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Today’s discussion

Closed session

• Detailed *in vitro* testing methods and results

Open session

• **Introduction**
  – *John Stewart*; Purdue President and Chief Executive Officer
  – *Craig Landau, MD*; Purdue Chief Medical Officer

• Addressing opioid abuse
• Polyethylene oxide excipient
• Bioequivalence
• Approach to *in vitro* testing
• Summary of *in vitro* testing results
• Interpretation of in vitro findings
• Conclusions
Intact OxyContin releases oxycodone HCl over twelve hours
The controlled-release mechanism of the current OxyContin dosage formulation is easily overcome.

**Graph:**
- **OXycodone HCl**
- **Percent released**
- **Time (Minutes)**

- **Crushed OxyContin**
- **Intact OxyContin**

- **Mortar & pestle**
- **Two spoons**
- **Pill crusher**

- **Intact**

- **0 10 20 30 40 50 60**
Physical crushing of OxyContin underlies many routes of abuse and misuse

<table>
<thead>
<tr>
<th>Route of admin</th>
<th>What happens to tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physical</td>
</tr>
<tr>
<td>Abuse</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Intact</td>
</tr>
<tr>
<td></td>
<td>Crush</td>
</tr>
<tr>
<td>Nasal</td>
<td>Crush</td>
</tr>
<tr>
<td>Rectal</td>
<td>Crush</td>
</tr>
<tr>
<td>Smoke</td>
<td>Crush, vaporize</td>
</tr>
<tr>
<td>Inject</td>
<td>Crush</td>
</tr>
<tr>
<td>Patient error</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Crush</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
</tr>
</tbody>
</table>
Purdue pursued multiple technologies to reformulate OxyContin to mitigate abuse and misuse

- **November 2007**
  - Initial NDA submitted
  - 10-40 mg

- **May 2008**
  - First Advisory Committee

- **October 2008**
  - FDA Complete Response Letter

- **March 2009**
  - NDA resubmitted
  - 10-80 mg
  - In vitro study program

- **September 2009**
  - Second Advisory Committee

- **Early 2000s**
  - Purdue began reformulation efforts

- **2007**
  - First NDA submitted
  - 10-40 mg

- **2008**
  - FDA Complete Response Letter

- **2009**
  - NDA resubmitted
  - 10-80 mg
  - In vitro study program
We consulted experts in drug abuse and tablet tampering

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bob Bianchi</td>
<td>President, Bianchi Consulting, Ltd.; VP and Chief of Scientific and Technical Affairs, Prescription Drug Research Center; Former Laboratory Director, DEA</td>
</tr>
<tr>
<td>Bruce Burlington, MD</td>
<td>Sole Proprietor, DB Burlington Associates; Former Head of Regulatory Affairs, Wyeth; Former Deputy Director Med Affairs, FDA; Former Head of Investigational New Drugs Division (Center of Biologics); FDA, Former Head of Center for Medical Devices and Radiological Health, FDA</td>
</tr>
<tr>
<td>Ronald W. Buzzeo, RPh</td>
<td>Chief Regulatory Officer, Cegedim Dendrite Compliance Solutions</td>
</tr>
<tr>
<td>Sandra Comer, PhD</td>
<td>Associate Professor of Clinical Neurobiology, Division on Substance Abuse, Columbia</td>
</tr>
<tr>
<td>Ed Cone, PhD</td>
<td>Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins; Former Chief of the Chemistry and Drug Metabolism Section, NIDA</td>
</tr>
<tr>
<td>Ed Sellers, MD, PhD</td>
<td>VP, Kendle International Early Stage; Professor of Pharmacology, Medicine and Psychiatry, University of Toronto</td>
</tr>
<tr>
<td>Herb Kleber, MD</td>
<td>Professor of Anesthesia &amp; Critical Care, University of Chicago</td>
</tr>
<tr>
<td>Jim Zacny, PhD</td>
<td>Professor of Psychiatry and Director, Division on Substance Abuse, Columbia University</td>
</tr>
</tbody>
</table>
We have modified our approach in three ways

• We redesigned our *in vitro* testing based on input received from FDA and the Advisory Committee

• We will simultaneously introduce all seven strengths of reformulated OxyContin tablets

• We are not seeking labeling language regarding *in vitro* testing, “abuse deterrence,” “tamper-” or “abuse-resistance”
Today’s discussion

Closed session

• Detailed *in vitro* testing methods and results

Open session

• Introduction

• Addressing opioid abuse
  – *Pamela Bennett, RN, BSN; Executive Director, Healthcare Alliance Development*

  • Polyethylene oxide excipient
  • Bioequivalence
  • Approach to *in vitro* testing
  • Summary of *in vitro* testing results
  • Interpretation of in vitro findings
  • Conclusions
Prescription drug abuse: Working together

• There is no single solution to prescription drug abuse

• All interested stakeholders need to work together

• Efforts must be sustained
Overview: Purdue programs to address prescription drug abuse

- Detecting abuse and diversion
- Advancing Prescription Monitoring Programs
- Working with law enforcement and healthcare professionals
- Building public awareness
Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System
Forty states have enacted PMPs
Educating law enforcement and healthcare professionals

• **Purdue Law Enforcement Liaison & Education Department**
  – Training more than 62,000 law enforcement and healthcare professionals

• **Healthcare professional education**
  – Unrestricted grants
  – Reaching more than 1.2 million healthcare providers
Building public awareness – select highlights

- Partnership for a Drug-Free America
- “Medicine Cabinet” Public Service Campaign
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• Addressing opioid abuse

• **Polyethylene oxide excipient**
  – *Craig Landau, MD; Purdue Chief Medical Officer*

• Bioequivalence

• Approach to *in vitro* testing

• Summary of *in vitro* testing results

• Interpretation of *in vitro* findings

• Conclusions
Use of polyethylene oxide (PEO) excipient enabled us to develop a bioequivalent reformulation.

