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Prescription Drug Abuse and Need of Abuse Deterrent Formulations: An Overview

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ABSTRACT

Abuse, misuse and diversion of drug substance are one of the most growing problems of United States and all over the world. The most critical challenge in combating the problem of drug abuse is to balance the control of prescription drugs along with continued access for legitimate use. To overcome the increasing problem of drug abuse, development of abuse deterrent formulation can prove an effective tool. This review provides an overview of abuse, modes of abuse, drugs with abuse potential, and different approaches for development of abuse deterrent formulations. Due to high mortality and morbidity, Opioids are the drug of choice for development abuse deterrent formulation. Hence draft guidance of US F.D.A. (US Food and Drug administration) for evaluation and labeling of abuse deterrent Opioid formulations are also under the scope of this review.

Keywords: Drug abuse, FDA, deterrent, formulations

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INTRODUCTION

Prescription drugs are developed by manufacturers and, once the federal government has been convinced that a drug is safe and efficacious, it is released for use. Access to these drugs is then controlled by designated health care professionals, and patients are responsible for complying with the recommendations for their appropriate use. However over the past decade, there have been growing concerns about the harm - abuse and addiction, as well as serious injury and death - caused by the use of prescription and over-the-counter drugs. Prescription drugs are the second-most abused category of drugs in the United States, following marijuana[1].

Drug abuse refers to non medical use with the specific intent to create a desired alteration in mental state or physical performance. This altered state may be euphoria in the case of opioids, anaesthetics, and sedatives. Alternatively, as stimulants may be used to enhance weight loss, academic performance, or wakefulness[2]. Prescription drug abuse can be defined as any intentional use of a medication with intoxicating properties outside of a physician's prescription for a bonafide medical condition, excluding accidental misuse. This definition of abuse includes use of medications prescribed for another user, even if for a physical condition, because this behavior can be risky[3]. When taken as directed for legitimate medical purposes, prescription drugs are safe and effective. However, they are just as dangerous and deadly as illegal drugs when used for non-medical reasons. Because prescription drugs are legal, they are easily accessible, often from a home medicine cabinet. Further, some individuals who abuse prescription drugs, particularly teens, believe these substances are safer than illicit drugs because they are prescribed by a healthcare professional.

In order to control and prevent the growing problem of drug abuse, various strategies have been in use. For over a century, the U.S. Food and Drug Administration (hereafter FDA) has applied the principles of science, evidence, and common sense to protect public health and safety in America. Development of abuse deterrent formulations is one of the significant and important strategies to save lives and protect public health epidemic of prescription drug abuse.

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving[4]. Abuse-deterrent formulations are designed to thwart willful attempts by consumers to extract the active ingredient or to otherwise blunt the euphorigenic effects from unapproved methods of administration[5]. In current review we intend to discuss the drugs with abuse potential, need of abuse deterrent formulations and few successful approaches of development of

abuse deterrent formulation. Draft guidance by FDA for evaluation and labeling of opioid formulations is also covered in this review.

Search methodology:

A search of Elsevier, Springer was conducted covering the period between January 1, 2000 and April 21, 2013. Search term included "abuse deterrent", "abuse resistant", "tamper resistant", "drug formulations" and "drug abuse". The reference lists of selected articles were reviewed. FDA website was searched for details of marketed products and guidance for industry. Emphasis was placed on various modes of abuse, drugs with abuse potential, marketed abuse deterrent formulation and evaluation and labeling of abuse deterrent opioid formulations.

DRUGS HAVING ABUSE LIABILITY:

Abuse potential has been defined as the ability of a drug to produce positive subjective or reinforcing effects, which is thought to be predictive of risks for "addiction"[6]. Abuse liability from a regulatory and public health perspective refers not only to abuse potential, but also to all factors impacting the risk of misuse, abuse, or diversion. Such factors include therapeutic indication, availability, ease of synthesis, context of use, and risk for misuse or diversion. Abuse liability also includes the potential for negative outcomes resulting from abuse (e.g., addiction, overdose, or toxicity)[6]. Sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes are the psychoactive effects of drug with abusable potential[7].

Prescription drugs:

Non medical use of prescription drugs is a serious problem however all the prescription drugs are not abused equally due to difference in abuse potential. Table 1 provides a short list of categories of prescription drugs with high abuse potential.

