CONFIDENTIAL

FDA Advisory Committee on Reformulated OxyContin

Public session
September 24, 2009

Today's discussion

Closed session

- Detailed *in vitro* testing methods and results

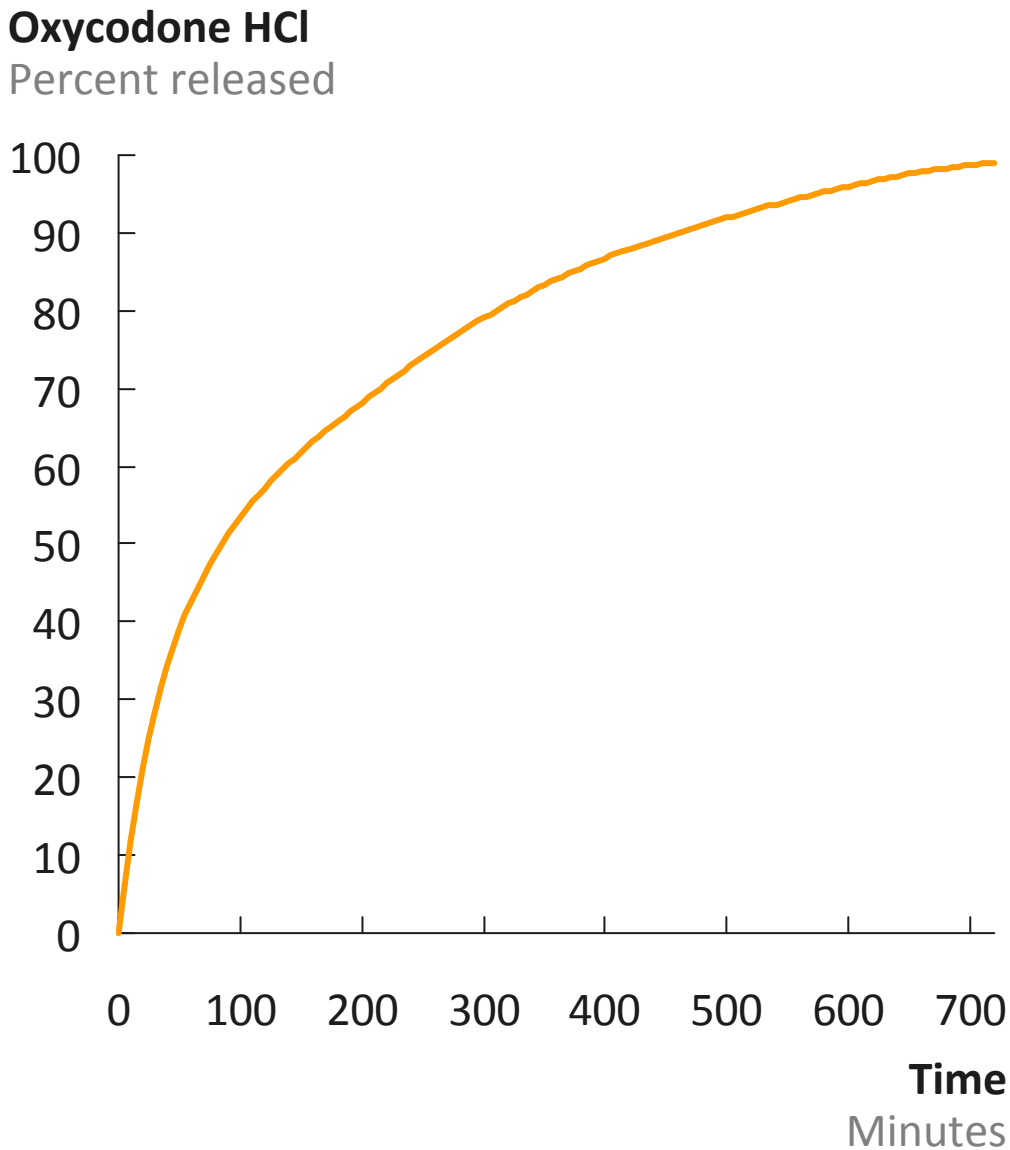
Open session

- **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

Crushed OxyContin

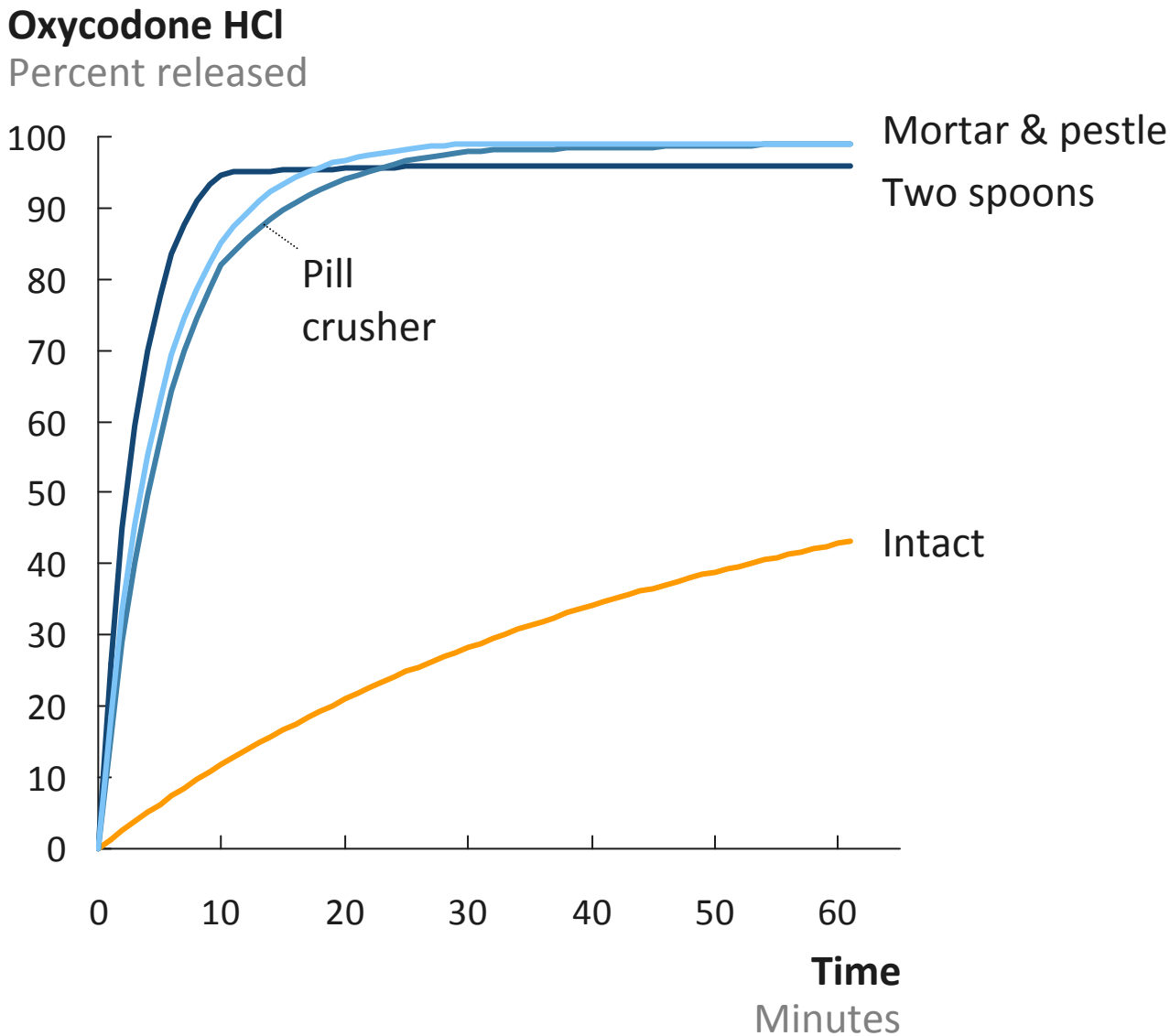
Intact OxyContin



The controlled-release mechanism of the current OxyContin dosage formulation is easily overcome

Crushed OxyContin

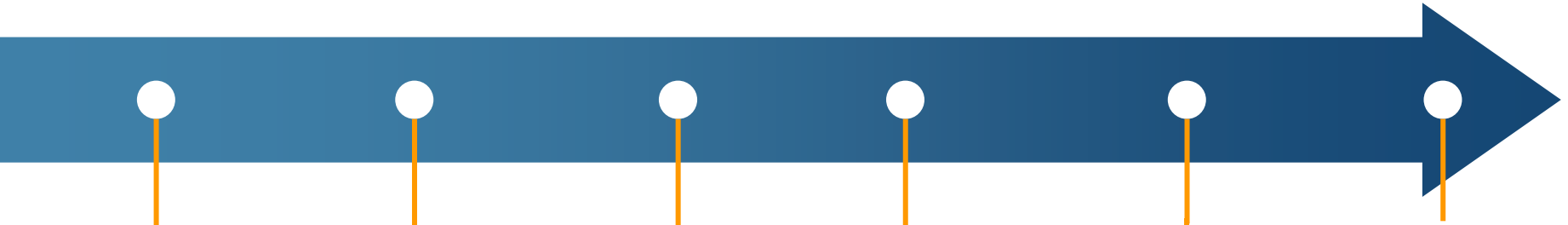
Intact OxyContin



Physical crushing of OxyContin underlies many routes of abuse and misuse

	Route of admin	What happens to tablets: Physical	What happens to tablets: Chemical
Abuse	Oral	Intact	
		Crush	
		Crush	Extract
	Nasal	Crush	
	Rectal	Crush	Extract
	Smoke	Crush, vaporize	
	Inject	Crush	Extract
Patient error	Oral	Crush	
		Intact	Swallow with alcohol

Purdue pursued multiple technologies to reformulate OxyContin to mitigate abuse and misuse



Early 2000s
- Purdue began reformulation efforts

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

We consulted experts in drug abuse and tablet tampering

Bob Bianchi	President, Bianchi Consulting, Ltd.; VP and Chief of Scientific and Technical Affairs, Prescription Drug Research Center; Former Laboratory Director, DEA
Bruce Burlington, MD	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
Ronald W. Buzzeo, RPh	Chief Regulatory Officer, Cegedim Dendrite Compliance Solutions
Sandra Comer, PhD	Associate Professor of Clinical Neurobiology, Division on Substance Abuse, Columbia
Ed Cone, PhD	Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins; Former Chief of the Chemistry and Drug Metabolism Section, NIDA
Ed Sellers, MD, PhD	VP, Kendle International Early Stage; Professor of Pharmacology, Medicine and Psychiatry, University of Toronto
Herb Kleber, MD	Professor of Anesthesia & Critical Care, University of Chicago
Jim Zacny, PhD	Professor of Psychiatry and Director, Division on Substance Abuse, Columbia University

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”

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  - ***Pamela Bennett, RN, BSN;*** *Executive Director, Healthcare Alliance Development*
- Polyethylene oxide excipient
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- Approach to *in vitro* testing
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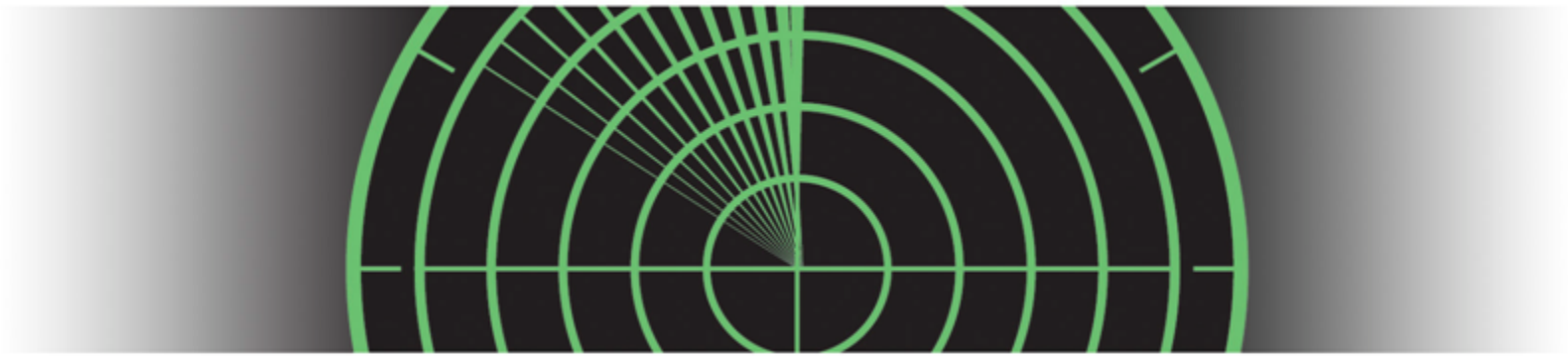
Prescription drug abuse: Working together

- 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

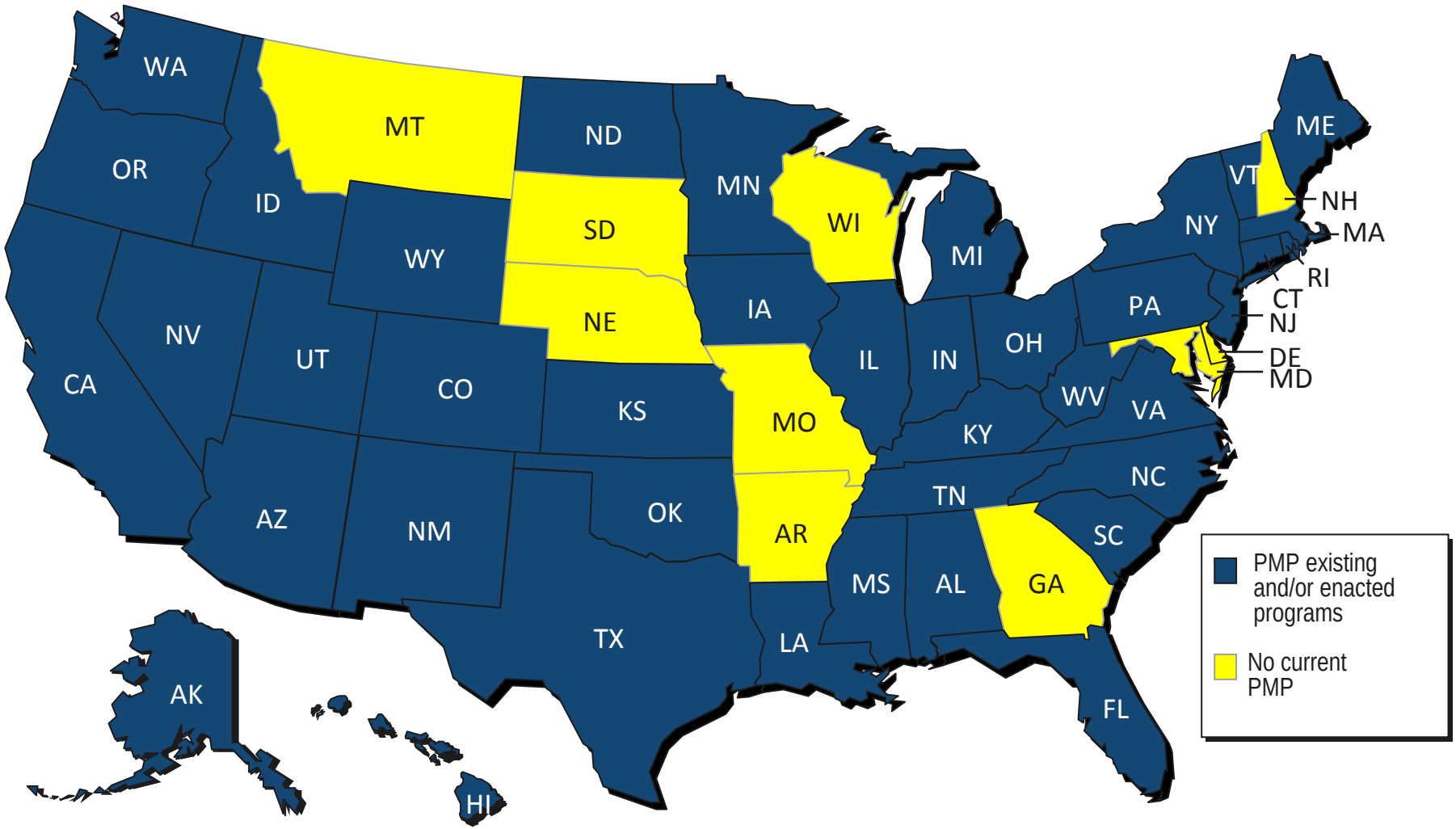
RADARS®
SYSTEM



Researched **A**buse, **D**iversion, and

Addiction-**R**elated **S**urveillance **(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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- **Polyethylene oxide excipient**
  - ***Craig Landau, MD;*** *Purdue Chief Medical Officer*
- Bioequivalence
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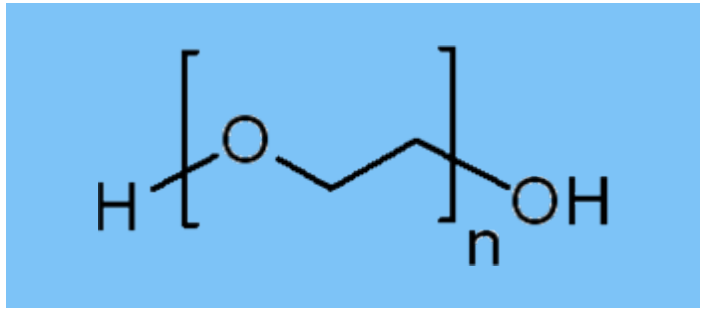
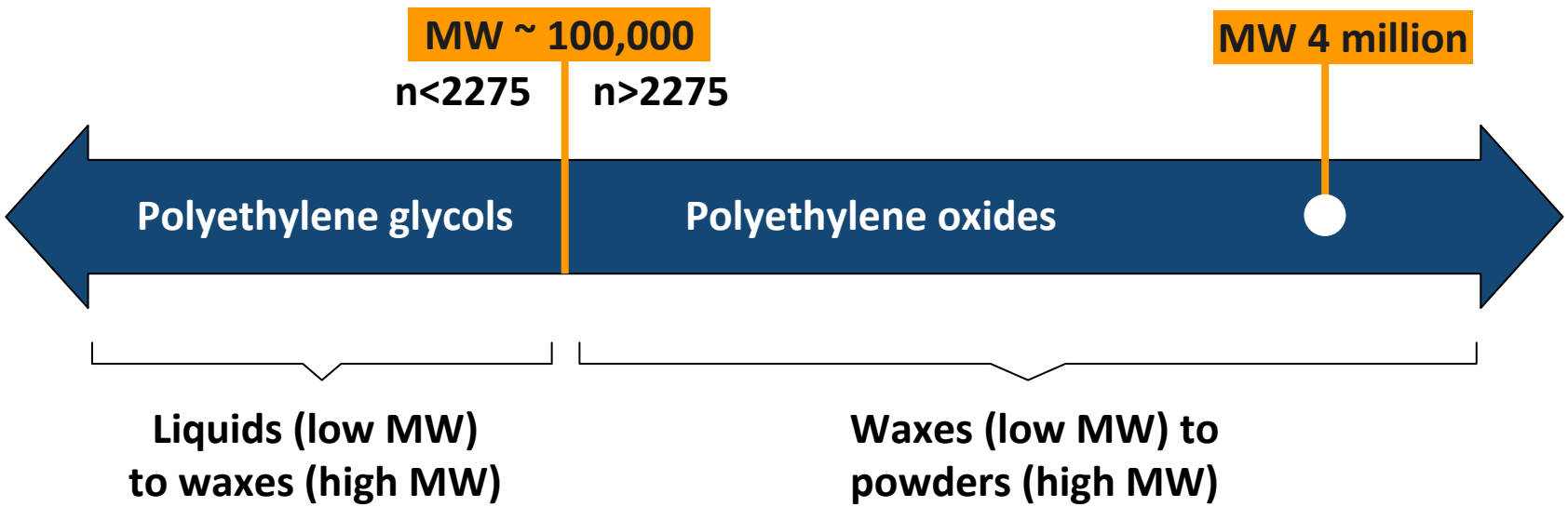
Use of polyethylene oxide (PEO) excipient enabled us to develop a this bioequivalent reformulation