Polyethylene

MW ~ 100,000
n<2275

MW 4 million
n>2275

Polyethylene glycols

Polyethylene oxides

Liquids (low MW) to waxes (high MW)

Waxes (low MW) to powders (high MW)
PEO is found in many common over-the-counter medications

<table>
<thead>
<tr>
<th>OTC medication</th>
<th>API (active ingredient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Vicks Formula 44e Cough &amp; Chest Congestion Relief Liquid</td>
<td>dextromethorphan hydrobromide, guaifenesin</td>
</tr>
<tr>
<td>Pediatric Vicks Formula 44m Cough &amp; Cold Relief Liquid</td>
<td>chlorpheniramine maleate, dextromethorphan hydrobromide</td>
</tr>
<tr>
<td>Sudafed Nasal Decongestant Tablets</td>
<td>pseudoephedrine hydrochloride</td>
</tr>
<tr>
<td>Theraflu Thin Strips Daytime Cold &amp; Cough</td>
<td>dextromethorphan hydrobromide, phenylephrine hydrochloride</td>
</tr>
<tr>
<td>Theraflu Thin Strips Nighttime Cold &amp; Cough</td>
<td>diphenhydramine hydrochloride, phenylephrine hydrochloride</td>
</tr>
<tr>
<td>Vicks Formula 44 Cough Relief Liquid</td>
<td>dextromethorphan hydrobromide</td>
</tr>
<tr>
<td>Vicks Formula 44E Cough &amp; Chest Congestion Relief Liquid</td>
<td>dextromethorphan hydrobromide, guaifenesin</td>
</tr>
<tr>
<td>Vicks Formula 44M Cough, Cold &amp; Flu Relief Liquid</td>
<td>acetaminophen, chlorpheniramine maleate,</td>
</tr>
<tr>
<td></td>
<td>dextromethorphan hydrobromide</td>
</tr>
</tbody>
</table>
PEO is also found in many well-known prescription medications

<table>
<thead>
<tr>
<th>Prescription drug</th>
<th>API (active ingredient)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procardia XL</strong></td>
<td>nifedipine</td>
<td>vasospastic angina</td>
</tr>
<tr>
<td>FDA – 1989</td>
<td></td>
<td></td>
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<tr>
<td><strong>Glucotrol XL</strong></td>
<td>glipizide</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>FDA – 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DynaCirc CR</strong></td>
<td>isradipine</td>
<td>hypertension</td>
</tr>
<tr>
<td>FDA – 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Covera HS</strong></td>
<td>verapamil HCl</td>
<td>hypertension and angina</td>
</tr>
<tr>
<td>FDA – 1996</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ditropan XL</strong></td>
<td>oxybutinin chloride</td>
<td>urinary incontinence &amp; nocturnal enuresis</td>
</tr>
<tr>
<td>FDA – 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Concerta</strong></td>
<td>methylphenidate</td>
<td>ADHD</td>
</tr>
<tr>
<td>FDA – 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proquin XR</strong></td>
<td>ciprofloxacin HCl</td>
<td>uncomplicated urinary tract infections</td>
</tr>
<tr>
<td>FDA – 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glumetza ER</strong></td>
<td>metformin HCl</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>FDA – 2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jurnista</strong></td>
<td>hydromorphone HCl</td>
<td>moderate to severe chronic pain</td>
</tr>
<tr>
<td>EMEA – 2006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary: Important properties of polyethylene oxide

• Slow water uptake by polyethylene oxide makes it an ideal excipient for controlled release formulations.

• After treatment via a specific manufacturing process, polyethylene oxide excipient confers tablet hardness.

• Polyethylene oxide has been safely used in oral medications for decades.
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• Introduction
• Addressing opioid abuse
• Polyethylene oxide excipient

**Bioequivalence**

– *Stephen Harris, MD; Purdue Executive Director of Clinical Pharmacology*

• Approach to *in vitro* testing
• Summary of *in vitro* testing results
• Interpretation of in vitro findings
• Conclusions
Significance of drug bioequivalence testing

Bioequivalence
• The absence of a major difference in oxycodone exposure
• Assessed statistically by standard FDA methodology: 90% Confidence Intervals for PK comparisons within 80%-125% acceptance range

Therapeutic equivalence
• Bioequivalence provides primary support for therapeutic equivalence between a test formulation and its reference comparator

Role of bioequivalence determinations
• ANDAs: Support generic drug applications
• NDAs: Demonstrate equivalence of development and commercial formulations
• Post approval: Support manufacturing changes
Six pivotal human studies assessed bioequivalence and two assessed dose-proportionality

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Fed Study</th>
<th>Fasted Study</th>
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</thead>
<tbody>
<tr>
<td>10 mg BE</td>
<td>OTR1002</td>
<td>OTR1003</td>
</tr>
<tr>
<td>40 mg BE</td>
<td>OTR1004</td>
<td>OTR1005</td>
</tr>
<tr>
<td>80 mg BE</td>
<td>OTR1008</td>
<td>OTR1009</td>
</tr>
<tr>
<td>10-40 mg Dose-Prop</td>
<td>Fasted: OTR1006</td>
<td></td>
</tr>
<tr>
<td>40-80 mg Dose-Prop</td>
<td>Fasted: OTR1012</td>
<td></td>
</tr>
</tbody>
</table>

