Development of Tamper Deterrent Formulations: State of the Pharmaceutical Industry

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Abstract: Prescription drug abuse is a significant and growing health and socio-economical problem in the US and the world. According to the 2008 UN World Drug Report, the number of people who have consumed an illicit drug at least once in 2006/2007 reached 240 million, roughly 6% of the world population aged 15 to 64. In the last few years, pharmaceutical manufacturers started developing new formulations specifically designed to provide tamper deterrent features. The initial focus of these development activities was extended release opioids, owing to their dominant share of reported prescription drug abuse. Tamper deterrent formulations (TDF) for other drugs of abuse, including stimulants and sedatives are also in various stages of development. Three major challenges face the development of TDF: the increased sophistication of the tampering methods used by abusers, the ambiguity of the regulatory requirements for labeling and marketing and the exaggerated expectations of what these formulations can deliver. This review details the approaches used by pharmaceutical manufacturers to impart tamper deterrent features into their formulations; the *in vitro* and *in vivo* tests that have been proposed or used to assess the performance of TDF; and the current regulatory landscape.

Keywords: Abuse, tamper deterrent, extended release, opioids, formulations.

INTRODUCTION

Prescription drug abuse is a growing major health and socio-economical problem. It is estimated that in the US alone, diversion and abuse of prescription drugs cost the public and private medical insurers $72.5 billion in 2009 [1]. According to the 2008 National Survey on Drug Use and Health (NSDUH), an estimated 20.1 million Americans aged 12 or older (8.0 percent of the population older than 12) were illicit drug users in the month preceding the survey [2]. Illicit drug use includes marijuana, cocaine, heroin, hallucinogens, and inhalants; and the non-medical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives. Globally, it is estimated that 4.0-5.8% of the world population aged 15-64 (172-250 million persons) have used illicit drugs once in the 12 months preceding the survey in 2007 [3]. In 2008, prescription pain relievers and marijuana were nearly equally used (2.2 million persons each) by new initiates of illicit drug use aged 12 or older followed by tranquilizers (1.1 million persons) [2]. From 2001 to 2005, unintentional deaths involving prescription opioids increased 114 percent and treatment admissions increased 74 percent [1]. These surveys and others, indicate that prescription drug abuse is a major public health problem in the US and globally.

Several factors contribute to the increase of illicit use of prescription drugs. Most notably is the increased availability and exposure to prescription drugs. Recent data from the Drug Enforcement Agency (DEA) revealed that the aggregate production of most controlled substances significantly increased from 2000 to 2010 [4]. The number of prescriptions dispensed for major opioids have been steadily increasing from 2005 to 2009. The relatively easier and safer access to these drugs compared to illegal substance of abuse like cocaine or heroin also contributes to the increase in prescription drug abuse. Studies suggest that more than half of prescription drug abusers get their medication free from a friend or a family member who holds the prescription [2]. In addition, there is a major underestimation of the risk associated with casual illicit prescription drug use. Nearly half of teens (grade 7-12) do not believe there is a great risk in abusing prescription medicine and 30% believe prescription pain relievers are not addictive [5].

Prescription drugs of abuse include opioids, stimulants, sedatives and tranquilizers. As seen in Fig. (**1**), opioids are the product of choice for many abusers in the US [2]. Opioids are a family of molecules that can bind to the opioid receptors inside the body. They have been available commercially for many decades to treat varying degrees of pain. Other clinical but limited uses for opioids include cough, diarrhea and anxiety due to shortness of breath. Several extended release opioid formulations have been introduced into the market in the last two decades. Extended release products are designed to contain an increased amount of the active ingredient (i.e., an opioid) in combination with an extension release barrier that allows the active ingredient to be released over a longer period of time. For the non-drug abuser the extended release product helps control pain evenly and over a longer period of time. Unfortunately, extended release products are more attractive to the abusers due to the increased drug load that can be made immediately available should the release extension barrier get compromised. This immediate availability of the extended release product drug load is referred to as dose dumping. It is not clear how much, if any, the introduction of extended release opioid products has contributed to the increased illicit drug use. However, due to their increased attractiveness to

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abusers, the need for extended release formulations that can resist dose dumping upon tampering has never been greater. This review focuses on the development of the so called tamper deterrent formulations (TDF) for opioid products.

