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Risk identification, risk assessment, and risk management of abusable drug formulations☆

Curtis Wright IV, E. Douglas Kramer, Mary-Ann Zalman, Meredith Y. Smith, J. David Haddox *

Risk Management and Health Policy, Purdue Pharma L.P., One Stamford Forum, Stamford, CT 06901-3431, USA

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Abstract

There is a demand for pharmaceutical products with reduced abuse liability. These products must meet three tests to be successful. They must be safe for patients, be less likely to injure the abuser, and be less desirable for abuse by established drug abusers relative to existing products on a dose for dose (milligram-equivalent) basis. There is a need for standardization of the evaluation of abusable pharmaceuticals in the various stages of drug development from preclinical animal studies to postmarketing surveillance. Formulations with reduced abuse liability must: (1) be tested using standard animal, benchtop, and human pharmacokinetic methods that allow interpretation, (2) sufficiently reduce the recovery of abusable drug substance, or contain another ingredient to deter abuse, (3) not alter drug activity for patients in an undesirable or risky way, and (4) have an accurate pre-approval estimation of their reduced abuse liability, which is validated by adequate epidemiologic post-approval surveillance.

Keywords: Abuse potential; Prescription drug abuse; Regulation; Medical use

1. Introduction

Drug abuse involving medicinal products has been part of the American experience for well over a century (Musto, 2002). Periods of increased medical use of a drug product or class of products with abuse potential are usually followed by reports of abuse, medical or political concern, followed in turn by calls for increased restrictions on access. The language involved in the debate over drug control is often intemperate, the data are often suspect (Jenkins, 1999), the actions taken may or may not be effective in controlling the problem (Reed and Schnoll, 1986), and may have an adverse impact on patient care by reducing access to useful medications for patients without demonstrable benefit to the public health (Hoffman et al., 1991; Weintraub et al., 1991).

The expansion of the legitimate medical use of opioids (morphine, oxycodone, hydrocodone, fentanyl) and methylphenidate in the last decade of the 20th century coincided with an upturn in both drug experimentation among the adolescent population in the United States (cannabis and Ecstacy (3-4-methylenedioxymethamphetamine, MDMA)) (Substance Abuse and Mental Health Services Administration (SAMHSA), 2003a) and in the worldwide increase in illicit production since the mid-1980s of opium and coca, the starting materials for production of heroin and cocaine (United Nations Office on Drug Control and Crime Prevention (UNODCCP), 1999; United Nations Office on Drugs and Crime (UNODC), 2003).

Since the 1990s there has been an increased frequency of reports of non-medical use of opioids in the United States (SAMHSA, 2002a,b,c, 2003a,b, 2004). This increased frequency has been associated with increases in their medicinal use as well (Zacny et al., 2003; Gilson et al., 2004; Novak et al., 2004). There are significant concerns over hydrocodone abuse, oxycodone abuse (which some attribute to the introduction of OxyContin) and fentanyl abuse associated with increased prescriptive use of the transdermal (Duragesic®) and transmucosal (Actiq®) forms of the drug.

One of the results of this concern over prescription drug abuse has been a re-examination of the basic attitudes toward drug safety by all parties. Prior to widespread reports of abuse of OxyContin, most experts considered adverse events related to abuse and diversion of pharmaceuticals to be important events,

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* Corresponding author. Tel.: +1 203 588 7667; fax: +1 203 588 6242.
E-mail address: dr.j.david.haddox@pharma.com (J.D. Haddox).

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but primarily either a law enforcement or an addiction medicine problem to be addressed by drug scheduling and improved access to treatment. Concern over pharmaceutical abuse in the last few years has led to the inclusion of adverse events related to drug abuse (abuse, addiction, overdose) into the safety profile of the drug considered in treatment selection.

The public controversy over OxyContin abuse has changed public policy such that, in the United States at the present time, abuse of a pharmaceutical is considered part of the safety profile that should be considered by the FDA prior to approval of any drug with significant abuse liability. This always was considered, but now is considered to be a primary pre-approval concern, which should be managed through an appropriate Risk Management Plan in addition to control under the Controlled Substances Act (U.S. General Accounting Office (GAO), 2003; U.S. Department of Health and Human Services (DHHS), 2005a).