Two-way crossover studies in healthy adult subjects comparing:
Reformulated OxyContin (Test) to Current OxyContin (Reference)

Randomized, open-label, single-dose, healthy male & female subjects, naltrexone blockade

5-treatment, 4-period, incomplete block, crossover study in healthy adult subjects

3-treatment, 3-period, complete block, crossover study in healthy adult subjects
Statistical results from six pivotal and two dose proportionality studies demonstrate bioequivalence of the two formulations

### Bioequivalence studies

<table>
<thead>
<tr>
<th>Study number</th>
<th>N*</th>
<th>Dose</th>
<th>Condition</th>
<th>LS Mean Ratio (%)</th>
<th>Cmax 90% CI</th>
<th>AUCinf LS Mean Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTR1002</td>
<td>76</td>
<td>10 mg</td>
<td>Fed</td>
<td>105.0</td>
<td>101.06, 108.51</td>
<td>95.6</td>
<td>93.73, 97.53</td>
</tr>
<tr>
<td>OTR1003</td>
<td>76</td>
<td>10 mg</td>
<td>Fasting</td>
<td>102.0</td>
<td>99.35, 105.42</td>
<td>98.0</td>
<td>94.94, 101.19</td>
</tr>
<tr>
<td>OTR1004</td>
<td>76</td>
<td>40 mg</td>
<td>Fed</td>
<td>99.9</td>
<td>95.40, 104.52</td>
<td>92.6</td>
<td>90.11, 95.09</td>
</tr>
<tr>
<td>OTR1005</td>
<td>76</td>
<td>40 mg</td>
<td>Fasting</td>
<td>97.0</td>
<td>93.11, 101.13</td>
<td>94.4</td>
<td>91.93, 96.92</td>
</tr>
<tr>
<td>OTR1008</td>
<td>76</td>
<td>80 mg</td>
<td>Fed</td>
<td>110.0</td>
<td>105.21, 114.47</td>
<td>94.7</td>
<td>92.71, 96.64</td>
</tr>
<tr>
<td>OTR1009</td>
<td>76</td>
<td>80 mg</td>
<td>Fasting</td>
<td>103.0</td>
<td>98.67, 106.66</td>
<td>97.0</td>
<td>94.20, 99.81</td>
</tr>
</tbody>
</table>

### Dose proportionality studies

<table>
<thead>
<tr>
<th>Study number</th>
<th>N*</th>
<th>Dose</th>
<th>Condition</th>
<th>PK Metric</th>
<th>Slope</th>
<th>90% CI (Power Model)</th>
<th>Critical Range (Power Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTR1006</td>
<td>48</td>
<td>10-40 mg</td>
<td>Fasting</td>
<td>Cmax</td>
<td>1.06</td>
<td>1.03, 1.09</td>
<td>0.8390, 1.1610</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUCinf</td>
<td>0.959</td>
<td>0.935, 0.982</td>
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<tr>
<td>OTR1012</td>
<td>48</td>
<td>40-80 mg</td>
<td>Fasting</td>
<td>Cmax</td>
<td>0.845</td>
<td>0.771, 0.919</td>
<td>0.6781, 1.3219</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUCinf</td>
<td>0.967</td>
<td>0.907, 1.03</td>
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</table>

* Planned number of subjects
OTR1003: Fasted 10 mg bioequivalence

Mean concentration vs. time
OTR1002: Fed 10 mg bioequivalence

Mean concentration vs. time
OTR1009: Fasted 80 mg bioequivalence
Mean concentration vs. time

![Graph showing mean concentration vs. time for OTC 80 mg Fasted BE](image)
OTR1008: Fed 80 mg bioequivalence
Mean concentration vs. time
Conclusions from bioequivalence and dose proportionality studies

• Therapeutic equivalence of current OxyContin and reformulated OxyContin demonstrated by fasted and fed bioequivalence at 10, 40, and 80 mg tablet strengths

• Dose-proportional oxycodone exposures demonstrated across the full range of reformulated OxyContin tablet strengths (10, 15, 20, 30, 40, 60, and 80 mg)
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• Polyethylene oxide excipient

• Bioequivalence

• **Approach to *in vitro* testing**
  – *Edward Cone, PhD; Ex-Chief of Chemistry & Drug Metabolism, NIDA; Adjunct Professor of Psychiatry, Johns Hopkins*

• Summary of *in vitro* testing results

• Interpretation of in vitro findings

• Conclusions
## Introduction and qualifications:
### Basis for my expertise drug abuse and tampering methods

**Education**
- Mobile College, B.S., Chemistry, 1967
- University of Alabama, Ph.D., Chemistry, 1971
- University of Kentucky, Postdoctoral Fellow, 1972

**Employment**
- National Institute on Drug Abuse, Lexington, KY, 1972-1984
- National Institute on Drug Abuse, Baltimore, MD, 1984-1998
- Retired from USPHS, 1998
- ConeChem Research, LLC, 1998-present
- Consultant to Pinney Associates, 1998-present

**Areas of expertise**
- Chemistry of drugs of abuse
- Pharmacokinetics & metabolism
- Pharmacology
- Forensic toxicology
- Analytical methods for drug testing
- Chemical basis of drug “tampering”

**Publications**
- Over 240 publications on the chemistry and pharmacology of drugs of abuse
I appear today as an independent consultant from Pinney Associates. Pinney Associates is being paid by Purdue Pharma for my time.