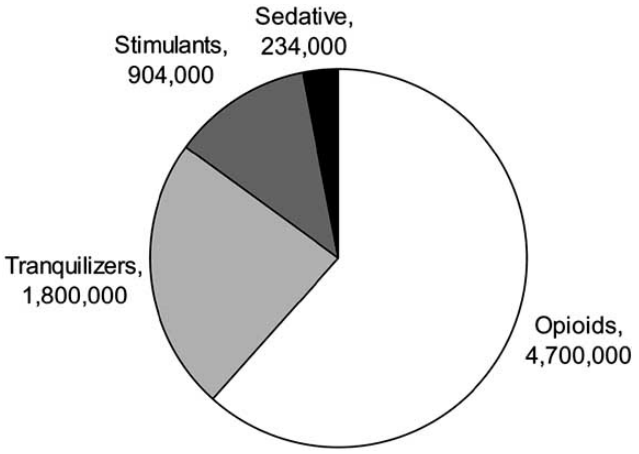

Fig. (1). Estimated number of Americans who used drugs non-medically in the past month (preceding the survey) in 2008 (based on data from ref. [2].

THE PHARMACEUTICAL INDUSTRY'S RESPONSE

The widespread problem of prescription drug abuse has incentivized the pharmaceutical industry to search for innovative solutions. The best approach to address prescription opioid abuse is to develop molecules that can alleviate pain but have no or minor euphoric and physical dependence effects. Thus far, no molecules with these attributes have been successfully identified. Accordingly, to tackle the problem of opioid abuse, pharmaceutical manufacturers are focusing on the development of TDF for existing molecules. The interest of pharmaceutical manufacturers in developing TDF increased with the passage of the Food and Drug Administration Amendments Act of 2007 which provided the FDA with the authority to require drug sponsors to submit and implement Risk Evaluation and Mitigation Strategy (REMS). In February 2009, the FDA sent letters to 16 manufacturers of 24 currently approved opioid products indicating their products require REMS [6]. Later that year, the FDA published its Guidance for Industry reflecting the agency's general views on the format and content of REMS [7]. As of today, there is no class-wide REMS for all opioids and sponsors are designing and implementing their own REMS. While it is still not clear how TDF could serve as part of any proposed REMS, the new regulatory requirement had brought attention to the importance of TDF. It is also interesting to note that some researchers have called for future generic product of abuse deterrent branded formulations to include the some abuse deterrent features [8].

In the last 8 years, hundreds of patent applications and numerous issued patents covering TDF have been filed or granted. However, despite the relatively high number of manufacturers who are interested in developing TDF, only a few products have reached phase III or have been successfully marketed (Table **1**). This limited success is attributable to the limited number of opioid molecules that make economical sense to reformulate as a TDF and the regulatory uncertainty associated with TDF approval and the ability to differentiate from a marketing perspective.

SELECTING THE BEST TDF APPROACH

Nearly all of the TDF technologies announced by pharmaceutical manufacturers or covered in patent publications can be classified into one of the following three approaches:

1. Use of physical barrier
2. Use of chemical barrier
3. Use of deterrent agent

From the manufacturer's point of view, selecting a TDF from the list of available technologies can be a complicated endeavor. Each approach has its pros and cons in terms of effectiveness in addressing the issue, complexity of clinical development and uncertainty of regulatory success. Attempts to evaluate and compare the potential ability of each approach have been published [9, 10]. However, the real effectiveness of each approach (let alone comparison among approaches or technologies) won't be adequately assessed without post launch epidemiological studies. Because the effectiveness of the approaches is unproven, it is difficult to favor a more complicated approach over a simpler one at this time.