Opioids (Narcotics):

The term "opiate" refers to a drug derived from opium poppy, such as morphine and codeine. "Opioid" is a much broader term, encompassing opiates and other agents capable of binding to the μ-opioid receptor and producing morphine like clinical effects[2]. Opioids are the class of drugs that are most frequently used for nonmedical purposes[8]. In 2007, the number of overdose deaths from prescription opioids outnumbered deaths from heroin and cocaine combined. As demonstrated by figure 1, opioids have surpassed marijuana as the most common drug for individuals initiating drug abuse[9]. According to data from medical examiners and the records of Prescription Drug Monitoring Programs (PDMPs) and opioid treatment programs, the majority of drug overdose–related deaths in West Virginia in 2006 were associated with nonmedical use and diversion of prescription opioid analgesics[10]. The potential of an opioid to produce euphoria

is related to the efficiency with which it penetrates the blood–brain barrier and its binding characteristics at the μ-opioid receptor. Distribution into the central nervous system is facilitated by organic functional groups that enhance lipid solubility. By binding to the μ-opioid receptors, opioid agonists enable release of dopamine in the mesolimbic system to produce euphoria[11, 12].

Table 1: Categorization of Prescription drugs with potential for nonmedical use[2]

Sr no.	Category	Indication	Examples[a]
1	Opioids (narcotics)	Acute or chronic pain	Propoxyphene, codeine, oxycodone, hydrocodone, meperidine, hydromorphone, methadone, morphine, butrophanol, pentazocine, tramadol
2	Sedatives-hypnotics	Sleep aids, insomnia, seizure disorders	Methaqualone, pentobarbital, secobarbital, butalbital, temazepam, amobarbital, butabarbital, triazolam, Phenobarbital, ethchlorvinyl
3	Stimulants	Narcolepsy,attention deficit/hyperactivity disorder, short term weight reduction	Amphetamine, benzphetamine, dextroamphetamine, diethylpropion, levmetamfetamine, mazindol, methamphetamine, methylphenidate, pemoline, phendimetrazine, phenmetrazine, phentermine.
4	Transquilizers	Anxiety and panic disorders	Alaprazolam, buspirone, carisoprodol, chlordiazepoxide, clonazepam, clorazepate, dipotassium, cyclobenzaprine, diazepam, flunitrazepam, hydroxyzine, lorazepam, meprobamate, oxazepam

a According to National survey on drug use and health (NSDUH)

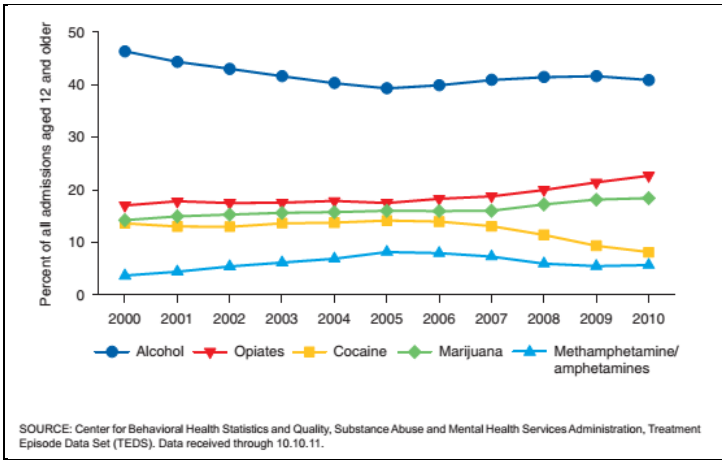

Figure 1: Primary substances of abuse at admission: 2000-2010 (Source: TEDS[13])

Sedative and Tranquilizers / CNS Depressants:

Benzodiazepines are used primarily as sedatives or anxiolytics, although they have other uses, including as hypnotics and anticonvulsants. Benzodiazepines achieve their effect by enhancing the function of the neuronal γ-aminobutyric acid mediated chloride channels. Benzodiazepine abuse contributes significantly to prescription drug abuse. ED visits involving nonmedical use of benzodiazepines increased 36% from 2004 to 2006. Abuse of benzodiazepines tends to occur in conjunction with abuse of other medications. Typically, they should not be combined with any

other medication or substance that causes CNS depression, including prescription pain medicines, some OTC cold and allergy medications, and alcohol[2]. Death from benzodiazepine overdose alone is a rare event; most often, a combination of benzodiazepine with other sedative hypnotics and/or ethanol is found to be the cause. Using CNS depressants with these other substances—particularly alcohol—can affect heart rhythm, slow respiration, and even lead to death[14]. Opioid dependent patients are known to abuse benzodiazepines for complementary psychoactive effects.