2. Perceived risk of abuse

A difference exists between the actual risk of drug abuse as measured by drug abuse specialists and scientists and the perceived risk from drug abuse of concern to the public. The public health concerns of the experts focus on the intrinsic rewarding properties of the drug as measured experimentally in the individuals most likely to abuse it. Their conclusions are based on comparative medical and scientific data for the drug substance (Sellers et al., 2003). The public, on the other hand, rarely has access to the facts available to a research scientist. Instead, the public must form its assessment of the situation from perceptions of the risks based on reports in the public domain for a specific drug product. Perceived risk can be quite different from "real" risk at the level of the general public (Slovic et al., 1980). For perceived risk, media mentions can act as a surrogate for real frequency, anecdotes replace medical and scientific data, and the emotional power of a single well-publicized event replaces comparative assessment of overall morbidity.

Thus, while the experts are rightly concerned about the risk of abuse in the high-risk population as a matter of public health, the public may be more concerned about dangers faced by the low-risk populations of which they are members. While the primary public health concern of physicians focuses on the prevalence and consequences of non-medical use of drugs by those with established histories of illicit substance use, the public may be more concerned about cases where experimentation by an adolescent manifests in a fatal overdose or in their own risk of being harmed by a medication intended to be helpful.

Because the two types of risk exist in society today (both the *actual*, most probable risks of drugs with abuse potential and the *perceived* risks of great concern to the public), any discrepancy or misalignment in these two classes of risk poses scientific, medical, regulatory, political and law enforcement problems. Social agencies must respond to perceived risk to maintain the confidence of the public, yet should craft responses that are science-based and effective in addressing the problems posing the greatest risk to the public health. In consequence, risk modification actions need to address both the public's risk and the public's trust. The next generation of new drugs and new formulations of existing, approved pharmaceuticals may need to address *both* the common and expected abuse problems of public health concern to experts and those less frequent events that are of great concern to the public.

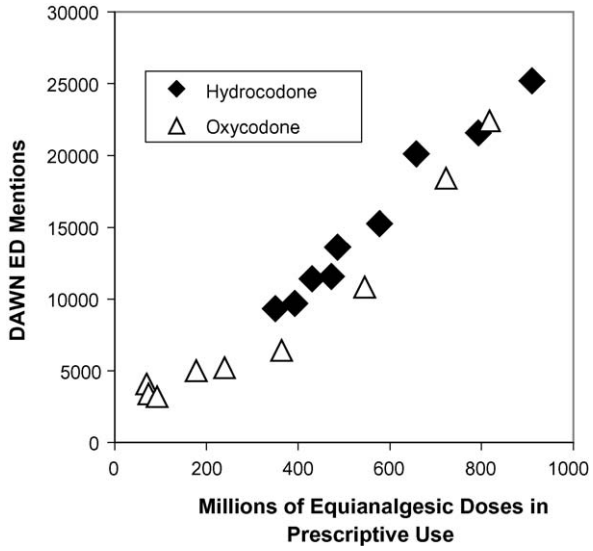

Fig. 1. The rate of Drug Abuse Warning Network (DAWN) Emergency Department (ED) mentions for hydrocodone and oxycodone for the years 1994–2002, corrected for the extent of use and potency. Source: Drug Abuse Warning Network & IMS Health's National Prescription Audit™ (cited with permission).

3. The most common abuse problem

The most likely problem for a new formulation is the risk of diversion and abuse by known abusers (Cicero et al., 1999). This kind of abuse problem is predictable, is the rationale for control via drug scheduling, and results in the majority of adverse medical consequences. As seen in Fig. 1, for the years 1994–2002, the number of DAWN (Drug Abuse Warning Network) ED (emergency department) mentions for hydrocodone and oxycodone is proportional to kilogram morphine-equivalents of the opioid available in prescriptive use (Dasgupta et al., in press). These data suggest that when a new pharmacologically-similar medication such as a new opioid, benzodiazepine, or stimulant, is introduced into medical practice, the extent of abuse expected under the established system of diversion control is a predictable function of the drug's availability, potency, and diversion profit potential (acquisition cost for medicinal use compared to sale price in the illicit market).

4. Less "liking" per milligram-equivalent

The first goal for the pharmaceutical designer intent on developing a product with less abuse liability is that the new drug substance or dosage form must be less desirable for abuse by established drug abusers, relative to existing products, on a dose for dose (milligram-equivalent) basis. There are multiple strategies being proposed to make new products that are less desirable than current products. Table 1 gives a partial listing of methods currently either discussed or under development.