One factor that has been proposed as a guide to selecting a TDF is the corresponding molecule abuse pattern. Studies have shown that not all opioids are abused at the same rate or using the same route. Extended release oxycodone and immediate release hydrocodone are by far the most abused by recreational abusers, as well as, abusers with a history of addiction compared to other opioids, stimulants and sedatives [9, 11]. The available data suggest that the oral route is the most preferred route for recreational abusers who use hydrocodone, which is rarely injected [9, 12]. It is important to note that all hydrocodone products available in the US market contain other analgesics that can have an effect on the abusers' route preference. It is not clear how a hydrocodone-only product will be abused when it becomes available. For extended release oxycodone, snorting was found equally favored [9] or even more preferred for abusers with history of addiction [11]. A sizable proportion of the individuals surveyed also abused oxycodone through the injection route [12]. The oxycodone abuse pattern was also found to be dynamic with abusers moving from oral to snorting and injection as they continue to abuse the drug over a period of time [13]. Extended release morphine is abused nearly equally through the oral and snorting routes but it shows the highest prevalence of injection as a route of abuse compared to oxycodone and hydrocodone [12]. The hydromorphone preferred route of administration is injection [14]. While these findings indicate different molecules may have different preferred abuse patterns, the data available are limited and the abuser patterns are dynamic and responsive. These factors make it difficult to conclude a certain TDF technology or approach would be better suited to a certain molecule.

Perhaps a simpler way to select a TDF technology is to consider the abusers' common techniques to tamper with the product prior to administration. Regardless of the molecule,

Table 1. Opioids TDF in Phase III or Beyond

Product (Company)	Approach	Regulatory Status
Extended Release hydrocodone bitartrate (Cephalon)	Physical Barrier	o Phase III
Extended release tapentadol (Johnson &Johnson and Grunenthal)	Physical barrier	o NDA submitted in December 2009
Remoxy™ Controlled release oxycodone HCl (Pain Therapeutics and King Pharmaceuticals)	Physical barrier	o NDA submitted in June 2008 and granted priority review status in August 2008 o November 2008, FDA Advisory Committee discuss the NDA o December 2008, the company announced receipt of FDA complete response letter citing the NDA was not approved in its present form but cited no additional clinical trials required[1] o In July 2009, the company announced that based on a meeting with the FDA, the company is expecting to resubmit the NDA mid year 2010 and reiterated no additional clinical trials required but cited the need for 6-month stability data[2]
Reformulated Oxycontin® Controlled release oxycodone HCl (Purdue Pharma)	Physical barrier	o NDA submitted in November 2007 o May 2008, first FDA Advisory Committees meeting to discuss the NDA o September 2009, second FDA Advisory Committees meeting to discuss the NDA o April 2010, FDA grant approval on bioequivalence basis o Expected launch in 2010
Acurox® immediate release oxycodone HCl (Acura Pharmaceuticals and King Pharmaceuticals)	Deterrent agent (niacin/irritant)	o NDA submitted in January 2009 and granted priority review status in February 2009 o June 2009, the company announced the receipt of FDA preliminary review letter and indicated the PDUFA date is likely to be missed[3] o July, 2009, the company announced the receipt of FDA complete response letter and indicated there were issues regarding the potential abuse deterrent benefit of the product but cited no additional clinical trials required[4] o April 2010, the FDA advisory Committees voted they don't have enough evidence to support the product approval o May 2010, the company announced plan to resubmit the NDA without niacin in early 2011[5]
Embeda® extended release morphine Sulfate (King Pharmaceuticals)	Deterrent agent (naltrexone as opioid antagonist)	o NDA submitted in June 2008 and was granted priority review in August 2008 o November 2008, FDA Advisory Committees discuss the NDA o August 2009, FDA approved the product

[1][24]; [2][25]; [3][40]; [4][41]; [5][42].

available data suggest the following are the most common abusers' techniques; ingestion of intact product alone or with alcohol, chewing and ingestion, crushing and ingestion, crushing and snorting, and crushing and extraction in a small amount of water for injection. Complex extraction techniques have also been described in abusers' internet exchanges but these are limited to a small percentage of sophisticated abusers. Most, if not all, TDF in development aim to address methods used by recreational abusers who typically don't resort to complicated extraction techniques when using the drug for recreational purposes. Based on this list of abusers' methods, crushing is by far the most used technique to prepare the dosage form for administration. Accordingly, crush resistant (physical and chemical barriers) or crush deterrent (sequestered deterrent agent) elements must be an integral part of any TDF. An intact TDF must also be resistant to alcohol (and preferably other solvents) to avoid dose dumping in situations where the abuser ingests the intact product with alcohol.

