

EXTRACTABILITY HOW SHOULD IT MEASURED?

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Tufts Meeting - Boston, MA September 7-8, 2006



Background

- Prescription drug abuse is the fastest rising category of drug abuse, second only to cannabis in terms of drug-related hospital emergency department visits (ONDCP 2004b).
- Emergency department visits resulting from non-medical use of prescription analgesics increased 163 percent between 1995 and 2002 (Ibid.).
- According to DEA, 18 of the top 25 drugs most often examined by forensic laboratories in 2003, are available as prescription drugs. (DEA, NFLIS, 2003)



BACKGROUND

- An estimated 6.2 million Americans reported past month use of prescription drugs for non-medical purposes.
- Nearly 14 percent of youth between the ages of 12 and 17 have used such drugs, which include pain relievers, sedatives/tranquilizers, or stimulants, for non-medical purposes at some point in their lives. (National Survey on Drug Use and Health, 2002)



Background

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



TYPES OF ABUSERS*

- Health care professionals – easy access, educated
- Hard core opioid addicts – prefers heroin to Rx
- Hard core Rx – converts SR to IR
- Polydrug/Rave – uses anything available
- Casual – low tolerance, alcohol & marijuana
- Patient abuser – scammer, doctor shopper

* **Sidney H. Schnoll, MD, PhD**

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



INFORMATION SOURCES

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
- <https://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)

News group:

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

Amazon.com



GOVERNMENT RESPONSE

- **Controlled Substances Act 1970**
 - Substances placed in one of five schedules based on:
 - Relative potential for abuse
 - Accepted medical use
 - Relative dependence potential
- **National Synthetic Drugs Action Plan 2004**
 - Primarily focuses on illicitly produced drugs
 - It also discusses selected pharmaceutical products which are sometimes diverted from legitimate commerce.
 - **“Regardless of the venues in which they are used, the problems posed by licitly produced pharmaceutical products are distinct from those pertaining to clandestinely produced drugs and the approaches to prevent their illegal trafficking like wise vary.”**



GOVERNMENT RESPONSE

- **Synthetic Drug Control Strategy 2006**
 - Companion document to the National Synthetic Drug Action Plan
 - Reduce abuse or non-medical use of prescription drugs by 15% by the end of 2008.
 - Establish a balance between patient availability and reduction of prescription controlled drug abuse.



GOVERNMENT RESPONSE

- **Risk Minimization Action Plan (RiskMAP) 2005**
 - FDA's guidance document does not establish legally enforceable responsibilities.
 - Guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations.



GOVERNMENT RESPONSE

■ Risk Minimization Action Plan (RiskMAP) 2005

Provides guidance to industry on the development, implementation, and evaluation of risk minimization action plans for prescription drug products, including biological drug products. In particular, it gives guidance on (1) initiating and designing plans called risk minimization action plans or RiskMAPs to minimize identified product risks, (2) selecting and developing tools to minimize those risks, (3) evaluating RiskMAPs and monitoring tools, and (4) communicating with FDA about RiskMAPs, and (5) the recommended components of a RiskMAP submission to FDA.



INDUSTRY RESPONSE

- **Development of abuse resistant delivery systems**
 - Oros® – osmotic pump
 - Encapsulated pellets
 - Addition of antagonists
 - Capsules within capsules
 - Rel-Ease™ - Ionic complexation
 - Packaging
 - Reservoir transdermal patch
 - Pro-drugs
- **Benefit to industry**
 - Enhanced corporate image
 - Fewer litigation actions
 - Increased market share
 - Lower schedule – more doctors will prescribe
 - Perceived as safer leading to increased prescriptions



Diversion methods

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



SCHEDULING

- The DEA 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 remove them from scheduling
- Eight criteria considered in making scheduling decisions
 - Actual or potential for abuse and history of abuse are directly related to extractability
- **Neither the DEA nor the FDA have objective criteria to measure extractability**



