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Risk based *in vitro* performance assessment of extended release abuse deterrent formulations

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ABSTRACT

High strength extended release opioid products, which are indispensable tools in the management of pain, are associated with serious risks of unintentional and potentially fatal overdose, as well as of misuse and abuse that might lead to addiction. The issue of drug abuse becomes increasingly prominent when the dosage forms can be readily manipulated to release a high amount of opioid or to extract the drug in certain products or solvents. One approach to deter opioid drug abuse is by providing novel abuse deterrent formulations (ADF), with properties that may be viewed as barriers to abuse of the product. However, unlike regular extended release formulations, assessment of ADF technologies are challenging, in part due to the great variety of formulation designs available to achieve deterrence of abuse by oral, parenteral, nasal and respiratory routes. With limited prior history or literature information, and lack of compendial standards, evaluation and regulatory approval of these novel drug products become increasingly difficult. The present article describes a risk-based standardized *in-vitro* approach that can be utilized in general evaluation of abuse deterrent features for all ADF products.

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1. Introduction

Opioid drugs are well known for their analgesic properties (as pain-relievers), for their ability to produce respiratory depression and their high potential for abuse. Consequently, while remaining as the leading therapeutic option for the treatment of both acute and chronic pain (Cheatle and Barker, 2014; Frank et al., 2014; Lusted et al., 2013), prescription opioids continue to be drugs of choice for those who abuse drugs. The number of opioid prescriptions dispensed in the United States (US) has seen a steady increase in the last decade, accompanied with a parallel escalation in the instances of abuse and/or misuse of these drugs (Budman et al., 2009; U.S. Department of Health and Human Services, 2013), and in many cases associated with serious consequences. It has been reported that the number of deaths related to prescription opioid drugs now exceeds the number of deaths involving all illicit drugs such as heroin and cocaine combined (CDC, 2014). In addition to morbidity and mortality, abuse of prescription opioid drugs is associated with high economic costs. The average direct health care costs for an opioid abuser is eight times higher than for non-abuser (White et al., 2005). According to the 2011 US National Survey of Substance Abuse Treatment Services (N-SSATS), around 1 million patients sought treatment for drug abuse resulting in significant loss of productivity (Substance Abuse and Mental Health Services Administration, 2013). The total economic impact of prescription opioid drug abuse rose from $8.6 billion in 2001 to $55.7 billion in 2007 (Birnbaum et al., 2011; Meyer et al., 2014; Strassels, 2009).

Understanding the underlying factors that contribute to drug abuse is critical to formulate solutions to this multifaceted problem. Broadly speaking, the availability and cost of the prescription opioid drug products, social acceptability, and popularity among peers are common factors (Butler et al., 2010b; Hays, 2004). The majority of approved opioid drugs, currently available, are designed for oral administration, *e.g.*, tablets, capsules, solutions *etc.* (Fig. 1) making them easy targets of abuse. Indeed, a number of recent drug preference studies show oral tablets to be the major source of abuse/misuse of prescription opioids (Sellers et al., 2013; Sellers et al., 2006). The opioids with

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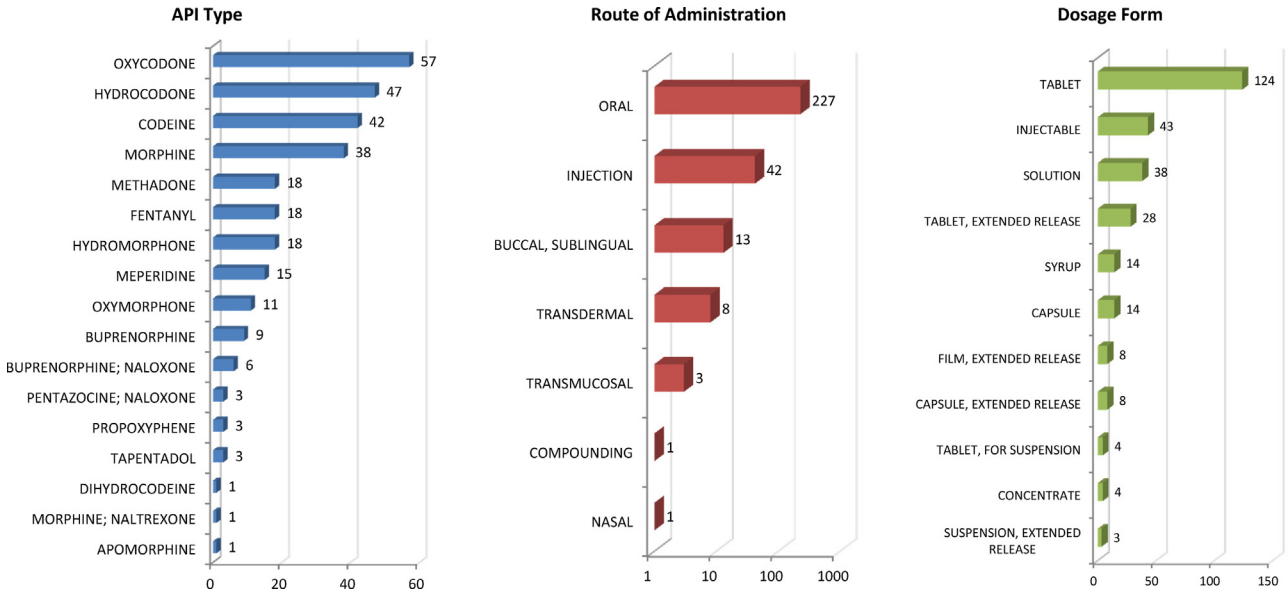