Polyethylene



PEO is found in many common over-the-counter medications

OTC medication	API (active ingredient)
Pediatric Vicks Formula 44e Cough & Chest Congestion Relief Liqui	dextromethorphan hydrobromide, guaifenesin
Pediatric Vicks Formula 44m Cough & Cold Relief Liquid	chlorpheniramine maleate, dextromethorphan hydrobromide
Sudafed Nasal Decongestant Tablets	pseudoephedrine hydrochloride
Theraflu Thin Strips Daytime Cold & Cough	dextromethorphan hydrobromide, phenylephrine hydrochloride
Theraflu Thin Strips Nighttime Cold & Cough	diphenhydramine hydrochloride, phenylephrine hydrochloride
Vicks Formula 44 Cough Relief Liquid	dextromethorphan hydrobromide
Vicks Formula 44E Cough & Chest Congestion Relief Liquid	dextromethorphan hydrobromide, guaifenesin
Vicks Formula 44M Cough, Cold & Flu Relief Liquid	acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide

PEO is also found in many well-known prescription medications

Prescription drug	API (active ingredient)	Indication
Procardia XL FDA – 1989	nifedipine	vasospastic angina
Glucotrol XL FDA – 1994	glipizide	type 2 diabetes
DynaCirc CR FDA – 1994	isradipine	hypertension
Covera HS FDA – 1996	verapamil HCl	hypertension and angina
Ditropan XL FDA – 1998	oxybutinin chloride	urinary incontinence & nocturnal enuresis
Concerta FDA – 2000	methylphenidate	ADHD
Proquin XR FDA – 2005	ciprofloxacin HCl	uncomplicated urinary tract infections
Glumetza ER FDA – 2005	metformin HCl	type 2 diabetes
Jurnista EMEA – 2006	hydromorphone HCl	moderate to severe chronic pain

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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- **Bioequivalence**
  - ***Stephen Harris, MD;*** *Purdue Executive Director of Clinical Pharmacology*
- Approach to *in vitro* testing
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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

10 mg BE	Fed: OTR1002	Two-way crossover studies in healthy adult subjects comparing: Reformulated OxyContin (Test) to Current OxyContin (Reference)
	Fasted: OTR1003	
40 mg BE	Fed: OTR1004	
	Fasted: OTR1005	
80 mg BE	Fed: OTR1008	
	Fasted: OTR1009	
10-40 mg Dose-Prop	Fasted: OTR1006	5-treatment, 4-period, incomplete block, crossover study in healthy adult subjects
40-80 mg Dose-Prop	Fasted: OTR1012	3-treatment, 3-period, complete block, crossover study in healthy adult subjects

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

Statistical results from six pivotal and two dose proportionality studies demonstrate bioequivalence of the two formulations

Bioequivalence studies

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

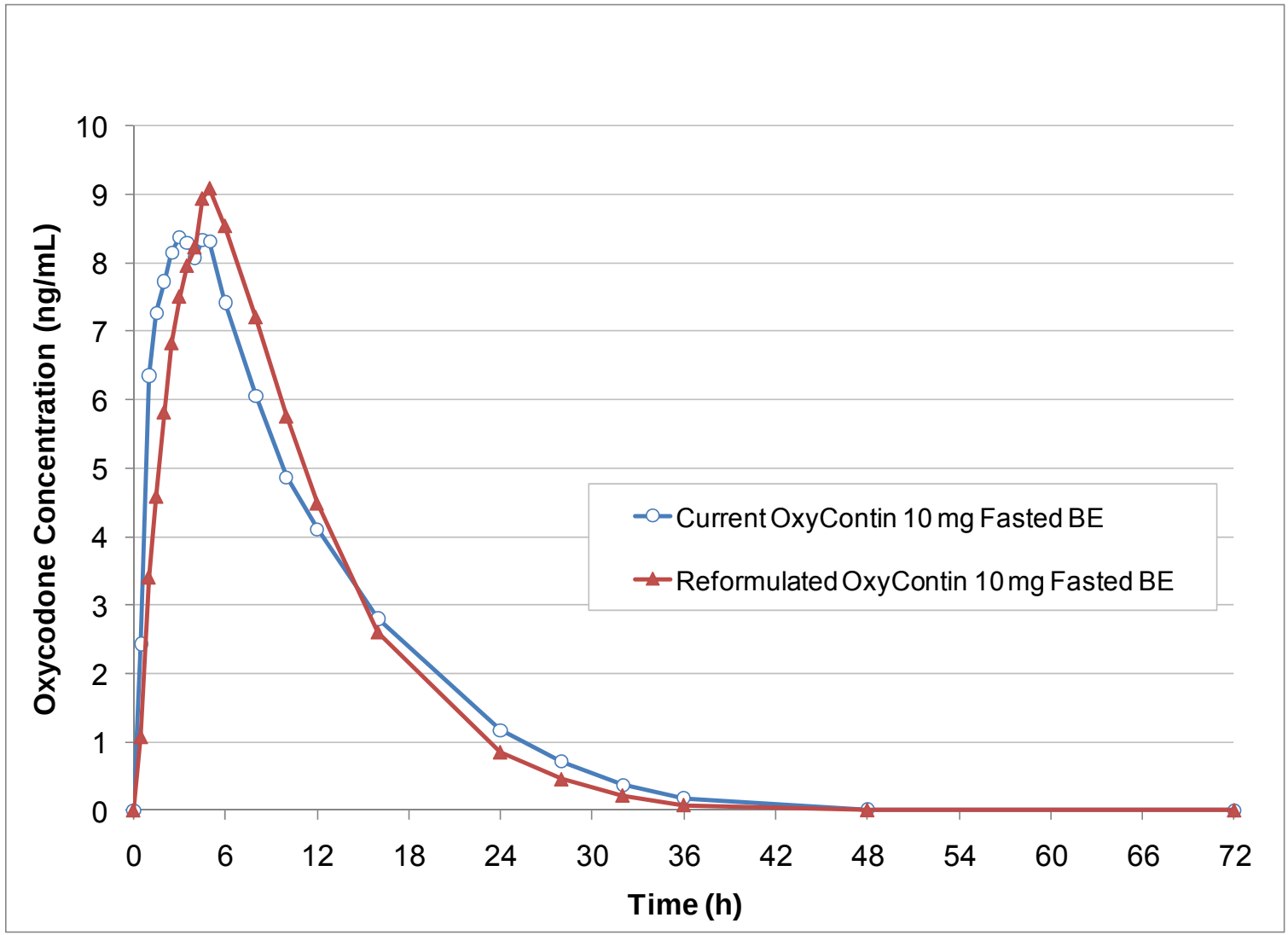
Dose proportionality studies

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

* Planned number of subjects

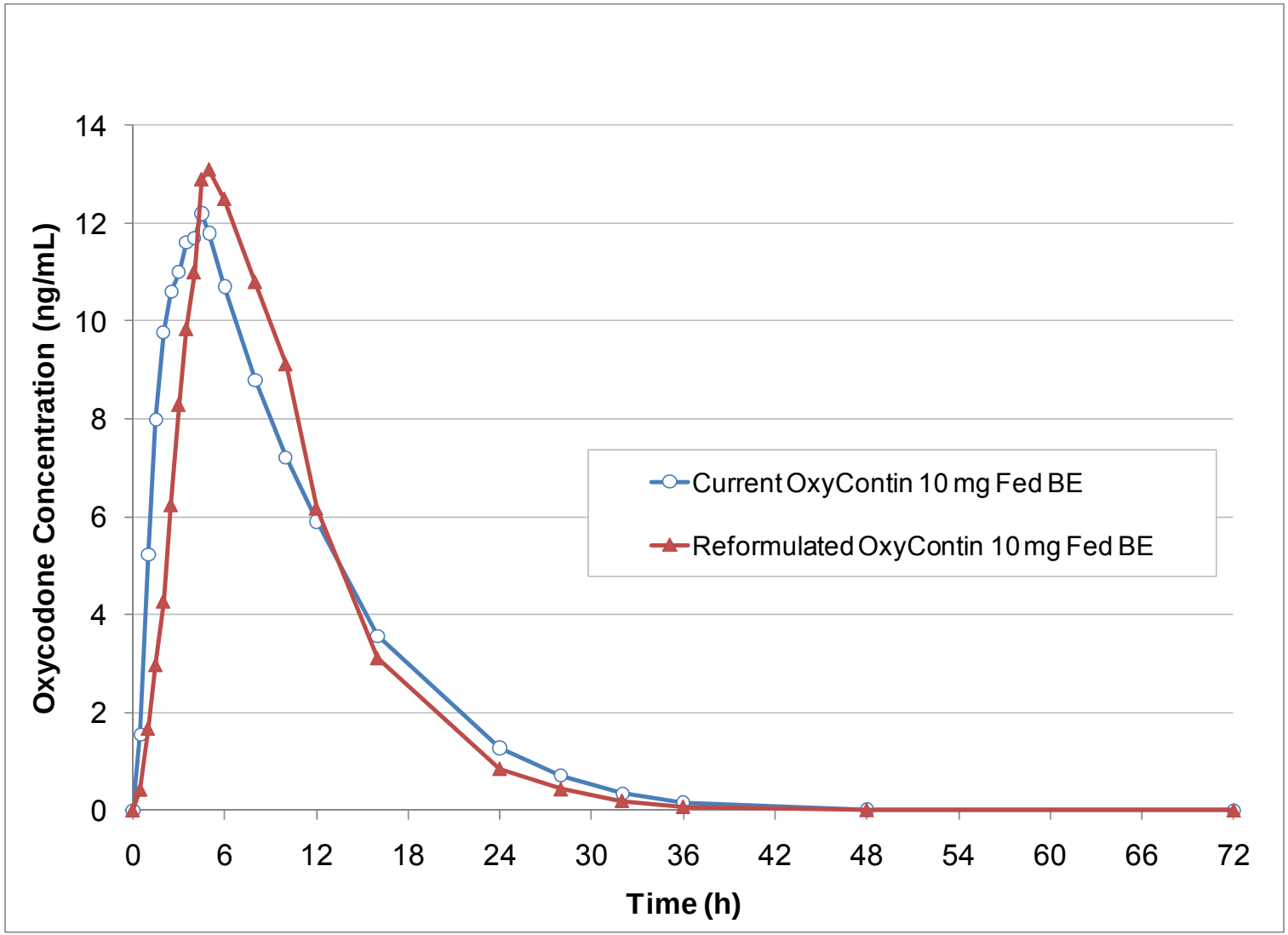
OTR1003: Fasted 10 mg bioequivalence

Mean concentration vs. time



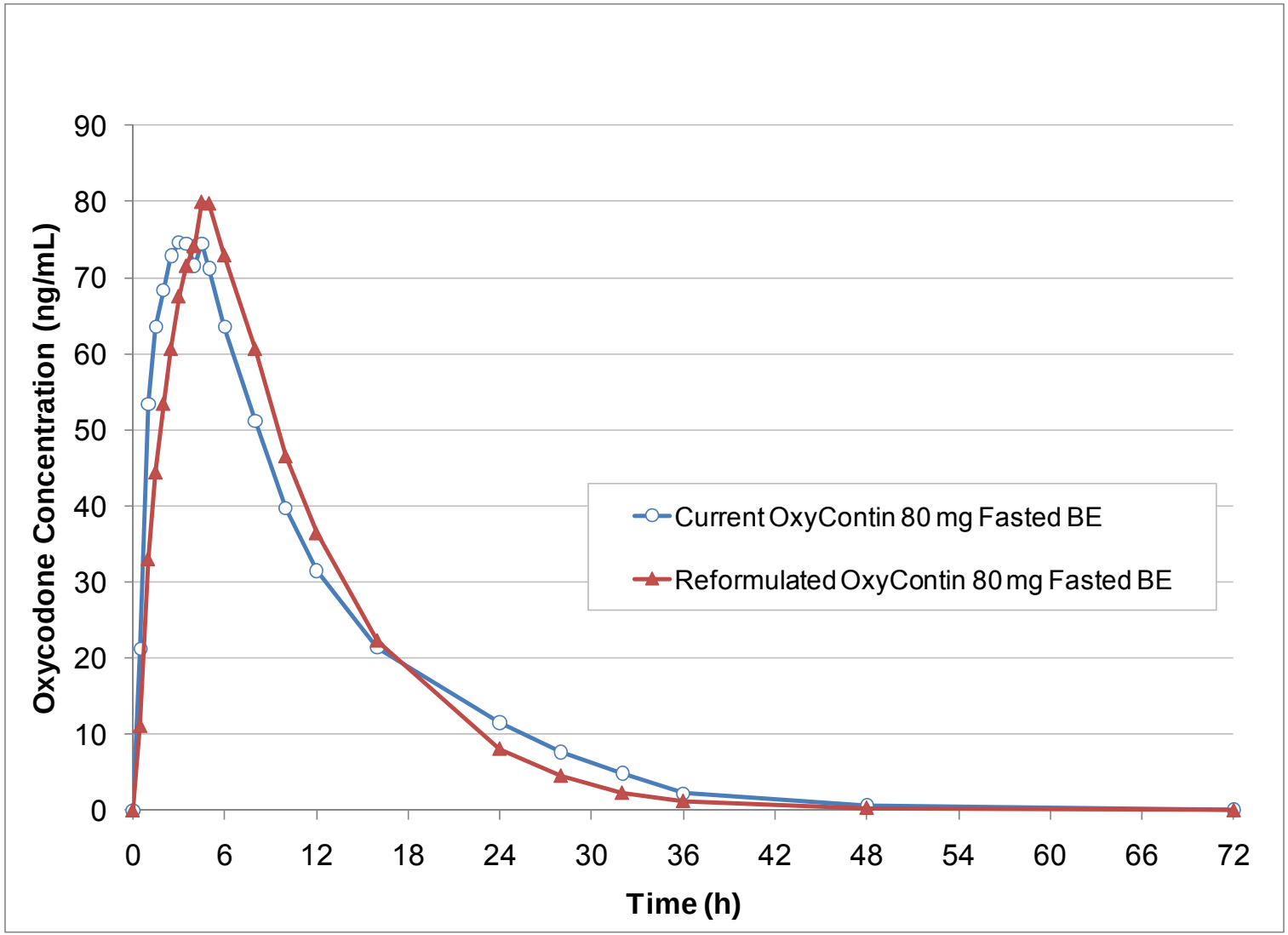
OTR1002: Fed 10 mg bioequivalence

Mean concentration vs. time



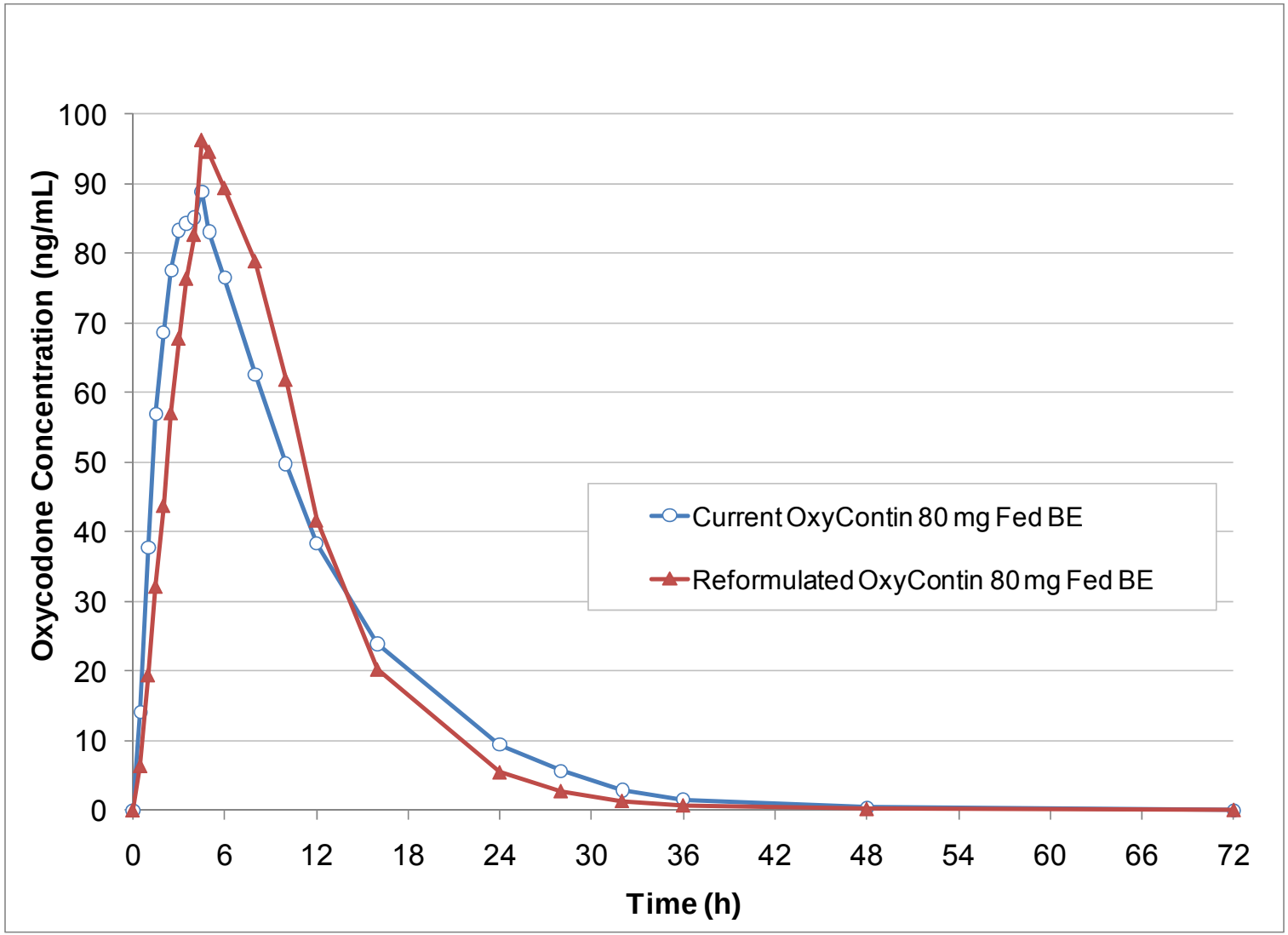
OTR1009: Fasted 80 mg bioequivalence

Mean concentration vs. time



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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- **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
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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
- Commissioned Officer in US Public Health Service, 1973-1998
- 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

Disclaimer

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

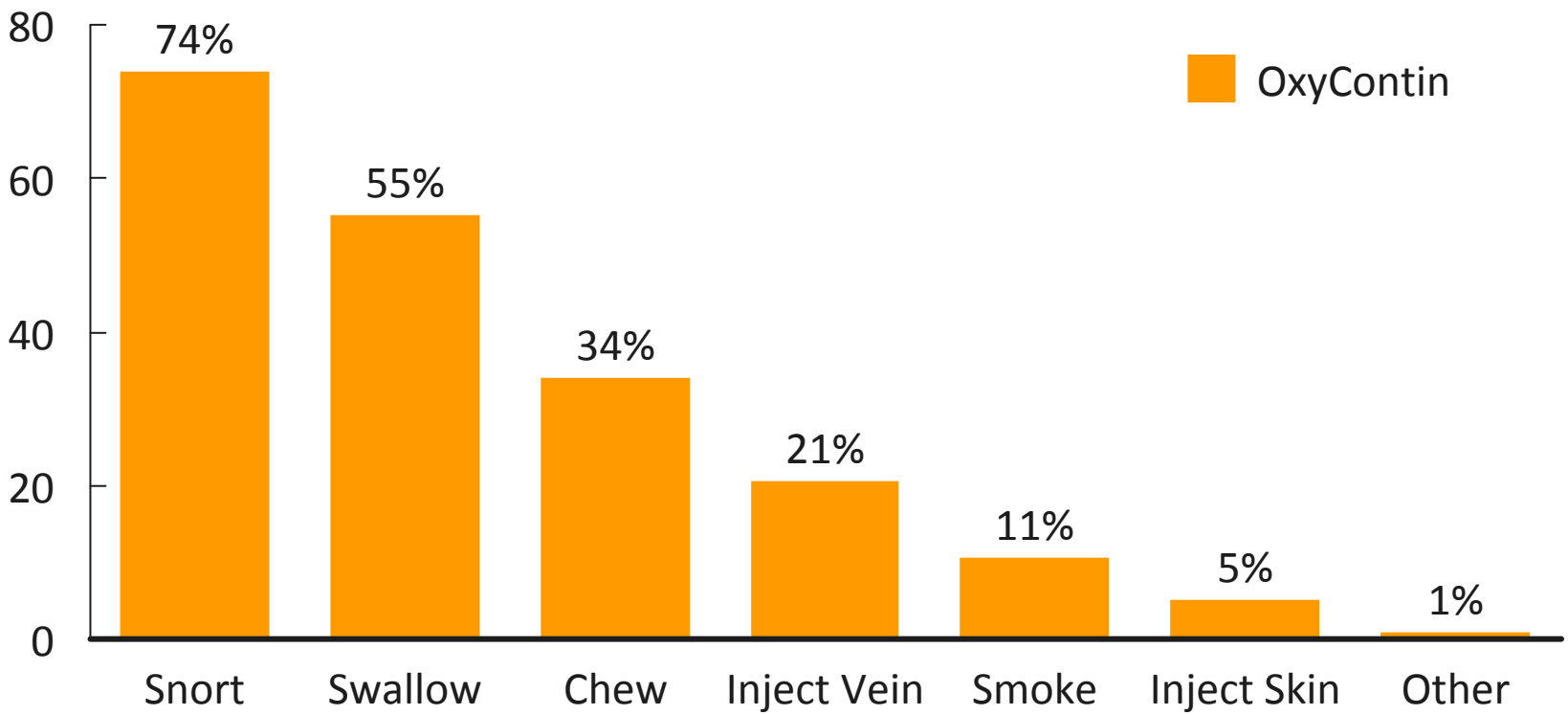
The views presented today are my own.

