Abuse Deterrent Formulation Science
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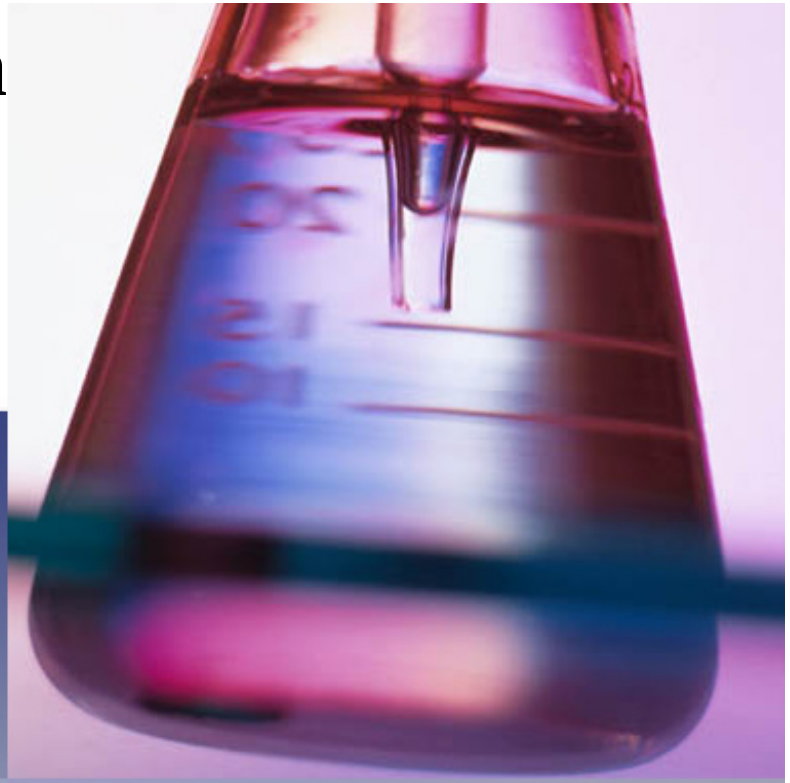
Bethesda MD



TAMPERABILITY/EXTRACTABILITY OF PRESCRIPTION DRUGS

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BACKGROUND

- Prescription drug abuse is the fastest rising category of drug abuse in the US, **second only to cannabis** and synthetic cannabinoids (ONDCP – Drug Control Strategy 2011).
- Prescription drug abusers increased to 16.7 million in 2012 from 14.7 in 2011 (NSDUH 2012)
- According to DEA, **17 of the top 25 drugs** most often examined by forensic laboratories in 2011, are available as **prescription drugs**. (DEA, NFLIS, 2011 mid year report)

BACKGROUND

- **What caused this phenomenon**?
  - Prescription drugs do not fall under the clandestine cloud of illegal drugs such as heroin, ecstasy or methamphetamine
  - Drugs are FDA approved
  - Friends and family use them
  - Prescription drugs are more available due to the development of new products and increased sales

Drugs are frequently obtained free of cost, over 70 percent of people who abused prescription pain relievers got them from friends or relatives, while approximately 5 percent got them from a drug dealer or from the Internet.*

**Results from the 2009 National Survey on Drug Use and Health (NSDUH): National Findings*, SAMHSA (2010).

DIVERSION METHODS

- Doctor shopping or other prescription fraud
- Illegal online pharmacies
- Theft and burglary (from residences, pharmacies, etc.)
- Receiving from friends or family, often for little or no cost
- Over prescribing (negligent or intentional over prescribing by physicians)
- Stereotypical drug dealing (selling pills to others)

INFORMATION SOURCES

- **Most abusers do not have technical training and get their information on abuse and extraction methods from friends, publications or the Internet**

Web sites

- http://www.courtinfo.ca.gov/opinions/revpub/A100018.DOC
- http://www.rhodium.ws/chemistry/
  http://www.erowid.org/index.shtml
- http://www.totse.com/en/drugs/speedy_drugs/166004.html
- http://www.the-hive.ws/forum/forums.pl
- http://nepenthes.lycaeum.org/Drugs/DXM/extract.html
- http://www.erowid.org/chemicals/dxm/faq/dxm_chemistry.shtml (good detail)
- http://www.bluelight.ru/

News group:

- Alt.drugs, Alt.drugs.hard, Rec.drugs, Lycaeum

Amazon.com

INDUSTRY RESPONSE

- Development of abuse resistant delivery systems
  - Reformulation - Oxycontin
  - Oros® – osmotic pump (POLYOX)
  - Encapsulated pellets
  - Addition of antagonists or aversion ingredients
  - Capsules within capsules
  - Rel-Ease™ - Ionic complexes
  - Packaging
  - Reservoir transdermal patch
  - Pro-drugs
  - ADPREM
  - Dose counting devices
  - Implants
- Benefit to industry
  - Enhanced corporate image
  - Fewer litigation actions
  - Increased market share
    - Lower schedule ? – more doctors will prescribe
    - Labeling concessions – more doctors will prescribe
    - Perceived as safer – more doctors will prescribe
- Patient/Public Benefit
  - Reduced abuse and subsequent health care costs

SCHEDULING

- The DEA in concert with FDA has been delegated the authority to add or transfer substances between schedules if the substance has a potential for abuse and meets the criteria for a particular schedule or they can be completely removed from scheduling
- Scheduling based on eight factor analysis

EIGHT FACTORS

The 8 factors are specified in the Controlled Substance Act (CSA) as:

(1) The drug/substance actual or relative potential for abuse

(2) Scientific evidence of the drug/substance pharmacological effect, if known

(3) The state of current scientific knowledge regarding the drug/substance

(4) The drug/substance history and current pattern of abuse

(5) The scope, duration, and significance of abuse

(6) What, if any, risk there is to the public health

(7) The drug/substance psychic or physiological dependence liability

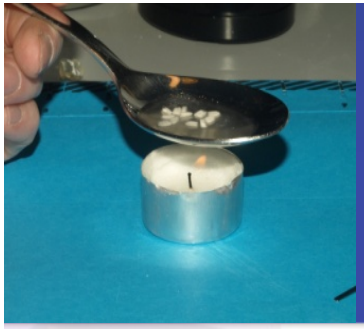
(8) Whether the drug/substance is an immediate precursor of a substance already controlled under this subchapter

ABUSE METHODS

- **Physical – oral, snorting, smoking**
  - Multiple doses
  - Heating or cutting patches
  - Particle size reduction -
    - Chewing
    - Grinding – hammer, coffee grinder, kitchen utensils
- **Extraction –oral, nasal, smoking, IV**
  - Solvent extraction to remove excipients or additatives and/or concentrate active ingredient

DEFINITIONS

- Tampering – physical manipulation
  - Crushing
  - Physical separation components (beads, layers, gel)
  - Heating, freezing, crisping, microwaving
- Extractability – chemical manipulation of a product to remove, concentrate and/or purify the active ingredient performed using **commonly available equipment and chemicals**
- Procedures may be used individually or in combination – crushing is frequently the first step



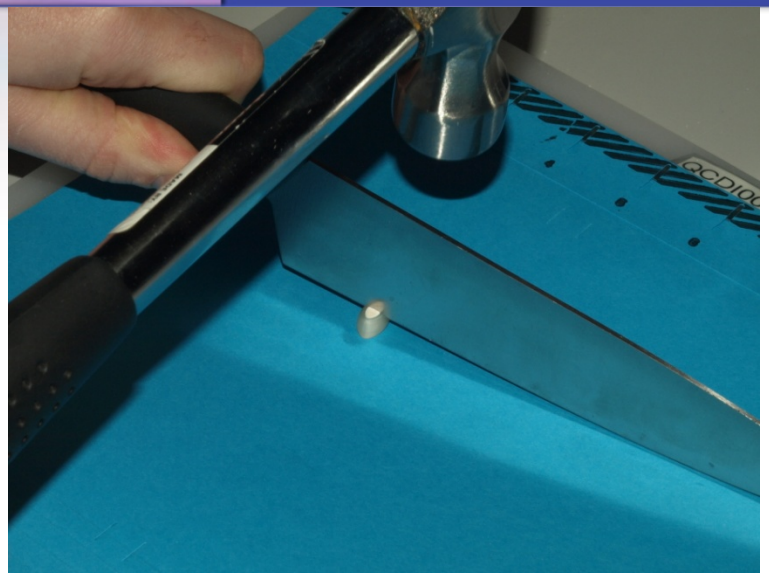
IN-VITRO EXPERIMENTS aka KITCHEN CHEMISTRY