Table 1
Strategies to reduce desirability for abuse

1. Strategies to slow rate of onset and peak effect
Pro-drugs slowly metabolized to active drugs
Tamper-resistant controlled-release dosage forms
2. Strategies to prevent tampering to enhance subjective effects
Sequestered aversive agents, inactivating agents or colorants
3. Strategies to limit dose-escalation
Partial agonist drugs
Agonist–antagonist combinations of drugs
4. Strategies to deter abuse by physically dependent persons
Antagonist mixtures which precipitate withdrawal with misuse

Table 2
Rating scale for degrees of tamper resistance

Level 0, no preparation needed for abuse
Level 1, readily prepared for abuse by all routes
Level 2 ,readily prepared for abuse by some routes
Level 3, requires extraction with simple solvents
Level 4, extracted only with advanced solvents
Level 5, not readily recovered with common methods[a]
Level 6, resistant to re-manufacture[b]

[a] Requires time, equipment and materials making abuse less practical than formulations with lower levels of tamper resistance.
[b] Separation results in low yields, requires costly industrial equipment or requires special expertise.

The most common strategy reported by the industry to reduce desirability for abuse is to create a tamper-resistant dosage form that increases the degree of difficulty required to recover its active pharmaceutical agent. While casual abusers may take a pharmaceutical intact for its psychoactive effect, experienced abusers often progress to snorting, sniffing, smoking or injecting their drugs, which are more reinforcing methods of administration. The reinforcing effects of drugs of abuse are related to the rate and extent of presentation of the drug to the central nervous system. Alterations in pharmacodynamic effect with alterations in the speed of onset of drug effect have been reported for most classes of drugs of abuse (Javaid et al., 1978; Griffiths et al., 1984; De Wit et al., 1992; Mumford et al., 1995; Marsch et al., 2001; Volkow and Swanson, 2003).

Tampering with oral or transdermal dosage forms to make them available by more efficient routes of administration is a well-established abuser practice. A study of new abusers of OxyContin shows that, in a specific subpopulation (i.e. young, females), crushing and snorting is the most common route of abuse (Dasgupta, 2003). Injection of crushed OxyContin was also prevalent among abusers. Dosage forms that are easy to prepare for abuse by multiple routes are most attractive, while dosage forms that resist such manipulation have been reported as less attractive (Brookoff, 1993). This raises the question as to the degree of difficulty needed to materially affect abuser preference and the methods to be used to quantify such "tamper-resistance". If reducing the ease or the efficiency of tampering is to be a credible strategy to reduce abuser desirability, then the methods used must be appropriate to the technology available to the abusers and predictive of the outcome.

4.1. Tamper resistance

Tamper resistance technologies are versatile. Patent references and press releases are found referring to "uncrushable" dosage forms which resist all but the most aggressive treatment with organic solvents, "bioactivated" dosage forms which require exposure to specific enteric conditions for release of active agents, "sequestered" dosage forms which release aversive or neutralizing agents only upon crushing, and other less conventional ideas. Since no modification of a dosage form can lower the abuse potential below that of the product used as intended, such reductions are likely to be quantitative, not qualitative or absolute. Tamper resistance technologies incrementally reduce the desirability for abuse of the dosage form by making it difficult or inefficient to free the active drug for abuse. Table 2 gives an example of an industrial rating scale for such products.

4.2. Compared to what standard?

Most current dosage forms have little or no intrinsic resistance to tampering for intranasal, transmucosal, oral or parenteral abuse. Over the last decade, as has been shown above, most drugs in a given schedule of control are relatively similar to each other in abuse liability once relative potency is taken into account. If products with reduced abuse potential (at premarket assessment) and lower actual abuse liability (measured post-approval) are to be developed, statements of relative abuse potential must be quantitatively expressed relative to a known comparator.

If a drug substance is currently on the market in an existing dosage form that is subject to significant abuse (e.g., oxycodone), obvious comparators are placebo and the most commonly marketed form of the drug involved in abuse. For a new drug not already on the market, a suitable comparator is the drug most frequently abused in the proposed indication or market segment based on the anticipated route of non-medical use. For example, if a new immediate-release oral opioid for acute pain is anticipated to be orally abused, the relevant comparator would be a hydrocodone combination product; if it is anticipated to be snorted or injected, the comparator might be oxycodone; and if the anticipated problem is transmucosal abuse, fentanyl.

4.3. Managing expectations

Even the most successful formulation strategies cannot reduce the abuse potential of a drug substance below that of the product taken as directed. If a drug has significant abuse potential improvements, its formulation can only reduce, not eliminate, abuse. It is likely, however, that tamper resistance can make a product significantly less vulnerable (Baum et al., 1987).