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]

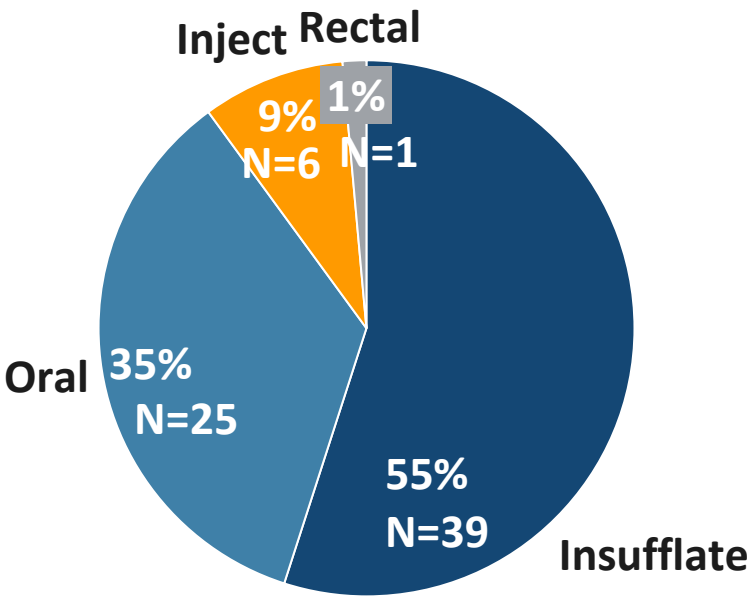


1 Respondents who had used OxyContin in the past 30 days
SOURCE: Katz et al. (2008) Clin J Pain. 24(6):528-35

Routes of administration vary by population

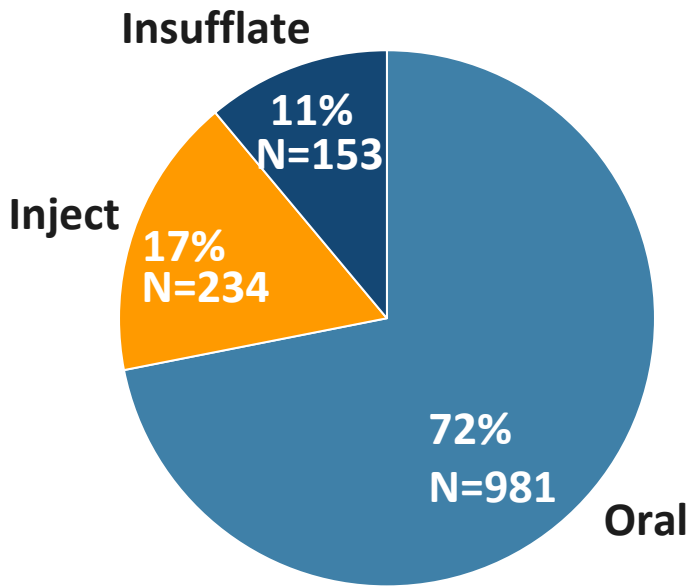
Recreational abusers

Cone 2009
N=51 respondents,
N=71 responses,
Percentage of responses



Abusers entering treatment

Carise et al 2007
N=1,368 respondents,
Percentage of respondents



SOURCE: Cone Internet Survey, 2009; Carise, et. al., 2007

How abusers typically manipulate tablets for abuse

Physical fragmentation

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

- Electric appliances

Chemical procedures

- Simple extraction
  - Aqueous solvents

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

Administration tools

- 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."

http://www.drugs-forum.com/forum/showthread.php?t=85217

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.opiophile.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

High scientific rigor of testing

- All dose strengths
- Taken to failure limit
- High and low temperatures
- Extended measures - 18 and 24 hours
- Comparison to current OxyContin
- Statistically calculated replicates
- Validated methods
- Independent laboratories
- Blind conditions

High relevance to "real world" methods

- Crushability: cutting, grinding, powdering
- Dissolution
- Effect of alcohol on "dose dumping"
- Extraction (simple and complex methods)
- Injection (syringeability and injectability)
- Nasal insufflation (snorting/sniffing)
- Smoking

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- **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

Goals

- Characterize the physicochemical properties of the reformulation
- Compare the performance of the two formulations
- Test the formulations to complete failure

Design

- Get input from experts in “real world” extraction of oxycodone HCl for abuse
- Test time, effort and equipment required to reduce particle size
- Ensure scientific robustness of studies

We replicated "real world" tablet manipulation scenarios in the lab

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

We had a comprehensive approach to ensure our data was robust and meaningful

How we determined the number of replicates

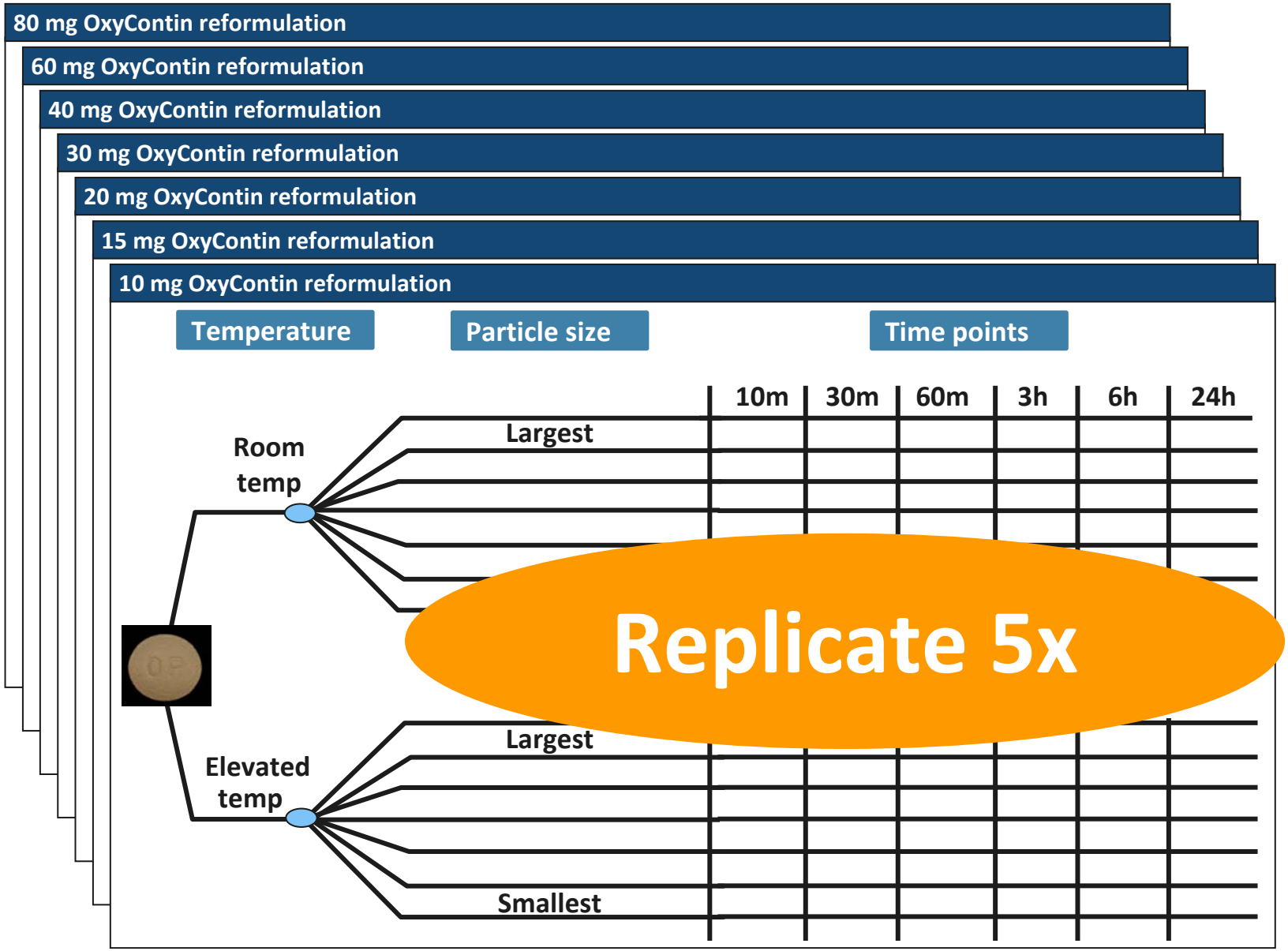
- Guided by internal experiments
- Produce results with observed mean within 10% of true mean with 95% confidence

Results for both formulations

- Reformulated OxyContin
  - N = 5 for small volume extraction (12,132)
  - N = 6 for dissolution (3,312)
  - N = 5 for IV and smoking (866)
- Current OxyContin
  - N = 3 for all studies

Our study designs were rigorous and comprehensive

Design EXAMPLE: Small volume extraction in Simple Solvent 1



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

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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

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

Results: Reformulated OxyContin is difficult to crush

Test tool	Ability to crush tablet to small particles	
	Current OxyContin	Reformulated OxyContin
Tool 1	✓ (fine powder)	✗
Tool 2	✓ (fine powder)	✗
Tool 3	✓ (fine powder)	✗
Tool 4	✓ (fine powder)	✗
Tool 5	✓ (fine powder)	✗
Tool 6	✓ (fine powder)	✗
Tool 7	✓ (fine powder)	✓ (fragments, shavings)
Tool 8	✓ (fine powder)	✗
Tool 9	✓ (fine powder)	✗
Tool 10	✓ (fine powder)	✗
Tool 11	✓ (fine powder)	✓ (fragments, slices)
Tool 12	✓ (fine powder)	✗
Tool 13	✓ (fine powder)	✗
Tool 14	✓ (fine powder)	✗
Tool 15	✓ (fine powder)	✓ (fragments, particles)
Tool 16	✓ (fine powder)	✓ (granulated particles)

✓ 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

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		Intact	Swallow with alcohol	Dissolution in ethanol and simulated gastric fluid	3

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

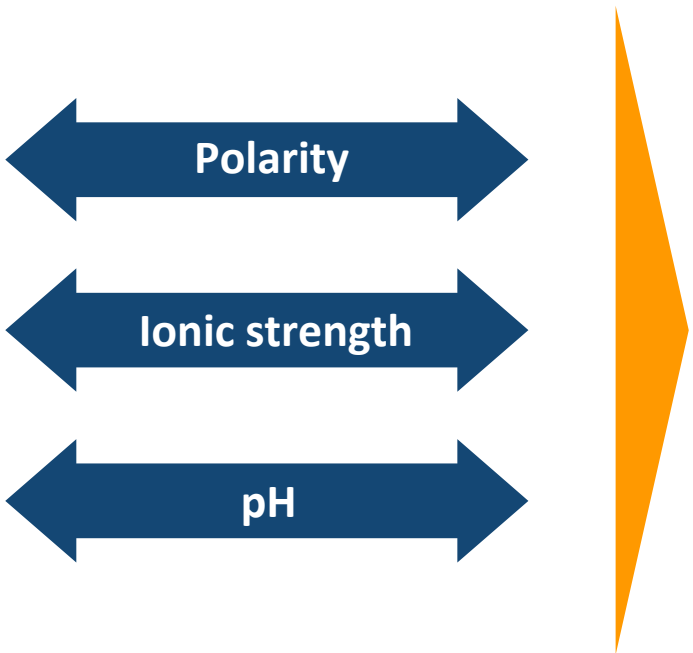
Perform extraction

- Solvent volume:
  - 30 mL
- Solvent types:
  - Ingestible
  - Non-ingestible
  - pH buffers
- Temperature:
  - Room
  - Elevated
- Agitation:
  - 100 rpm

Conduct analysis

- Determine amount of extractable oxycodone HCl
- Test a variety of time points
  - 10, 30, 60, 180, 360 min., and 24 hours

Solvents were selected to cover a wide range of chemical properties



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

Similar
Faster, P<0.05

Solvent	Time:	10 minutes			60 minutes			18 hours		
	Particle size band:	large	medium	small	large	medium	small	large	medium	small
Ingestible	Simple Solvent 1	7	53	75	20	88	84	91	93	93
	Simple Solvent 2	[illegible]	[illegible]	38	16	71	41	87	95	74
	Simple Solvent 3	[illegible]	[illegible]	45	13	74	57	57	99	88
	Simple Solvent 4	[illegible]	[illegible]	60	10	50	79	57	55	87
	Simple Solvent 5	2	39	81	12	58	82	44	92	86
	Simple Solvent 6	0	18	100	0	20	63	0	28	55
pH buffers	pH A	3	35	58	13	56	65	68	84	89
	pH B	3	36	60	13	74	73	66	86	86
	pH C	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	65	49	97	87
	pH D	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	71	17	84	84
Non-ingestible	Advanced Solvent 1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	87	96	97	88
	Advanced Solvent 2	1	13	43	5	30	41	44	57	88
	Advanced Solvent 3	0	23	123	0	27	127	0	67	15

28% reformulation vs. 28% OxyContin

16% reformulation vs. 13% OxyContin

19% reformulation vs. 15% OxyContin

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

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

Goal

Patient error

Assess whether reformulated OxyContin will “dose dump” oxycodone HCl in a simulated scenario of patients taking tablets together with alcoholic beverages

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

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

“Dose dumps” in ethanol?

- No
- Yes

Reformulation tablet strength	Particle size		
	Small	Medium	Large
10 mg			
15 mg			
20 mg			
30 mg			
40 mg			
60 mg			
80 mg			

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

	Route	Physical	Chemical	How we tested in the lab	Study No.
Abuse	Oral	Intact		N/A	N/A
		Crush		Manipulation of tablets via manual and electrical tools	1
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	Smoke	Crush, vaporize		API extraction via vaporization	5
	Inject	Crush	Extract	Syringability and injectability	5
Patient error	Oral	Crush		Manipulation of tablets via multiple manual tools	1
		Intact	Swallow with alcohol	Dissolution in ethanol and simulated gastric fluid	3

Goal

Abuse

Assess whether reformulated OxyContin tablets can be injected using an insulin syringe (type typically available to abusers)

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

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

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)

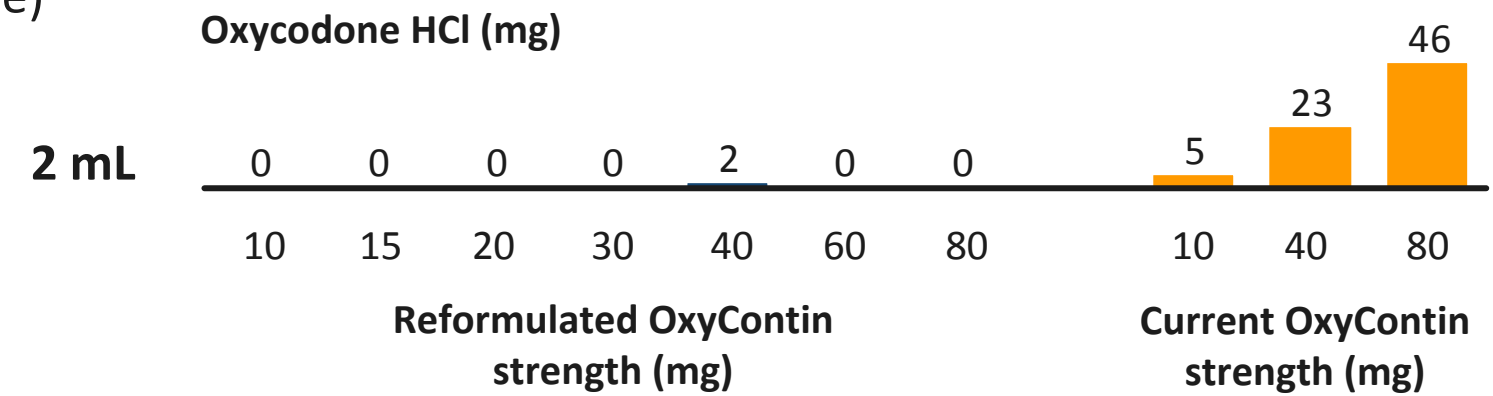
- Temperature
- Time
- Solvent: water

- 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

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

Syringability
(27 gauge)



Conclusion: Reformulated OxyContin is resistant to intravenous use

✓ Easy
✗ Difficult or impossible

Intact tablet

Current OxyContin

Reformulation

We replicated “real world” tablet manipulation scenarios in the lab

	Route	Physical	Chemical	How we tested in the lab	Study No.
Abuse	Oral	Intact		N/A	N/A
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	Inject	Crush	Extract	Syringability and injectability	5
Patient error	Oral	Crush		Manipulation of tablets via multiple manual tools	1
		Intact	Swallow with alcohol	Dissolution in ethanol and simulated gastric fluid	3

Goal

Abuse

Simulate “smoking” of reformulated OxyContin and compare to known controls that are efficient for smoking

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

	Test substance	Yield
Reformulated OxyContin	10 mg	✗
	15 mg	✗
	20 mg	✗
	30 mg	✗
	40 mg	✗
	60 mg	✗
	80 mg	✗
OxyContin	10, 40, 80 mg	✗
Controls	Negative control	✗ (18%)
	Positive control	✓ (68%)
Reference*	Reference 1	✓ (80%)
	Reference 2	✓ (80%)
	Reference 3	✓ (98%)

✗ Low
✓ High

SOURCE: NIDA Research Monograph 173 "Pharmacokinetics, Metabolism, and Pharmaceutics of Drugs of Abuse," 1997, page 201

Conclusion: Reformulated OxyContin is inefficient for use via smoking

✓ Easy
✗ Difficult or impossible

Intact tablet

Successful smoking of API

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

Kendle
Real people. Real results.®

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

Kendle
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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

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Real people. Real results.®

- **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

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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 dont get how that works with all the binders and fillers thats in oxy. I tried it once and it was very disgusting and i didnt 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

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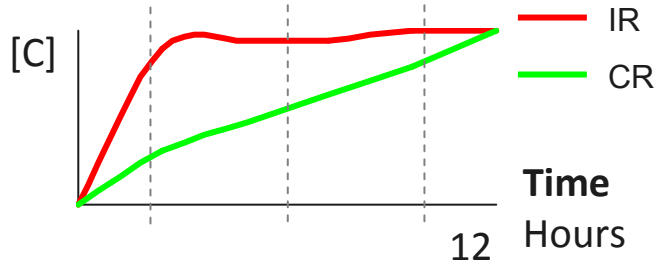
in vitro **dissolution of intact and manipulated tablets**

Goals:



- Consider safety of the product:

My interpretation

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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

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Real people. Real results.®

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

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	Route	Physical	Chemical	Anticipated impact of reformulation
Abuse	Oral	Intact		No improvement
		Crush		Better
		Crush	Extract	Better
	Nasal	Crush		Better
	Rectal	Crush	Extract	Better
	Smoke	Crush, vaporize		Better
	Inject	Crush	Extract	Better
Patient error	Oral	Crush		Better
		Intact	Swallow with alcohol	No dose dumping

My interpretation: Reformulation offers an overall improvement in safety profile across at-risk populations

