Abuse-Deterrent Studies for Controlled Drugs – A Changing Landscape

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INTRODUCTION

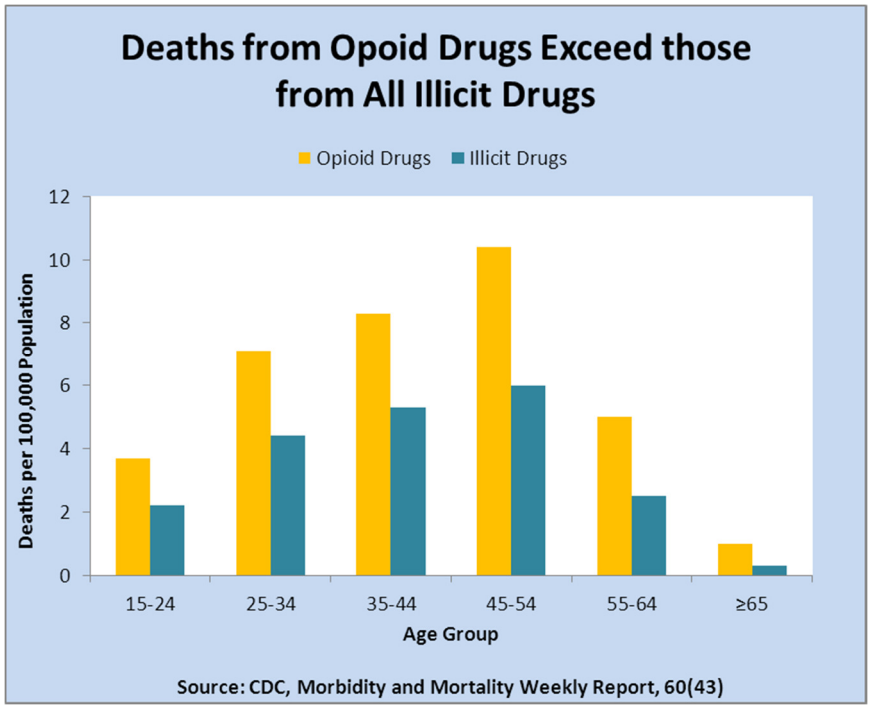
Prescription drug abuse is the Nation's fastest-growing drug problem and has been classified as an epidemic by the Centers for Disease Control and Prevention.[1] Abuse in this case can be defined as intentional misuse of prescription pharmaceuticals to obtain a desirable physiological or physical effect. Prescription drug abuse is the second most abused category of drugs after marijuana,[2] and the abuse of opioid painkillers, primarily oxycodone, hydrocodone and oxymorphone, has become the largest component of prescription drug abuse in the United States. These drugs have typically been abused by chewing, crushing a tablet into a fine powder before snorting it, or dissolving a crushed powder in water before IV injection.

Governmental and regulatory bodies, such as the U.S. Food and Drug Administration (FDA), have made significant investments towards the reduction of the misuse of prescription drugs. Engineering abuse-deterrent properties into prescription forms of drugs with abuse potential has become a primary strategy towards abuse prevention. In April 2015, The U.S. FDA issued a final guidance to assist the pharmaceutical industry with developing drug products with potentially abuse-deterrent properties. FDA Commissioner Margaret A. Hamburg, M.D., has stated that, “We feel this is a key part of combating opioid abuse.”[3]

[1] Paulozzi, et al., *J Clin Psychiatry*. 2011; 72(5):589-592

[2] National Survey on Drug Use and Health, 2010, U.S. Department of Health and Human Services.

[3] FDA News Release, April 1, 2015, “FDA issues final guidance on the evaluation and labeling of abuse-deterrent opioids” (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm)



THE COST OF ABUSE

Prescription drug abuse is a growing national epidemic. Deaths from prescription painkillers (drugs such as Vicodin® (hydrocodone), Oxycontin® (oxycodone) Opana®(oxymorphone) and methadone) have reached epidemic levels in the past decade. They are the most common type of prescription drug taken illicitly[4] and the number of overdose deaths from prescription painkillers is now greater than those of deaths from all other illicit drugs combined.

