

OPIOID OVERDOSE PROTECTION: AN INEVITABLE NEED TO ADDRESS AN ALARMING EPIDEMIC

In 2015, opioids were responsible for the overdose deaths of more than 33,000 Americans, and nearly half of these deaths involved a prescription opioid. Deaths from prescription opioids have more than quadrupled since 1999, indicating an alarming and growing trend.¹

To address this epidemic, manufacturers have been developing abuse-deterrent formulations (ADFs) of opioids designed to prevent the release of excess opioid when a controlled-release formulation is manipulated or to prevent the manipulation of a formulation for unintended routes of administration such as insufflation or intravenous (IV) administration. The Food and Drug Administration (FDA) has noted the importance of this initiative and in 2015 published a final guidance for industry specific to opioid ADFs.² The FDA also launched the Opioids Action Plan, which includes a strategy to expand access to ADFs to discourage abuse.³

While currently marketed ADFs target the prevention of manipulation and administration of opioids by unintended (nonoral) routes, there are no available ADFs that specifically address the oral overingestion of intact opioids. Developing such technologies is challenging given that the full therapeutic dose needs to be bioavailable to the pain patient but excessive exposure needs to be minimized when higher than therapeutic doses are taken.

Technological approaches to developing overdose protection mechanisms vary. One approach is to introduce excipients that either limit release of the opioid from the formulation or limit its absorption when ingested in larger than intended amounts. A second approach is a prodrug mechanism that requires the opioid to be cleaved from the drug molecule by a physiological enzyme. With higher doses, the enzyme may become saturated and thereby limit exposure to the opioid. Currently, several manufacturers are developing technologies that may curb excess consumption of their opioid formulation. For example, one company is developing an overdose protection technology that relies on a pH-dependent polymer system for opioid release. Included in the formulation is an alkaline buffering agent. Under

administration of single tablets, the gastric pH remains low and the release of opioid retains its immediate-release characteristics. However, when multiple tablets are combined, the pH of the gastric fluid in the stomach is increased by the buffering agent, resulting in a retardation of opioid release.⁴

Labeling claims for overdose protection technologies would presumably follow the current FDA guidance on abuse-deterrent opioids, with Category 1, 2, and 3 labeling claims from *in vitro*, pharmacokinetic, and human abuse potential studies, respectively.² Currently, there is no guidance on the inclusion of safety data related to respiratory function for ADF opioids; however, at high doses, one would expect that respiratory function would be less depressed by an opioid with an overdose protection technology compared to a non-protected opioid. Therefore, a unique aspect of clinical ADF studies would be the inclusion of respiratory depressant effects as a safety measure. Such studies could examine respiratory function following single and multiple tablet administration. Based on past studies, noninvasive measures used to evaluate respiratory depression included an increase in end-tidal CO₂, a reduction in O₂ saturation, and/or a reduction in respiratory rate.⁵⁻⁷ Such studies would require a positive control (ie, opioid without overdose protection) and be conducted in an opioid-experienced population that could be exposed to opioid without a naltrexone cover (eg, non-dependent recreational opioid users).

Category 1 testing involves various chemical and physical manipulation techniques to determine if an ADF can be defeated. As reported by Setnik and Cone,⁸ *in vitro* testing of an opioid protection technology requires that the formulation be tested under conditions thought to warrant overdose protection (eg, combining multiple pills) and determining if there are physical/chemical methods to circumvent the protective properties.

Category 2 testing using pharmacokinetic studies can serve as an important proof-of-concept to demonstrate that the opioid is bioavailable at therapeutic concentrations but is blunted under circumstances of excessive consumption. It will be essential to test the technologies against various foods and drugs that may overcome the overdose protection. The nature and extent of these trials depends

on the mechanism of the protection technology and the Category 1 in vitro results. For example, food effect studies would determine if there are differences in fed/fasted conditions under excessive oral administration. The types of food should also be considered (eg, CYP enzyme inhibitors to assess technologies that utilize enzyme inducers, beverages with different polarities and pH levels).

Human abuse potential studies are the basis of Category 3 testing that examines the effectiveness of a formulation in the recreational drug user population. For overdose protection, a relevant study would be oral administration under conditions of excessive consumption. Such a study may demonstrate that dose escalation can blunt opioid effects. Other routes of administration should be considered if the overdose protection technology includes barriers to deter intranasal and IV use.

Preventing the oral overconsumption of opioids is an important step in mitigating the consequences of opioid abuse and misuse. Currently, the technologies to circumvent excessive oral consumption are in development and are not available in any marketed ADFs. Such technology will have unique attributes that need to be appropriately characterized. All abuse-deterrent technologies can at some point be defeated as they are ultimately designed as a drug delivery system; however, it is important to keep in mind that these formulations are intended to provide incremental improvements over the existing formulations that have no barriers in place.

Beatrice Setnik, PhD,
VP Scientific Affairs,
Early Phase,
INC Research, Raleigh, North Carolina;
Adjunct Professor,
Department of Pharmacology and Toxicology,
University of Toronto,
Toronto, Canada.

REFERENCES

1. Centers for Disease Control and Prevention: Drug overdose deaths in the United States continue to increase in 2015. Available at: <https://www.cdc.gov/drugoverdose/epidemic/index.html>. Accessed February 15, 2017.
2. US Department of Health and Human Services: Food and Drug Administration. Center for Drug Evaluation and Research: Abuse-Deterrent Opioids – Evaluation and Labeling. Guidance for Industry. April 2015.
3. US Department of Health and Human Services: Food and Drug Administration: Fact Sheet—FDA Opioids Action Plan. Available at: <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>. Accessed February 15, 2017.
4. Patent PCT/US2015/014690: Abuse-Resistant Drug Formulations with Built-In Overdose Protection. Kashiv Pharma, LLC. Available at: <http://patents.justia.com/patent/20160346274>. Accessed August 3, 2017.
5. Cashman JN, Dolin SJ: Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth*. 2004; 93(2): 212-223.
6. Overdyk FJ, Carter R, Maddox RR, et al.: Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. *Anesth Analg*. 2007; 105(2): 412-418.
7. Sivilotti M, Messenger DW, van Vlymen J, et al.: A comparative evaluation of capnometry versus pulse oximetry during procedural sedation and analgesia on room air. *CJEM*. 2010; 12(5): 397-404.
8. Setnik B, Cone EJ: Establishing “abuse-deterrence equivalence” for generic abuse-deterrent opioid formulations: A proposed development framework. *J Opioid Manag*. 2016; 12(2): 96-100.