Industry Testing of Opioids for Differential Schedule Control Purposes: Abuse-Deterrent Formulations

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Abstract

Drug deterrence should not be viewed as “abuse proof” or “diversion proof”. If the abuse deterrent formulation (ADF) provides for a C_max and half-life of parent compound that is conducive to maintain plasma opiate levels or abate drug withdrawal then compromising of the drug deterrence formulation seems irrelevant to the majority of street consumers - those that consume an opiate outside the scope of medical practice. It is an error in judgment to think that all opiate dependent street drug-seekers of pharmaceutical grade opioids are looking to inject snort, or smoke extracted drug product. Under the Comprehensive Drug Abuse and Control Act of 1970 (CSA) substances are controlled by chemical nomenclature and scheduled in one of 5 levels of controlled access to the drugs. The CSA does allow for differential scheduling of specially designed formulations of a given drug substance due to the reduced likelihood of access to the drug through ADF strategies. The inclusion of “special testing” in standard preclinical screening should be based on established and known trends and patterns of clandestine laboratory or street use of similar drug products. This review is intended to describe typical patterns of drug diversion and standardized methods used to administer the drug outside the scope of medical practice, or to divert for drug extraction. These may have relevance to the testing of new product formulations that are being developed as tamper-resistant or tamper-proof products with the intent of requesting differential scheduling.

ABSTRACTIONS

FDA: Food and Drug Administration; DEA: Drug Enforcement Administration; ADF: Abuse Deterrent Formulation; API: Active Pharmaceutical Ingredient; BUP: Buprenorphine

INTRODUCTION

There are two competing interests in the development and sale of opiate-based medicines within healthcare and law enforcement agencies. The Food & Drug Administration is charged by Congress (and statutes) to ensure safe and effective drugs are available for the legitimate treatment of pain. Untreated pain is associated with unnecessary suffering, progression of underlying diseases, depression, decreased enjoyment of life, and reduced productivity. In contrast, the Drug Enforcement Administration is charged with the enforcement of international treaty obligations as well as Congressional mandates to prevent diversion of drugs from the legitimate supply chain while maintaining sufficient bulk materials for medical use and research.

International drug control treaties [1-3] bind the U.S. government health and law enforcement agencies to limit the access to psychotropic drugs and dependence producing drugs, in part, through the enactment of the long standing Comprehensive Drug Abuse and Control Act of 1973, also known as the Controlled Substances Act [4] (CSA). The development of effective, non-addicting pain medications is a public health priority set by the National Institutes of Health [5], and the development of abuse-deterrent formulations (ADFs) is a health priority for the FDA, as well [6]. In the recent FDA guidance document the health agency acknowledged:

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. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Under the FDA guidance document, the evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier routes. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases. Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product.

It should not come as a surprise that new “lock tight” formulations designed by pharmaceutical industry pharmacologists are “unlocked” by an avid drug seeker soon following market release. It’s been said, “A lock does no more than keep an honest man, honest.” [7]. No one formulation can be expected to deter all types of opioid-abusive behaviors and no product is likely to be abuse proof in the hands of clear and determined abusers [8-13]. Drug seekers are extremely resourceful and show little “brand loyalty” to a particular opiate derivative when other drugs are available [14]. It’s been said that “necessity is the mother of invention” and the motivation to establish a sustainable source of pharmaceutically pure opiates by a drug seeker establishes the necessity.

Methodologically, the abuse liability studies to assess the relative likelihood of diversion from the products intended purpose and route of administration should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). The manufacturer has to “think outside the box”. Most pharmaceutical pharmacologists spend their days in pristine, almost antiseptic GMP-environments and have had little training or experience in clandestine laboratory or “kitchen-extraction” methodologies. Testing should provide information sufficient to fully characterize the product’s abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing in vitro studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product. This review is to familiarize the reader to some basic but standard sources of information, extraction methodologies, and street “locksmith” techniques used to divert pharmaceutical grade opiates to use outside the scope of standard medical practice.