Stimulants:

"Stimulants" refers to medications that enhance alertness by increasing circulating catecholamines, particularly dopamine, norepinephrine, and, at higher doses, serotonin. Stimulants may induce the release of catecholamines and may block their reuptake by competitive inhibition. The most commonly abused prescription stimulants include amphetamine/dextroamphetamine and methylphenidate. The abuse of prescription stimulants has become common among students ever since these drugs were introduced for the treatment of attention deficit/hyperactivity disorder. Nonmedical use of stimulant medication is most common among college aged students (18–24 years). Among this population, the most common motive for non medical use of prescription stimulants was to increase their focus and concentration in order to enhance academic performance. Delivery of the drug to the central nervous system is rapid when abused intranasally or intravenously, and therefore these routes are preferred by those abusing stimulants for their euphorigenic effects. The oral route is preferred by those misusing the stimulant to enhance wakefulness and maintain alertness[14].

Anesthetic:

Anesthetics induce reversible changes in the perception of and reaction to pain and reversible loss of responsive reflexes. When the anesthetic effects wear away, there is amnesia to events in the immediate past. Anesthetics encompass inhalational, intravenous, subcutaneous, intramuscular, topical, and oral agents. They may be used in combinations at varying doses to produce the desired psychoactive effects along a continuum of sedation and analgesia. Anesthetics interact with many neuronal proteins to induce these effects, and numerous ion channels contribute to their mechanisms of action. Although abuse of anesthetic agents does occur, it contributes to a very small portion of prescription drug abuse. Abuse of anesthetic drugs is more likely to be identified among the health-care professionals who have access to anesthetics in their daily clinical practice. Reports of anesthetic abuse usually relate to anesthesiologists, in whom the rate of substance abuse disorders is thought to be higher than in

other physicians[14].

OTC (Over the counter) drugs[15]:

Over-the-counter (OTC) medications, such as certain cough suppressants, sleep aids, and antihistamines, can be abused for their psychoactive effects. This typically means taking doses higher than recommended or combining OTC medications with alcohol, or with illicit or prescription drugs. Either practice can have dangerous results, depending on the medications involved. Some contain aspirin or acetaminophen (e.g., Tylenol), which can be toxic to the liver at high doses. Others, when taken for their "hallucinogenic" properties, can cause confusion, psychosis, coma, and even death. Cough syrups and cold medications are the most commonly abused OTC medications. In 2010, for example, 6.6 percent of high school seniors took cough syrup"to get high." At high doses, dextromethorphan—a key ingredient found in cough syrup—can act like Phencyclidine / Pentachlorophenol (PCP) or ketamine, producing dissociative or out-of-body experiences[14].

Table 2: Some common categories of medicines/therapeutic groups implicated in OTC abuse[15]

Sr. no.	Medicine/therapeutics group	Example	Countries identified
1	Non opiate cough medicines	Dextromethorphan	France, Hungary, USA
2	Sedative antihistamines	Diphenhydramine	France, Humngry, Jordan, UK, USA
3	Decongestant	Pseudoephedrine	France, Jordan, UK, USA

Nonprescription medications are just as likely a cause of poisoning as prescription drugs. While medication abuse is a major problem, restricting our concerns to prescription drug abuse fails to acknowledge the major contribution of nonprescription agents to healthcare resource utilization. A significant number of adults are at risk of unintentionally overdosing on over-the-counter (OTC) pain medication, according to a new study in the US by Dr. Michael Wolf, from Northwestern University in Chicago, and his colleagues. The ease of access to OTC drugs presents a challenge to patient safety as many individuals may lack the necessary health literacy skills to self-administer these medicines appropriately. Indeed, individuals make independent decisions that match an OTC product to a self-diagnosed symptom or condition[15].