A remaining difficulty is to assess and conclude how much resistance or deterrence is good enough. Attempts to establish an *in vitro* extractability rating system to be used by manufacturers and regulators has been published [15] but none, according to the authors' knowledge, has been adopted by the FDA. Manufacturers engaged in developing TDF have conducted numerous *in vitro* tests simulating abusers techniques such as crushing and solvent extraction and some of the outcomes of these tests were made public during FDA advisory committee meetings and conference presentations. However, little is known about the details of each manufacturer's methods, rendering any comparison between technologies or product very difficult. Several manufacturers have also conducted pharmacokinetics and abuse liability studies in humans to assess the performance of TDF after tampering. The data generated from these studies is very useful for assessing the potential ability of these TDF to deter abuse. However, it will take several years after these TDF are launched and multiple, well controlled epidemiological studies to assess the level of deterrence achieved by these products when they are on the street.

Another factor to consider in selecting a TDF technology is the inherent complexity of the dosage form. For some of the proposed TDF technologies, the physical and chemical barriers used to impart crushing resistance are also designed to afford solvent resistance. In other approaches, different formulation components are included to address different abuser methods. This increases the complexity and the risk of commercial failure of the designed product. Therefore, it

is very important to ensure that not only does the TDF technology afford resistance against crushing and solvent extraction, but that it can also lend itself well to known manufacturing techniques and can maintain its stability (including crushing and solvent resistance) over the target shelf life. It is also equally important to consider the safety, stability and regulatory status of the excipients used to impart the needed attributes. While the use of novel excipients can improve the product's Intellectual Property (IP) position, new excipients often carry the risk of toxicological, regulatory and sometimes manufacturing uncertainty. If the performance attributed to the novel excipient can be matched using approved excipients, the novel excipient's IP advantage is moot. Accordingly, the novel excipient must impart performance attributes significantly above and beyond other approved materials to justify the additional increase in complexity and uncertainty in getting the regulatory approval.

USE OF PHYSICAL BARRIERS

Most of the abusers' tampering techniques involve crushing. Thus a common feature in many of the new TDF is the introduction of a physical barrier to impart crushing and solvent extraction resistance. Physical barriers have been used to control drug release from dosage forms for decades. However, since all traditional extended release dosage forms were not designed with abuse deterrence in mind, nearly none of them have good resistance against crushing or solvent extraction. Therefore, new formulation approaches were sought by several pharmaceutical companies. For example, controlled release oxycodone has been available commercially in the US as Oxycontin® since 1996. Abusers have found it very easy to compromise the release extension barrier by crushing or chewing the tablets. Therefore Oxycontin was one of the most abused products in the last 10 years. The manufacturer of Oxycontin reformulated the product to enhance its resistance against crushing and solvent extraction and the new formulation is expected to be launched later in 2010.

To avoid unnecessary complications, the same formulation components that control the drug release are used to impart crushing and solvent resistance. This can be achieved through prudent selection of excipients (and combinations thereof) and dosage form designs. Physical barriers can be in the form of a thick and strong coat on a drug-loaded core [16]. The core can be in the form of small particles, tablets or capsules. Or the drug can be distributed through a matrix that can be made of fat or wax [17, 18], gelling polymers [19, 20] or plastic polymers [21]. In all cases, the excipients are selected to impart crushing and solvent resistance owing to their physicochemical properties and how they are used within the dosage form. Another approach relies on simply making very strong tablets that are hard to break with commonly available utensils such as spoons, cigarette lighters, porcelain mugs etc. Some technologies use more than one of the above components to maximize the resistance. Examples of physical barrier-based TDF that have reached phase III or beyond include Remoxy™, reformulated Oxycontin, extended release tapentadol and extended release hydrocodone bitartrate (Table **1**).