Our intention is not to provide a “how to” source of information to non-scientists. Based on the information we are providing, any academically-trained pharmacologist should be able to consolidate the information and incorporate it into their standard laboratory tests conducted with “lock tight” protection. Drug diversion is the intentional delivery of GMP-grade active pharmaceutical ingredients from the structured “closed” supply chain for the purpose of drug administration outside the scope of medical practice. In the FDA’s drug deterrence guideline they clearly acknowledge the fact that a product that is promoted to have abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must, in the end, be able to deliver the opioid to the patient, there may always be some abuse of these products. The critical issue that requires resolution is how much “hypothetical risk” has to be lowered before drug control review on the formulation meets the international and national standards for differential schedule control.

It should be paramount to all manufacturers of opiate-based medications to acknowledge that, for centuries, opiate alkaloids have served as currency. Their value in an industrial society characterized by the fast pace, highly competitive, and stressful environments of both work and home should not be underestimated. While the medical community has repeatedly demonstrated that opiates are not effective in the treatment of chronic pain, manufacturing quotas of metric tons of opiate derivates are approved yearly by the U.S. Drug Enforcement Administration. The prescription of a pain medication, like morphine, hydrocodone, oxycodone, or hydromorphone, is the best source of high quality, uncut opioid sought by all illicit end users. Standard heroin supplies are generally poor quality; cut several times down the supply chain, or have the potential of being laced or supplemented with unknown chemicals to boost the purity of the street sample (i.e., talc, Levamisole, synthetic clan-lab fentanyl). For those individuals seeking to “feel normal”, “prevent feeling sick”, or to “tune out” the tablet, capsule, patch, or lollipop opiate need no tampering or extraction methods applied. Swallowing the tablet, capsule, or pill is the end goal for the majority of people using opiates outside the scope of medical practice. Statistics from emergency rooms are a nice adition to standard grant applications, but the majority of opiate drug seekers take the drug “as directed” by the intended route of administration - just without a prescription. However, for those who seek the “euphoria”, “rush”, or “coasting” associated with snorting or injecting powdered product then extraction techniques become a priority.

With the growth of the internet and its associated search-engines it doesn’t take a novitiate long to find “chat rooms”, “blogs”, or document libraries that provide information as to the best methods to compromise the final formulated product:
Many cookbooks, instruction manuals, and "how to" guides for the clandestine manufacturing of psychoactive substance are available through bookstores, web-based book suppliers and even local libraries. These books not only give detailed instructions on how to manufacture illicit drugs in your kitchen, they also provide step-by-step procedures and descriptions of standard kitchen equipment that can substitute for laboratory glassware or standardized chemistry apparatus. Here are just 3 of these sources of information available to the interested reader at any bookstore:


The diversion of pharmaceutical products from the intended route-of-administration or for the intended use of the product that is described on the FDA-approved label is not always governed by an interest to modify the "rate-of-change" in plasma drug concentrations (i.e., snort, or inject the drug). Ultra-high potency opiates (> 20 to 160 mg active compound per tablet in some formulations) have the interest of the drug seeker because of the confidence in the pharmaceutical purity of the active ingredient contained within them - an opiate abuser in withdrawal doesn't feel well. Feeling the rush from an injection has long since diminished by tolerance development in most of the heroin users of diverted medications.

The FDA guidance document highlights the need for opioids without abuse-deterrent properties to remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed. As a general framework, FDA has characterized abuse-deterrent formulations:

Physical/chemical barriers - Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.

Manufacturers have utilized standard pharmaceutical hardness testers (such as PTB 111E, Pharma Test Apparatus AG, Hainburg, Germany) to demonstrate the resilience to crushing of the final opiate formulations. The hardness test results are used to defend the argument that the formulation is resistant to illicit attempts to achieve a final powdered form of the API that can be used for insufflations or dissolved and heated for IV injection.