The views presented today are my own.
My work with Purdue Pharma on reformulated OxyContin began in October 2008

- **October 2008:** Member of Purdue’s expert panel on modes of abuse and misuse
- **November 2008:** Member of expert panel on physicochemical methods of drug tampering
- **November 2008 – March 2009:** Advisory role on design and execution of *in vitro* tampering studies of reformulated OxyContin
- **December 2008:** Inspected the 3rd-party laboratory performing the studies
- **January 2009:** Attended Purdue’s FDA meeting on approaches to *in vitro* testing
- **February 2009:** Reviewed results from *in vitro* studies
- **March 2009:** Authored a portion of the introduction to Purdue’s NDA
Recreational abusers of OxyContin prefer insufflation as a route of administration

Route of administration survey (N=896)
Percentage of respondents

1 Respondents who had used OxyContin in the past 30 days
Routes of administration vary by population

**Recreational abusers**
Cone 2009
N=51 respondents,
N=71 responses,
Percentage of responses

- Oral: 35% (N=25)
- Insufflate: 55% (N=39)
- Rectal: 1% (N=1)
- Inject: 9% (N=6)

**Abusers entering treatment**
Carise et al 2007
N=1,368 respondents,
Percentage of respondents

- Oral: 72% (N=981)
- Insufflate: 11% (N=153)
- Inject: 17% (N=234)

SOURCE: Cone Internet Survey, 2009; Carise, et. al., 2007
How abusers typically manipulate tablets for abuse

<table>
<thead>
<tr>
<th>Physical fragmentation</th>
<th>Chemical procedures</th>
<th>Administration tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scrapers</td>
<td>• Simple extraction</td>
<td>• Oral (swallow or crush)</td>
</tr>
<tr>
<td>• Kitchen graters, grinders</td>
<td>• Aqueous solvents</td>
<td>• Insufflation (credit card, straw)</td>
</tr>
<tr>
<td>• Mortar &amp; pestle</td>
<td>• Alcohol</td>
<td>• Injection (insulin syringe)</td>
</tr>
<tr>
<td>• Pill cutters, crushers</td>
<td>• Acids</td>
<td>• Rectal (needle-less syringe)</td>
</tr>
<tr>
<td>• Electric appliances</td>
<td>• Advanced extraction</td>
<td>• Smoking (foil, lighter)</td>
</tr>
<tr>
<td></td>
<td>• pH adjustments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Organic solvents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Purification</td>
<td></td>
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<tr>
<td></td>
<td>• Liquid/liquid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Precipitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Filtration</td>
<td></td>
</tr>
</tbody>
</table>

- Scrapers
- Kitchen graters, grinders
- Mortar & pestle
- Pill cutters, crushers
- Electric appliances

- Simple extraction
  - Aqueous solvents
    - Alcohol
    - Acids
- Advanced extraction
  - pH adjustments
  - Organic solvents
- Purification
  - Liquid/liquid
  - Precipitation
  - Filtration

- Oral (swallow or crush)
- Insufflation (credit card, straw)
- Injection (insulin syringe)
- Rectal (needle-less syringe)
- Smoking (foil, lighter)
Tablet characteristics that abusers dislike

**Hardness**

“(Tablet)...is definitely not in any crushable form...If you want to get the full bang...put the pill in a glass of water and wait for...all to be released...will take as long as if you swallowed em.”

Cone, DAD, 2006

**“Gel”**

“DO NOT SNORT THIS STUFF! You will be pulling massive amounts of thick sticky gel...out of your nasal cavity.”


**Work**

I don’t know man...seem to gel more ...I guess waiting 2 to 4 hours for it to seep into 70 ml of solution on a hot plate or stove might work, but that is quite a bit of work.

http://forum.oopiophile.org/showthread.php?t=25339
Principles of abuser 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

• A “resistance” barrier to tampering consists of time x effort x resources

• As the barrier to tampering increases, the frequency of tampering diminishes

SOURCE: Cone, Drug Alcohol Depend, 2006
Overview of how I advised Purdue

1. Helped Purdue team identify current and potential physicochemical tablet tampering methods employed by opioid abusers.

2. Ensured design scope was broad enough to anticipate creativity of abusers.

3. Provided input on how to translate “real world” abuser tablet manipulations into reproducible laboratory methods.

4. Input on analytical and methodological details to ensure high scientific validity, accuracy and reproducibility.

5. Looked for unanticipated weaknesses in the reformulation.
Purdue’s *in vitro* testing was scientifically rigorous and simulated relevant “real world” abuser tablet manipulations

<table>
<thead>
<tr>
<th>High scientific rigor of testing</th>
<th>High relevance to “real world” methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All dose strengths</td>
<td>• Crushability: cutting, grinding, powdering</td>
</tr>
<tr>
<td>• Taken to failure limit</td>
<td>• Dissolution</td>
</tr>
<tr>
<td>• High and low temperatures</td>
<td>• Effect of alcohol on “dose dumping”</td>
</tr>
<tr>
<td>• Extended measures - 18 and 24 hours</td>
<td>• Extraction (simple and complex methods)</td>
</tr>
<tr>
<td>• Comparison to current OxyContin</td>
<td>• Injection (syringeability and injectability)</td>
</tr>
<tr>
<td>• Statistically calculated replicates</td>
<td>• Nasal insufflation (snorting/sniffing)</td>
</tr>
<tr>
<td>• Validated methods</td>
<td>• Smoking</td>
</tr>
<tr>
<td>• Independent laboratories</td>
<td></td>
</tr>
<tr>
<td>• Blind conditions</td>
<td></td>
</tr>
</tbody>
</table>
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• Bioequivalence

• Approach to *in vitro* testing

• **Summary of *in vitro* testing results**
  – **Judy Lee, PhD; Purdue Senior Director, Analytics/Preformulation**