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

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- Bioequivalence
- Approach to *in vitro* testing
- Summary of *in vitro* testing results
- 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

CONFIDENTIAL

Q&A Backup Slides

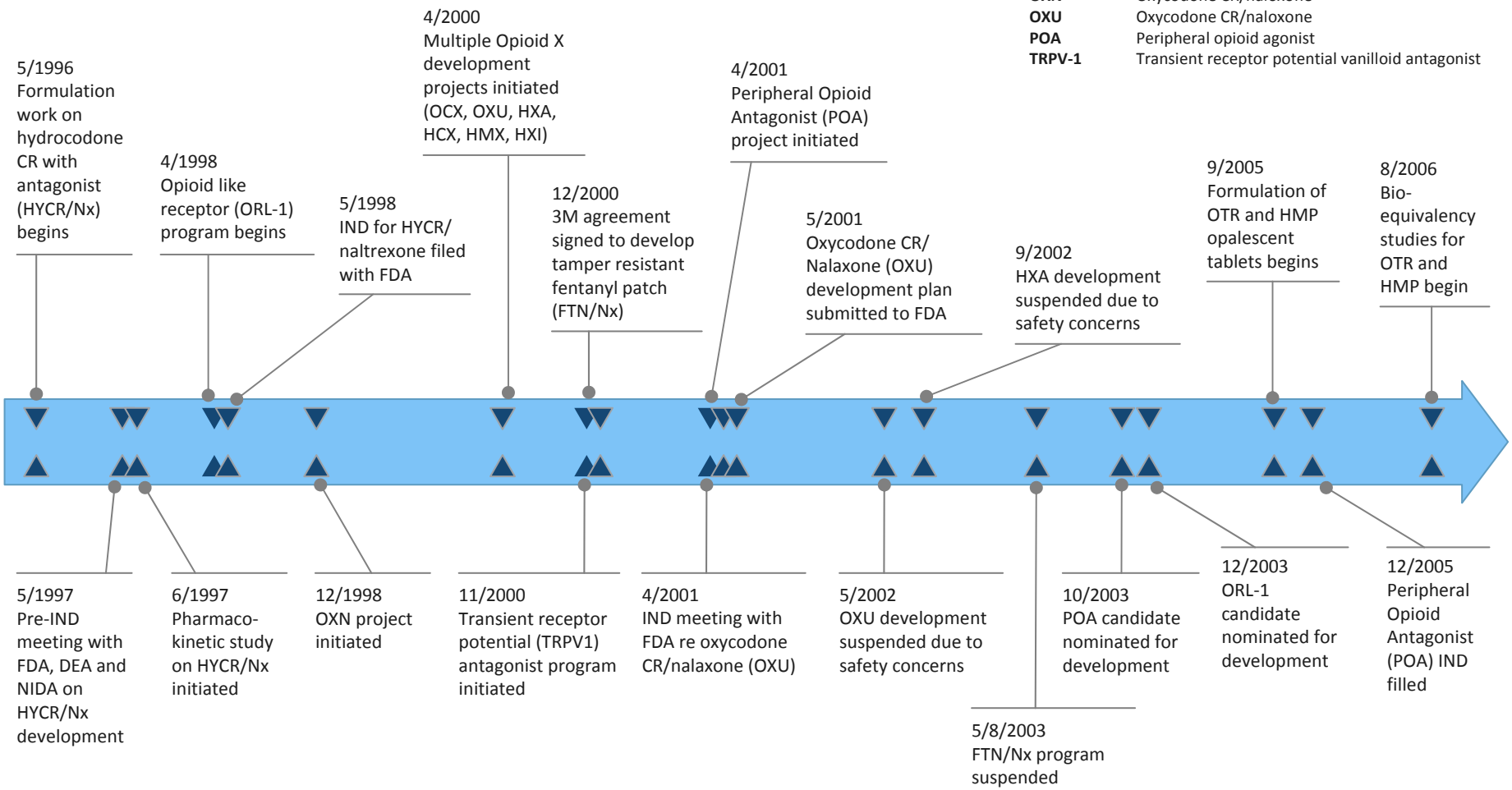
Q&A
September 24, 2009

BACK UP contents

1. **Development history**
2. Value of CR opioids and oxycodone
3. Bioequivalence
4. PEO (properties, toxicity)
5. *In vitro* studies (design, data, statistics, interpretation)
6. *In vivo* studies (PK and likability)
7. Anticipated impact of reformulation on abuse
8. Risk mitigation (epidemiology, current actions and plans, REMS)
9. Commercial (label, marketing, “switch” timeline)

Purdue research and development of analgesics with lower abuse potential

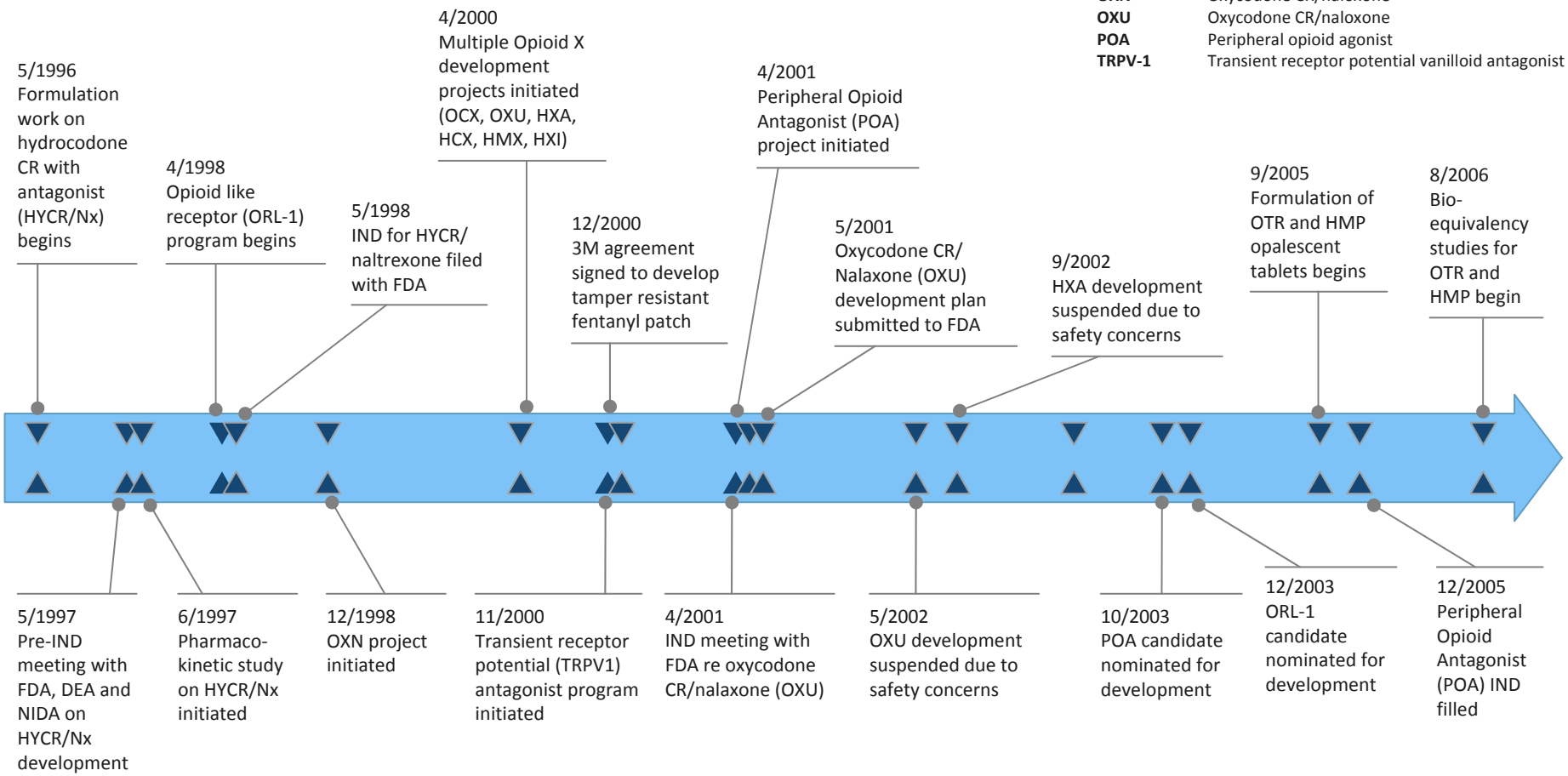
HCYR/Nx	Hydrocodone CR/naloxone or naltrexone
HCX	Hydrocodone CR/naltrexone
HMP	Hydromorphone tamper-resistant
HMX	Hydromorphone CR/naltrexone
HXA	Hydrocodone IR/APAP/naltrexone
HXI	Hydrocodone IR/naltrexone
OCX	Oxycodone CR/naltrexone
ORL-1	Opioid-like receptor agonist
OTR	Oxycodone tamper-resistant
OXN	Oxycodone CR/naloxone
OXU	Oxycodone CR/naloxone
POA	Peripheral opioid agonist
TRPV-1	Transient receptor potential vanilloid antagonist



Total expenditures to date: $275 million

Purdue's ongoing research related to abuse resistant opioid analgesic formulations

HCYR/Nx	Hydrocodone CR/naloxone or naltrexone
HCX	Hydrocodone CR/naltrexone
HMP	Hydromorphone tamper-resistant
HMX	Hydromorphone CR/naltrexone
HXA	Hydrocodone IR/APAP/naltrexone
HXI	Hydrocodone IR/naltrexone
OCX	Oxycodone CR/naltrexone
ORL-1	Opioid-like receptor agonist
OTR	Oxycodone tamper-resistant
OXN	Oxycodone CR/naloxone
OXU	Oxycodone CR/naloxone
POA	Peripheral opioid agonist
TRPV-1	Transient receptor potential vanilloid antagonist



Total expenditures to date: $260 million

Timeline of Purdue reformulation research

Jan. 1990	• Kaiko first explores use of opioid antagonists to reduce side effects of opioid therapy
Oct. 1993	• Kaiko develops draft publication on "Effect of Naltrexone on Bioavailability of Controlled Release Morphine Sulfate"
May 29 1996 gap in info	• Formulation work on hydrocodone CR single entity and hydrocodone CR w/ antagonist (HYCR Plus or HYCR/Nx) begins
1Q 97	• Pharmacokinetic study HY970305 on HYCR Plus (Naltrexone) initiated
Apr-97	• R&D staff review status of HYCR Plus and prepare to request Pre-IND meeting with FDA, DEA and NIDA
May 14, 1997	• Pre-IND meeting with FDA, DEA and NIDA to discuss HYCR/Nx
June 1, 1997	• HYCR Plus project team formed
1997-1998	• HYCR Plus toxicology studies progress
Apr-99	• Executive Planning Team report on HYIR/Ntx states development goals of efficacy and abuse resistance
May-98	• IND for HYCR/naltrexone filed with FDA
Dec-98	• OXN project initiated with goal to reduce side effects (constipation)
Jun-99	• Purdue documents regulatory strategy for hydrocodone/APAP IR with naloxone, this project becomes HXA
1H 2000	• BWeingarten and Curtis Wright lead effort to prioritize development efforts
April 17, 2000	• Opioid X project team formed (OCX, OXU, HCX, HMX, HXI)
June 15, 2000	• BWeingarten issues memo detailing organization and priority of Opioid X projects
Jun-2000	• Development of hydrocodone CR single entity product suspended in favor of HXA
April 23, 2001	• IND meeting with FDA re CR oxycodone/Nalaxone (OXU)
May 29, 2001	• Purdue submits development plan for CR oxycodone with Nalaxone to FDA
May 14, 2002	• CR oxycodone/Nalaxone (OXU) development suspended due to safety concerns
Sep-02	• HXA development discontinued due to safety concerns (high liver enzyme counts from APAP)
2003	• Opiod X toxicology and Phase I and II studies progress
Jul-04	• CR oxycodone/naltrexone (OCX) development suspended due to safety concerns
2Q 2005	• Formulation of oxycodone MEMs suspended due to alcohol dissolution concerns
2H 2005	• Formulation of OTR and HMP opalescent tablets begins
Dec-05	• Peripheral Opioid Antagonist (POA) IND filed, currently on Clinical Hold
Aug-06	• Bioequivalency studies for OTR and HMP begin

CDER Controlled Substance Staff (CSS)

Conclusions:

1. This application covers the reformulation of all dosage strengths. Detailed in vitro testing to characterize tamper-resistant properties was conducted on all dosage strengths of reformulated OxyContin.
2. As a product that is bioequivalent to OxyContin, all oxycodone blood levels produced by the intact reformulated product are expected to be the same as those produced by OxyContin at all points in time after oral administration.
3. The proposed reformulation of OxyContin may provide enhanced protection over that provided by the currently available OxyContin for the intended population against dose dumping when tablets are accidentally crushed or chewed.
4. The tamper resistant properties of the reformulated OxyContin are limited. However, the tamper resistance characteristics of reformulated OxyContin may provide an advantage over the currently available OxyContin.

Reference: CSS Background AC Paper - N22272 - 082409

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TBDFDA's statement on the Advisory Committee's position on restricting OxyContin's indication to severe pain

"FDA approved OxyContin for "moderate to severe" pain rather than just "severe" pain for several reasons. First, pain is not monotonic, and even in patients with chronic painful conditions, their pain tends to wax and wane. Patients with chronic pain may rate their pain as severe one day and only have more moderate levels on another. Further, it is clear from a number of scientific studies that if one looks at significant functional impairment as a threshold for defining significant pain (which is a subjective assessment), many patients with such dysfunction will only rate their pain as moderate or moderately severe, rather than severe. Therefore, patients with pain that importantly limits their daily activities may only rate their pain subjectively as moderate or moderately severe. The question of whether OxyContin and other potent opiates should be limited to severe pain only was posed to the Advisory Committee in the September 2003 meeting. The committee strongly recommended that FDA maintain the indication to include moderate pain. Misuse and abuse of a drug is not driven by FDA's approved indication." (emphasis added)

SOURCE: Letter, Amit K. Sachdev, Associate Commissioner for Legislation, FDA, to The Honorable Mark E. Souder, April 26, 2004.

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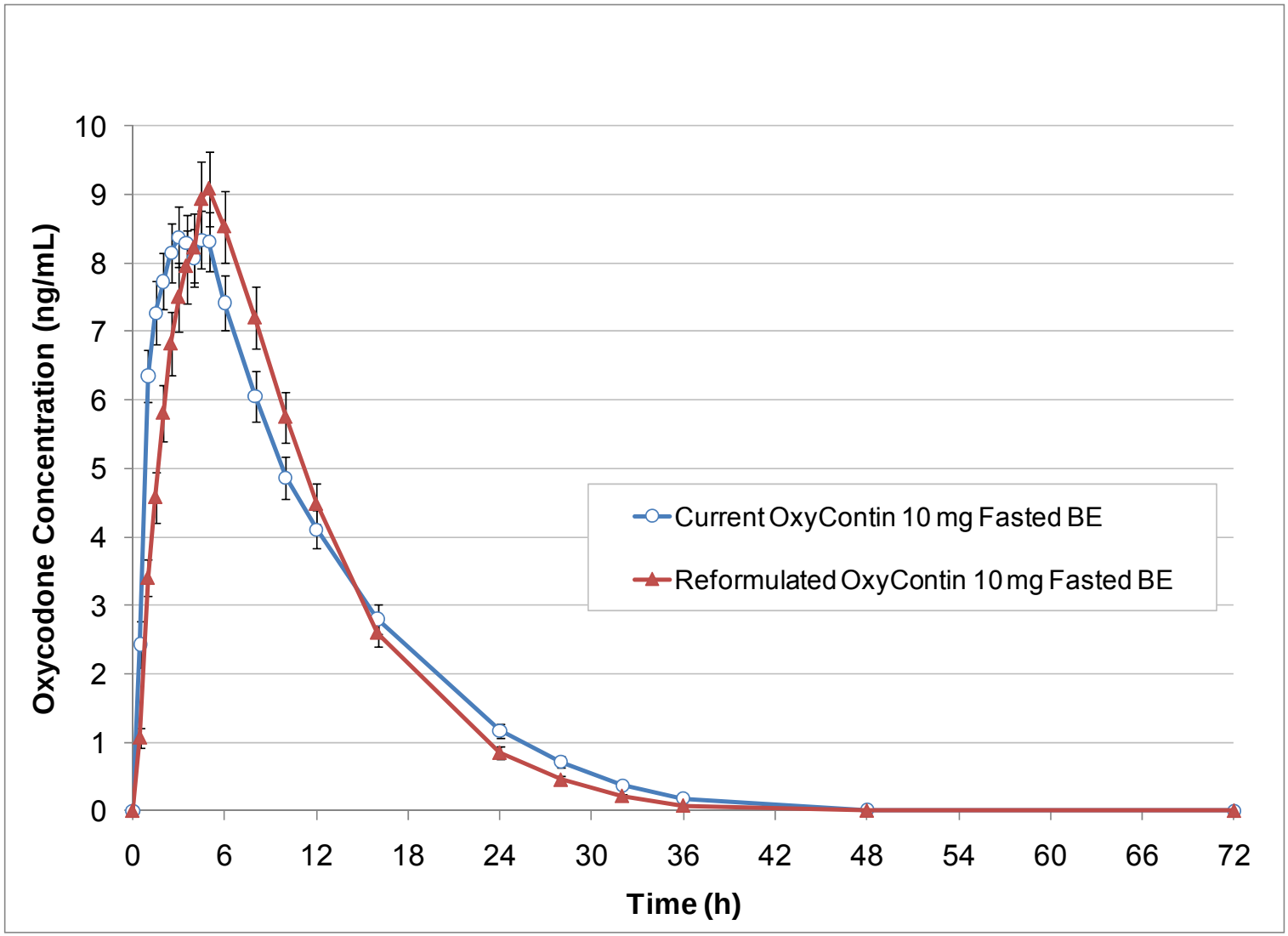
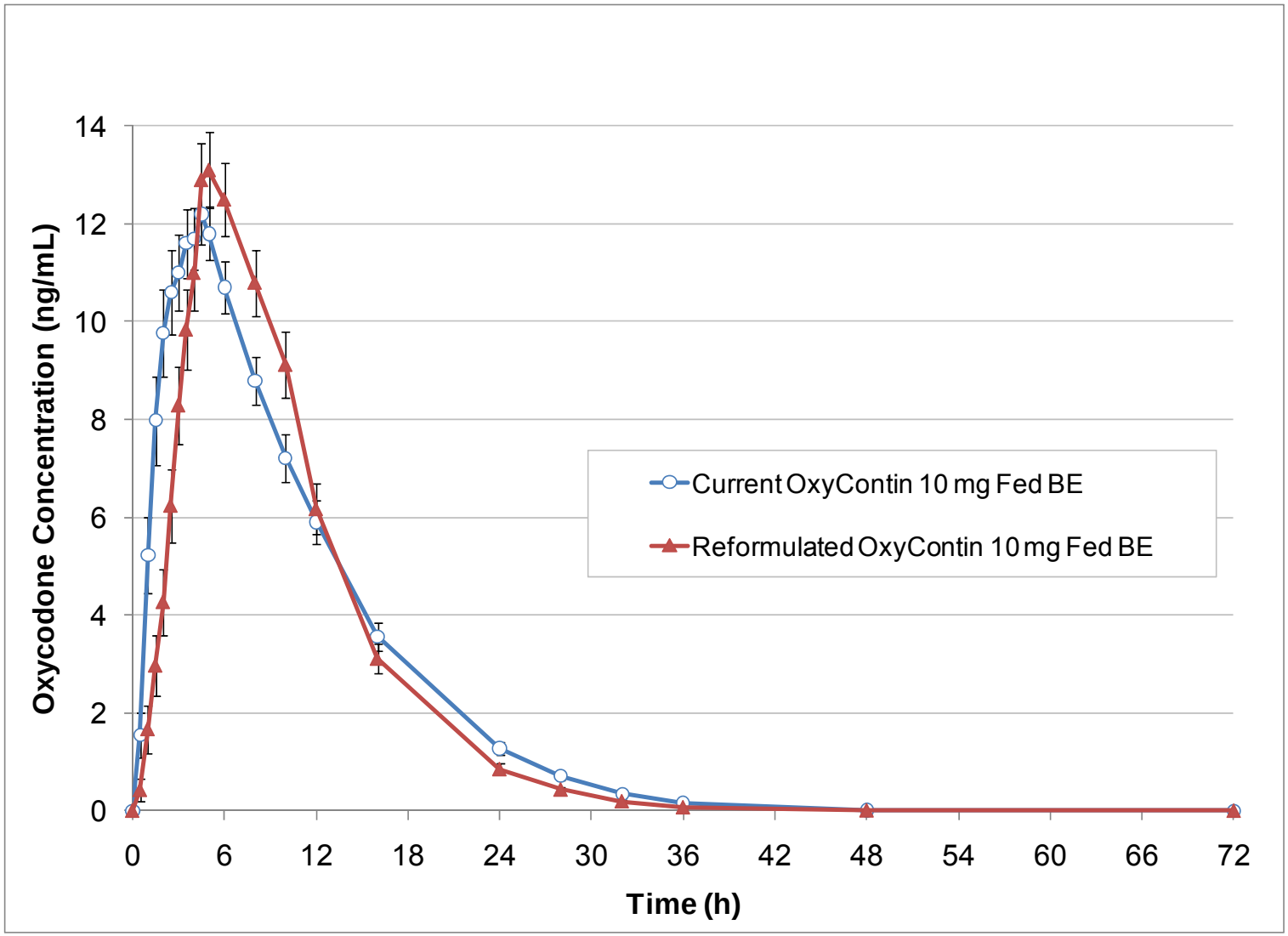
OTR1003: Fasted 10 mg bioequivalence