NEED FOR ABUSE DETERRENT FORMULATION[16]:

The Centers for Disease Control and Prevention has classified prescription drug overdoses as an epidemic. National data show that by 2010, drug overdose deaths were the second leading cause of injury death in America. Additionally, the overall drug overdose death rate in the United States roughly tripled between 1991 and 2011, and in 2007 about 100 people per day died from

drug overdoses in the U.S[17]. According to the recent Monitoring the Future study – the Nation's largest survey of drug use among young people – prescription drugs are the second-most abused category of drugs after marijuana. In addition, the latest National Survey on Drug Use and Health shows that over 70 percent of people who abused prescription pain relievers got them from friends or relatives, while approximately 5 percent got them from a drug dealer or over the Internet[18]. Further, opiate overdoses, once almost always due to heroin use, are now increasingly due to abuse of prescription painkillers. In our military, illicit drug use increased from 5% to 12% among active duty service members from 2005 to 2008, primarily due to non-medical use of prescription drugs.

The number of prescriptions filled for opioid pain relievers – some of the most powerful medications available – has increased dramatically in recent years. From 1997 to 2007, the milligram-per-person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams, an increase of 402%. In addition, in 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48%. As the figure 2 below demonstrates, drug induced deaths were the second highest cause of death after motor vehicle fatalities during the year 1999-2007 [19].

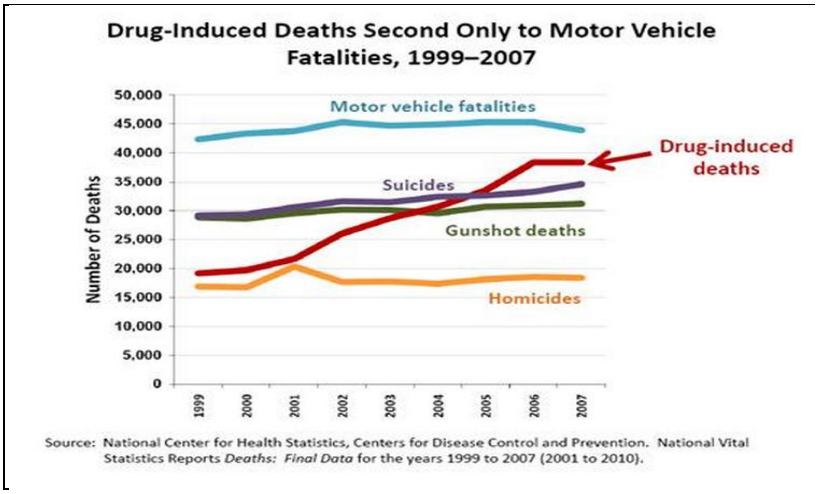

Figure 2: Drug induced deaths in U.S from 1999 to 2007. [Source: National center for health statistics, Center for disease control and prevention]

Since drug abuse is a systemic problem, with failures to recognize and prevent potential abuse occurring at many points in the system –from development and distribution of the pain medications, to the physician's office, and even to the patient's home, tackling this public health problem will require multifaceted solutions. Several strategies have already been proposed, in the hope that, if implemented together, they could reduce morbidity and mortality from drug abuse.

One of the promising strategy is to develop innovative formulations to make the drug less convenient ('abuse resistant') or less desirable ('abuse deterrent') to abusers because the easier a formulation is to alter more rapidly it provides the onset and euphoria or anxiolysis and so the more attractive it is to abusers. Abuse-deterrent formulations are not necessarily resistant to tampering, but contain substances that are designed to make the formulation less attractive to abusers.

MODES OF ABUSE:

Abusers commonly tamper with drug products prior to administration. Manipulation of the dosage form is typically done to enhance euphoria, and to make the drug suitable by alternate routes of administration (e.g. intravenous (IV), nasal)[20]. Certain modified release prescription drug products have been formulated to deliver up to 12 h or more of a medication from a single dose, making them very prone to abuse. However abusers damage such type of formulations and allow all or most of the medication to quickly be released at once, which can best be described as a "dose-dumping" effect. Some of the most common and preferred modes of abuse are briefly described below:

Crushing / Chewing:

Crushing or chewing easily destroyed the tablet's controlled-release mechanism, offering a quick "rush" or "heroin-like" high in the user upon administration. In addition, the co-ingestion of alcohol can alter a slow-release delivery system causing "dose dumping" of the drug into the bloodstream[21].

Intravenous injection:

Because a particular dose of a drug especially opioid analgesic, is typically more potent when administered parenterally as compared to the same dose administered orally, one mode of abuse of oral medications involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any suitable vehicle for injection) in order to achieve a "high". Such extraction is generally as easy as dissolving the dosage form using an aqueous liquid or a suitable solvent.