Historically, all diversion-proof tablets analyzed by experienced "special testing laboratory" personnel (e.g. Drug Enforcement Administration, Special Testing and Research Laboratory, Dulles, VA) or a motivated drug seeker easily "break the code" with in a few trials using standard clandestine laboratory methods. As stated above, no one formulation can be expected to deter all types of opioid-abusive behaviors and no product is likely to be abuse proof in the hands of clear and determined abusers [8]. The claims of a reduction in abuse of these new products is the dilemma faced by drug control regulators who must comply with national and international initiatives to reduce diversion from the supply chain yet retain access to those drugs for legitimate medical need. To date, we know of no definitive monetary gain or loss based on which specific schedule an opiate is placed at the time of the NDA review. MS-Contin™, Oxycontin™, Opana™, and other high potency opiates in Schedule II, the strictest schedule of control for drugs deemed to have "medical use" by the FDA, have had astronomical yearly sales as listed in the IMS Health pharmaceutical databases published yearly in the Pharmacy Times. There is little indication that schedule status has influenced the prescription patterns, retail sales, or their payment by the patient or their insurance carrier.

Compromised opioid tablets

There seems to be a generally held presumption that the drug seeker will attempt to use a heavy implement (hammer) to crush the pills for administration. The street user knows the value of the conservation of energy. Drug seeking, thefts, or engagement in illicit behaviors to achieve currency to buy more drugs is often times arduous. The street pharmacologist or drug seeker should not be presumed or expected to expend much energy on a pill-by-pill extraction method. Figure (1) shows the typical utensils used by "mom and pop" drug diverters to compromise the physical barriers imposed by patented manufacturing techniques.

Depending on the intent of the user, individual (left image) or group supplies of powered materials (right image) can be crushed using a commercially available manual (left image) or electric pill crushers (right image). The manual pill crushers are available at any local pharmacy. Legitimate retail suppliers of the commercial grade electric models are available on the internet or they can be obtained by theft (Figure 2).

Moderate scale conversion of prescription opiates from pill to powder is easily conducted with standard kitchen appliances such as a stand-alone or multi-speed motorized spice or coffee grinders. Receiving a prescription for 60 tablets of Endo Pharmaceuticals’ Opana ER™ tablets will provide an adequate source of high potency oxymorphone substrate that can be used for insufflations, for further extraction methods to assist IV street users, or for sale. If a personal use supply is needed, other kitchen equipment is often recruited into the diversion process (Figure 3).
Nutmeg graters or microplanars are oftentimes used to convert pill into powder. When the kitchen department of the local hardware store or department store is short of supply of these kitchen accoutrements, the drug diverter may look to the bathroom department (Figure 4).

It’s not a large shift in methods to move from nutmeg planar to callous removers to break down hard pills to usable powder. And when all else fails, the internet promotes the use of common items in the tool-box.

Website information promotes the use of hand-held electric rotary tools to grind down prescription tablets to powder (Figure 5; left panel) and also promotes the use of standard jewelry ultrasonic cleaning tanks filled with common household solvents to extract the intended API from the legitimate formulation packaging or from the rough-cut tablets.

Once crushed into “pill crumbles” or to fine powder the opiates need not be targeted for IV dose administrations. Rough cut pill crumbles that expose the inner matrix of the pills and compromises the slow or extended release formulations can be simply spooned or sprinkled into the central area of a facial tissue or a square of toilet paper (Figure 6A). The ends of the paper are twisted around the central pile of loose materials (Figure 6B). The wadded drug load is then swallowed with or without liquids.
The thin degradable paper prevents tasting the crushed tablets and dissolves rapidly in the stomach. This is a method commonly referred to as "parachuting" the drug.

Similarly, the rough cut drug product or "pill crumbles" can be placed into a 4-6 ounce saline retention enema (over-the-counter preparation with lubricated tip) and injected into the anus to the lower bowel [15-18]. The absorption area of the lower bowel provides for a rapid onset of action. On the street this procedure may be referred to as "booty bumping" or "booty shooting".