Mean (+/- 2 SE) concentration vs. time



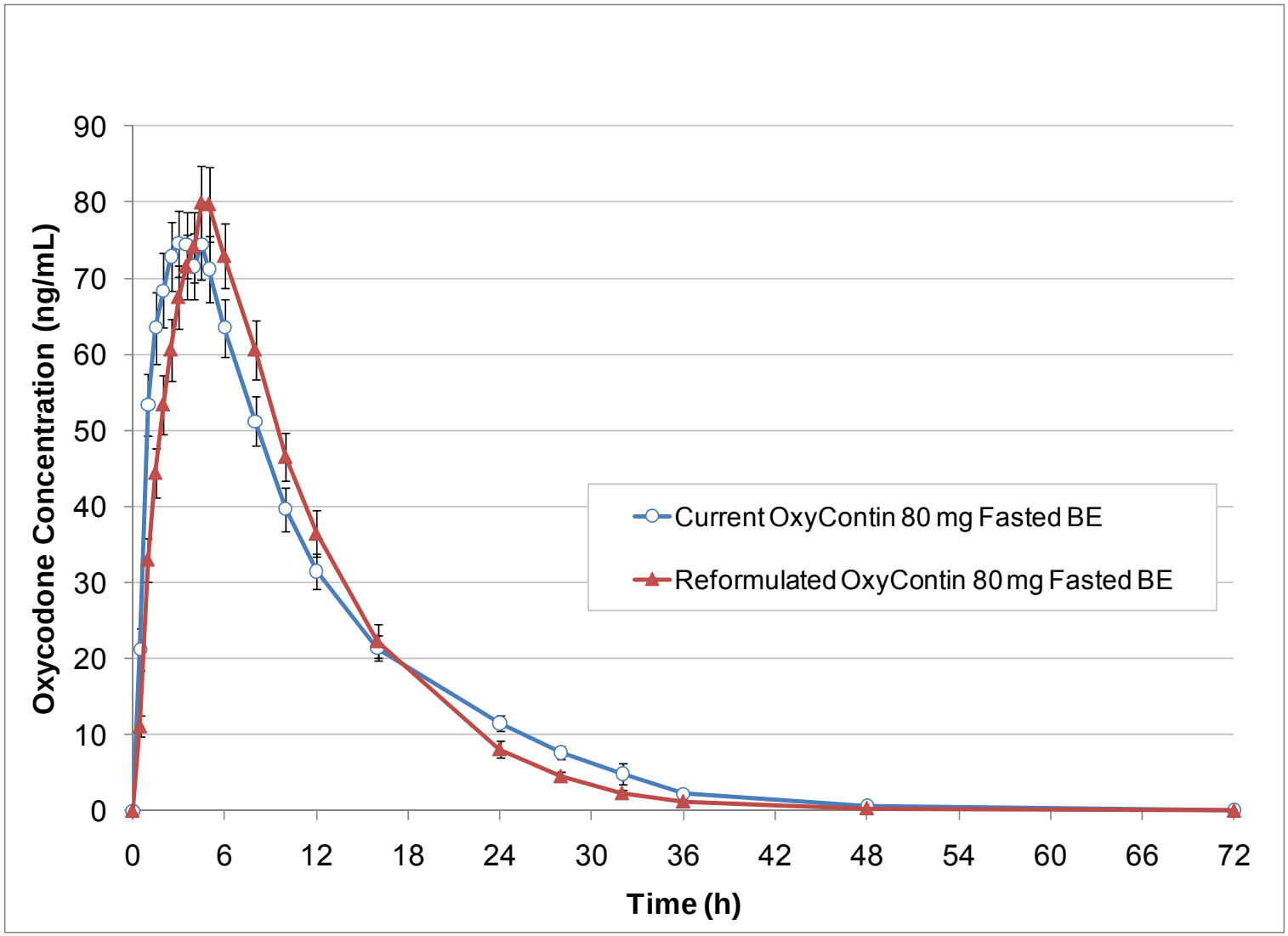
OTR1002: Fed 10 mg bioequivalence

Mean (+/- 2 SE) concentration vs. time



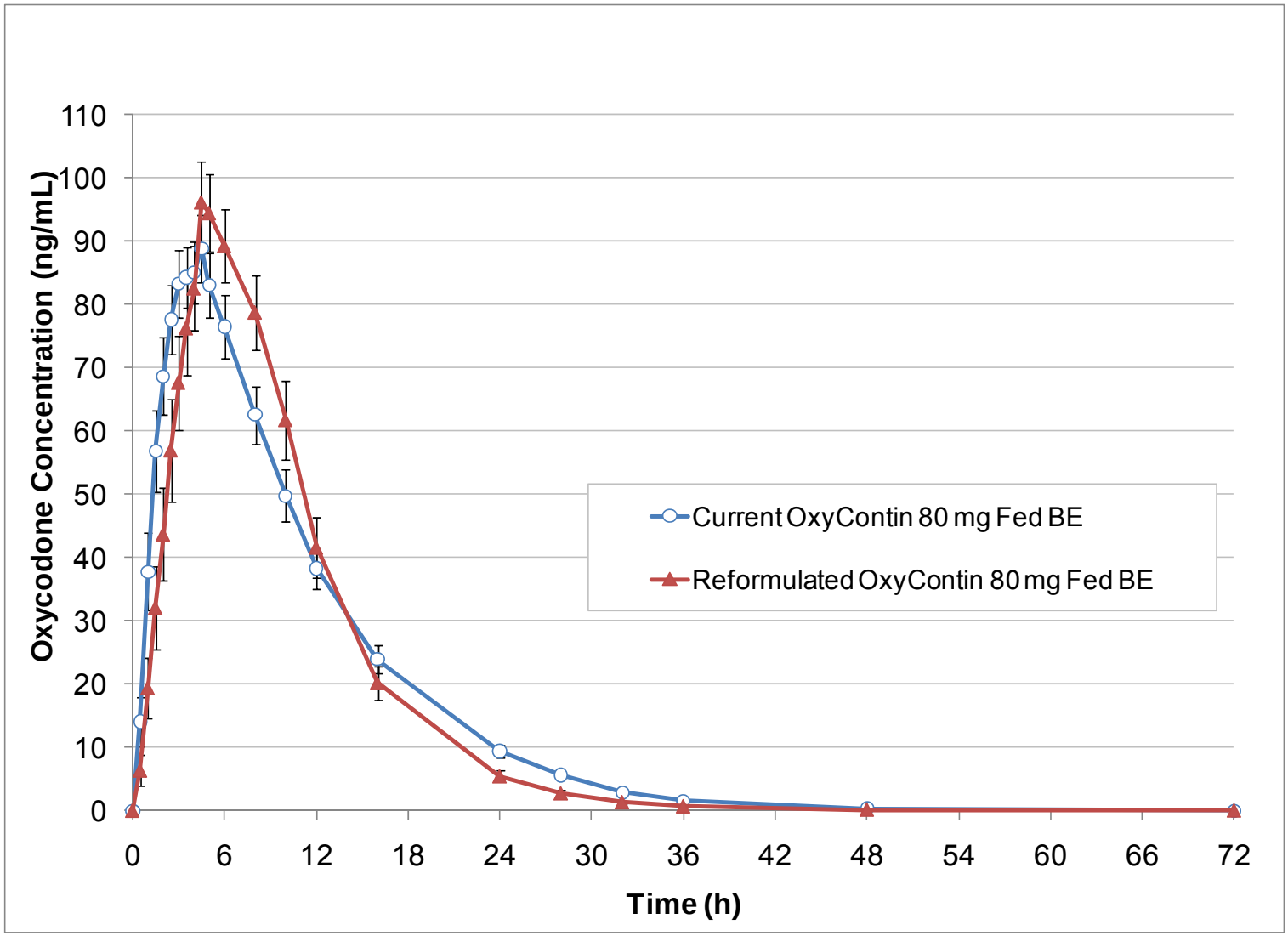
OTR1009: Fasted 80 mg bioequivalence

Mean (+/- 2 SE) concentration vs. time

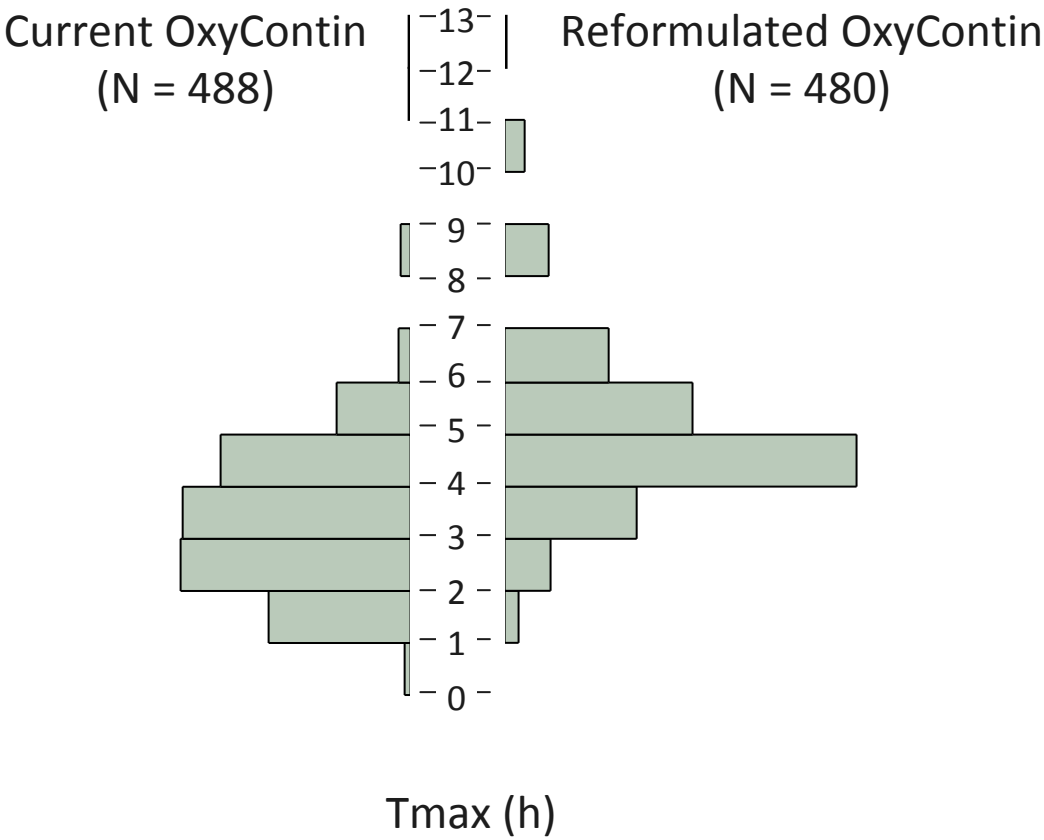


OTR1008: Fed 80 mg bioequivalence

Mean (+/- 2 SE) concentration vs. time



Tmax distributions and descriptive statistics combined Tmax data from all six bioequivalence studies



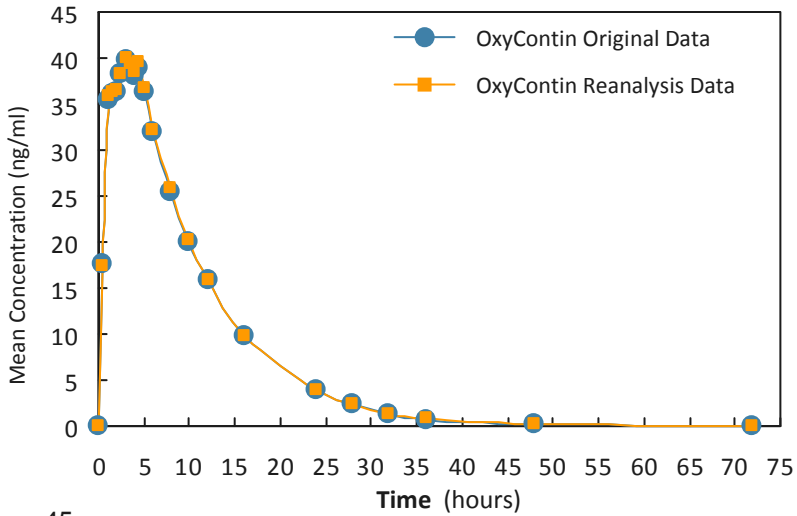
Tmax	Current OxyContin	Reformulated OxyContin
N	488	480
Median	3.0 h	4.5 h
Mean	3.2 h	4.7 h
CV	46%	32%
Range	0.5 - 12 h	1.0 - 12 h

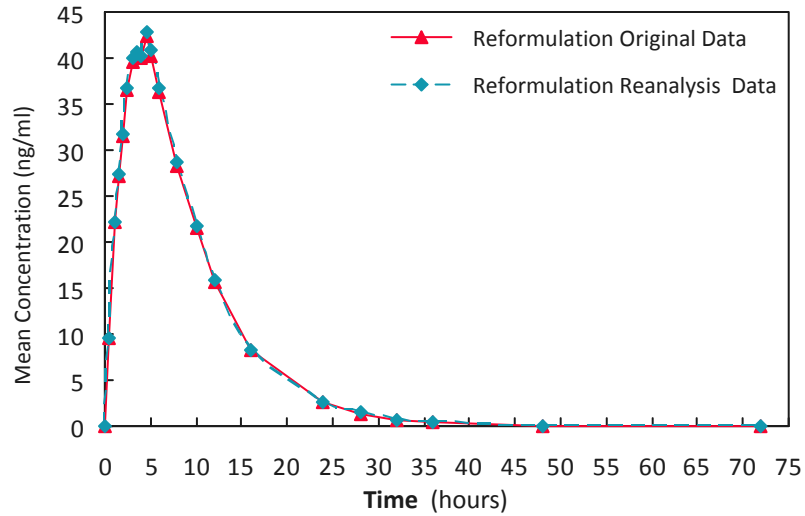
Tmax and Tmax difference descriptive statistics combined Tmax data from all six bioequivalence studies

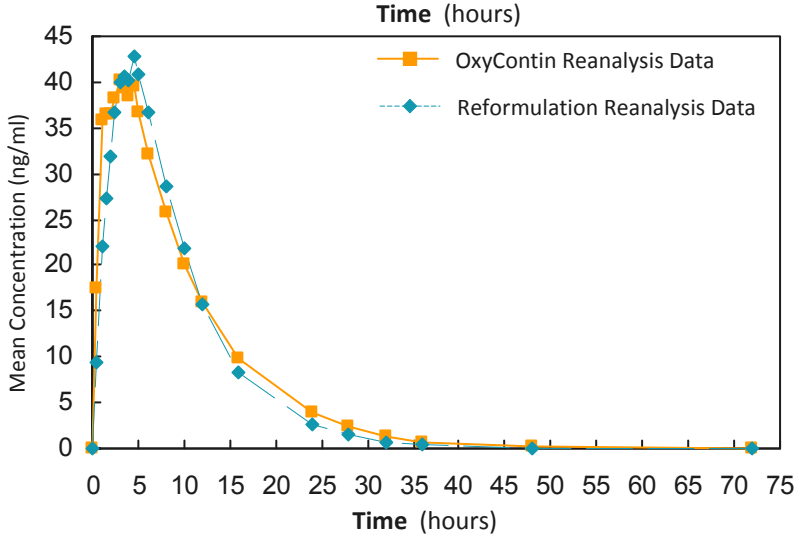
Tmax	Current OxyContin	Reformulated OxyContin
N	488	480
Median	3.0 h	4.5 h
Mean	3.2 h	4.7 h
CV	46%	32%
Range	0.5 - 12 h	1.0 - 12 h

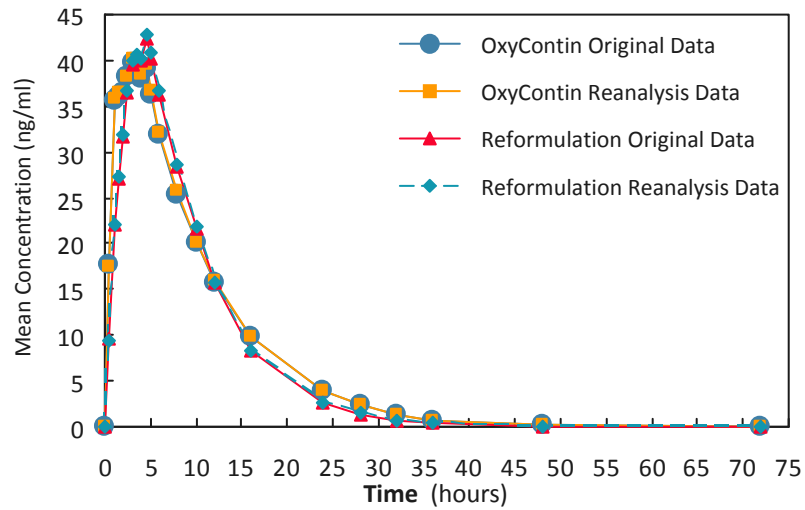
Percentiles	Tmax Difference Reformulated - Current (N = 462)
100% (Maximum)	9.5 h
75%	2.5 h
50%	1.5 h
25%	0.0 h
0% (Minimum)	-7.5 h

Reformulation is bioequivalent to OxyContin *before* AND *after* removal of six subjects