Remoxy is an extended release oxycodone gel-cap product based on the use of a novel, high viscosity and hydrophobic excipient sucrose acetate isobutyrate [22]. A new drug application (NDA) for Remoxy was filed in June 2008. During the FDA advisory committee meeting in 2008, the sponsoring company presented numerous *in vitro* and *in vivo* data on the performance of the dosage forms under simulated tampering testing conditions [23]. The company later received a complete response letter from the FDA in December 2008 indicating the NDA was not approvable in its current form but the company also cited no additional clinical trials were required [24]. The company then announced that it expects to resubmit the NDA in 2010 [25].

The reformulated Oxycontin product is based on the use of gel forming polymer which is melted during the manufacturing process and upon cooling the polymer fuses to impart plastic-like properties to the product [26]. The polymer also gels in presence of many solvents. The new formulation was submitted to the FDA in 2007. During the FDA Advisory Committee Meeting in 2009, the sponsoring company presented *in vitro* data on the performance of the new formulation under a variety of test conditions. However, the company presented no *in vivo* data at the advisory committee meeting. The reformulated product NDA was approved in April 2010 and is expected to be marketed later in the year. The extended release hydrocodone product is based on the use of combinations of polymers to impart resistance against crushing and solvent extraction. The product is currently undergoing testing in phase III.

A few other companies have announced new opioid TDF products entering phase I using physical barrier approaches. These include once a day extended release oxycodone [27, 28], extended release morphine, oxycodone and hydrocodone [29].

USE OF CHEMICAL BARRIER

The chemical barrier approach is based on chemically modifying the drug *via* the formation of a covalent bond with other carriers to form a prodrug. In some cases, the prodrug is absorbed intact and the drug release is initiated through enzymatic cleavage of the formed linkage in the intestinal wall, liver or in the blood. In other cases, the prodrug is digested in the gastrointestinal tract enzymatically and/or non-enzymattically and the drug is absorbed in its original form. In both cases, the rate of drug release is controlled by how fast the enzymes or other digestive agents break the linkage which is highly dependent on the type and strength of the formed linkage. The formed prodrug does not release the original drug upon tampering unless the formed linkage is broken which requires the use of strong chemicals or enzymes.

Two linkages have been the focus of several pharmaceutical manufacturers, namely amidic and ester linkages. The amidic linkage can be formed between the drug molecules and a single amino acid like lysine or small oligopeptide (15 or fewer amino acids). Examples include d-amphetamine [30], hydromorphone [31] and hydrocodone [32]. The ester linkage is formed between a hydroxyl group on the drug and a carboxylic group on the carrier [33]. No opioid prodrug has made it yet to phase III or beyond. A d-

amphetamine prodrug has been approved and launched in the US under the trade name Vyvanse®. According to the approved product label, the prodrug demonstrated less subjective response in a human abuse liability study compared to an equivalent dose of the immediate release d-amphetamine after oral and intravenous administration [34]. However, higher oral doses of the prodrug produced increases in the positive subjective responses that were statistically indistinguishable from that of the immediate release d-amphetamine [34].

Other chemical interactions proposed to impart tamper deterrent features include complexation with ion exchange resin [35, 36] and with metal cation/fatty acid [17]. An oxycodone TDF based on the interaction with metal cation and fatty acid has been tested in phase I clinical studies [37].

