to potential routes of abuse while still maintaining the targeted release profile. Fill materials may be soft, hard, waxy, or paste-like and may contain water-insoluble materials or suspended solids. These can modify the viscosity to prevent powdering and snorting, resist injection after moderate dilution, inhibit dose dumping in alcohol, and otherwise hamper extraction for use via alternative routes of administration. This ADF technology is highly flexible and comprises a number of elements that can be combined to maximize the abuse-deterrent properties and to provide the appropriate release profile. The elements include:

- High-melting-point excipients that resist liquefaction at an injectable temperature,
- Taste modifiers that resist covert administration, snorting, and dose dumping,
- Water-insoluble excipients that resist extraction and adulteration by drinking,
- Soluble excipients that allow release modulation,

- Waxy excipients that resist dose dumping, snorting, and injection,
- Viscosity modifiers that resist low-volume dissolution, injection, and dose dumping, and
- Dyes that resist adulteration.

An early example

Some years ago Lonza developed an abuse-resistant ER levorphanol product—a potent opiate intended to treat severe pain. It was originally only available as an IR product, and the target product profile was set to allow once-daily dosing. The abuse profile was to resist abuse via injection, insufflation, and extraction.

The development of this type of product starts with the ER element, which must be balanced against the abuse-deterrent properties. To make a liquid fill meet a circa 12-hour release profile, the most common approach is to use—as the primary mechanism of release—a thermo-softening waxy solid that contains a pore-forming material to allow diffusion. Additional solids are then used in order to modify the viscosity if there is an attempt to manipulate the formulation in low-volume solutions. A great deal of Category 1 characterization is then required to demonstrate the abuse-deterrent properties in the lab and to optimize both the abuse deterrence and release profile in harmony.

For injection, the usual test method is to dilute the product in relatively low-volume solutions with different solvents and then to attempt to syringe it through various sizes of needle (Figure 3).

For insufflation, tests seek to create particles that are of suitable size to be inhaled, with the size generally determined using a sieve (Figure 4). For liquid-based formulations, a range of powder flow enhancers are added to ensure the formulation is further challenged.

Extraction in a range of solvents is also conducted, as this procedure can be used to directly abuse the drug load or to further manipulate it for abuse via other routes.

FIGURE 5

Resistance to solvent extraction of abuse-deterrent ER forms of levorphanol [3]

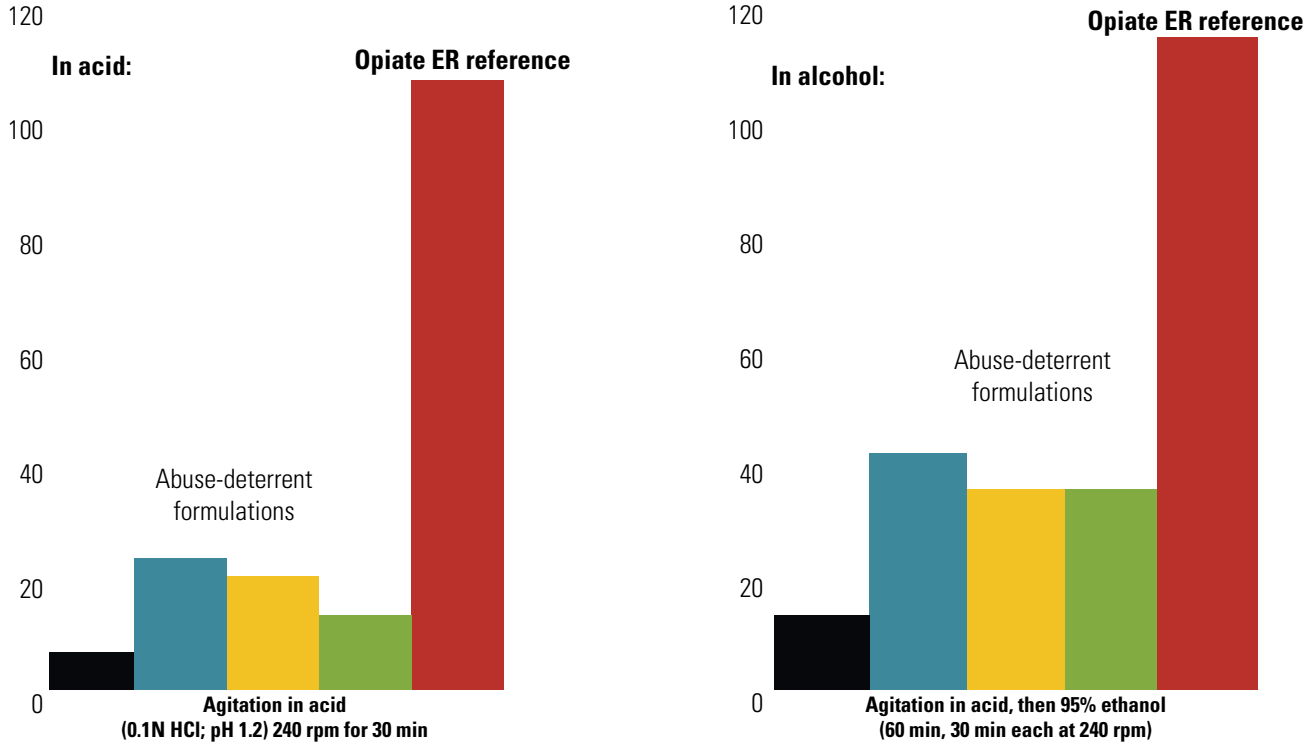


TABLE 1

PK paramater	LFHC test formulations versus IR reference-listed drug (levorphanol)				
	IR levorphanol	Form A	Form B	Form C	Form D
T_{max} (h)	2.4	10.36	12.29	9.15	11.53
C_{max} ratio (%)	100	40.89	29.97	32.01	26.66
AUC_{inf} Ratio (%)	100	99.27	92.89	86.99	82.16
% decrease in abuse quotlent (C_{max}/T_{max}) cf. IR formulation		90.6	95.2	91.6	94.5

Category 1 testing also calls for trials to ensure that dose dumping of the ER product will not occur if it is ingested with alcohol, as this also provides one of the most common accidental overdose routes (Figure 5) [7].

Finally, it must be shown that the product produces the clinical pharmacokinetics profile that is essential to ensure that the target product profile is met. In the levorphanol example, four prototype abuse-deterrent dosage forms of levorphanol ER were tested against the IR version of levorphanol in an analytically masked, fasted, single-dose five-way crossover bioavailability study. Fifteen healthy, non-smoking subjects aged 18 to 45 were assigned to each treatment period, with a 7- to 14-day washout between treatments.

In conclusion, the formulation technology, regulation, and understanding in the area of prevention of abuse of prescription medications will continue to develop rapidly in the coming months and years. ADFs form one useful approach in the arsenal that is being generated to combat this abuse crisis. LFHC technology has been demonstrated to be a highly flexible and effective ADF option. *T&C*

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