**Extraction of API from tablets (for injection, insufflations, or other routes of administration)**

Multiple internet chat rooms, blogs and social video platforms provide detailed methods of "cold" drug extraction. Once the tablets have been deconstructed into particles or powder, standard solvents are used for extraction of the API. For cold extraction techniques the solvents vary but they generally are common easily accessible supplies such as:

- Ethanol – vodka, Everclear®, gin
- Denatured alcohol
- Isopropyl alcohol
- Methanol
- Lighter Fluid
- Camp stove/Lantern fuel, aka ‘White Gas’ or Naptha

To buffer or adjust pH, household white vinegar, baking soda, drain cleaner, or lye are often promoted. A series of mixing, settling or resting, freezing and acclimating back to room temperatures set into motion the removal of the API from the matrix with the final solutions filtered using standard coffee filters within 8 hours of extraction initiation. With a full months prescription of high potency opiate tablets (for example, b.i.d. dosing - 60 pills; 80 mg tab of Oxycontin® = 4.8 grams of oxycodone) in their possession there is no immediacy to replenishing his/her drug supply. By doctor shopping another cache will soon follow – this is the dilemma for drug control policy makers and law enforcement agencies required to ensure the "closed system" is maintained.

**Dermal formulations – the fentanyl patch**

The Duragesic Patch®, also known as the Fentanyl Transdermal System, is approved for the transdermal administration of the highly potent Schedule II narcotic. According to the approved label, the patch is indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age and older when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The patch is NOT intended for use as an "as-needed" or PRN analgesic. The lowest fentanyl dose patch will deliver 25 micrograms of fentanyl per hour when applied dermally. Using the conservatively based conversion charts on the FDA-approved label, this patch is equivalent to administering 60-134 mg per day of orally administered morphine. To an opiate-dependent abuser who wants to prevent withdrawal, or a legitimate outpatient in a methadone reduction program who has been informed that his daily compliment is being cut, the psychotropic effects of the "high potency" opiate contained within the patch becomes attractive. Most of the patients don't need to inject, they simply seek a plasma concentration that is stable, of long duration, and above some perceived threshold of awareness. Most often the drug seeking is based on a need to avoid declining plasma concentrations that might elicit withdrawal. The user seeks only the comfort of the "nod" to know he/she has sufficient drug load to maintain feeling "normal".

The key concept for unlocking the dermal patch is heat [19-22]. Steeping the fentanyl patch in a cup of hot water to produce a consumable and surreptitious opiate tea [23], or placing the patch on the arm and wrapping the arm with a heating pad [24,25] or simply apply a dermal patch while laying under a heating blanket will compromise the patch and provide easy delivery of the opioid that is approximately 100 fold more active than morphine.

In one study, fentanyl patches that had been applied to the patient for 3 days were cut open, solubilized in methanol, and diluted with water. The used and removed 2.5 microgram patch retained 28% to 49% of the original quantity of pharmaceutical grade fentanyl and the 10 microgram patch retained 45% to 84% of the drug load [26]. It should not come as a surprise why opiate users looking to maintain their preferred drug state seek the fentanyl patch. Placing the patch in a glass with vodka or gin for a few hours would be deadly if consumed by an opiate novice looking to have a good time. Direct heat or solvent extraction is not the only route of diversion. It has been reported that simply chewing the patch like bubble-gum releases the API from mechanical crushing by the teeth and the warmth of the oral cavity [22]. In one case reported in the literature the patch was removed from the oropharynx from an emergency room patient during resuscitation attempts [27] and two monkeys succumbed to transdermal patch consumption following application for post-surgical pain control in a research facility [28].