ABUSE METHODS

- **Physical – oral, snorting, smoking**

- Crushing

- Chewing

- Grinding – hammer, coffee grinder, kitchen utensils

- removal of abuse barrier – cut patch

- Multiple doses

- Heating patches

- **Extraction –oral, nasal, smoking, IV**

- Solvent extraction to remove excipients and/or concentrate active ingredient



SOLVENT EXTRACTION EXPERIMENTS

- Information I can share was presented at the American Pain Society annual meeting. Janssen sponsored study to compare the extractability of fentanyl from reservoir and matrix patches. All extractions were performed using chemicals and equipment available to the general public. Identification and purity of extracts confirmed by GC/MS/MS



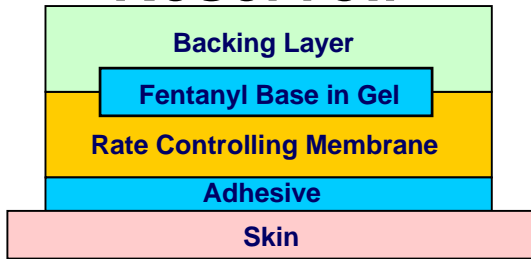
Fentanyl Transdermal Systems

- The DURAGESIC reservoir patch is a form-fill-seal design that contains a suspension of fentanyl base in a water/ethanol and hydroxyethyl cellulose solution.
- The matrix patch is a drug-in-adhesive formulation that contains fentanyl base dissolved in polyactylate adhesive.

Fentanyl Transdermal Systems



DURAGESIC® Reservoir



Fentanyl Generic





Products Extracted

- Duragesic® 10 mg/patch – 100µg/hr
- Matrix 18.4mg/patch -100µg/hr

- Water
- Rubbing alcohol (IPA)
- Vodka (40% ethanol)
- Vinegar
- Bacardi 151 rum
- Methyl alcohol