• Interpretation of in vitro findings

• Conclusions
Our goals drove the designs of our tamper testing

<table>
<thead>
<tr>
<th>Goals</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Characterize the physicochemical properties of the reformulation</td>
<td>• Get input from experts in “real world” extraction of oxycodone HCl for abuse</td>
</tr>
<tr>
<td>• Compare the performance of the two formulations</td>
<td>• Test time, effort and equipment required to reduce particle size</td>
</tr>
<tr>
<td>• Test the formulations to complete failure</td>
<td>• Ensure scientific robustness of studies</td>
</tr>
</tbody>
</table>
We replicated “real world” tablet manipulation scenarios in the lab

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</tr>
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<td>Intact</td>
<td></td>
<td></td>
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</tr>
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<td>vaporize</td>
<td></td>
<td></td>
<td></td>
</tr>
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<tr>
<td></td>
<td>Intact</td>
<td>Swallow</td>
<td>Dissolution in ethanol and simulated gastric fluid</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with alcohol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
We had a comprehensive approach to ensure our data was robust and meaningful

<table>
<thead>
<tr>
<th>How we determined the number of replicates</th>
<th>Results for both formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Guided by internal experiments</td>
<td>• Reformulated OxyContin</td>
</tr>
<tr>
<td>• Produce results with observed mean within 10% of true mean with 95% confidence</td>
<td>– N = 5 for small volume extraction (12,132)</td>
</tr>
<tr>
<td></td>
<td>– N = 6 for dissolution (3,312)</td>
</tr>
<tr>
<td></td>
<td>– N = 5 for IV and smoking (866)</td>
</tr>
<tr>
<td></td>
<td>• Current OxyContin</td>
</tr>
<tr>
<td></td>
<td>– N = 3 for all studies</td>
</tr>
</tbody>
</table>
Our study designs were rigorous and comprehensive.

Design EXAMPLE: Small volume extraction in Simple Solvent 1

<table>
<thead>
<tr>
<th>Particle size</th>
<th>Temperature</th>
<th>Time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest</td>
<td>Room temp</td>
<td>10m, 30m, 60m, 3h, 6h, 24h</td>
</tr>
<tr>
<td>Largest</td>
<td>Elevated temp</td>
<td>10m, 30m, 60m, 3h, 6h, 24h</td>
</tr>
<tr>
<td>Smallest</td>
<td>Room temp</td>
<td>10m, 30m, 60m, 3h, 6h, 24h</td>
</tr>
<tr>
<td>Smallest</td>
<td>Elevated temp</td>
<td>10m, 30m, 60m, 3h, 6h, 24h</td>
</tr>
</tbody>
</table>

- 80 mg OxyContin reformulation
- 60 mg OxyContin reformulation
- 40 mg OxyContin reformulation
- 30 mg OxyContin reformulation
- 20 mg OxyContin reformulation
- 15 mg OxyContin reformulation
- 10 mg OxyContin reformulation

Replicate 5x
We took multiple steps to eliminate bias

• Studies were outsourced to contract research organizations (CROs)
• Transferred testing methods to CROs
• CRO analysts blinded to samples to the extent possible
• External consultants conducted CRO site visits and helped interpret data
• Quality assurance and statistical analysis were also performed externally
We replicated “real world” tablet manipulation scenarios in the lab

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<td>N/A</td>
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<td>Crush</td>
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<td>Crush, vaporize</td>
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<td>API extraction via vaporization</td>
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</tr>
<tr>
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<td>Crush</td>
<td>Extract</td>
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</tr>
<tr>
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<td></td>
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<td>Intact</td>
<td>Swallow with alcohol</td>
<td>Dissolution in ethanol and simulated gastric fluid</td>
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</table>
Study 1 – manipulation of tablets

Goals

**Abuse**
Simulate expected abuser approaches to intentionally crush or fragment tablets to swallow, insufflate directly or add to solvent to extract oxycodone

**Patient error**
Understand likelihood that tablets can be accidentally crushed by patients, or intentionally crushed by caregivers with a pill-crusher or knife
Study 1 – manipulation of tablets

**Methods: Identify techniques to develop a standardized set of samples for further testing**

**Identify tools**
- Choose common household tools
- Use multiple types of each tool

**Create samples**
- Identify the broad range of particle sizes
- Divide range into 6 bands
- Reproduce bands using lab equipment
Study 1 – manipulation of tablets

Results: Reformulated OxyContin is difficult to crush

<table>
<thead>
<tr>
<th>Test tool</th>
<th>Ability to crush tablet to small particles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current OxyContin</td>
</tr>
<tr>
<td>Tool 1</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 2</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 3</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 4</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 5</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 6</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 7</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 8</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 9</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 10</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 11</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 12</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 13</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 14</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 15</td>
<td>✅ (fine powder)</td>
</tr>
<tr>
<td>Tool 16</td>
<td>✅ (fine powder)</td>
</tr>
</tbody>
</table>

✅ Could be crushed
❌ Could not be crushed
Conclusions

• Current OxyContin tablets are crushable and have a binary response to any form of tablet manipulation

• Reformulated tablets are hard, require time and effort to reduce their size, and have a graded response to any form of tablet manipulation

• Many household tools cannot crush reformulated OxyContin but can crush current OxyContin
We replicated “real world” tablet manipulation scenarios in the lab

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<td></td>
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</tr>
<tr>
<td></td>
<td>vaporize</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
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</table>


Studies 2 & 4 – small volume extraction

**Goal**

**Abuse**

Simulate the scenario of an abuser attempting to extract oxycodone HCl from intact or crushed tablets in small volume of liquid to ingest orally or inject.
**Methods: Evaluate API release of reformulated OxyContin after small volume extraction in solvents**