USE OF DETERRENT AGENTS

The third approach to impart tamper deterrent features into opioid products is the use of deterrent agents. Several agents have been proposed including opioid antagonists, flushing agents like niacin, emetic [38], diuretics and capsaicin [39]. Two main approaches have been proposed to include the deterrent agent; the first relies on the use of small amount of the deterrent agent in the dosage form to deter the abuser from ingesting multiple dosages. The second relies on the use of sequestered deterrent agent which is not released except when the dosage form is crushed. An example of the first approach is Acurox® (Table **1**), an immediate release oxycodone product to which niacin and local irritant were added in relatively small amounts in addition to gelling agent. The NDA for this product was submitted to the FDA in January 2009 and granted priority review. In June 2009, the company announced the FDA would miss its PDUFA date [40] and a month later the company announced receipt of FDA complete response letter indicating there were issues with the potential abuse deterrent benefits of the product [41]. During the FDA advisory committee meeting in April 2010, doubts were raised about the effectiveness of using niacin as a deterring agent and the potential risk of niacin-induced flushing in patients. However, the FDA did state that other excipients present in the formulation that gel to deter injection and perform as in irritant during nasal abuse could be considered advantageous in the fight to prevent tampering. The company then announced it will resubmit the NDA for the product without the niacin [42].

USE OF OPIOID ANTAGONISTS AS DETERRENT AGENTS

The use of an opioid antagonist can be considered as the earliest approach to address opioid abuse problems. Several products containing opioid agonist/antagonist combinations have already been approved in the US and the world including Talwin® Nx (pentazocin/naloxone 50/0.5 mg; approved in the US in 1982), Valoron N (tilidine/naloxone 50/4 mg; approved in Germany), Targinact® (Oxycodone/Naloxone 2/1; approved in the UK) and Suboxone® (Buprenorphine/Naloxone 4/1; approved in the US in 2002). Since naloxone has very low oral bioavailability, the addition of this antagonist in relatively low doses was not expected to intervene with the drug analgesic effect when the product is administered orally, but to deter abusers from intravenous injection. The available data on the effect of using naloxone on changing abuse patterns are not conclusive. For example, the abuse of Talwin seems to have diminished after the introduction of Talwin NX [43]; however, it has been argued that the effect can be attributed to the availability of cheap heroin at the same time [9]. In addition, there were reports of addicts who still abused Talwin NX through the intravenous route [44, 45] and patients experiencing no overall decrease in the drug-induced euphoria with Talwin NX [45]. On the other hand, a survey of intravenous opioid abusers in Finland revealed the addition of naloxone to buprenorphine may have reduced its likeability and street value [46].

In 2009, the FDA approved Embeda® (Morphine sulfate/Naltrexone HCl 25/1). It is the first product to use naltrexone as an antagonist. Unlike naloxone, naltrexone is orally bioavailable and the combination product includes the antagonist in a sequestered form *via* the application of thick polymeric coating. The product is designed so that naltrexone has no clinical effect if the product is administered as directed but if the product is crushed, the antagonist is released in a significant amount. According to the Embeda approved label, a well designed abuse likeability study on 32 non-dependent, recreational opioid users revealed that 69% of subjects showed some degree of a decrease in euphoria with crushed Embeda compared to the same dosage of immediate release morphine [47]. The label also reflects a considerable, individual variability in the degree of reduction in drug liking and euphoria [47]. The data suggested that adding sequestered naltrexone afforded an incremental improvement in reducing drug liking after crushing, however, the real effectiveness of naltrexone in changing morphine abuse patterns is yet to be established. Other manufacturers have also showed interest in developing extended release opioids using the opioid antagonist approach [48-50].

REMAINING CHALLENGES

While the pharmaceutical manufacturers speed up their activities to develop innovative TDF, they are still facing major challenges regarding the clarity of the regulatory approval. A few years ago, when the concept of TDF was surfaced, the increased sophistication of abusers' tampering techniques posed serious questions on the validity of any claim of tampering deterrence. In the early FDA Advisory Committee meetings to discuss TDF, some of the committee members questioned the reliability of the proposed technologies in combating sophisticated abuser's techniques. In some instances, the reviewers even contemplated rejecting the new TDF on the ground that perceiving the new formulation as "safer" from abuse perspective can cause more harm than good. As more TDFs were discussed in these FDA Advisory committee meetings, a growing understanding that none of these new formulations will be abuse proof has emerged. The FDA Draft Guidance on the assessment of abuse potential of drugs concurs that TDF are expected to provide incremental improvement in combating abuser's tampering technique [51]. The guidance clearly stated that "the concept of abuse deterrence is viewed as the introduction of some limits or impediments to abuse, as