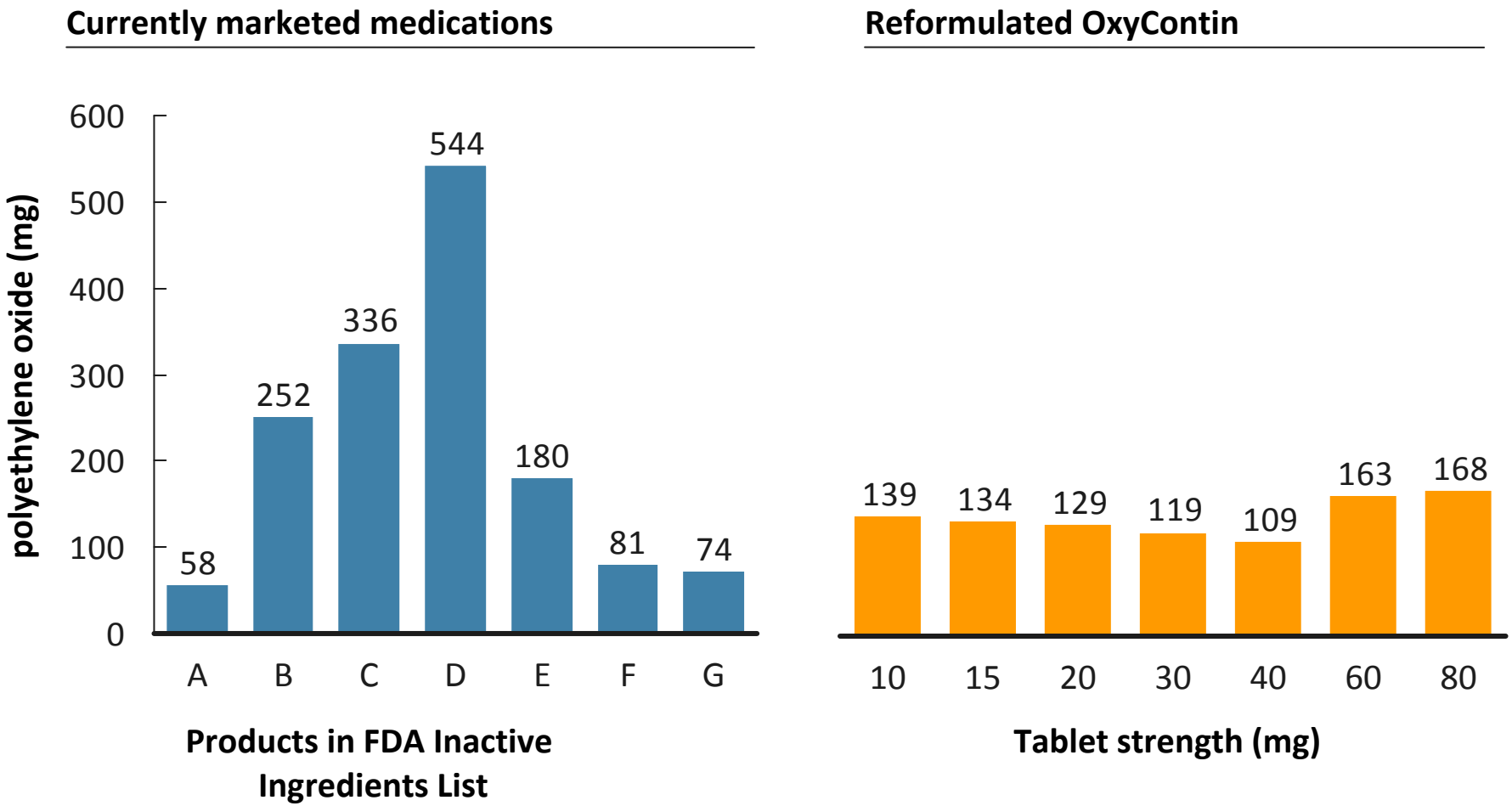




BACK UP contents

1. **Development history**
2. Value of CR opioids and oxycodone
3. Bioequivalence
4. **PEO (properties, toxicity)**
5. *In vitro* studies (design, data, statistics, interpretation)
6. *In vivo* studies (PK and likability)
7. Anticipated impact of reformulation on abuse
8. Risk mitigation (epidemiology, current actions and plans, REMS)
9. Commercial (label, marketing, “switch” timeline)

Reformulated OxyContin contains less polyethlene oxide than other currently marketed medications

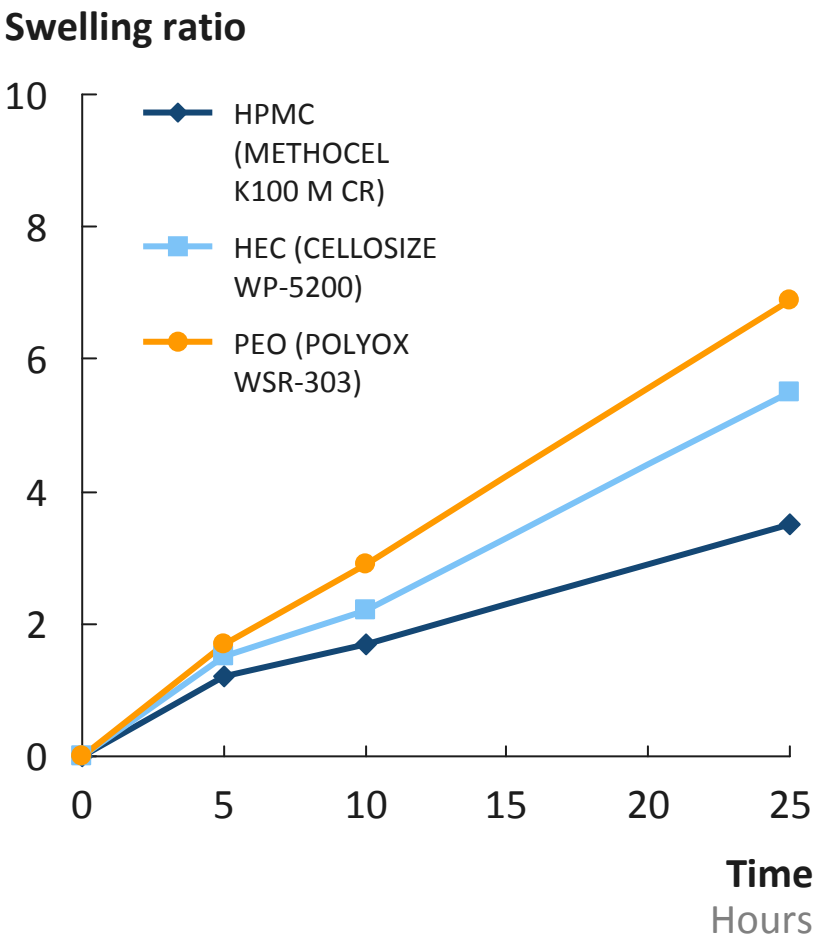


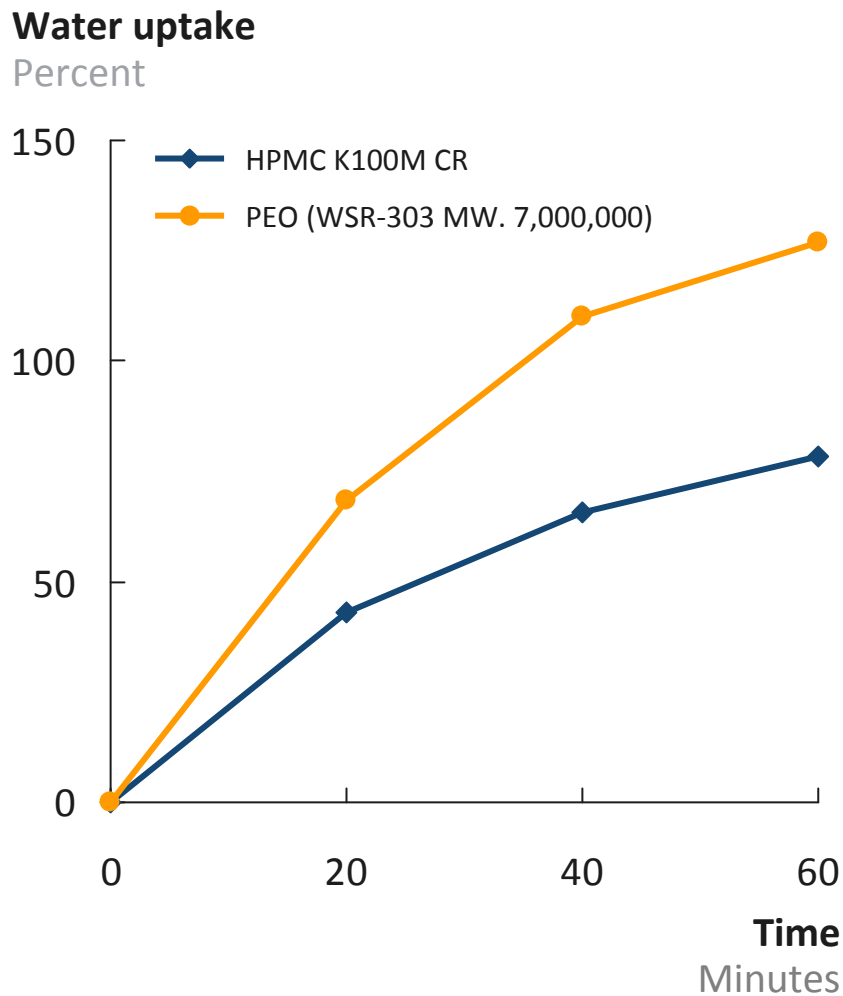
SOURCE: FDA Inactive Ingredients List (last updated July 10, 2009)

Comparison of PEO in reformulated OxyContin compared to approved human drugs

- PEO in reformulated OxyContin is 167.5 mg (80 mg OxyContin tablet) equal 0.00334 g PEO/kg/day
- PEO in approved human drug is up to 543.9 mg per unit equals 0.0119 g PEO/kg/ day

Swelling of water soluble polymers





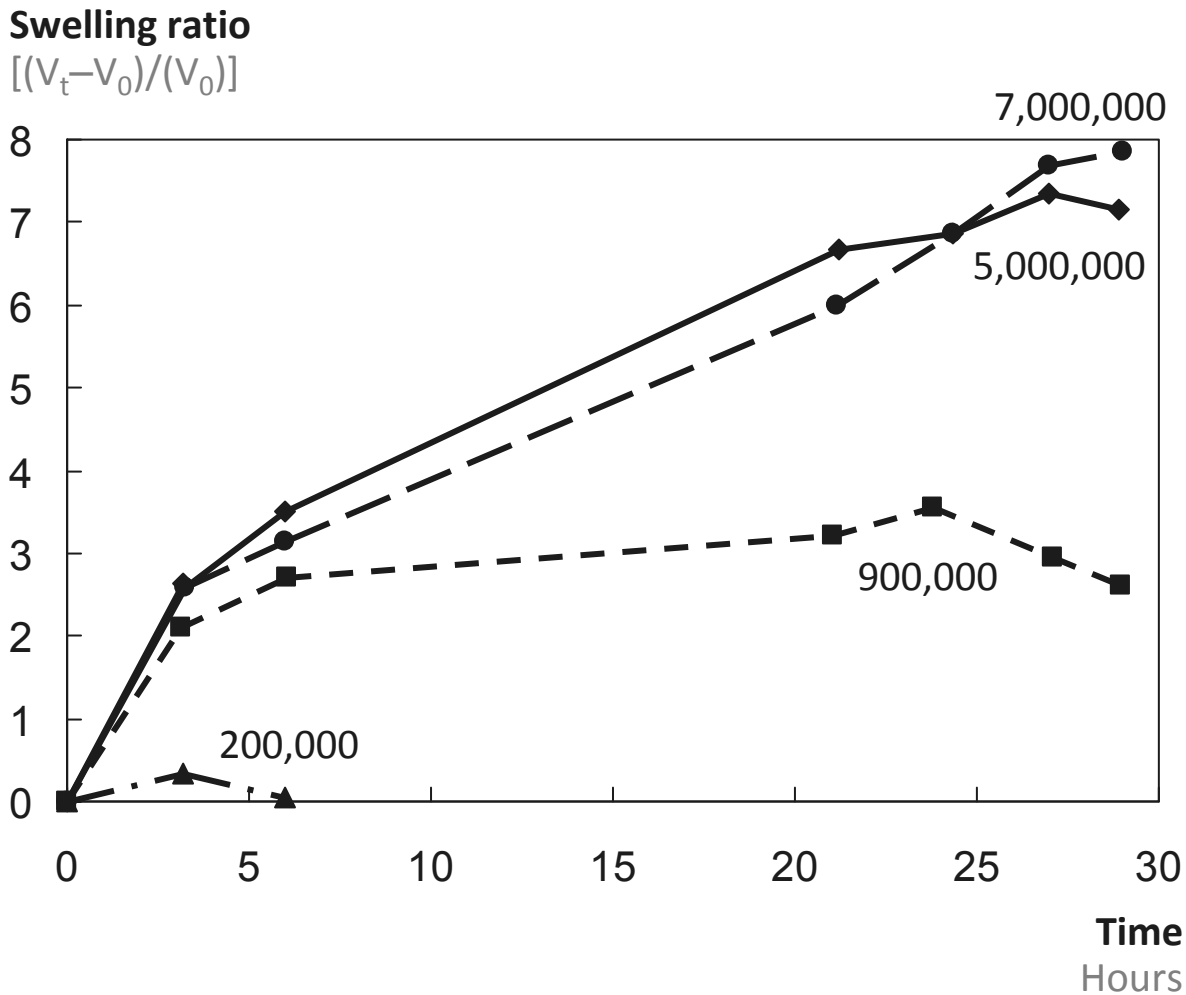
POLYOX NF grades

POLYOX NF grades	Approximate[1] molecular weight	Viscosity rage at 25°C, cP		
		5% solution	2% solution	1% solution
WSR N-10 NF	100,000	30-50		
WSR N-80 NF	200,000	55-90		
WSR N-750 NF	300,000	600-1,200		
WSR 205 NF	600,000	4,500-8,800		
WSR-1105 NF	900,000	8,800-17,600		
WSR N-12K NF	1,000,000		400-800	
WSR N-60K NF	2,000,000		2,000-4,000	
WSR-301 NF	4,000,000			1,650-5,500
WSR Coagulant NF	5,000,000			5,500-7,500
WSR-303 NF	7,000,000			7,500-10,000

1 Based on rheological measurements. Value obtained by other methods including light scattering and gel permeation chromatography, may not be directly comparable – The physical property data listed are considered to be typical properties, not specifications; FP grades (96% through #60) available for N-80 NF, N-60K NF, 301 NF, Coag NF, 303 NF; SFP grades (96% through 100%) available for N-60K NF and 303 NF

Polyethylene oxide – rate of water uptake

Swelling capacity of polyethylene oxide (Polyox WSR) – measured for four molecular weight grades; 28mm tablets in 300 ml of water



SOURCE: Handbook of Pharmaceutical Excipients – Fourth Edition

Polyethylene oxide animal toxicity studies

PEO animal oral toxicity studies (feeding)*

Study	**Highest dietary concentration** (Percent)	**Daily dose** (g/kg/day)	**Effect**	**Equivalent total human PEO dose in** a 50 kg person (g/day)	**Reformulated OxyContin tablets per day for equivalent 50 kg human PEO dose** (# of tablets)
Rat 90 day	20	18.40	• Decrease BW gain • "kidney tubular cloudy swelling"		
Rat 2 year	5	2.76	• No effect	138	824
Dog 2 year	2	0.56	• No effect	28	167

* PEO in reformulated OxyContin equals 167.5 mg (0.1675 g) in an 80 mg OxyContin tablet

SOURCE: Smyth H F et.al. Experimental toxicity of a high molecular weight polyethylene oxide. Toxicol Appl Pharmacol 16, 442-445,1970

Polyethylene oxide animal toxicity studies

PEO animal oral toxicity studies* (parameters evaluated)

Rat 2 year	Dog 2 year
• Diet consumption	• Body weight change
• Mortality	• Mortality
• Body weight change	• Liver & kidney to body weight ratios
• Life span	• Hemoglobin
• Liver & kidney to body weight ratios	• Hematocrit
• Hematocrit	• Red and white cell total count
• Incidence of neoplasms	• Differential white cell count
• Histopathology	• Serum urea nitrogen
	• Serum alkaline phosphatase
	• BSP retention
	• Histopathology (26 tissues)

SOURCE: Smyth H F et.al. Experimental toxicity of a high molecular weight polyethylene oxide. Toxicol Appl Pharmacol 16, 442-445,1970

Polyethylene oxide characteristics in Study 5

Finding	Concen-tration (Percent)	Volume (mL)	Tablet strength (mg)
• Not syringe-able	8.3	2	80
• Injectable only with heat or 18 gauge needle	1.1*	10	40

* Viscosity approximately 1,500 to 3,500 centipoises equal to 160 to 372 x the viscosity of no effect dose in rat IV single dose study.

Polyethylene oxide rat intravenous single dose toxicity study

Results

N	Concentration (Percent)	Viscosity 30°C (Centipoise)	Volume (mL)	Dose (mg/kg)	Effect
4	0.010	7.5	4.0	4.0	None
4	0.025	9.4	4.0	10.0	None
4	0.050	11.9	2.5	12.5	Lethal
4	0.100	17.2	0.3	3.0	Lethal

SOURCE: Smyth H F et.al. Experimental toxicity of a high molecular weight polyethylene oxide. Toxicol Appl Pharmacol 16, 442-445,1970

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Statistical calculation of *in vitro* study sample size

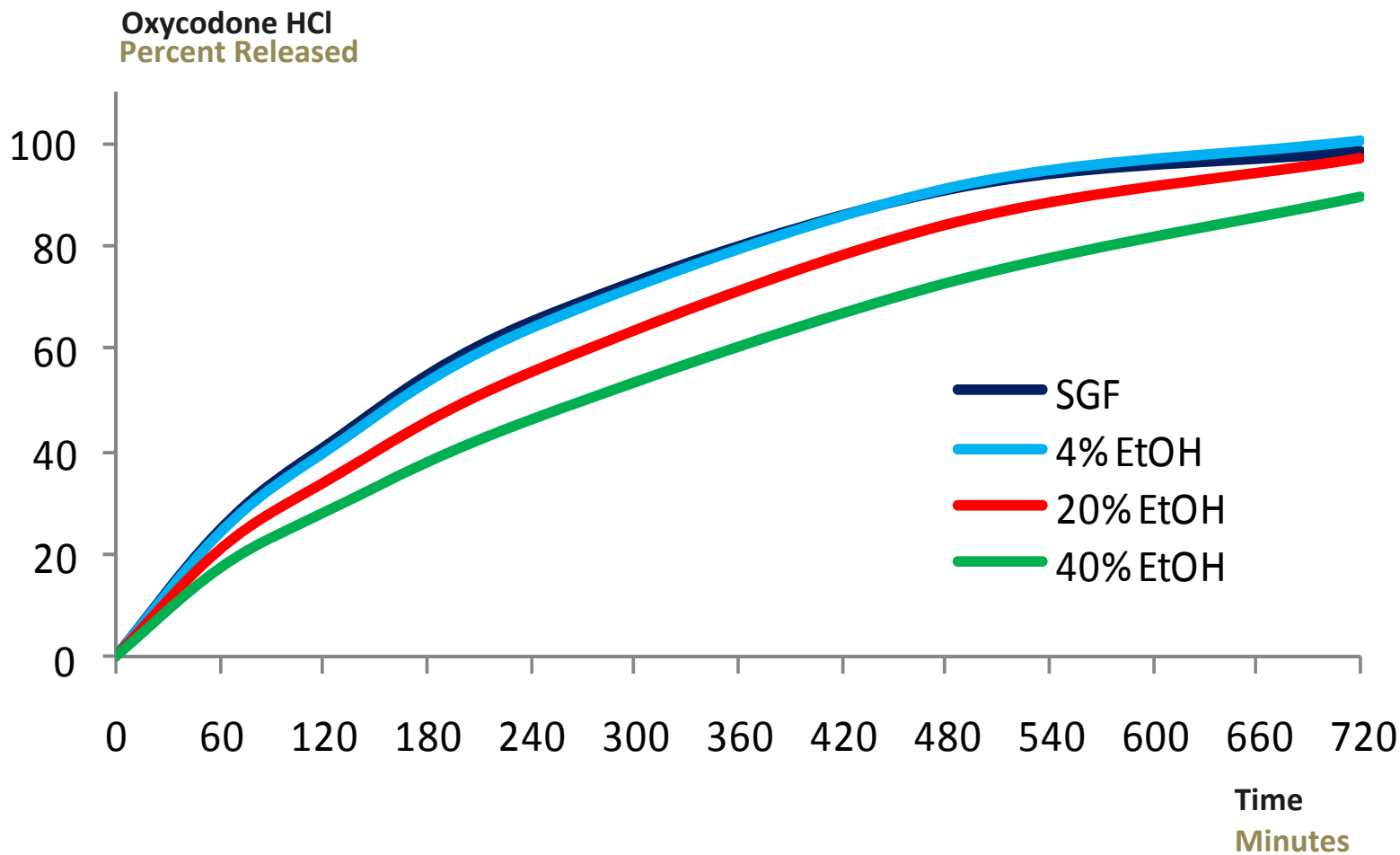
Process

1. We generated data internally for bands 2, 4, 5, and 6 of the 80 mg. reformulated treatment. Three measurements were taken for each band.
2. The standard deviations of the triplicate measurements were calculated at 5 time points (10, 30, 60, 120, and 240 minutes)
3. The average of the 20 standard deviations was calculated.
4. The estimate of the standard deviation was used to compute sample size estimates such that the 95% confidence interval for the sample means is less than ± 10% of the population mean.