Addiction overdoses and deaths involving non-medical prescription drug use, especially narcotic pain relievers, have risen dramatically over the last decade. A 2006 Study estimated that the total cost at that time in the United States of nonmedical use of prescription opioids was $53.4 billion[5]. Of this total, $42 billion was attributable to lost productivity, $8.2 billion to criminal justice costs, $2.2 billion to drug abuse treatment, and $944 million to medical complications. Given that indicators of prescription drug abuse (e.g., overdoses, deaths, emergency department visits and treatment admissions) have increased since 2006, and that opioids are just one class of abused prescription drug, current costs stemming from their illicit use are likely to be substantially greater. The United States Government has recognized this and taken steps to stem this epidemic of abuse.

[4] National Drug Threat Assessment 2013, US DEA

[5] Hansen et al. (2011) Economic costs of nonmedical use of prescription opioids. *Clinical Journal of Pain*, 2:3.

GOVERNMENT ACTION

In 2011, the U.S. Government published a comprehensive strategy for responding to America's prescription drug abuse crisis that included a requirement for the development of abuse-deterrent formulations (ADF's) for prescription drugs[6]. In support of this initiative, the FDA published a guidance on the evaluation and labeling of abuse-deterrent opioids that was codified into law in April 2015[7]. This guidance provides the FDA's current thinking on how studies should be conducted to prove that a pharmaceutical formulation has abuse-deterrent properties. Proving that a proposed product has abuse-deterrent properties is a threefold task. Laboratory-based *in-vitro* manipulation and extraction studies lay the groundwork for subsequent pharmacokinetic studies and clinical abuse potential studies.

Following this trend, in May, 2015, Health Canada announced that legislation would be introduced to block generic formulations of opioid painkillers that do not have abuse-deterrent properties[8]. This action mirrored a similar action by the U.S. FDA, in 2013, who announced that generic oxycodone formulations would not be approved without abuse-deterrent properties[9].

And recently, in May 2016, the FDA released a draft guidance that defines the principles for the *in vitro* evaluation of the abuse-deterrent properties of generic solid oral opioid drug products.

Clearly, these actions by the U.S. FDA and Health Canada represent a policy shift that drug manufacturers will need to respond to with the development of ADF's for current and future drug applications.

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[6] https://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf

[7] https://www.federalregister.gov/articles/2015/04/02/2015-07562/abuse-deterrent-opioids-evaluation-and-labeling-guidance-for-industry-availability

[8] http://news.nationalpost.com/news/canada/federal-government-reversing-its-decision-to-allow-generic-oxycontin-as-addictions-surge

[9] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm

ABUSE – DETERRENT STRATEGIES

Several formulation strategies are currently employed to reduce or eliminate the potential for the abuse and misuse of psychoactive pharmaceuticals. These are:

Physical or chemical barriers – Formulations that physically limit the ability of products to be mechanically or chemically modified for the purpose of abuse.

Agonist/antagonist combinations – Formulations that include an agent that blocks the desired properties of the product when the product is abused.

Aversive properties – Formulations that include an agent that makes the product unpalatable or toxic when the product is abused.

Delivery systems – Modified release products that limit the possibility of rapid absorption of the active through a sustained-release mechanism or modification of drug bioavailability.

New molecular entities and prodrugs – Chemical entities designed to release the controlled substance through novel biochemical action, thereby limiting bioavailability if the product is manipulated for the purpose of abuse.

Combination formulations – A combination of two or more of the aforementioned approaches.

Novel approaches – Formulation technologies not captured in the previous categories.

CURRENT PRODUCTS

As of September, 2014, seven products had been approved by FDA with claims of abuse deterrence.

Approved Abuse-Deterrent Formulations								
Product	Active(s)	Company	Indication	Abuse Reduction Strategy	Approved	Dosage Form	First Approval	Current Status
Vyvanse	Lisdexamfetamine	Shire	ADHD	Prodrug, ER	Global	Oral, Capsule	2007 (US)	Marketed
Embeda	Morphine, Naltrexone	Pfizer	Pain	Antagonist, ER	US	Oral, Tablet	2009 (US)	Off Market
Targin	Oxycodone, Naloxone	Purdue Pharma	Pain	Antagonist, ER	US, EU, Other	Oral, Tablet	2009 (EU)	Marketed
Oxycontin (Abuse Resistant)	Oxycodone	Purdue Pharma	Pain	Physical, ER	US, Canada	Oral, Tablet	2010 (US)	Marketed
Opana ER (Crush Resistant)	Oxymorphone	Endo	Pain	Physical, ER	US	Oral, Tablet	2011 (US)	Marketed
Oxecta	Oxycodone	Acura	Pain	Physical	US	Oral, Tablet	2011 (US)	Marketed
Nexafed	Pseudoephedrine	Acura	Allergies	Physical	US	Oral, Tablet	2012 (US)	OTC
Global – includes US, EU, Japan and various other markets								
Source: Drug-Development. & Delivery (2014) Vol.14 No 9, p. 41								

Additionally in 2014, there were at least 53 applications being considered by the FDA that had been formulated with abuse-deterrent properties[10]. With so many products in the pipeline, the need for *in-vitro* abuse-deterrent testing expertise has increased significantly.