opposed to the outright elimination of abuse". While this represents a major improvement in assessing regulatory risk for the pharmaceutical manufacturers, a major residual risk is the lack of well defined testing procedures and acceptance criteria to judge the success of the introduced "limits or impediments to abuse". As described above, an *in vitro* extractability rating system to evaluate TDF has been published [15] but none is adopted by the FDA. Each manufacturer relies on internal and external expertise and the available limited information from competitors Advisory Committee meetings to design their "*in vitro* simulated tampering protocol". The contents of these protocols can be discussed with the FDA prior to NDA filing. However, with no clear success criteria, the outcome of executing these protocol fall short from securing regulatory acceptability, especially when these products continue to be the subject of Advisory Committee meeting discussions and voting.

Another challenge facing the developers of TDF is the ambiguity regarding the value these formulations can bring to their business. TDF are more complicated, more expensive to develop and carry higher regulatory risk compared to standard formulations. With the recent passage of the health care reform bill and the expected pressure on drug pricing, the financial incentive to develop TDF is questioned especially when the real benefit of these formulations will not be adequately assessed for years after the product is marketed (after conducting well controlled epidemiological studies). The FDA has expressed concerns about allowing the results of *in vitro* simulated tampering studies in the label since the data might provide the abusers with the needed knowledge to successfully extract the drug. The two approved TDFs (Embeda and reformulated Oxycontin) do not include any of these data in their labels. It is expected, however, that the FDA will allow the results of human abuse potential studies in recreational drug users in the product label (the Embeda label includes it; the sponsor of the reformulated Oxycontin did not conduct the studies). It is not clear if the FDA would allow the outcome of post marketing epidemiological studies in the product label. The inclusion of this data in the product label clearly provides a differentiating tool for the product. However the value of this differentiation in terms of Formulary adoption, physician acceptance, pricing and market penetration is yet to be established.

CONCLUSION

Prescription drug abuse continues to present significant health and socio-economical challenges in the US and the rest of the world. In response, numerous pharmaceutical manufacturers are engaged in developing new formulations that carry some tampering deterrent features. Several of these formulations are based on the use of physical and chemical barriers to impart drug extraction resistance. Others are based on the use of one or more deterrent agent. While the publication of the FDA [51] and Health Canada [52] Guidance on the assessment of abuse potential of drugs are steps in the right direction, the regulatory pathway for these products is still far from clear. The added complexity of these TDF and the lack of universally acceptable methods and criteria to assess and compare their effectiveness are the main causes of the regulatory uncertainty. It is generally believed that the true added value of these formulations will not be realized until well controlled epidemiological studies are conducted after these products are launched.

CONFLICT OF INTEREST

The authors of this paper are employed by Cephalon, Inc. who is engaged in the development of tamper deterrent products. The views expressed in the paper are those of the authors and do not necessarily represent the views of Cephalon, Inc.

Key Learning Objectives:

- Prescription drug abuse continue to pose major health and socio-economical problems globally
- Several pharmaceutical manufacturers are engaged in the development of tampering deterrent dosage forms for drugs of abuse but few have reached phase III clinical development or beyond
- Three major approaches are used to impart tampering deterrence: physical barrier, chemical barrier and deterrent agents
- There are no standardized and widely accepted procedures to test for abuse deterrence features *in vitro* or *in vivo*. Pharmaceutical manufacturers rely on internal and external experts to devise testing methods
- The regulatory landscape is evolving and with the continuous submission and approval of tampering deterrent products, some of the regulatory uncertainty will be alleviated
- The true added value of tampering deterrent formulations will not be realized until well controlled epidemiological studies are conducted after these products are launched

Future Research Questions:

- What are the best *in vitro* and *in vivo* testing methods to use in assessing tampering deterrent formulations during development? Can these methods be standardized among all formulations?
- What kind of post launch epidemiological studies is needed to assess the true values of tampering deterrent formulations? How much of the information collected in these studies can be added to the products labels and what kind of claims these products would be allowed to have?
- What is the true effect of these products on reducing the problem of prescription drug abuse?

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