Smoking:

Smoking, or inhalation by volatilization, is another method of tampering. This is a potent route of drug administration, offering rapid absorption of drug into the circulation with immediate reinforcing effects. One method of volatilizing drug from a tablet is by placing the powder from a crushed tablet on to aluminum foil and using a heat source (e.g. cigarette lighter) under the foil. Drugs with high vapor pressures (e.g. amphetamines) are more likely to be abused by

volatilization techniques[22]. Consequently, the route of smoking delivers drugs relatively quickly and is considered more addictive than the other routes like swallowing, which deliver the drugs more slowly. In still another form of abuse, the opioid is extracted from the powder obtained by combination of the dosage form (optionally dissolving in a suitable liquid) and inhaling the (dissolved or powdered) opioid.

Nasal snorting:

In another mode of abuse, the corresponding dosage forms are communicated, for example ground, by the abuser and administered, for example, by inhalation. The abused active ingredient in the powder is absorbed through the lining of the nasal passages providing the abuser with a rapid onset of euphoric effects.

Diversion:

Drug abusers may also try to extract the desired pharmaceutical ingredient(s) from other undesired components in a dosage form. For such extraction, the product may be mixed with a suitable solvent (e.g. water, soda, alcohol), allowing the drug to solubilized, and be separated from the other undesirable and insoluble components.

E.g. Pseudoephedrine (PSE) is a widely used nasal decongestant available in many non-prescription and prescription products. It can be misused for the clandestine production of methamphetamine, a highly addictive, illicit drug abused by an estimated 1.1 million Americans annually. PSE products facilitate a straight forward conversion of PSE products to be misused for the clandestine production of methamphetamine. Two of the three most popular processes follow two general processing steps. (1) Dissolving the PSE tablets in a solvent to isolate purified PSE and (2) a chemical reduction of the PSE to methamphetamine for drying into crystals. The third method, or the "one-pot" method, involves the direct chemical reduction of the PSE to methamphetamine in the presence of the tablet's inactive ingredients[23].

Prevalent tampering methods of abused prescription drugs include chewing (mastication), snorting (insufflation), and IV injection. These forms of administration give rise to an accelerated rise in levels of the abusable drug, relative to oral administration, providing the abuser with the desired result. Hence targeting these modes of abuse was the key to the success of currently available marketed abuse deterrent formulations.

VARIOUS APPROACHES FOR DEVELOPMENT OF ABUSE DETERRENT FORMULATIONS:

The final formulation of an abuse-deterrent product must be safe, effective, and less favorable to abuse, misuse, and possibly addiction. The formulation should also have some way to decrease,

discourage or even prevent someone from achieving a rush or euphoria from its misuse and abuse. Common manufacturing approaches being employed to produce abuse-deterrent formulations include:

Physical barrier:

Physical barriers can change the physical form of an oral drug rendering it less amenable to abuse. Physical barriers can prevent chewing, crushing, cutting, grating, or grinding[4]. Formulations listed under this category offer some type of physical characteristic that prevents tampering and ensuing abuse. These dosage forms restrict access to the active drug component and tend to enclose, shelter, or trap the drug even after tampering. Formulations of this nature are presumed to be less appealing to potential abusers since they prolong both the time and effort needed for manipulation. For example, if a drug in a tablet was being primarily abused by snorting, it could be formulated so as to be tough, inflexible, and crush resistant. This would make it problematic for nasal insufflations, and conceivably lead to a decrease in this type of abuse.

Chemical Barrier:

In formulation based on chemical barrier approaches either add a chemical substance to, or perform a chemical modification on, an abused drug. With the former, the chemical excipient may sometimes have a pharmacological effect in addition to the active drug. This effect is not considered desirable and is not part of the therapeutic benefit of the prescribed product. However, since these excipients can be considered "active", we define them as "active excipients". This labeling helps to distinguish them from other "inactive excipients" used in manufacturing the dosage form. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents[4]. For chemical modifications, we are referring to changes made to the base structure of an abused drug that does not significantly alter the principal structure. This may include changing salt forms of the drug or slight modifications to form prodrugs. More significant changes to a drug structure may also be done when designing a new chemical entity that is less desirable to abuse or addiction. Although this may be another promising approach, the authors of this paper consider this to be drug discovery and not formulation; therefore this review does not include a discussion on this topic.

