



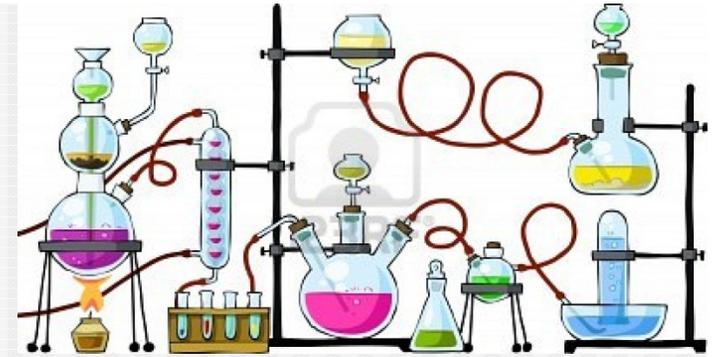
Implications Of *In Vitro* Testing Of ADFs For Industry And Real World Abusers

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Disclaimer

- Dr. Cone is an employee of Pinney Associates, a consulting firm that consults with clients' marketing, business development, research and development, scientific and regulatory affairs, government affairs, and legal divisions, throughout all stages of a product's lifecycle.
- No specific product will be discussed in this presentation.

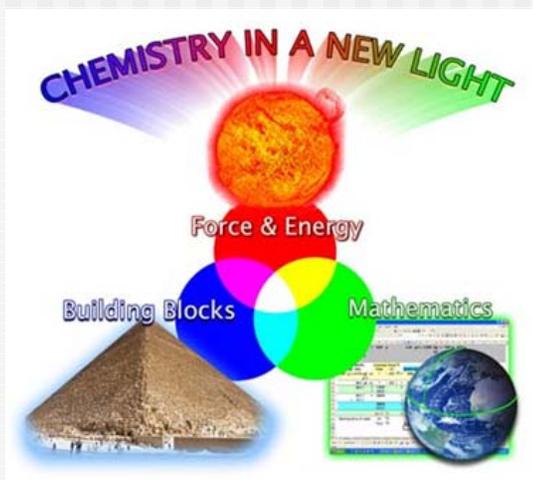
Outline:



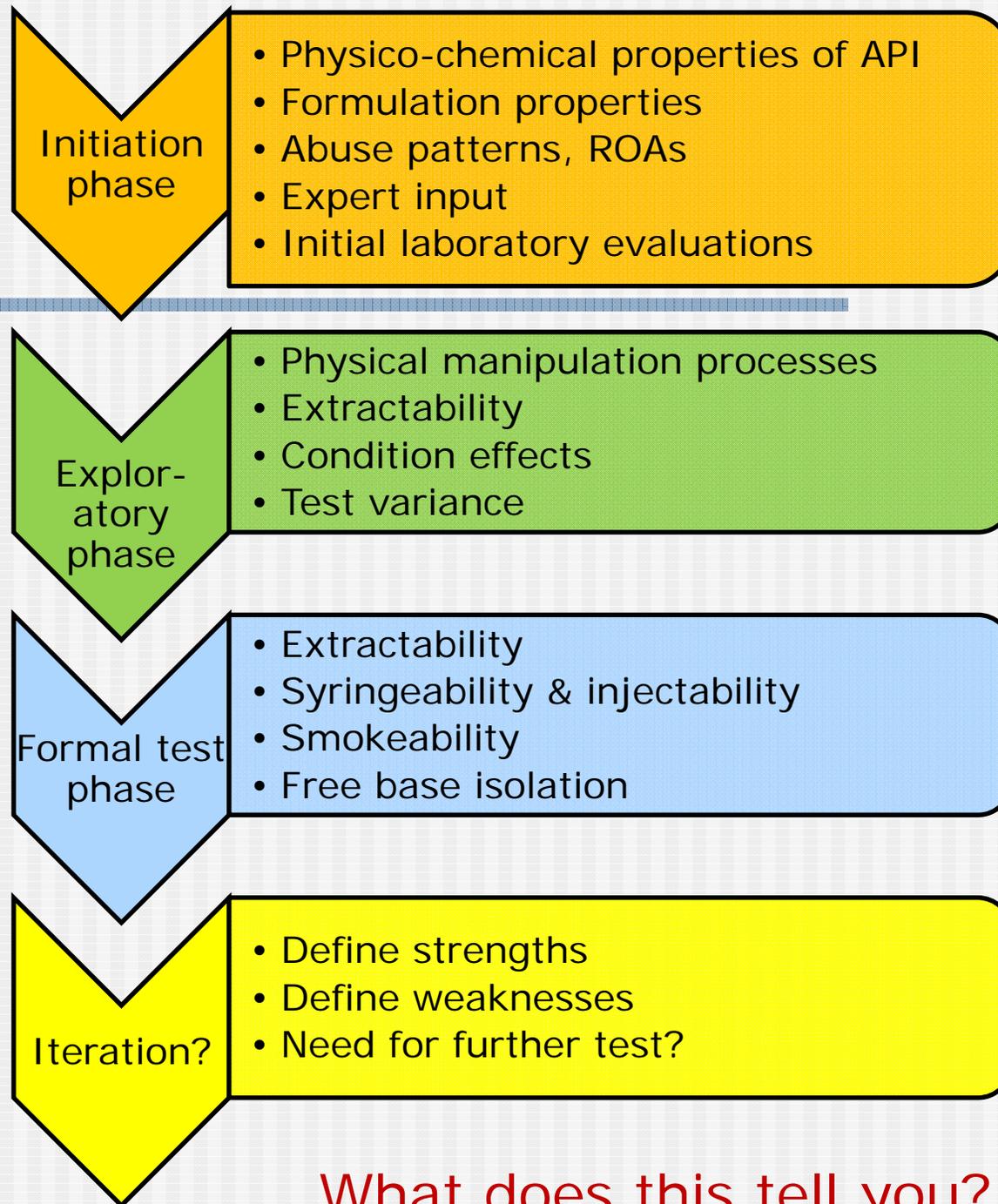
- Evolving science and changing attitudes
- Brief overview of laboratory ADF tests
- Implications for industry
 - Why *in vitro* studies should be done as completely and as early as possible
- Real-world abusers
 - Impact on common practices
 - Potential to change preferences

Industry Chemists Need To Think Like a Kitchen Chemist

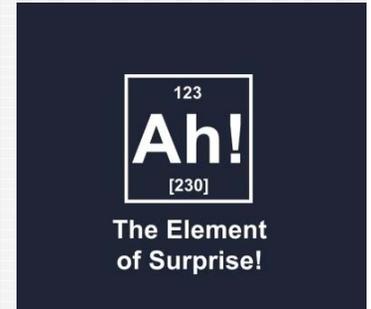
- New science
- Major challenge for Pharma chemists
- Large hurdle to change thinking patterns
- Multiple inputs are required
 - Abuse experts
 - Literature
 - Internet



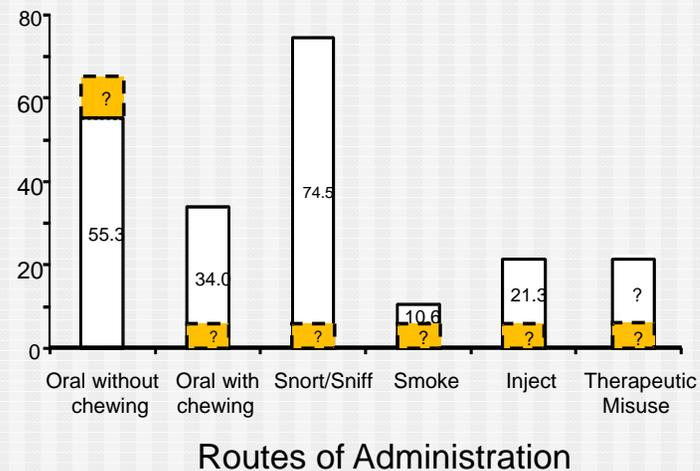
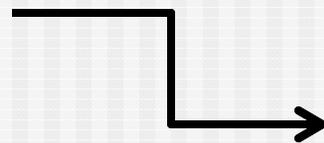
Overview: *In Vitro* Schema for ADFs



Value of Laboratory ADF Assessments To Industry?