Reduced tamper vulnerability comes at a price. Recent presentations on at least one product showing promising reductions in apparent abuse potential (Friedmann et al., 2004) also showed a pronounced fed-fasting effect on pharmacokinetics (C_{max} fasting 3.88 ng/mL, C_{max} fed 10.93 ng/mL; 282% increase) (de Kater et al., 2004). This and similar findings with agonist-antagonist combinations (Sunshine et al., 1988) show that abuse-

resistant formulations cannot be judged on the basis of abuse-resistance alone, but must also prove safe, tolerable, and effective in patients. An abuse-resistant formulation which is not safe and effective in the treatment of patients is not an advance in therapeutics.

Thus, there is a four-fold test for new tamper resistant formulations. Experience has shown that practical new formulations must: (1) be benchtop tested using methods that are sufficiently standardized so as to allow interpretation, (2) reduce the recovery of uncontaminated or "abusable" drug substance by an amount sufficient to be useful in deterring abuse, (3) not alter drug activity for patients in an undesirable or risky way, and (4) have the pre-approval finding of reduced abuse potential confirmed by post-approval surveillance.

4.4. The problem of human testing of tampered dosage forms

The strongest evidence available of reduced abuse liability for a pharmaceutical is a properly conducted human abuse liability study. Experts and human laboratory facilities are available that are knowledgeable in this area, and the results of these studies have proven highly predictive of the abuse liability of drug substances, but the inclusion of abuse liability studies in the phase 1 portfolio for commercial new drug applications has not always gone smoothly. Ethical and safety concerns may pose significant resistance to the conduct of these types of studies in laboratories not accustomed to this research, and the doses used are such that interpretation may be complicated. To be successful, human abuse liability studies must be conducted in drug-abusing populations, with appropriate designs and controls to allow for interpretation, in a manner that is of acceptable risk to the subjects. Regulatory agencies and sponsors must be prepared to accept the validity of these data for purposes of decision-making.

It is easy for regulators to require a study that Institutional Review Boards for human subject protection will not allow to be conducted, or for regulatory officials in different nations to disagree with the dose, dose range, or comparators used for a particular study. There are many things that abusers and people suffering from addiction do that are sufficiently unsafe so as to be of unacceptable risk to any responsible human subjects review board. Therefore, however urgent the need, many of the activities of abusers cannot be safely studied. When studies cannot be performed in safety, they must not be considered.

There is a need for thoughtful review and expert agreement on when human abuse liability testing is necessary and how it should be performed. Examples of typical problems involve testing intranasal abuse (How safe is insufflating ground drug product? Is it the same as insufflating a pure solution?), testing parenteral abuse (Do we try to filter and inject extracted drug product after heating it in a teaspoon, or do we administer a suitable parenteral dosage form at a dose based on recovery from benchtop tampering studies?) or transmucosal abuse (How does one safely test abuse techniques that have been associated with abuser deaths?). Evaluating these issues is very different from testing the efficacy or safety of a product when it is used as directed, and is subject to practical and ethical constraints that are always difficult, and often present insurmountable barriers to accomplishment.

Human abuse liability testing should be conducted in drug-experienced subjects able to differentiate the effects of drug and placebo, where the trial conditions and comparators address the hypothesis under test and where the experimental administration of tampered (risky) dosage forms is kept to the minimum number of studies, subjects and doses needed to determine the truth or falsity of the hypothesis. Many dosage form-drug abuse issues can be successfully addressed by animal, benchtop and human pharmacokinetic studies. If the data from such studies are clear, human abuse liability testing should not be done. In the case of high-risk products or where claims of reduced abuse potential are not self-evident, one or two judiciously selected and designed human studies are appropriate. Human studies where the knowledge base is such that no one experienced in the field seriously doubts the result should not be performed. Examples of such situations would be products containing amounts of aversives already shown to be poorly tolerated (e.g. human trials of injecting intravenous capsaicin) or cases where benchtop or pharmacokinetic studies show the yield upon a broad range of tampering techniques to be de minimus.

5. Overdose risk

Most members of the general public and their physicians do not feel any personal sense of risk when they are told that known drug abusers or people suffering from drug addiction are abusing pharmaceuticals. Such behavior is expected, and is considered (in part) to involve some degree of a voluntary assumption of risk undertaken by the participant. Members of the public are concerned, however, with the risk that an adolescent will experiment with abuse of a pharmaceutical, and then overdose and suffer a fatal or disabling outcome. No one wants a foolish act by an adolescent to become a permanently disabling or lethal event. Lower priority, but related and significant risks are also of concern to the public. Parents worry that the abuse of a pharmaceutical may be considered by adolescents to be "safe" or of "low risk", and become so common that it acts as a "gateway" drug into illicit drug abuse in the schools with attendant morbidity and later involvement with illicit drugs. Pharmacy owners, health care professionals, and the public at large are also concerned that the profits from diversion of pharmaceuticals can be so high as to foster serious criminal behavior with its attendant risks.

