EDITORIAL

Abuse-deterrent formulations of opioids: Many questions still to answer

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The societal disruption in America triggered by widespread abuse of opioids has led to billions of dollars spent in search of comprehensive remedies.[1] To date, no single solution has been completely effective in reducing the consequences of opioid misuse despite the consumption of federal, state, and local resources and the best designs of scientists and clinicians. One response that is being implemented by the pharmaceutical industry at the direction of the United States Food and Drug Administration (FDA), as a portion of the extensive federal program to a significant public health problem, is the creation and implementation of abuse-deterrent formulations (ADFs) of opioids.[2] These new technologies are designed to limit the ability of users to manipulate the drug formulation and separate opioid from excipients, a process which allows for abuse by inhalation or injection. These modes are calculated to profoundly increase the immediate "high" that the abuser experiences, and are strongly associated with the development of addiction.[3] In the case of intravenous injection of manipulated extended-release/long-acting (ER/LA) opioids, death is a relatively common consequence and has driven much of the national anxiety about opioid abuse.

After nearly five years of careful planning, regulatory guidance and numerous studies attempting to determine whether ADFs are indeed efficacious in reducing opioid abuse; many old questions are still unanswered while new issues continue to arise. Can the use of ADFs be expected to reduce addiction to prescription opiates in the near term, or are the technologies meant to deter abuse so weak that kitchen chemists will continue to find methods to efficiently extract opioid despite ever more sophisticated formulations? Can these methods of negating ADF technology be performed at scale, allowing for the dumping of large quantities of opioid on the illicit drug market? Do the newest ADFs save lives, or do they only drive abusers to other formulations of prescription and illicit drugs that have weaker or no abuse-deterrent technology? Perhaps most important, with the presence of ADFs, will clinicians, previously chastened by the knowledge that increased prescribing leads to greater injury and death, and in the face of weak Risk Mitigation Strategies, increase the number of prescriptions written for chronic opioids in the belief that new formulations are completely safe?

To deter abuse of prescription opioids, new methods for drug opioid packaging have been crafted by industry, including the addition of opioid-blocking agents (naltrexone, naloxone), physicochemical methods that deter physical manipulation, or combinations of several methods. Sponsors perform all the design of these agents, the manufacturing process, and the complex testing that occurs after production of the drug with guidance from FDA scientists, clinicians, and pharmacologists. At the behest of Congress, these agents are evaluated by the FDA Advisory Committee on Analgesics and Anesthetics and the Drug Safety and Risk Management Advisory Committee before a final decision from the FDA clearing the compound for marketing.[4] These Committees are composed of experts from outside of the Agency with broad knowledge and experience in clinical drug use, epidemiology, pharmacology, and biostatistics. The FDA does not always follow the advice of this group of well-informed clinicians and scientists. However, recently there has been significant political pressure to consider these Committee's deliberations closely in their final decision. The evaluation of new formulations of opioids is complicated, especially given the political pressures of the time, and decisions by the Agency are not always transparent.

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Time is required to derive certain data pre- and post-marketing and to assure that the data that is provided by industry can be validated. Two types of data are mandatory to determine the success or failure of any new drug technology. First, laboratory and clinical studies demonstrating the efficacy of the change in the formulation of the drug must provide evidence of the safety of the parent compound. Also, studies that prove that the new drug technology is effective in deterring abuse must be performed. These efficacy studies are usually small as measured against the population of patients that will be eventually exposed to the new formulation and cannot be expected to reveal every problem with efficacy or even with safety. Post-marketing studies are therefore critical in showing whether the new formulation is safe for all patients and, whether abuse is indeed deterred. In the five years that the Agency has been licensing ADFs, comprehensive reviews of post-marketing data have been rare. For the Agency to make public, such an analysis, a significant safety signal must be identified, and this finding has occurred only once. Without just cause to examine industry data in public, the Agency cannot, by law, release internal documentation to the Advisory Committee or others for further analysis. But, within the Agency, an examination of proprietary information is ongoing.

Complete post-marketing data analysis is of particular importance as the Agency creates a knowledge base on what could be a new drug class. The continued evaluation of the consequences of the release of ADFs is a unique requirement for the Agency's analysts and the information that they will require to comprehend the complexities of the release of this new drug class are being developed coincident with the release of even newer opioids, with improved formulations, on the market. The Agency recognizes the need for new information as old data is analyzed, but inevitably must rely on industry to provide that information. Companies may not have the required population data, or the information that is available may be unfavorable for the continued marketing of the drug. Thus, a company delay for months or longer before supplying information that is requisite for the immediate licensing of the drug. Because of the inability of the Agency to immediately have the information that is required, it is likely that five or more years will pass before a complete picture is obtained of class efficacy, safety, and the relative success of the various technologies that are being marketed.