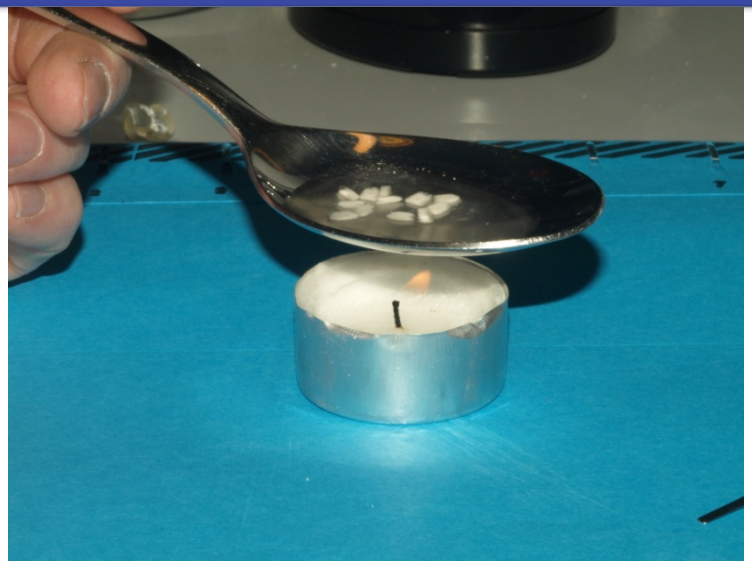
- **Every product is different**; therefore each requires a unique set of experiments developed under the standardized tests to assess tamperability.
- **Sponsor knows product's vulnerabilities** and should develop experiments in concert with abuse experts based on product knowledge and current abuse methods of similar products using **commonly available chemicals and equipment**.
- Standardized laboratory extractions must be developed for each dosage form, e.g. tablets, capsules, patches, liquids, IR, SR using **solvents & equipment commonly available**.
- Consider testing all dosage strengths

IN-VITRO EXPERIMENTS

- Develop written protocols that produce statistically valid, reproducible results.
  - Include related comparator product
  - Include controls
  - Include quality assurance procedures
  - All experiments must be conducted at least in triplicate
  - Use graphs and charts to illustrate data
  - Experiments should be conducted by an independent laboratory that is blinded to the fullest extent possible in addition to in house laboratory experiments
  - Take photographs to illustrate results

INJECTABILITY





Photos by permission, Egalet, Copenhagen DK, 2010.

PHYSICAL MANIPULATION

- Particle size reduction is generally the first step.
- Experiments should be attempted at RT and ET as well as after physical manipulation (heating, freezing, microwaving, crisping)
- Use a variety of available manual and electric tools
- Set practical time limits (Egalet study- 80% of subjects would spend 3-10 minutes tampering)
- Smallest particle size generally produces the most desirable result.

SOLVENT EXTRACTION

- Solvents of different pH and polarity
  - Soaked and stirred
  - RT and elevated temperature (ET)
  - Ground and intact
  - Percolated
  - Single solvent (ingestible e.g. alcohol, water - non-ingestible e.g. paint thinner, acetone)
  - Multiple solvents - aqueous /pH adjustments & immiscible solvents

ABUSE METHODS

- All modes of abuse must be considered if relevant
  - Oral – the most commonly encountered
  - Nasal – crushing followed by snorting
  - Smoking – crushing/extracting/smoking –
  - IV – hard core abusers requiring immediate most intense result

EXTRACTABILITY RATING

Neither the DEA nor FDA have objective criteria to measure/evaluate extractability, YET.

Ideally, a rating system should be developed that would result in a quantitative score that regulators and industry officials could use to determine the relative extractability of any pharmaceutical product.

EXTRACTABILITY RATING

- Objective metrics must be established –
  - Abuser knowledge and skill required
  - Number of steps required
  - Amount and cost of equipment and chemicals
  - Amount of time expended
  - Percent recovery and purity
  - Other active & inactive ingredients recovered
  - Physical characteristics of extract – viscosity, color, odor, syringability

Summary

- No objective measure exists to measure tamperability/extractability
- Each product/system requires unique experiments designed to address vunerabilities
- Use independent laboratory & abuse experts
- Consider all modes of abuse & all strengths
- Include photographs, graphs & charts where appropriate
- **No product has been proven to be tamper proof**

Thank you

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