ABUSE-DETERRENCE STUDIES

When an ADF formulation is developed, significant thought has gone into how the product may be abused and how it has been engineered to prevent this. The FDA requires that scientifically rigorous laboratory-based *in-vitro* manipulation and extraction studies be performed with the goal of evaluating how easily the ADF properties may be defeated or compromised. A well designed *in-vitro* study is essential to meet the FDA requirement, and may even reduce the scope (and cost) of subsequent pharmacokinetic and clinical studies.

Designing an effective *in-vitro* abuse deterrent study is not as straightforward as it seems. Dosage forms may be tablets, capsules, patches or injectables and may use one or more of the aforementioned ADF strategies. Each dosage form presents different

[10] Kararli T., et al. 2011, What's in the Pipeline? Abuse-Deterrent Products, *Drug Dev. & Del.*, 14 (9):38-42.

challenges and will require an experimental design unique to that product. For these reasons there are several key concepts and questions that need to be addressed when designing *in-vitro* abuse-deterrent studies.

- What types of physical manipulation should be used? Abuser strategies differ from drug to drug and formulation to formulation, and the manipulation challenges should reflect actual and speculative abuse techniques. Can the product be crushed, ground or cut? When is a particular challenge technique too onerous to be considered realistic for a method of abuse?

- Extractability and solubility studies should be designed around a thorough understanding of the chemical characteristics of the active drug and excipient components of the formulation. Recreational abusers can be surprisingly sophisticated in their methods and it is important to match and slightly exceed this level of sophistication when building a justification for ADF performance.

- What is a valid comparator? For example, oxycodone is sold as both immediate-release (IR) and extended-release (ER) formulations. If you are developing a new oxycodone ADF, do you compare your product to ER only, or both ER and IR? What do you use for a valid comparator if there are multiple ADF formulations available? Careful experimental design may also demonstrate that a novel ADF formulation is superior to previously marketed products.

- Analytical methodology may be challenging due to the wide variety of matrices encountered in an abuse-deterrent study. It is not unusual for the typical solvents used in these studies, acetone, mineral spirits, vinegar, etc., to be incompatible with standard analytical methodology, and secondary handling, such as evaporation/reconstitution or liquid-liquid extraction may be necessary for accurate measurement. The use of positive controls is essential to prove that a low recovery results from the action of the ADF and not just poor solubility or poor extraction of the active drug. If the ADF presents a physical deterrent, analytical methods should be specific and accurate for the controlled drug. If an antagonist is part of the formulation, the methods need to measure both active drug and antagonist for all challenge tests.

- Drugs that may be crushed and inhaled should be characterized for particle size while those that might be injected should be evaluated for the ease or difficulty of pushing the extracted drug through a syringe. Particle size distribution of manipulated drug should be performed using laser light-scattering techniques.

- Careful observations and variations during manipulation studies, crushing, grinding, etc., may be used to establish blinding mechanisms for subsequent clinical trials.

The important thing to know is that there is no “one size fits all” approach to *in-vitro* abuse deterrent studies and experience with these studies is essential to their success. A well designed and executed *in-vitro* abuse-deterrence study will set the stage for successful pharmacokinetic and clinical studies.

WHY ALCAMI?

ALCAMI is an experienced partner for performing *in-vitro* abuse-deterrent studies. The Alcami Development Laboratories have designed and executed several *in vitro* abuse-deterrent studies for a variety of dosage forms and ADF strategies for several different clients over the last 5 years. Given the dynamic regulatory landscape surrounding ADF’s, it is important to partner with a company who has proven experience completing studies that comply with the FDA’s guidance for abuse-deterrence.

ABOUT ALCAMI

Alcami is a world class supplier of comprehensive pharmaceutical development and manufacturing services. With seven sites across the globe, Alcami’s combined capabilities include API development and manufacturing, solid state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (oral solid dose and parenteral), packaging, and stability services.