<table>
<thead>
<tr>
<th>Perform extraction</th>
<th>Conduct analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Solvent volume:</td>
<td></td>
</tr>
<tr>
<td>– 30 mL</td>
<td>• Determine amount of extractable oxycodone HCl</td>
</tr>
<tr>
<td>• Solvent types:</td>
<td></td>
</tr>
<tr>
<td>– Ingestible</td>
<td>• Test a variety of time points</td>
</tr>
<tr>
<td>– Non-ingestible</td>
<td></td>
</tr>
<tr>
<td>– pH buffers</td>
<td>– 10, 30, 60, 180, 360 min., and 24 hours</td>
</tr>
<tr>
<td>• Temperature:</td>
<td></td>
</tr>
<tr>
<td>– Room</td>
<td></td>
</tr>
<tr>
<td>– Elevated</td>
<td></td>
</tr>
<tr>
<td>• Agitation:</td>
<td></td>
</tr>
<tr>
<td>– 100 rpm</td>
<td></td>
</tr>
</tbody>
</table>
Studies 2 & 4 – small volume extraction

Solvents were selected to cover a wide range of chemical properties

- Polarity
  - Ingestible
    - Simple Solvent 1
    - Simple Solvent 2
    - Simple Solvent 3
    - Simple Solvent 4
    - Simple Solvent 5
    - Simple Solvent 6
  - Non-ingestible
    - Advanced Solvent 1
    - Advanced Solvent 2
    - Advanced Solvent 3
  - Buffers
    - pH A
    - pH B
    - pH C
    - pH D
Results: Early release of oxycodone HCl from the reformulation is slower or similar to current OxyContin

Oxycodone release expressed as percent of release from current OxyContin

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time:</th>
<th>10 minutes</th>
<th>60 minutes</th>
<th>18 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>large</td>
<td>medium</td>
<td>small</td>
</tr>
<tr>
<td>Ingestible</td>
<td>Simple Solvent 1</td>
<td>7</td>
<td>53</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Simple Solvent 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple Solvent 3</td>
<td>2</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Simple Solvent 4</td>
<td>2</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Simple Solvent 5</td>
<td>2</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Simple Solvent 6</td>
<td>0</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td>pH buffers</td>
<td>pH A</td>
<td>3</td>
<td>35</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>pH B</td>
<td>3</td>
<td>36</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>pH C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH D</td>
<td>6</td>
<td>68</td>
<td>53</td>
</tr>
<tr>
<td>Non-ingestible</td>
<td>Advanced Solvent 1</td>
<td>8</td>
<td>58</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Advanced Solvent 2</td>
<td>1</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Advanced Solvent 3</td>
<td>0</td>
<td>23</td>
<td>123</td>
</tr>
</tbody>
</table>

Legend:
- Similar
- Faster, P<0.05
Conclusions

• Smaller particles release oxycodone HCl faster than larger particles

• At time points tested that are relevant to abusers, the reformulation releases oxycodone HCl slower in all effective solvents tested
We replicated “real world” tablet manipulation scenarios in the lab

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<td></td>
<td>with alcohol</td>
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<td></td>
</tr>
</tbody>
</table>
Study 3 – alcohol “dose dumping”

Goal

Assess whether reformulated OxyContin will “dose dump” oxycodone HCl in a simulated scenario of patients taking tablets together with alcoholic beverages.
Study 3 – alcohol “dose dumping”

Methods: Determine if OxyContin in ethanol causes “dose dumping”

Perform dissolution

- Volume: 900 mL
- Solvents:
  - Simulated gastric fluid (SGF)
  - Ethanol in SGF
- Temperature: 37°C
- Agitation: 100 rpm

Conduct analysis

- Determine amount of extractable oxycodone HCl
- Time points: 10, 30, 60, 180, 360, 720 minutes
Study 3 – alcohol “dose dumping”

Results: Across bands and strengths, reformulated OxyContin does not “dose dump” in ethanol

```
<table>
<thead>
<tr>
<th>Reformulation tablet strength</th>
<th>Particle size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small</td>
</tr>
<tr>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td>15 mg</td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>30 mg</td>
<td></td>
</tr>
<tr>
<td>40 mg</td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td></td>
</tr>
</tbody>
</table>
```

“Dose dumps” in ethanol?
- No
- Yes
Study 3 – alcohol “dose dumping”

Conclusions

• Reformulated OxyContin does not “dose dump” in ethanol

• This holds true across bands and strengths
We replicated “real world” tablet manipulation scenarios in the lab

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<td>Swallow with alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study 5 – syringability and injectability

Goal

Assess whether reformulated OxyContin tablets can be injected using an insulin syringe (type typically available to abusers)
Study 5 – syringability and injectability

**Methods:** determine how much oxycodone HCl can be syringed and injected for potential intravenous abuse

<table>
<thead>
<tr>
<th>Perform extraction</th>
<th>Syringe or inject solution</th>
<th>Conduct analysis</th>
</tr>
</thead>
</table>

**Syringability** (ability to draw oxycodone HCl through needle into syringe)

- **Temperature**
- **Time**
- **Solvent: water**

- **Needle size:** 27 and 28 gauge
- **Syringe size:** 1 cc and 10 cc
- **Time to draw in:** up to 1 minute

- **Determine amount of oxycodone HCl that can be syringed**
- **Volume of solution that can be drawn into a syringe**
Study 5 – syringability and injectability

**Methods:** determine how much oxycodone HCl can be syringed and injected for potential intravenous abuse (continued)

Perform extraction  | Syringe or inject solution  | Conduct analysis
--- | --- | ---