The "hardened" dosage forms under development have been reported to have markedly lower yields upon tampering, which may act to protect the abuser (Friedmann et al., 2004). It is expected, but unproven, that "aversive-" or "antagonist-" containing dosage forms may act to protect the abuser by reducing overdose. It is possible that "agonist–antagonist" mixtures or "hardened" dosage forms may also act to reduce lethality risk in overdose situations. Such claims can usually be supported pre-approval only by animal testing in valid and predictive models, and not by clinical trials of overdose in humans. Some pharmacological effects (slow conversion of a pro-drug or antagonist effects) can be safely examined in clinical studies (e.g., respi-

ratory depression studies). Some effects can be demonstrated pharmacokinetically (enough antagonist is absorbed to reverse any practical level of opioid action), and some effects can be demonstrated in preclinical models of respiratory depression or other limiting toxicity. Current anesthetic research technology allows for non-destructive testing in animal models that is highly predictive of many human effects for some drug classes. Standards also need to be developed in this area to allow for responsible comparisons and for allowances for known covariates such as the concurrent effects of alcohol ingestion, which is a frequent part of abuse-related overdose in humans.

If a product is to be considered to be protective, testing should be conducted that involves probable drug–drug and polydrug interactive toxicity. One example would be if a novel dosage form of a new sedative is expected to provide some level of protection against overdose, it must be tested in a relevant species and model that includes alcohol co-administration, owing to the extremely high frequency of involvement of these two agents with fatal overdose (Cone et al., 2004). The rule here should be one of parsimony, since programs to study interactive toxicity routinely balloon out of control in size and complexity. If the most significant abuse-related interactive toxicity with a class of pharmaceuticals is either known or can be elucidated, then the testing should address this *most likely common problem*, not all possible interactions at all possible doses.

6. Physicians' concerns about patient safety

One consequence of pre-existing abuse being common, and iatrogenic abuse or addiction being uncommon is that new drug formulations are rarely studied in high-risk populations. Review of the Warnings, Precautions, and Safety guidances for most abusable drugs in the Physician's Desk Reference reveals that very few drugs were ever studied in patients at high risk for abuse and diversion of their study medication as the direct result of active exclusion of such patients from clinical studies on ethical grounds. It is now clear that this situation, which is similar to the situation in pediatrics a decade ago, has excluded a clinically-relevant population from study, and has had a similar result, specifically, a paucity of information as to the relative risk of different medications in this class, relative to one another, in high-risk populations.

One consequence of the low risk of abuse or diversion in genuinely low-risk patients is that physicians are concerned about *any* additional risk to patients posed by tamper-resistant or abuse-resistant medications. Rightly or wrongly, physicians rely on their clinical skills to avoid prescribing to patients with unmanaged pre-existing drug problems and perceive most of their patients as low-risk, non-abusing patients with legitimate medical need for controlled substances. Given the recent increases in prescription drug abuse, this means that new formulations must be sufficiently studied such that any increased risk to low-risk patients, relative to conventional formulations, is acceptable. This includes both serious irreversible adverse events or common, non-serious adverse events. The only exceptions where an increased risk may be acceptable to physicians are cases involving geographic areas or practice settings where abuse has become a significant local problem, prescribing for patients already known to be in the high-risk category, or in cases where the formulation has potential for increased efficacy or tolerability even under normal conditions of use.

7. Numerators, denominators, rates and paradoxical effects

If a drug has been tested pre-approval and credibly found to have a lesser abuse potential than alternative therapy, this does not guarantee that the benefits of the drug will be accepted. This is because postmarketing surveillance for abuse typically does not consider the benefit to patients. Therapies that are more widely used because they are safer may be erroneously perceived as presenting a greater risk of abuse.

Such a situation has occurred with buprenorphine, the mu-opioid receptor partial agonist. As discussed by Jasinski et al. (1978), buprenorphine is judged to have a lower abuse potential than codeine or propoxyphene in formal abuse liability studies, and has other properties consistent with reduced abuse liability (Strain et al., 1992; Walsh et al., 1994; Strain et al., 1995; Walsh et al., 1995). Because of these and other properties, buprenorphine has been widely used for substitution treatment in France since 1996. Reports from France show an 80% reduction in opioid overdose deaths following the introduction of buprenorphine substitution treatment in primary care (Ministry of the Interior, 1999). Considerable attention, however, focuses on the relatively few cases of overdose associated with buprenorphine therapy, some of which appear to have been reported more than once (Reynaud et al., 1998; Tracqui et al., 1998a,b; Kintz, 2001).