Fig. 1. A select list of currently approved opioid analgesics drug products from Drugs@FDA database. Some of the products may not be available currently on the market. Left: number of approved products based on API; Middle: number of approved products based on route of administration; Right: List of dosage forms for oral route of administration. Last accessed on July 29th, 2014.

the most drug product approvals in the US market, *i.e.*, oxycodone, hydrocodone, codeine and morphine, are also the most abused ones (Pergolizzi et al., 2012; Raffa et al., 2012). Beside the availability of drug products, properties such as onset and duration of action, the intensity of the effect, and the dependence potential of the active pharmaceutical ingredient (API) also contribute to the high incidence of prescription opioids abuse (Calderon and Klein, 2014).

An abuser may choose to ingest multiple doses of a drug product or may manipulate (*e.g.*, crush, cut, chew, grind, heat, and/or dissolve) the drug product to yield a high amount of opioid that could be easily abused via ingestion, snorting, inhaling, injection, or smoking. The preferred route of abuse is governed by a number of factors such as the type of abuser and their tolerance level, and varies based on the geographical location and demography of the abuser (Butler et al., 2010b; Hays, 2004; Katz et al., 2011). The more experienced abuser prefers injection route while the oral route is favored by non-experienced and occasional abusers (Katz et al., 2011, 2007; Pergolizzi et al., 2012). Overall, oral route is the route of choice followed by snorting and injection (Budman et al., 2009; Butler et al., 2010a; Hays, 2004; Katz et al., 2011, 2008; Sellers et al., 2013) (Fig. 2). Yet, the highest mortality and severe morbidity rates are associated with the parenteral and nasal routes (Katz et al., 2011).

Despite the sizable human and economic costs associated with the abuse of prescription opioid drugs, these medications are essential for improving the care and outcomes for millions of Americans living with chronic pain (APS, 2000). One way of providing safer prescription opioids while limiting their abuse, is to develop opioid formulations with design features that prevents or deters abuse, commonly refer to as abuse deterrent formulations (ADF). For example, a pentazocine drug product containing naloxone was approved by the US Food and Drug Administration (FDA) in 1982 (Raffa et al., 2012) but now discontinued. The naloxone component of this agonist-antagonist combination is designed to block the pentazocine's positive effects when the product is abused. Various other design features have been used, including making it difficult to manipulate the drug product *e.g.*, by

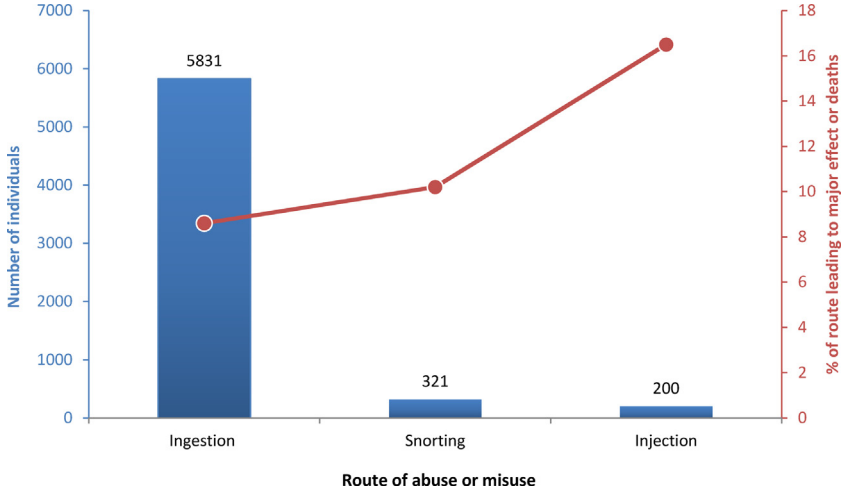

Fig. 2. Number of patients in treatment for substance abuse and percentage leading to major health effect or death, by routes of administration. Source: Data from 2006 Treatment Episode Data Set (TEDS) Highlights (Katz et al., 2011).