**Syringability** (ability to draw oxycodone HCl through needle into syringe)

- Temperature
- Time
- Solvent: water

- Needle size: 27 and 28 gauge
- Syringe size: 1 cc and 10 cc
- Time to draw in: up to 1 minute

- Determine amount of oxycodone HCl that can be syringed
- Volume of solution that can be drawn into a syringe

**Injectability** (ability to expel oxycodone HCl through needle after back-loading syringe)

- Temperature
- Time
- Solvent: water

- Needle size: 27 gauge
- Syringe size: 10 cc
- Time to expel: up to 1 minute

- Determine amount of oxycodone HCl that can be expelled
- Determine volume of solution that can be expelled
Study 5 – syringability and injectability

Results: Reformulated OxyContin is difficult to syringe or inject using an insulin syringe

**Syringability**

(27 gauge)

<table>
<thead>
<tr>
<th>Oxycodone HCl (mg)</th>
<th>2 mL</th>
<th>Reformulated OxyContin strength (mg)</th>
<th>Current OxyContin strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>
Study 5 – syringability and injectability

**Conclusion: Reformulated OxyContin is resistant to intravenous use**

- **Intact tablet**
  - Crush
  - Dissolve
  - Syringe
  - Inject
  - Easy
  - Difficult or impossible

- **Current OxyContin**

- **Reformulation**
  - Successful injection of oxycodone
We replicated “real world” tablet manipulation scenarios in the lab

<table>
<thead>
<tr>
<th>Route</th>
<th>Physical</th>
<th>Chemical</th>
<th>How we tested in the lab</th>
<th>Study No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Intact</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nasal</td>
<td>Crush</td>
<td></td>
<td>Manipulation of tablets via manual and electrical tools</td>
<td>1</td>
</tr>
<tr>
<td>Rectal</td>
<td>Crush</td>
<td>Extract</td>
<td>API extraction in small volume of different solvents</td>
<td>2 &amp; 4</td>
</tr>
<tr>
<td>Smoke</td>
<td>Crush, vaporize</td>
<td></td>
<td>API extraction via vaporization</td>
<td>5</td>
</tr>
<tr>
<td>Inject</td>
<td>Crush</td>
<td>Extract</td>
<td>Syringability and injectability</td>
<td>5</td>
</tr>
<tr>
<td>Patient error</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Crush</td>
<td></td>
<td>Manipulation of tablets via multiple manual tools</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Intact</td>
<td>Swallow with alcohol</td>
<td>Dissolution in ethanol and simulated gastric fluid</td>
<td>3</td>
</tr>
</tbody>
</table>
Study 5 – vaporization for inhalation

**Goal**

*Abuse* Simulate “smoking” of reformulated OxyContin and compare to known controls that are efficient for smoking
Study 5 – vaporization for inhalation

Methods: Simulate oxycodone HCl release through “smoking”

**Perform vaporization**

- **Conditions**
  - Heat block
  - Constant airflow
  - Collection with solid phase cartridge

- **Temperature optimized to maximize vaporization and minimize pyrolysis**
  - Reformulated OxyContin
  - Current OxyContin
  - Positive control
  - Negative control

**Conduct analysis**

- Determine amount of oxycodone HCl that can be vaporized
Results: The efficiency of smoking reformulated OxyContin is low

<table>
<thead>
<tr>
<th>Test substance</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reformulated OxyContin</td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>✗</td>
</tr>
<tr>
<td>15 mg</td>
<td>✗</td>
</tr>
<tr>
<td>20 mg</td>
<td>✗</td>
</tr>
<tr>
<td>30 mg</td>
<td>✗</td>
</tr>
<tr>
<td>40 mg</td>
<td>✗</td>
</tr>
<tr>
<td>60 mg</td>
<td>✗</td>
</tr>
<tr>
<td>80 mg</td>
<td>✗</td>
</tr>
<tr>
<td>OxyContin</td>
<td></td>
</tr>
<tr>
<td>10, 40, 80 mg</td>
<td>✗</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Negative control</td>
<td>✗ (18%)</td>
</tr>
<tr>
<td>Positive control</td>
<td>✓ (68%)</td>
</tr>
<tr>
<td>Reference*</td>
<td></td>
</tr>
<tr>
<td>Reference 1</td>
<td>✓ (80%)</td>
</tr>
<tr>
<td>Reference 2</td>
<td>✓ (80%)</td>
</tr>
<tr>
<td>Reference 3</td>
<td>✓ (98%)</td>
</tr>
</tbody>
</table>

Study 5 – vaporization for inhalation

**Conclusion: Reformulated OxyContin is inefficient for use via smoking**

- Intact tablet
- Crush
- Vaporize w/o pyrolyzing
- Successful smoking of API

✅ Easy
❌ Difficult or impossible

**Positive control**

**Current OxyContin**

**Reformulation**
Summary of *in vitro* findings

These data indicate that reformulated OxyContin tablets:

• Are difficult to crush

• Release oxycodone HCl slower than current OxyContin tablets in a range of solvents, even when reduced to particles

• Do not “dose dump” oxycodone HCl in ethanol, even when reduced to particles

• Are difficult to syringe or inject via an insulin syringe

• Release oxycodone HCl inefficiently via vaporization
Today’s discussion

Closed session

• Detailed in vitro testing methods and results

Open session

• Introduction
• Addressing opioid abuse
• Polyethylene oxide excipient
• Bioequivalence
• Approach to in vitro testing
• Summary of in vitro testing results

• Interpretation of in vitro findings
  – Dr. Edward Sellers, MD, PhD; Professor Emeritus of Pharmacology, Medicine and Psychiatry, University of Toronto

• Conclusions
Introduction and qualifications: Basis for my expertise in drug abuser behavior and preferences

Professor Emeritus, University of Toronto
• Long experience with drugs with dependence and addictive potential
• Published more than 600 peer reviewed scientific papers

WHO, Member of the Expert Committee on Drug Dependence

Past President of ASCPT and CPDD

Former VP and Medical Director of Addiction Research Foundation

VP, Kendle International Early Stage
• A world-leading contract research organization
• Works across therapeutic areas
• Offers full range of early- to late-stage services
Disclaimer

I appear today as an independent consultant from Kendle. Kendle is being paid by Purdue Pharma for my time.