Because of this reporting bias, it is critical that the abuse potential and abuse-resistance of new medications be established in pre-approval testing. It is also essential that methods for controlled scientific observations concerning comparative abuse liability of different substances with similar indications achieve broad acceptance in the medical community. When a new drug is subjected to postmarketing surveillance, the methods used must conform to accepted epidemiological standards. The importance of adequate epidemiologic study to validate the pre-approval assessment of abuse potential cannot be overestimated. Such an effort to quantitatively examine the buprenorphine-associated deaths in France confirmed that the *rate* of buprenorphine-associated deaths was less than that associated with methadone in the same indication (Auriacombe et al., 2001).

Such comparative observations are essential if unwarranted changes in prescribing practices are to be avoided. Unwarranted changes in prescribing have occurred in the past and were associated with serious negative public health consequences. For example, general practitioners in Scotland stopped prescribing buprenorphine for analgesia because of concern about its non-medical use; this was associated with an increase in opioid overdose deaths (Hammersley et al., 1995). Conditions placed on benzodiazepine prescribing in New York State, led to an increase in prescribing of less desirable alternatives (Weintraub et al., 1991).

8. Postmarketing surveillance of drugs with abuse potential

Consistent with the call for standards for assessing comparative abuse potential during the pre-approval period, there is a corresponding need for accepted methods concerning the conduct of pharmacovigilance and pharmacoepidemiologic assessment in the postmarketing context (DHHS, 2005b). Concurrently, there has been the acknowledgement that many of the pharmacoepidemiologic practices in use at the present time are not well grounded scientifically.

The goals of postmarketing risk assessment include: (1) characterization of a product's risk profile in comparison to its benefits, (2) epidemiologically sound comparison of the product to those products providing similar benefit, and (3) the provision of accurate pharmacovigilance data for guiding informed decisions regarding risk minimization activities. In order to achieve these goals, both appropriate data and appropriate tools are needed. Postmarketing surveillance can be conceptualized as consisting of two phases: screening, and confirmation, corresponding to the hypothesis generating and hypothesis confirmation paradigm long familiar to the FDA. The purpose of the screening phase is to gain an accurate and comprehensive picture of the scope of the perceived abuse problem. Screening efforts are designed to detect potential signals, events, or clusters of events that exceed a threshold. Confirmation occurs in response to a potential signal and involves a more detailed investigation to confirm or disprove the existence of an actual abuse problem in a given location. Confirmation of a problem, in turn, triggers the development of a tailored risk minimization response. In order to fulfill these disparate functions, screening approaches must be highly sensitive, while confirmation requires greater specificity. There is a need for the development of a standard protocol for conducting postmarketing investigations to adequately differentiate real from perceived problems.

Important domains of impact to address in the screening phase include the individual, the health care system, the criminal justice system, and the workforce. Another relevant dimension, the continuum of drug involvement (i.e., from accidental overdose to addiction), should also be tapped. Reliance on a limited number of sources that sample from small select sections of the drug abuse continuum (e.g., treatment admissions data that are reflective of the drug addicted population only) can result in a distorted and potentially misleading picture that omits events of potentially greater significance to the general public such as adolescent overdose.

A number of extant datasets are available in the U.S. within the public domain that can provide relevant information. Examples that provide healthcare system-related information include DAWN, which collects information regarding drug-related visits to emergency departments and drug-related deaths in select jurisdictions and the National Survey on Drug Use and Health (NSDUH), an annual cross-sectional survey which provides estimates of the number of individuals abusing specific substances by state, region and nationally. Both are sponsored by SAMHSA. Similarly, Monitoring the Future (MTF), a federally-funded cohort study, tracks patterns of non-medical drug use among adolescents and young adults in the U.S.

In addition to these public sources, a host of proprietary sources exists as well. The Toxic Exposure Surveillance System (TESS) provides detailed data on individual cases involving intentional and unintentional exposure to prescription drugs and other substances reported to regional poison control centers nation-wide. This and health insurance administrative claims data can be obtained for a fee. The claims databases yield some information on the direct and indirect costs associated with prescription drug abuse among the employed population (Office of National Drug Control Policy, 2001).