- More than you know!
- Strengths and vulnerabilities of your product
- Comparator data
- Basis to support/inform PK and HAL studies
- Possibility to achieve specialized labeling
- Predictive value for safety and misuse?



Implications for Industry

- Provides orderly R&D pathway and decision framework for opioid ADFs, and.....
 - Methods to assess NCEs
 - Generic assessments
 - Other CNS-active drug classes
 - Complimentary studies
 - Use of prescription opioid abusers as an alternative means of assessment?

A Few Words About NCEs

- Unique pharmacology
 - Less abuse liability?
- Unique pharmacokinetics
 - Altered disposition, slower onset of effects?
- Prodrug
 - Tamper assessments needed
 - Conversion to active drug
- Precursor?
 - Chemical assessment needed for 8FA

A Few Words About Generic Assessments

- Bioequivalence is a given
- But equivalent abuse deterrence is NOT a given
- How to assess and compare to innovator
 - Identical formulations
 - Similar formulations (excipients are similar but not identical)
 - Generics with innovative excipients?
- *Equivalence (or better) in all tests*

A Few Words About Generic Assessments: Tampering Methods May Differ Depending Upon Generic Formulation

- **Bluelight.ru, Author: “gh0ul”, April, 2010**
The best way to prep 3 different brands of morphine
(<http://www.bluelight.ru/vb/threads/498083-The-best-way-to-prep-3-different-brands-of-MS-Contin>) (accessed Aug. 18, 2013)
 - Presents different recipes for injection preparation of the “Endo”, “Mallies”, and “Watson” generic versions of morphine
 - Procedures are relatively easy and fast
 - Each procedure is distinctly different; success is claimed for each

A Few Words About Other CNS-Active Drug Classes

- Tampering assessments are needed (required?)
- Strong possibility of tiered labeling
- Assessments should be based on:
 - Known and potential routes of abuse
 - Characteristics of active and formulation
 - Beware the comparator!

Complimentary Studies to *In Vitro* Assessments: Tamper Testing with Rx Opioid Abusers

- Vosburg et al (Addiction, 2013; DAD, 2012)
- Participants were experienced prescription opioid abusers
- Provided tools for preparation for intranasal and iv use
- Not allowed to administer drug
- Compared and ADF to a non-ADF product
- Self-report data and analyses of particle sizes and extracts
- Provided comparative data
- Limitations: motivation, age, innovation, small N

Industry Lessons Learned!

- There are built-in biases in Pharma; ADF assessments are counter-intuitive
- Incomplete assessments hamper approval
- Full disclosure is necessary and advantageous
“We know how to beat the product, but why should we disclose that?”
- Public disclosure of methods is verboten!
- Minor ADF weaknesses do not diminish a product’s value

Implications for Real World Abusers: Common Sense Principles of Tampering Behavior

- Although a few individuals will go to unusual lengths, most prefer fast and easy methods of tampering
- A bigger dose and a faster delivery mode is the desired goal, however it can be achieved
- As the barrier to tampering increases, the frequency of tampering diminishes

"I just want to take a moment and cheer from the side lines for the guerilla scientists and kitchen chemists of Team Junkie. You are seriously part of what makes the Internet still a great place. That, irregardless of whether abusing your OP80's is a Good Thing or not, the noosphere is moving history apace." (<http://www.bluelight.ru/vb/threads/523580-Experiment-Thead-New-Formulation-Oxycodone-Extraction/page5?p=8786891#post8786891>) Accessed 8/19/13



Implications for Real World Abusers

- Strong ADFs will be challenged
 - Increased frustrations
 - Spiraling rise of postings
 - Search for easier “targets”
- Weak ADFs will become exposed and abused

Implications for Real World Abusers



- Increased “doctor shopping” for easy formulations
- Turn to illicit
- Become more innovative
- Internet pseudoscience will continue to evolve
 - Focus on means to overcome polymeric matrices
 - Separate/deactivate antagonists
- Will “tampered” Rx products become available in the illicit market?

The End!

Where do we go from here?