The views presented today are my own.
Like Dr. Cone, my work with Purdue Pharma on reformulated OxyContin began in October 2008

- **October 2008**: Member of expert panel on modes of abuse and misuse
- **January 2009**: Attended Purdue’s closed FDA meeting to discuss their approach to *in vitro* testing
- **February 2009**: Reviewed results from *in vitro* studies
- **April 2009**: Worked with Purdue to design post-marketing studies
We can learn from abuser’s experiences with hard and hydrogelling formulations of other medications

Abuser views about injecting and snorting methylphenidate (Concerta)

“Concerta when crushed up and snorted has been known to completely clog up the nostrils as it turns into a slime. I wouldn't inject it, unless of course you want your blood to become the consistency of maple syrup. Concerta is only good for eating, no matter what you do with it. Edit: And even eating it is pointless.”

Abuser views about hydrogelling generic formulation

“In terms of potency, they should be no difference in any brand. However, some brands are a pain to crush, and if you want to sniff them, they turn to gel...”

Abuser views about smoking current OxyContin

“I've heard of people smoking oxycontin with success, but I don't get how that works with all the binders and fillers thats in oxy. I tried it once and it was very disgusting and I didn't feel anything from it. I even tried it with the instant release oxycodone 15 and 30 mg pills and that was just as bad as smoking a 40 mg oxycontin.”
Three axes of testing are important, but none are sufficient to exactly predict impact on “real world” opioid abuse.

Goals:
- Balance medication benefit with its safety and risks
- Balance safety for different populations with risk to different populations
- Consider safety of the product:
  - for its intended population
  - when used by non-patients
  - when used outside conditions of use

\[ \text{IR} \quad \text{CR} \]

\[ [C] \]

\[ \text{Time} \quad \text{Hours} \]

\[ 12 \]

\[ \text{Like} \quad \text{Dislike} \]

\[ \text{Time} \quad \text{Hours} \]

\[ 12 \]
My interpretation

Reformulated OxyContin’s public health benefits to patients are clear

Medication errors are less likely

• Crushing by patient or well-intentioned caregivers
• Accidental chewing by patients
My interpretation

Reformulated OxyContin also brings important incremental public health benefits for non-patients

For most, misuse and abuse are likely to decline
- The harder the tablet is, the less likely the behavior
- The tablet is more difficult to crush or easily chew
- Reductions also likely in intravenous and insufflation abuse

For those seeking delayed effect, impact on intact oral abuse is likely to be limited
My interpretation: Reformulation offers an overall improvement in safety profile across routes of administration.

<table>
<thead>
<tr>
<th>Route</th>
<th>Physical</th>
<th>Chemical</th>
<th>Anticipated impact of reformulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td></td>
<td></td>
<td>No improvement</td>
</tr>
<tr>
<td>Oral</td>
<td>Intact</td>
<td></td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td>Crush</td>
<td></td>
<td>Better</td>
</tr>
<tr>
<td></td>
<td>Crush</td>
<td>Extract</td>
<td>Better</td>
</tr>
<tr>
<td>Nasal</td>
<td>Crush</td>
<td></td>
<td>Better</td>
</tr>
<tr>
<td>Rectal</td>
<td>Crush</td>
<td>Extract</td>
<td>Better</td>
</tr>
<tr>
<td>Smoke</td>
<td>Crush, vaporize</td>
<td></td>
<td>Better</td>
</tr>
<tr>
<td>Inject</td>
<td>Crush</td>
<td>Extract</td>
<td>Better</td>
</tr>
<tr>
<td>Patient error</td>
<td>Crush</td>
<td></td>
<td>Better</td>
</tr>
<tr>
<td>Oral</td>
<td>Intact</td>
<td>Swallow with alcohol</td>
<td>No dose dumping</td>
</tr>
</tbody>
</table>
My interpretation: Reformulation offers an overall improvement in safety profile across at-risk populations

<table>
<thead>
<tr>
<th>Population at risk</th>
<th>Anticipated impact of reformulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental misusers</td>
<td>• More difficult to defeat controlled-release mechanism by chewing</td>
</tr>
<tr>
<td>Experimenters</td>
<td>• Likely reduction in casual use, and acute dose deaths</td>
</tr>
<tr>
<td>Recreational abusers</td>
<td>• Likely to shift drug choice, reducing OxyContin’s role as a gateway drug</td>
</tr>
<tr>
<td>Sophisticated addicts</td>
<td>• Likely to switch due to increased time and effort</td>
</tr>
<tr>
<td></td>
<td>• Effect possibly modest on highly motivated abusers and traffickers</td>
</tr>
</tbody>
</table>
Today’s discussion

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• Interpretation of in vitro findings

• Conclusions
  Craig Landau, MD; Purdue Chief Medical Officer
Conclusions

Reformulated OxyContin:

• Is bioequivalent to the current OxyContin formulation

• Is an advanced formulation because it should be
  – More difficult to prepare for abuse via multiple routes of administration
  – Less likely to be inadvertently crushed by patients or caregivers

• If approved, will replace the currently marketed product