**Agonist/Antagonist combination tablets**

From 1977 to 1981, Poklis [29] report a startling increase in the involvement of the partial-opiate-agonist, pentazocine, in combination with an antihistamine familiar to opiate addicts for the blockade of opiate-induced pruritis (tripelenamine). The combination was reverently referred to as “Ts and Blues”. Poklis reported increases in the: (a) sudden and violent deaths (62 homicides, 7 fatal intoxications), (b) emergency room visits (137 in 1980), (c) admissions to drug treatment programs (7.7% in 1978 up to 64% in 1981), and (d) police laboratory cases (100 in 1977 - 78 up to 700 in 1981) associated with the IV administration of the combination. Initial popularity of the drugs was related to the decline in the quality of street heroin (2.5% in 1977 reduced to 0.5% by 1979) and the lack of strict legal controls on the partial-opiate-agonist pentazocine (Talwin). The deterrent formulation, Talwin-NX, was manufactured and quickly marketed to reduce the opiate effects of the combination, if injected. In the 1984 NIDA Research Monograph, Senay & Clara [30] reported results of a study initiated in 1983 in the Chicago area. In that study participants described the Talwin-NX experience as:

Many of the subjects stated that Talwin NX, known to them as "footballs", "bananas", or "butterballs" were not as potent as T-21’s. One subject described the effects of Talwin NX as follows:
With the originals (peach colored T-21), I used to get a good nod and be able to wake up in the morning and feel cool, now with Talwin Nx I feel jittery when I wake and I have to go out and look for dope, i.e. heroin.” While Talwin-NX injectors in the study did report dysphoric effects (nausea, paranoia, diarrhea, abscesses, agitation and seizures) from IV administration of the drug, the subjects of the Senay & Clara [30] study did not stop their IV injection of the drug. They simply shifted the use of the drug to “boost” poor quality heroin from their street sources. The naloxone contained within the pentazocine tablet was not sufficient to block both opioid agonists in the injections.

Buprenorphine (BUP) was developed for the treatment of pain and as an adjunctive therapy for opioid dependence. As a partial mu agonist it was developed under a unique relationship between the National Institute on Drug Abuse (NIDA) and industry. BUP was attractive because it was believed to have limited opioid-induced respiratory depression and as a partial-agonist with relatively high affinity for the opioid receptor, it would block the effects of full agonist dose administrations by competitive binding at the mu receptor. BUP was approved in 1982 as a Schedule II substance and in 1985 schedule control was reduced to Schedule V. BUP could be prescribed for opiate maintenance therapy by registered family physicians and in response to indicators of growing abuse, the DEA moved the drug from CV to CIII in 2002. The increased availability of buprenorphine (BUP) did lead to its abuse, particularly if the dosage form could be injected intravenously. As early as 1993, NIDA was admonishing that self-administration of buprenorphine had been reported to occur in countries in which buprenorphine was easily available. Pharmacists and physicians in New Zealand noted increasing demands for buprenorphine [31,32]. Subsequently, abuse of buprenorphine among opioid addicts was reported in Ireland [33], Germany [34], Scotland [35], and Australia [36]. In most instances, addicts reportedly preferred the intravenous route of administration [37]. In 1993, during BUP development, the NIDA conducted abuse liability studies in clinical population of opiate users [38]. The NIDA concluded from their study that if buprenorphine became a widely used treatment for opioid dependence, drug diversion was likely to occur. And it did.

BUP was combined with naloxone in an attempt to diminish the diversion of the product to IV or insufflated routes-of-administrations. Walsh et al., [39] recently reported that BUP tablets with and without naloxone are being crushed (and sublingual films dissolved) and subsequently injected or insufflated intranasally [40-46]. For instance, two studies report that up to 30% of patients enrolled in BUP therapy were snorting their medication [47,48].

The Talwin-NX and Suboxone product histories suggest that abuse deterrent or tamper resistant formulations containing agonist and antagonist are not likely to prevent diversion or deter abuse [11]. Based on the experience with these two opiates, preclinical abuse liability studies designed to test combination drug products must include a demonstration that the naloxone or naltrexone API within each tablet is sufficient to block the subjective and physiological effects of the amount of opioid agonist API that exists in that same tablet. There is no deterrence to agonist/antagonist combination products if the functional antagonism of the agonist is not achieved within each tablet.