Prodrugs:

Chemically engineering prodrugs that require *in vivo* enzymatic cleavage to produce a pharmacological effect. It lacks opioid activity until transformed in the gastrointestinal tract[4]. The idea of this design is that the prodrug should be relatively inactive and exert its effect only

after it has gone through a metabolic process somewhere in the body to an active form. This would diminish abuse by those who choose to snort or inject the drug and attempt to bypass the GI tract for a faster onset of action. The biotransformation process of these precursor compounds in the GI tract, or elsewhere in the body, are the rate limiting step to activation. Therefore, when large amounts of Prodrug are administered, the enzyme pathways become saturated with drug and may prevent adverse effects of an overdose. Such enzyme kinetics may also delay the time to reach maximum plasma concentrations and thereby prevent a "rush" or "high" in the user.

Aversion:

Incorporation of an aversive ingredient (e.g., a flushing agent [niacin], emetic [ipecac], diuretic, or irritant [capsaicin]) intended to create an unpleasant experience and thereby deter further experimentation[4]. Aversive agents or "active excipients" are substances added to the formulation to produce an unpleasant effect in the user if the product is tampered with or overdosed. Modern versions of abuse-deterrent formulations using the aversive agent approach are currently being developed.

Agonist / Antagonist Combination:

An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse of opioids. The antagonist can be sequestered and released only upon manipulation of the product. Under normal dosing conditions, the antagonist remains unavailable and the system performs as a sustained-release opioid. If the formulation is physically or chemically manipulated, the opioid antagonist becomes available in the systemic circulation and blunts the opioid effects, including the psychotropic effects. Methods to segregate an opioid antagonist in a formulation may include coating multiparticulate pellets with polymers insoluble in the GI tract and impermeable to the antagonist. In this fashion, the antagonist is prevented from being released from an intact and un-tampered product.

Combination:

Since no single formulation strategy has yet been shown to be superior to another, it is common to see an abuse-deterrent formulation combining more than one approach in a final preparation.

Table 3: Marketed abuse deterrent formulations and their development approaches[24]

Sr. No	Trade name	Drug / Type of release	Available strengths (mg)	Developed by	Approach / Technology
1.	Oxecta	Oxycodone hydrochloride immediate release	5, 7.5	Pfizer; Acura Pharmaceuticals	Aversion
2.	Nexafed	Pseudoephedrine	30	Acura Pharmaceuticals	IMPEDE

Sr. No	Trade name	Drug / Type of release	Available strengths (mg)	Developed by	Approach / Technology
3.	Opana ER	Oxymorphine extended release	5, 7.5, 10, 15, 20, 30 and 40(RLD)	Endo Pharmaceuticals	INTAC
4.	Oxycontin	Oxycodone extended release	10, 15, 20, 30, 40 (RLD), 60 and 80	Purdue Pharma	Physical barrier
5.	Embeda	Morphine sulfate / Naltrexone extended release	20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, 100/4 (RLD)	King Pharmaceuticals	Antagonist
6.	Suboxone	Buprenorphine / Naloxone extended release	2/ 0.5, 8/2 (RLD), 4/1, 12/3	Reckitt Benckiser Pharmaceuticals	Antagonist
7.	Vyvanse	Lisdexamfetamine	20, 30, 40, 50, 60 and 70 (RLD)	Shire Pharmaceuticals	Prodrug
8.	Exalgo®	Hydromophone controlled release	8, 12, 16 and 32 (RLD)	Covidien Pharmaceuticals	Physical barrier / OROS

RLD: Reference listed drug

FDA GUIDANCE TO INDUSTRY FOR EVALUATION AND LABELLING OF ABUSE DETERRENT OPIOID FORMULATIONS:

In February 2009, the FDA announced that it was initiating a process under the FDA Amendments Act (FDAAA) that would require manufacturers of high potency opioids to institute risk evaluation and mitigation strategies (REMS). The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications[26]. Current section includes a brief introduction of guidance for industry by FDA for evaluation and labeling of abuse deterrent Opioid formulations.