Example calculation – Study 3 (dissolution in 900 mL of ethanol)

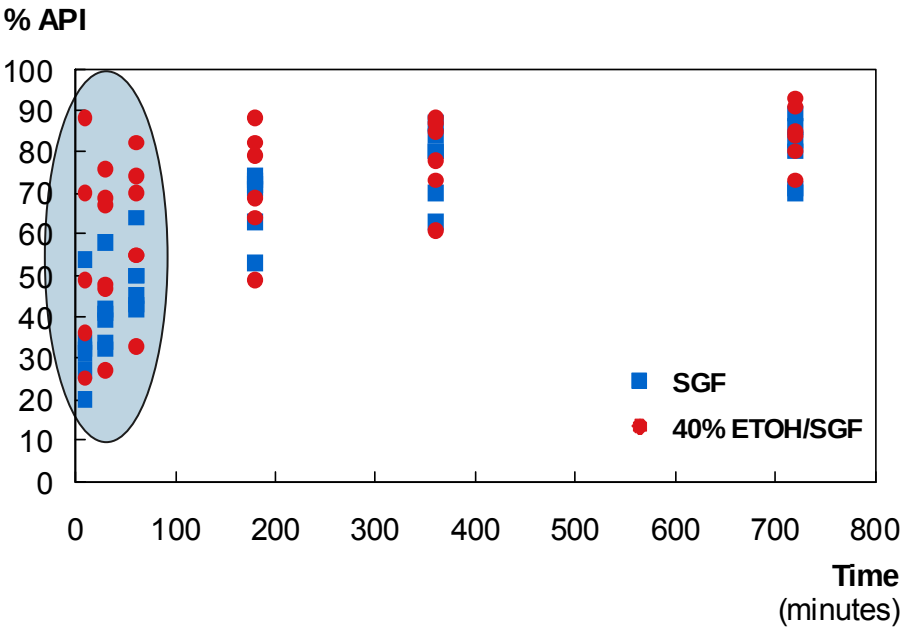
- The average of the 20 standard deviations from the internal study data was 8.
- With a sample size of 6 replicates, the 95% confidence interval for the population mean is the observed mean ± t(0.975, 5) x 8 / (sqrt(6)) or observed mean ± 2.57 x 8/sqrt(6) or observed mean ± 8.4.
- Thus, it was estimated that a sample size of 6 would result in the observed mean being within 10% of the true but unknown population mean.

Intact reformulated OxyContin tablets have a slower release in higher concentrations of ethanol

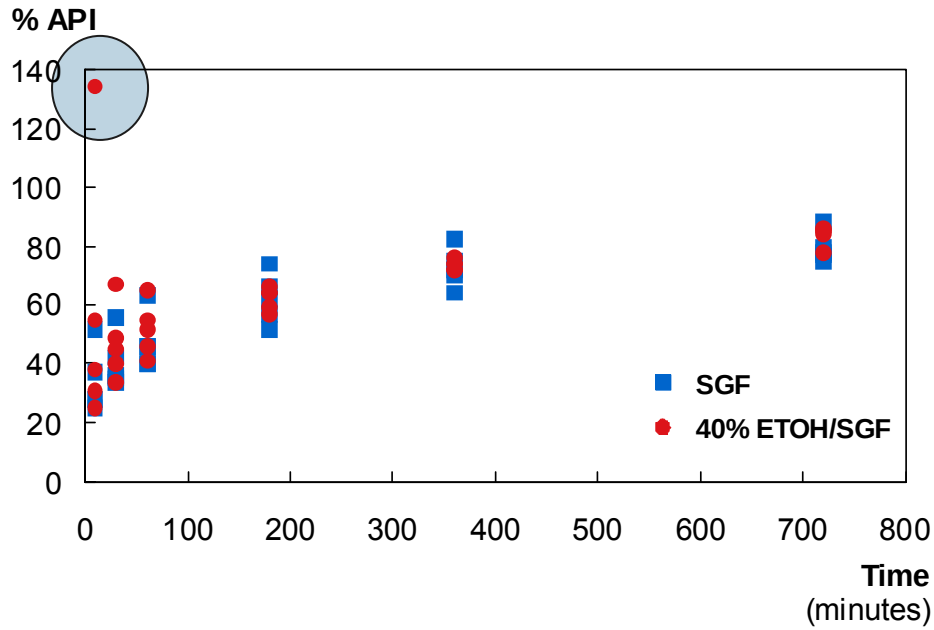


Study 3: Scattering of 10 min time point causes dissimilarity in dissolution profiles

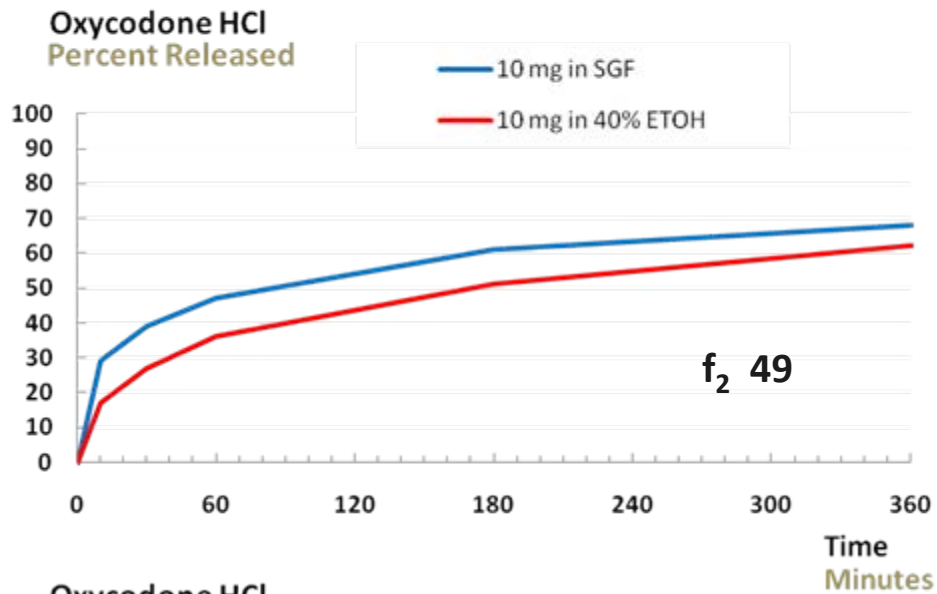
Band 6, 10 mg – scatter plot

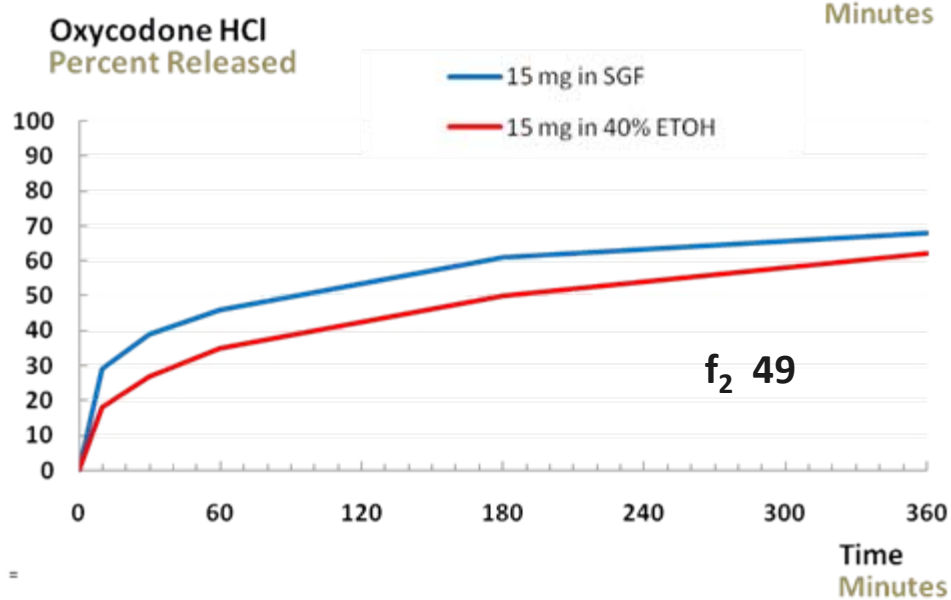


Band 6, 15 mg – scatter plot

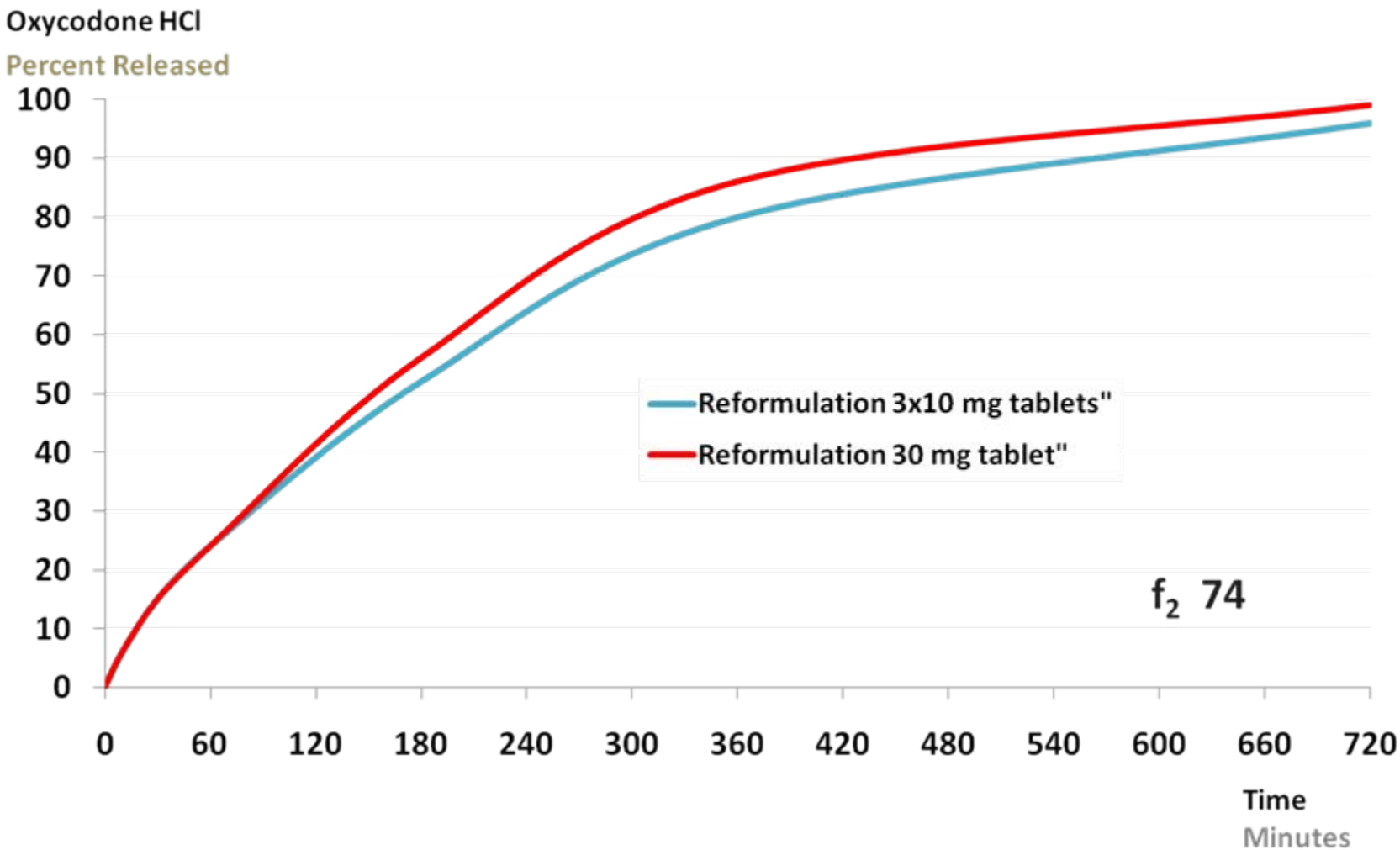


Study 3: Reformulation band 6 is slower in 40% EtOH than SGF

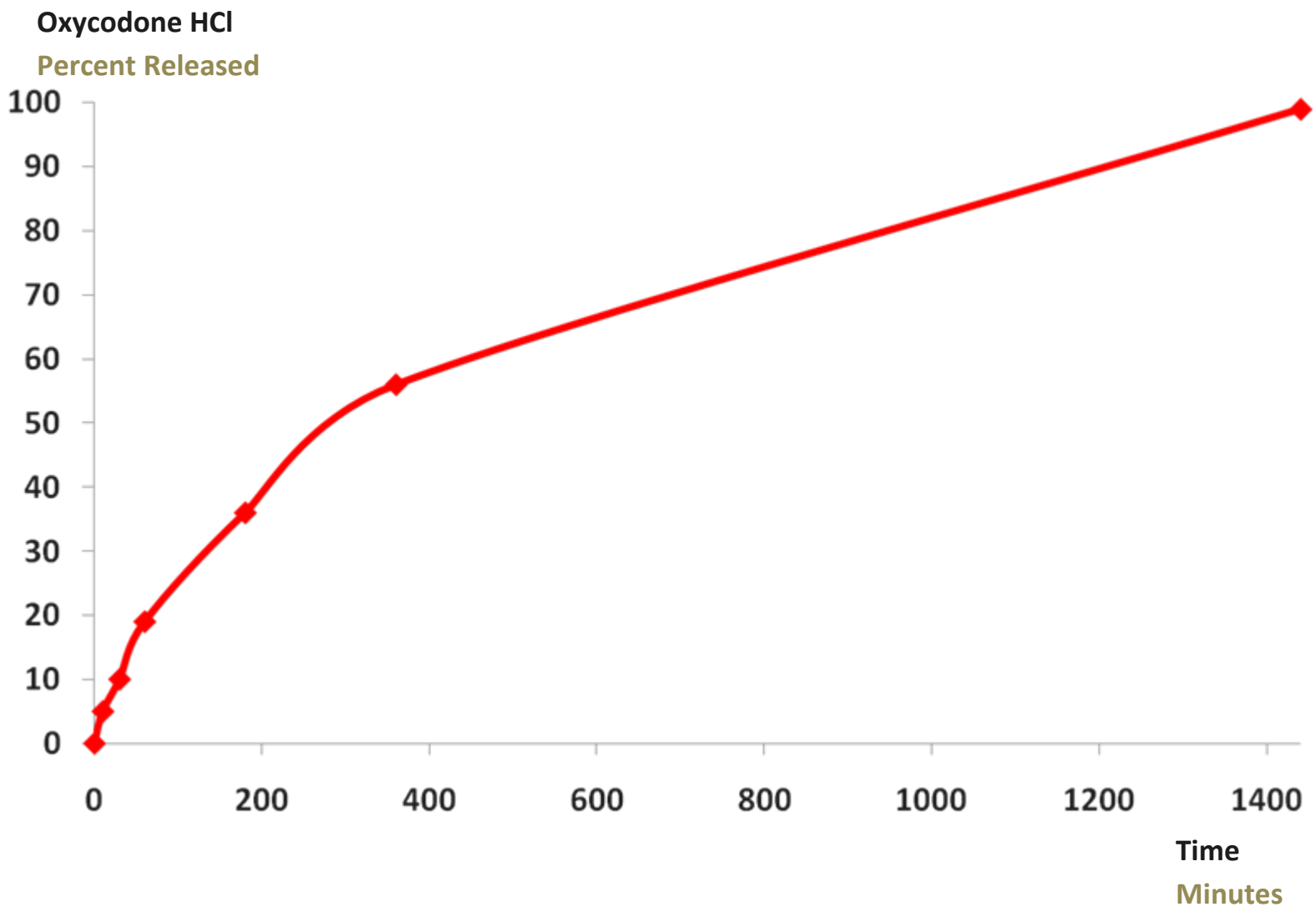




Dissolution rates are similar for 3 x 10 mg tablets and 1 x 30 mg tablet



3x80 mg tablets in 100 ml of SGF (37°C, no agitation) release all oxycodone HCl over 24hrs



Viscosity of solutions prepared for injection

Preparation Formulation- volume- time	Viscosity (mPa.s) at $10s^{-1}$	Reference (mPa.s)
OTR 80mg – 10ml – 10 mins	1020	Motor oil (650-1000)
OTR 80mg – 10ml – 60 mins	1200	Motor oil (650-1000)
OTR 80mg – 10ml – boil-0 min	310	Motor oil (650-1000)
OTR 80mg – 5ml – 10 mins	10500	Honey (10,000)
OTR 80mg – 5ml – 60 mins	15400	Honey (10,000)
OTR 80mg – 5ml – boil-0 min	4000	Motor oil (650-1000)
OxyContin 80mg – 2ml-0 min	3	Milk (3)
OxyContin 80mg – 2ml – boil-0 min	2	Water (1)

Study 5: Reformulated OxyContin cannot be syringed or injected with an insulin syringe

Syringability at Room Temperature (mg of API withdrawn into syringe)

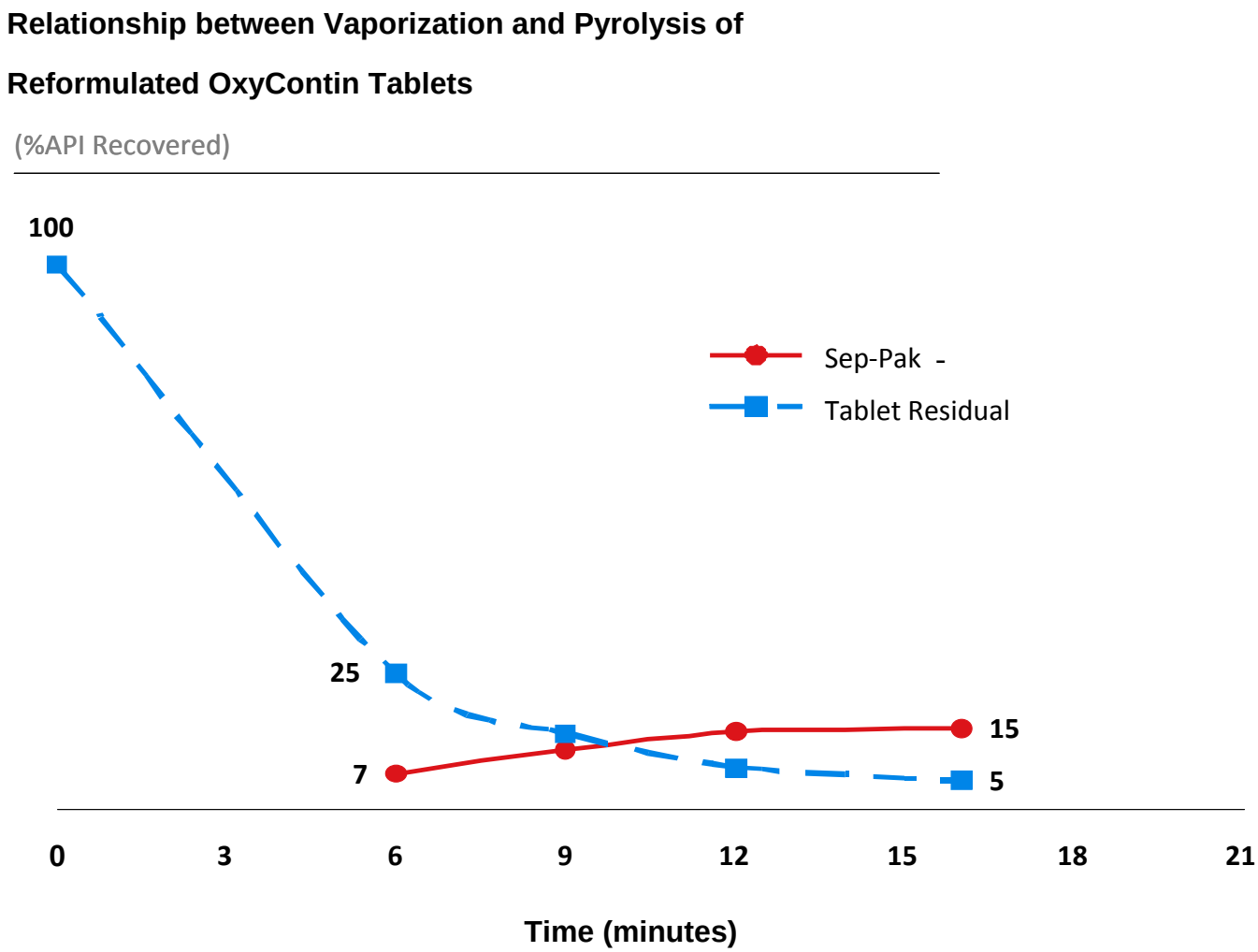
Needle Gauge	Prep Volume (mL)	Reform Oxy 10 mg	Reform Oxy 15 mg	Reform Oxy 20 mg	Reform Oxy 30 mg	Reform Oxy 40 mg	Reform Oxy 60 mg	Reform Oxy 80 mg	Oxy 10 mg	Oxy 40 mg	Oxy 80 mg
27	5	0	0	0	0	0	0	0	8	34	56
	10	1	1	1	2	4	0	4	N/A	N/A	N/A
25	5	0	0	0	4	0	0	9	N/A	N/A	N/A
	10	N/A	N/A	N/A	N/A	N/A	4	N/A	N/A	N/A	N/A
22	5	2	3	5	N/A	12	8	N/A	N/A	N/A	N/A
	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
18	5	5	7	15	17	22	19	21	9	37	67
	10	6	8	13	20	26	28	32	N/A	N/A	N/A