**DISCUSSION & CONCLUSION**

There is a clear motivation and pay-off for intentional diversion of opiates from the closed supply chain. At times, there seems to be a general sense of industry-wide naïveté or intentional myopia in regards to patterns of or motives for drug diversion and abuse. A chronic pain patient receiving prescriptions for a one month supply of high potency extended release opiates (60 tabs) and a second, ancillary prescription for immediate release opiates for “breakthrough” pain (60 tabs) is in no real need to modify the pharmaceutical formulations. If, however, the patient is unemployed and on disability, the drug ‘cache’ can easily become ‘cash’ by tampering with his/her prescriptions for parceling and subsequent sale. On the other hand, the street consumer achieves a supply through doctor shopping or other means of diversion with the intent of clandestine-laboratory extraction of the parent compound to supplement his/her own dependency or for sale to other drug seekers. History has demonstrated, that any means invented by an academically-trained pharmacologist or chemical engineer to hinder, diminish, or slow the access to pharmaceutically pure opiates contained within a formulation will be “unlocked” or “broken” within days following marketed release to the public. Diversion-proof or deterrent-proof formulations exist only within a vault within the walls of the pharmaceutical company. Once on the street, breaking the code of the “lock-tight” high purity single entity opiates are almost a foregone conclusion.

As described by Cicero, Inciardi, & Munoz [49] the 1997 Physician’s Desk Reference contained the statement, “delayed absorption, as applied by OxyContin® tablets, is believed to reduce the abuse liability of a drug”. This statement was approved by the FDA in the face of:

1. The worldwide “ecstasy epidemic” (3, 4 methylenedioxyamphetamine), a drug almost exclusively dosed by oral administration. The desired psychological onset of action of the entactogen following oral administration is 2 to 4 hours.

2. Anabolic steroid abuse was rampant with little, if any, immediate euphoric effects engendered by the drug itself, and

3. A wave of oral Ritalin abuse on college campuses around the nation [50-52]. Methylphenidate has an oral T<sub>max</sub> of approximately 2 hours for immediate release formulations and 4 to 5 hours using extended release formulations.

These drugs were known by the FDA and were showing up in National drug abuse statistical collections services (DAWN, TEDS, Monitoring the Future, etc.) of the National Institutes of Health at the time of NDA approval by the FDA. The slow onset action of these substances did not curtail or limit the abuse of these other scheduled controlled drugs. So, what was unique about extended release formulations? This may represent a classic example of industry hubris.

In enacting the recent Centers for Disease Control Pain Guidelines (CDC) [53,54] the agency and public health service advocates acknowledged that as the pendulum swings away
from the current environment of opioid overprescribing, improvements to patient and physician education, controlled substance tracking, abuse treatment programs, and better research in patient outcomes must be a priority. The continued investment in basic science research and the development of safer next-generation analgesics may be the ultimate solution to this considerable clinical and societal problem. Analysis of the effectiveness of abuse deterrence formulations must rely on the understanding of current methods of diversion and extraction of API from current and past attempts by the drug seeking population in order to provide a level of confidence in the technology and engineering design of future formulations. Recently, the FDA publicly stated that explicit claims of abuse deterrence would not be permitted in product labeling unless such claims were supported by double-blind controlled clinical trials demonstrating actual reduction in product abuse by patients or drug abusers [14]. What seems reasonable now is the addition of special testing of the formulations by experts with a known history of compromising strategies used within the subculture of clan lab chemistry.

Going forward, the pharmaceutical industry needs to retain a constant concern for the methodologies promoted for breaking the “lock-tight” formulations that might support bifurcated schedule control under the CSA. Internet libraries, chat rooms, drug forums, and blogs are relaying the valuable information from the street “locksmiths” and clan lab chemists whose sole purpose is to “crack the code”. No product should ever be considered tamper-proof or diversion-proof.

REFERENCES