Premarketing evaluation:

A. In Vitro Manipulation and Extraction Studies: To evaluate the ease with which the abuse deterrent mechanism of a product can be defeated

- Physical and chemical manipulation of the formulation so that opioid is in a form more amenable for abuse by desired routes of administration
- Separation and isolation of the opioid from the opioid antagonist
- Neutralizing the effects of an aversive agent by separation or other mean

In Vitro Manipulation and Extraction studies include:

a) Mechanical Evaluation:

It evaluates a variety of common household tools for cutting, grading and grinding test product formulation with comparison to appropriate extended release (ER) reference

product(s). It also includes evaluation of time and ease of manipulation, determination of particle size, examination of impact of first freezing or heating the formulation and chewing simulator with artificial saliva.

b) Chemical Extraction:

It evaluates ease of chemical extraction of opioid from test product (intact, crushed, cut and ground) and appropriate reference product(s) For agonist/antagonists formulations this would include isolation of the agonist from the antagonist. Extraction in solutions like water, beverages (or simulated beverages), household chemicals, buffers of different pH, and other chemicals constituting different polarities is also evaluated. Effect of extraction conducted under continuous agitation and at room and elevated temperature is done and percent opioid extracted is determined at selected time points out to 12 to 24 hours or until opioid is mostly extracted.

c) Preparation for Snorting, Inhalation, Intravenous Administration:

- Preparation for Intranasal: Being one of the modes of abuse, ease with which formulation is reduced to a form for nasal application is evaluated. During such evaluation, effect of product on lining of nasal cavity is also considered.
- Preparation for Inhalation: It includes evaluation of ease of manipulating formulation and opioid for smoking and co-relation between vaporization temperatures vs. degradation temperature is established.
- Preparation for Intravenous (i.v.) Injection: Evaluation of ease in obtaining small volume with sufficient opioid concentration for i.v. injection should be done. Syringeability and Injectability are the parameters those should be also evaluated.

Clinical pharmacokinetic Testing:

Determine the bioavailability and pharmacokinetic profile of tablets administered intact and manipulated (orally and intranasally)

Comparison of bioavailability:

- Test product (intact and manipulated) compared to reference ER product (intact and manipulated) and reference IR product.
- Swallowed and chewed product, possibility other routes of administration
- Effects of concomitant food and ethanol intake

Study Design: Open-label, randomized, single-dose, crossover design

Subjects: Healthy adult volunteers under opioid antagonist blockade

Plasma concentrations of opioid, and possibly opioid metabolites, followed as a function of time following dose administration. In the case of agonist/antagonist product formulations, plasma levels of antagonist are determined over time.

Pharmacokinetic Parameters:

- Peak plasma concentration (Cmax)
- Time to peak plasma concentration (Tmax)
- Area under the concentration versus time curve (AUC0-tand AUC0-inf)
- Others

Compromise of the release mechanism due to manipulation is indicated when analysis demonstrates:

- Cmax (manipulated) > Cmax (intact)
- Tmax (manipulated) < Tmax (intact)
- AUC0-t(manipulated) > AUC0-t(intact)

Human Abuse Liability studies:

Compare subjective effects produced by intact and manipulated test product, intact and manipulated ER reference product and IR reference product. It should include pharmacokinetic evaluation

Study Design: Randomized, placebo-controlled, single-dose, double-blind, crossover in a controlled setting Subjects: Approximately 30 opioid experienced, non-dependent volunteers who can discriminate the subjective reinforcing effects of opioid from placebo

CONCLUSION:

Virtually all drugs that produce psychoactive effects are abusable in one form or another, but not to the same degree. Opioids present the greatest challenge for the future of abuse deterrent drug technology. In fairness, however, it should be noted that other prescription drugs, including stimulants, depressants, sedatives, muscle relaxant, hypnotics, anxiolytics and even some over the counter drugs, contribute significantly to the nation's drug problem. As abuse, misuse and diversion of prescription as well as over the counter products have had a profound impact on the public health. A difficult balance between continuous supply of products with abusable drugs to the patients and restricted availability to abusers needs to be made. There appears to be great promise in the development of formulations that will decrease the abuse potential of medications. Many drugs with abuse potential have been made inherently less abusable through the use of abuse deterrent formulations and novel product designs. Current marketed abuse deterrent

formulations are of innovative design and are deterring drug abuse. Along with development of abuse deterrent formulations, FDA has published a blueprint for prescriber education for long-acting and extended-release opioids and now concomitant application of strategies like education, law enforcement, monitoring etc can very well help in dealing with the epidemic of drug abuse.

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