Ingesting large quantities of drug via the oral route is by far the most common method of abuse.[4] Currently, no formulation has been found to be effective in reducing this method of abuse. Also, and concurrently with the ongoing evaluation and licensing of new formulations by FDA, "chemists" in garages and kitchens worldwide are in search of methods to negate each new deterrence technology and extract a progressively higher percentage of opioid. Under ordinary circumstances, the evolution of more successful methods to deter abuse by industry would be expected. However, the sophistication of abusers who can rapidly study and diminish each incremental improvement in technology is noteworthy, as reported in these national news journals and on "Blue Light," an internet site that focuses on drugs of abuse.[5-9]

One of the unintended consequences observed in the creation of ADFs has been the movement of individuals from one drug of abuse to another if their drug of choice is changed to an ADF.[4] The current market continues to include many ER/LA and IR opioids without ADF technology, and this dramatically undercuts the ability of a few ADFs to affect the total market for opiates. Also, heroin, fentanyl, and other illicit opioids continue to be available to fill any gap produced by price pressure or lack of availability, creating one more reason that ADFs are not the entire solution in the resolution of a complex, multifaceted public health quandary. Another consequence of changes to the formulation of ER/LA opioids likely has been to alter the method of abuse with a particular drug of choice. As an example, changes meant to actively reduce the ability to use the drug for nasal inhalation, but with weak facility to deter the extraction of opioid, and conversion to a syringeable liquid has been observed.[11] This can and will lead to abusers changing their preferred mode of abuse to IV injection. Another significant issue for the Agency in pressing for the development of ADFs has been to cultivate an understanding of how the presence of one ADF on the market will affect the use and abuse of other opioids. Currently, most ADFs are classified as ER/LA and thus contain large quantities of the opioid within the formulation. Because of the high dose range, these formulations can readily supply abusers with opioid even if the extraction coefficient is relatively small.

Ideally, if ADFs were understood to be effective deterrents of abuse, all LA/ER opioids currently licensed without these technologies would be

eliminated from the market and replaced by those with effective deterrence. A rational regulatory policy would require that all immediate release formulations would need to be managed in a similar fashion. To say that such a comprehensive policy change would be difficult to implement is a gross understatement, but an examination of why the Agency could not sustain what would seem to be a rational approach is instructive.

First, the FDA is subject to litigation if policies promulgated by the Agency deter an organization from marketing a product unless that product is found to be unsafe, ineffective, or both. Company x has been selling a well-known opioid compound for some years but have not created a different ADF for their product. Company x would argue that their product, which has been on the market for many years is no less safe now than it ever was and that the requirement for a single company to shoulder a larger societal aim to reduce the abuse of opioids would not be supported by the Constitution or current federal law.

Second, the cost of reformulation of opioids is high and the price of ADFs that are labeled as such rises dramatically. Setting aside questions related to the appropriate use of opioids for chronic nonmalignant pain, such a dramatic increase in cost would place an unjustifiable burden on patients with cancer. The Congress would likely be inundated with millions of threats and promises from patients, physicians, and professional groups as well as the pharmaceutical industry. The Agency would not be able to sustain any such policy with this amount of political pressure.

Third, what of those patients that require liquid formulations? Currently, there are no ADF options available for children and those with difficulty swallowing. Removing all existing products that are liquid to deter abuse of opioids would, again, create a firestorm.

It is the current policy of the FDA to guide the pharmaceutical industry to create successful drug technologies that deter opioid abuse, to follow their progress closely, and, hopefully, to identify any safety concerns before marketing. This policy is rational in the face of the political and societal pressures that influence the creation of regulations based on federal law. It is, however, the slow road to success. Using this incremental approach to change the composition of opioids on the market, regulators can identify some of the unintended consequences of a profound shift in the marketing of a unique drug class. Unfortunately, these cannot be recognized quickly. The best that can be said is that, now, the entire regulatory process represents an opportunity to learn from past mistakes and to foster a new regulatory science.

ADFs of opioids reflect the best single technology that is currently available to reduce the nonmedical use of a whole class of drugs. However, this vehicle alone is insufficient to solve the problem completely. Dramatic and sustained reductions in addiction and death require that more effective risk mitigation strategies are created and that clinicians that prescribe opioids demonstrate an increased knowledge of the dangers of their long-term use. Resolution of prescription opioid misuse requires that every student in medical or nursing school graduates with a sophisticated understanding that pain control provided using opioids is balanced with the risks of prescribing this drug class to a given individual. Resolution requires that we continue to investigate the opioid molecule that has provided adequate analgesia for billions of patients over the four thousand years of our modern civilization, so that newer derivations that provide analgesia without tolerance, elevated risk of addiction, or respiratory depression can be revealed. Resolution also requires that we continue the search for unique compounds that will provide analgesia with fewer side effects and no risk of addiction. ADFs represent the first step along a long road that can lead to resolution. The next few years and the work of many scientists and clinicians will hopefully help us to answer some of the many questions that have been raised by this new pharmaceutical technology.

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