Several other attributes are vital to the adequacy of a surveillance system. These include: definitional consistency (e.g., definition of key categories such as misuse and abuse are not used consistently across pooled studies/data sources); representative geographic coverage and specificity; timeliness. Given the dynamic nature of prescription drug abuse, the latter two elements are especially important. Temporal and geographic specificity enables surveillance users to distinguish typologies of drug abuse as manifested in a geospatial context. This capacity is vital for informing effective policy responses, for developing predictive models regarding the trajectory of drug abuse within a given locality, and for planning, implementing, and evaluating the impact of risk minimization actions. A system with minimal lag time between actual occurrence of a drug abuse-related event and its detection by the surveillance system is superior in terms of sensitivity and permits a response to be undertaken that may help slow, or contain, an emerging or developing problem in a given area.

As many extant sources of data have shortcomings in one or more of these areas, there is a need for the inclusion of well-designed primary data collection initiatives within the surveillance framework. Possible examples include the establishment of key informant networks from among the research and drug treatment communities, and surveys of law enforcement and criminal justice populations.

Comprehensive and systematic approaches to selecting and collecting numerator information to include in the surveillance system are important. Careful selection of both the type and quality of numerator data is critical in order to protect against systematic bias in risk assessment, and more specifically, bias in signal detection. Studies incorporating active surveillance, which have less response bias than passive approaches, are another hallmark of a high quality surveillance operation.

To date, misuse, abuse or diversion of prescription drugs has most commonly been reported in terms of raw counts or relative percent change (Joranson et al., 2000; Zacny et al., 2003; Gilson et al., 2004; Novak et al., 2004). While such values provide information about the absolute magnitude of occurrence of abuse or diversion, standardized measures in the form of rates are needed to make valid comparisons of estimates across drugs and relevant categories such as age, gender, and geographic areas (Gail and Benichou, 2000). Rates can take into account differences in population, medical access, and the level of medicinal use of drugs that share the same class or indication, thereby permitting valid analyses of trends, comparisons of different products in

terms of the relative rate of associated abuse cases, and determination of a product's risk-benefit profile (Riegelman and Hirsch, 1996).

To date, no readily available data concerning the number of individuals at risk for abusing prescription drugs exist. In the absence of these data, various proxy measures or denominator "candidates" can be used. These include: (a) census data; (b) number of kilograms of chemical compound distributed; (c) number of prescriptions dispensed; (d) number of unique recipients of a dispensed drug (URDD) prescribed; or (e) URDD-days of exposure to the indicated drug or comparators. Census data are the least valuable for the purposes of inter-drug comparisons because they do not allow for adjustment of differences in the level of medicinal use across different products and compounds. Similarly, data on the number of kilograms of a pharmaceutical distributed at the retail level are publicly available only at the state level, do not adjust for differences in drug potency, and are not released on a timely basis (Joranson et al., 2000; Gilson et al., 2004; Novak et al., 2004). In contrast, the number of prescriptions dispensed for the drug of interest accounts partially for differences in potency and drug exposure (Zacny et al., 2003) but also has several limitations. It does not adjust for differences in the size of the average prescription across products. Far more prescriptions are dispensed for short-acting as opposed to long-acting medications but the prescribed days supply for the short-acting drugs is on average much smaller than that for long-acting medications. As with the number of prescriptions, estimates of the number of unique recipients of specific products for a designated region and time period are available, but at a price, from commercial vendors of retail prescription data. Advantages of using URDDs as a denominator are that it adjusts for differences in the level of medicinal use of each product and is expressed in units similar to the numerator. Most importantly, expressing the ratio of cases of abuse that occurred per number of URDDs provides a risk-benefit profile that can characterize both the absolute and relative burden of abuse imposed by a given drug on a given community, even though the risk may not necessarily be occurring to the individuals who benefit. Rates based on the number of URDDs, or URDD-days of exposure, however, do not count in the denominator those exposed via illicit means through drug diverted from the legitimate distribution chain, nor do they account for legitimate exposure through means other than outpatient retail channels, such as hospital pharmacies, long-term care facilities, hospice or direct administration to hospital inpatients.

Consensus regarding both the type and characteristics of numerator and denominator data to include in a prescription drug postmarketing surveillance system promises to enhance significantly the quality and applicability of assessment efforts. The utilization of standard epidemiologic principles and methods to the investigation and monitoring of prescription controlled substance abuse can advance the state of the art of prescription drug surveillance and help ensure that data are defensible when subjected to scrutiny by both lay and expert consumers. It is essential that drug regulatory decisions must be based on the best available science.