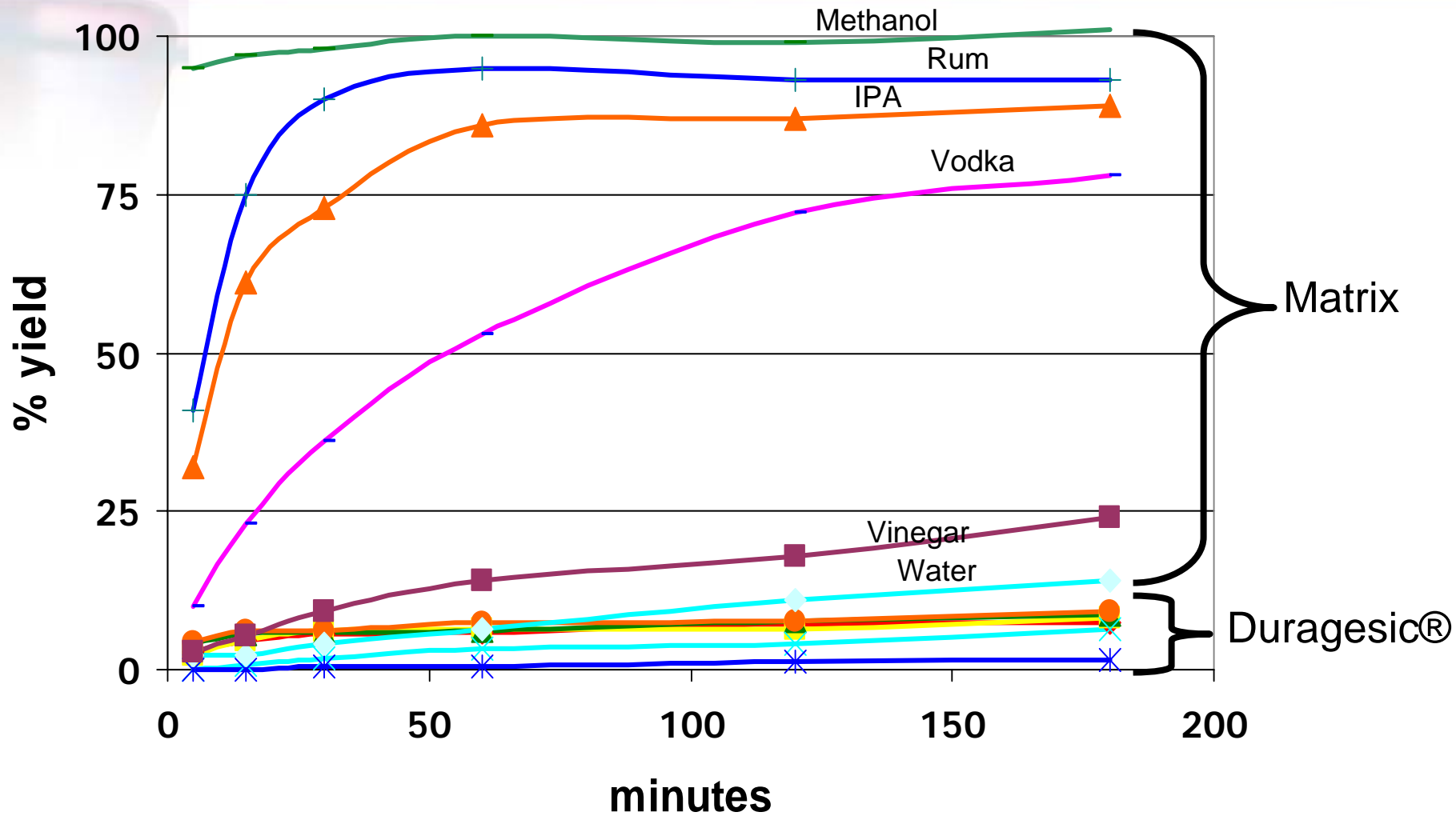
Extraction Techniques

Protective layers removed and intact patches subjected to extraction

- “Room temperature Soak” (party punch): each patch left undisturbed in 500 ml of each solvent at RT.
- “Elevated Temperature Soak”: each patch soaked in 500 ml of solvent at boiling point.
- “3 Hour Percolation”: each patch percolated with 750 ml of each solvent.



Room Temperature Soak





EXTRACTION EXPERIMENTS

- Although pharmaceutical companies and drug delivery development companies have their own laboratories, the objectivity of an independent laboratory is sought in addition to or instead of in house experiments
 - **National Medical Services Laboratory** – clinical laboratory with a forensic component conducted a variety of experiments
 - Extraction experiments have been completed or are in process for the extraction of fentanyl, pseudoephedrine, methylphenidate, morphine, oxycodone, hydrocodone, oxymorphone in single ingredient and combination products in immediate & sustained release preparations



EXTRACTION EXPERIMENTS

- Extractability is defined as the manipulation of a product to remove, concentrate and/or purify the active ingredient.
- Solvent extractions
 - Soaked and stirred
 - RT and elevated temperature
 - Ground and as is
 - percolated
 - Single solvent
 - Multiple solvents
 - pH modifications



EXTRACTABILITY RATING

- Standardized laboratory extractions must be developed for each type of dosage form e.g. tablets, capsules, patches, liquids, IR, SR, using solvents & equipment commonly available. All experiments must be conducted in triplicate to provide statistical validity and controls must be included.
- Participants should include chemists, addiction & pain management specialists, substance abuse professionals and substance abusers.



EXTRACTABILITY RATING

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



EXTRACTABILITY RATING

- Objective metrics must be established
 - Number of steps required
 - Amount of time expended
 - Percent recovery
 - Other active & in active ingredients recovered
 - Physical characteristics of extract – viscosity, color, odor



EXTRACTABILITY RATING

- Experiments must be conducted by an independent laboratory and grant funded independent of pharmaceutical industry funding
- Ideally the rating system would result in a quantitative rating that regulators could use to determine the relative extractability of any pharmaceutical product.