9. Pharmaceutical development; promotion and advertising claims

The high cost of development of a new product means that it cannot be made and sold at as low a cost as a "mature" or generic product that has already paid back the cost of development. If the product is to be sold at a profitable price it must be able to make justifiable claims that it is better (e.g., more effective, safer, better tolerated, has less risk in overdose, has less risk of abuse or diversion, etc.) than conventional therapy. Recent experience in the U.S. with claims (made pre-approval) that the coxibs (selective inhibitors of COX-1) should have less risk of patient injury due to lower gastrointestinal toxicity than conventional NSAIDs has undoubtedly made regulatory agencies reluctant to accept pre-approval safety claims that encourage rapid adoption and widespread usage.

The consequences for abusable drugs are that the current level of ICH (International Conference on Harmonisation on the Technical Requirements for Registration of Pharmaceuticals for Human Use)/FDA mandated chemistry and manufacturing, preclinical, clinical pharmacology and clinical testing impose a prohibitive barrier to capital investment unless a commercial investor can be assured that claims of lower risk of abuse (lower abuse potential) or lower risk if abused (improved patient and abuser safety) can be made for the product at the time of launch and initial promotion. Simply put, third-party payers will put a drug on formulary and reimburse its use only if there is substantial evidence that the result will benefit the patient, the prescriber, the public or the payer. This will require the establishment of a strong academic consensus as to the level of scientific evidence needed to support a claim of less abuse potential premarketing and to sustain it postmarketing. If the professional organizations are unable to make such a case, then it is unlikely that any of the promising inventions currently being considered will actually become a new drug. No one will risk millions of dollars in an investment if there is no assurance that supportable claims cannot be made that will result in a fair return.

10. The path forward

The path forward to managing claims for abuse-resistant drugs is to establish a set of common standards of surrogate evidence (benchtop, preclinical, human abuse liability and clinical studies) that would allow a regulatory agency to approve a new drug as having lower abuse potential at the time of approval. The new drug could then be examined in postmarketing studies to see if it were truly "abuse resistant" (less abuse or consequences of abuse relative to a suitable standard) after it has been placed on the market.

This strategy would require a reduced abuse potential claim to be proven by substantial evidence from adequate and well-controlled benchtop, animal, and human data that meets accepted standards, but not require that academic experts, FDA personnel or commercial developers take the risk of predicting the future (what will happen after the product is launched). No one can tell with certainty, in advance, what drug abusers will or will not do. Confirming these claims post-approval means that

Table 3
Needed standards in evaluating abusable pharmaceuticals

Standards for which drugs need abuse-liability/tamper-resistance testing
Methods for quantitative estimation of additional risk posed by tampering
Standard benchtop methods for tamper testing
Animal models of overdose suitable for dosage form testing
Animal models of abuse liability testing of intact and tampered dosage forms
Human laboratory testing methods for intact and tampered dosage forms
Standard methods for abuse and diversion evaluation in clinical trials
Standards for mandatory inclusion of high-risk patients in clinical trials
Terminology and standards for assessing and communicating level of abuse risk
Standards for phase IV study and pharmacovigilance of abuse risk(s)
Standards for selection, application and evaluation of Risk Management Programs
Standards for modification and amendment of ongoing Risk Management Programs

every such drug would have to be followed after approval to prove the truth of the claims. If a drug developed an unanticipated abuse problem after launch, the claims would be modified accordingly, the usage of the drug modified or, if appropriate, the drug could be removed from the marketplace. In order for such an approach to be effective, there must also be wide acceptance of epidemiologic principles of pharmacovigilance and risk management to assure that better, safer drugs are not inappropriately considered to have greater liability to abuse merely because they are more widely used.

It is very likely that any new product claiming to have significantly reduced abuse potential will have to undergo formal evaluation of its abuse potential prior to approval. Recent legislation requires DEA review of Risk Management Plans for all schedule II and other narcotic drugs requiring a procurement quota, making it similarly likely that any claim of reduced abuse potential will need to be substantiated postmarketing. Results of both pre-approval and postmarketing evaluations must be communicated to prescribers, patients and the public as part of the research, approval and labeling process. The public expects to know what the experts know about the safety of medicines as soon as the experts know it. In the case of medications with abuse potential, this will require that standards be established so as to allow meaningful, scientific evaluation, rather than the anecdotal and arbitrary judgments typical of this area of public policy in the past.

Table 3 sets forth the areas in which standards must be established so as to encourage the development of safer drugs and dosage forms to the benefit not only of the patients, but of abusers and adolescents at risk as well. It is felt that with the development of such standards and the movement of these concerns forward with regulatory agreement, the dual goals of patients having access to needed pain medications, and limiting the access of highly abusable products to those who would use them illicitly, can be achieved.

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