Study 5: Reformulated OxyContin cannot be syringed or injected with an insulin syringe

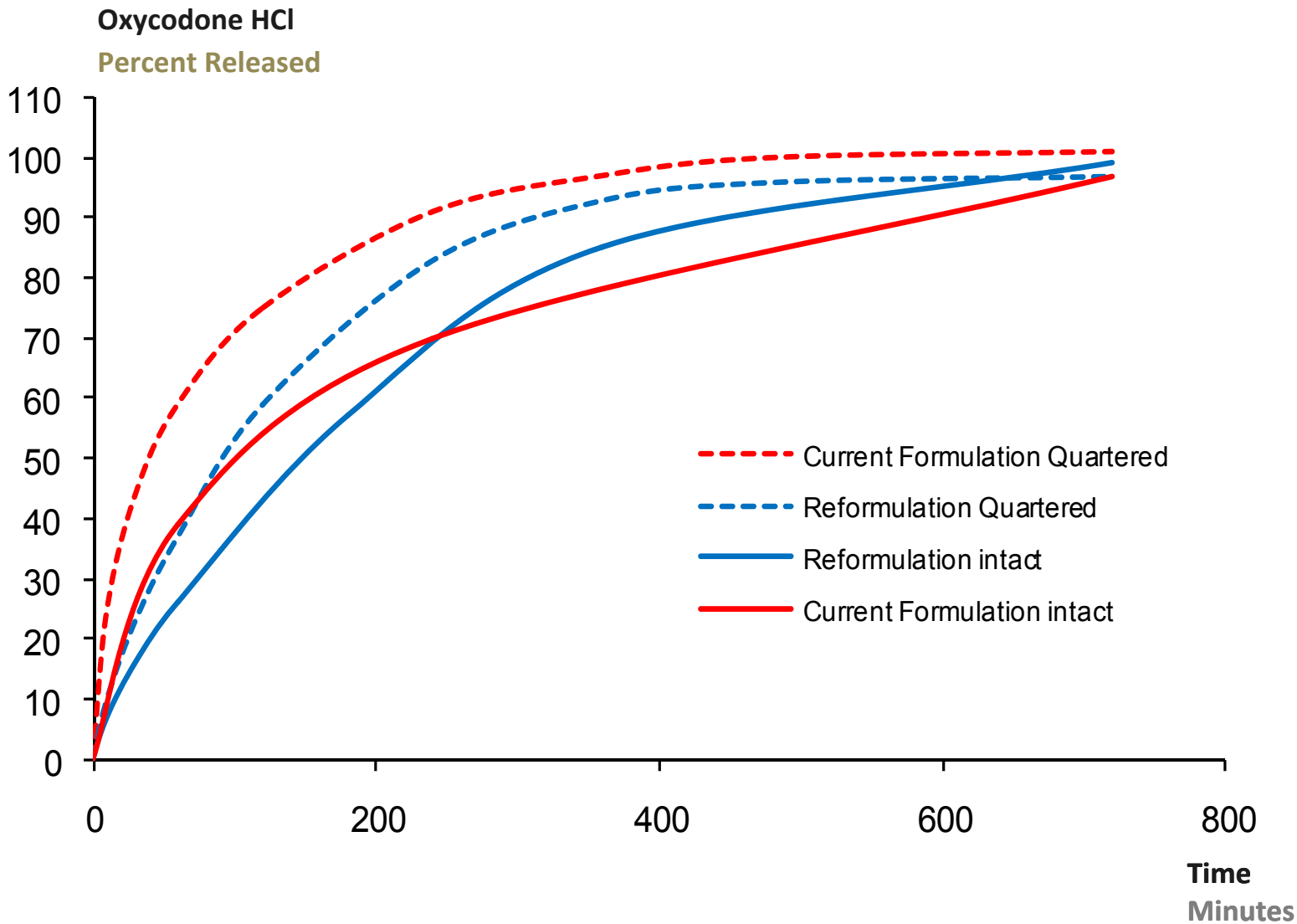
Syringability after Boiling (mg of API withdrawn into syringe)

Needle Gauge	Prep Volume (mL)	Reform Oxy 10 mg	Reform Oxy 15 mg	Reform Oxy 20 mg	Reform Oxy 30 mg	Reform Oxy 40 mg	Reform Oxy 60 mg	Reform Oxy 80 mg	Oxy 10 mg	Oxy 40 mg	Oxy 80 mg
28	2	0	0	0	2	0	0	0	5	23	46
27	5	0	0	4	6	0	0	0	10	37	71
	10	2	2	6	10	5	9	25	N/A	N/A	N/A
25	5	2	3	N/A	N/A	0	0	0	N/A	N/A	N/A
	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
22	5	N/A	N/A	N/A	N/A	12	0	15	N/A	N/A	N/A
	10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
18	5	4	9	14	22	29	35	54	8	34	66
	10	4	9	14	21	33	39	45	N/A	N/A	N/A

Study 5: Vaporization without pyrolization is difficult



Quartering the reformulated tablet does not result in dose dumping



Study 3: F2 Similarity Calculation

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

- The f2 metric is a model independent approach that is accepted by the FDA SUPAC MR Guide for the determination of similarity of dissolution profiles

- The f2 metric should be between 50 and 100 in order for the profiles to be considered similar

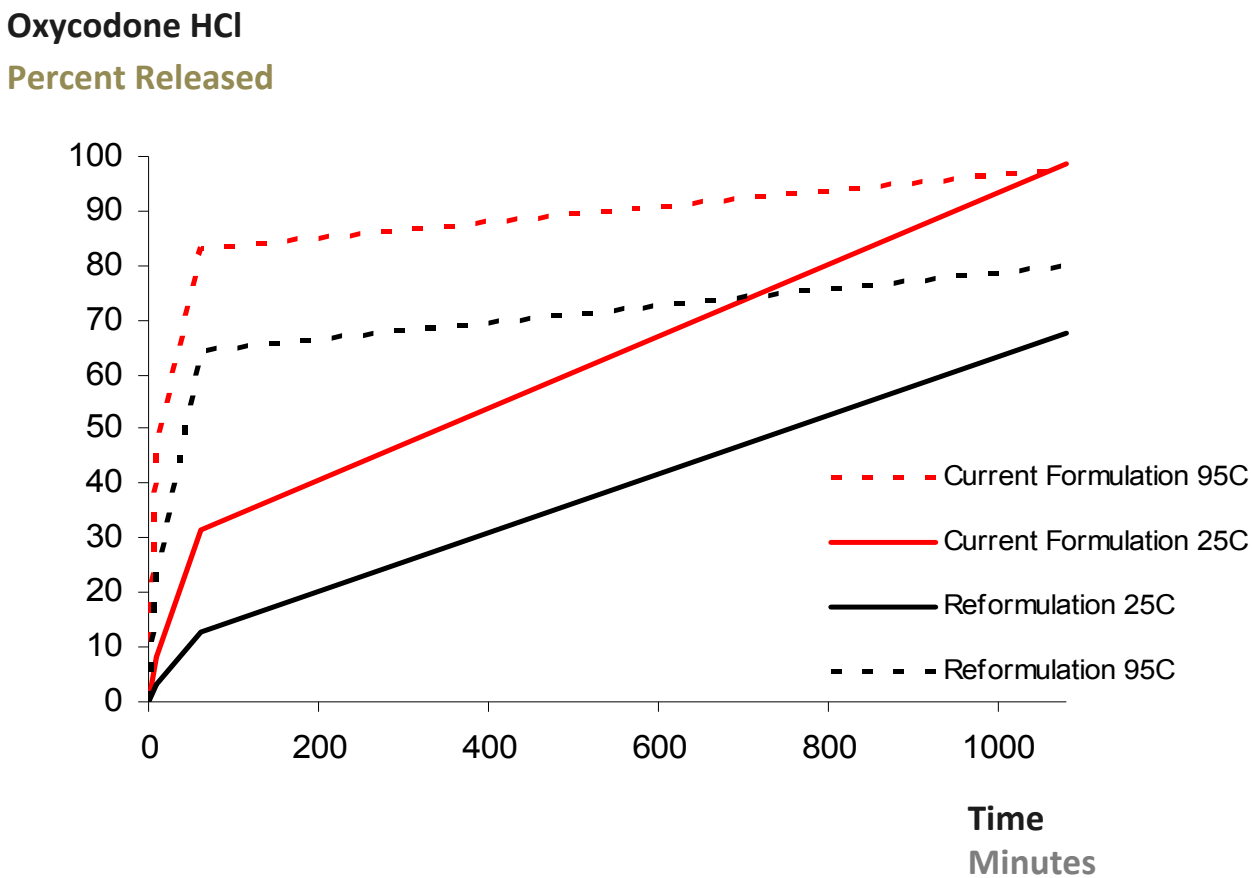
Study 3: F2 Similarity Calculation

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t-T_t)^2]^{-0.5} \times 100\}$$

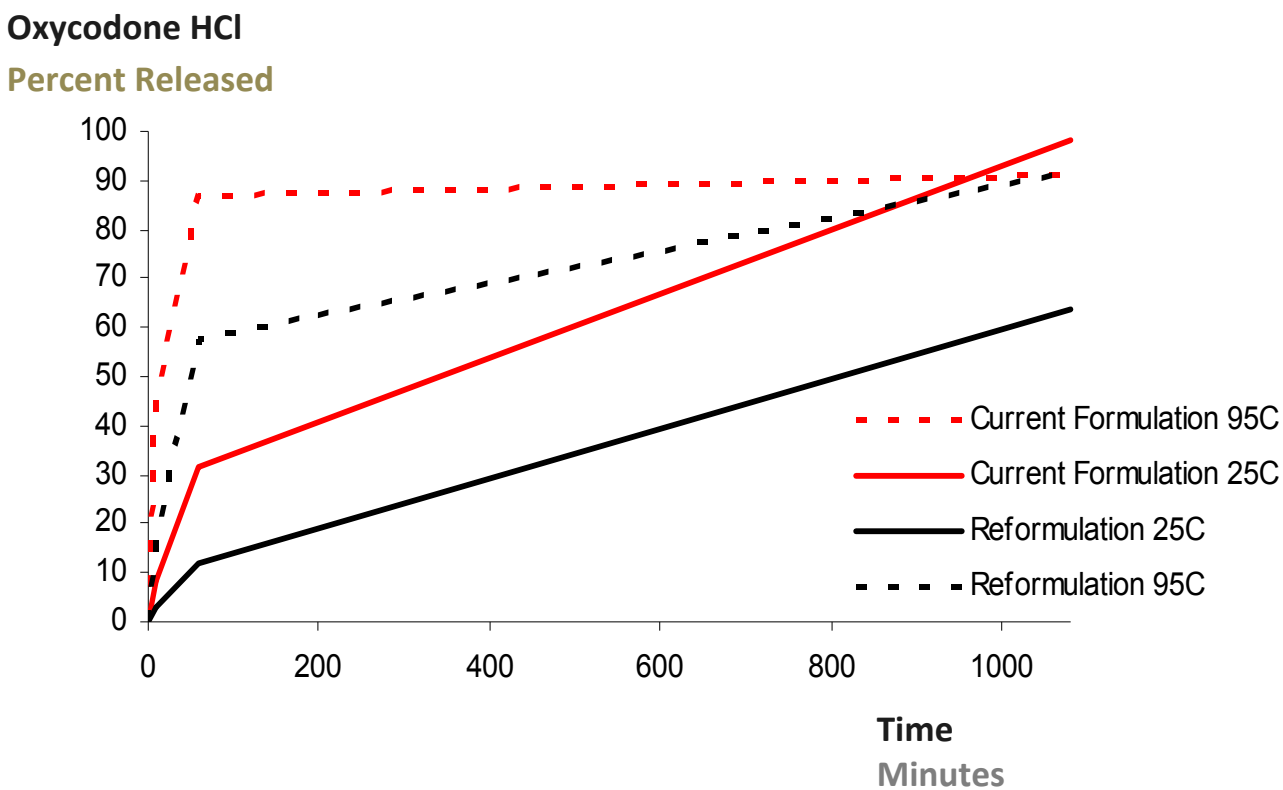
Where:

LOG = logarithm to base 10
n = number of sampling time points
$\sum$ = summation over all time points
R_t = dissolution at time point t of the reference (unchanged drug product, i.e., pre change batch)
T_t = dissolution at time point t of the test (changed drug product, i.e., post-change batch)

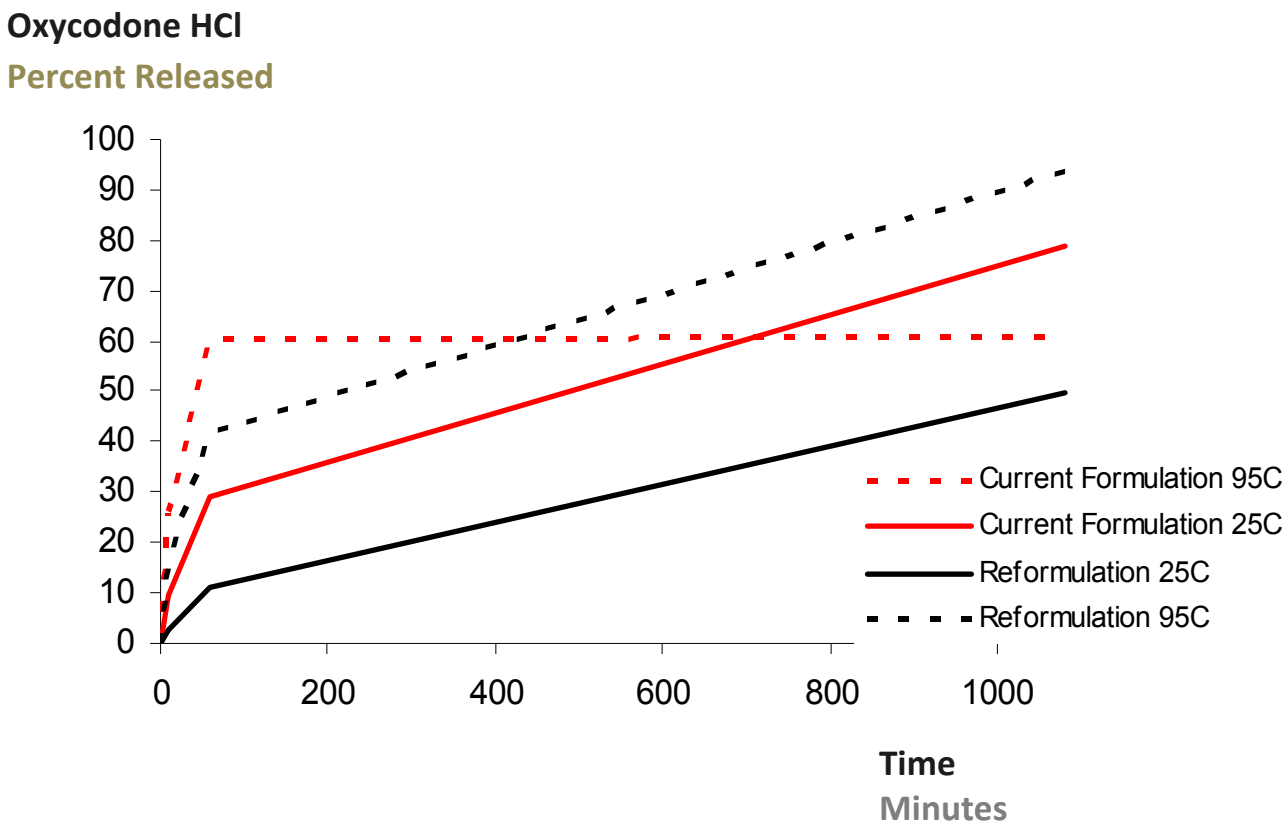
Current formulation vs. reformulation of intact tablets in pH 1 media (0.1N HCl) at room temperature and 95°C



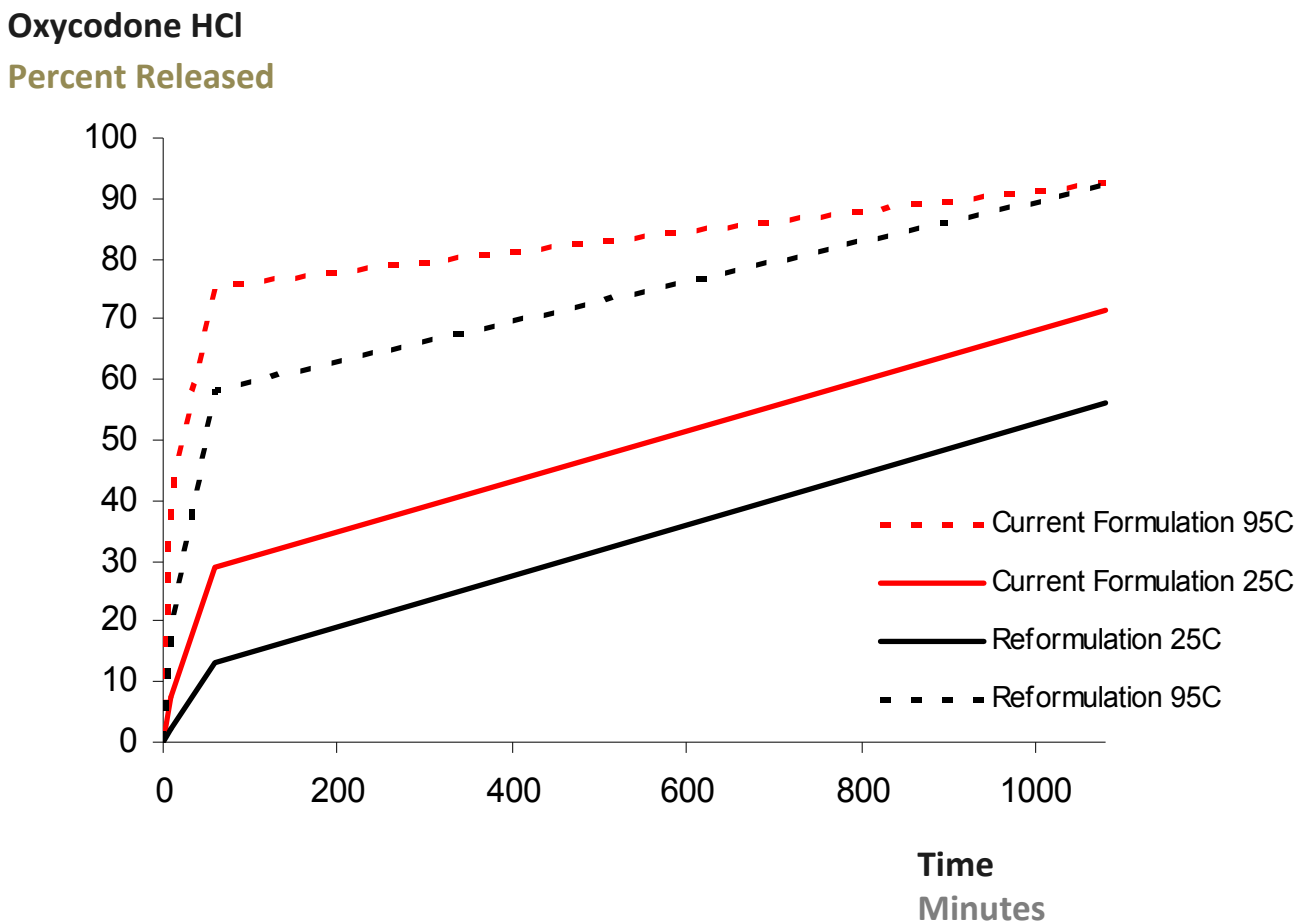
Current formulation vs. reformulation of intact tablets in pH 3 buffer at room temperature and 95°C



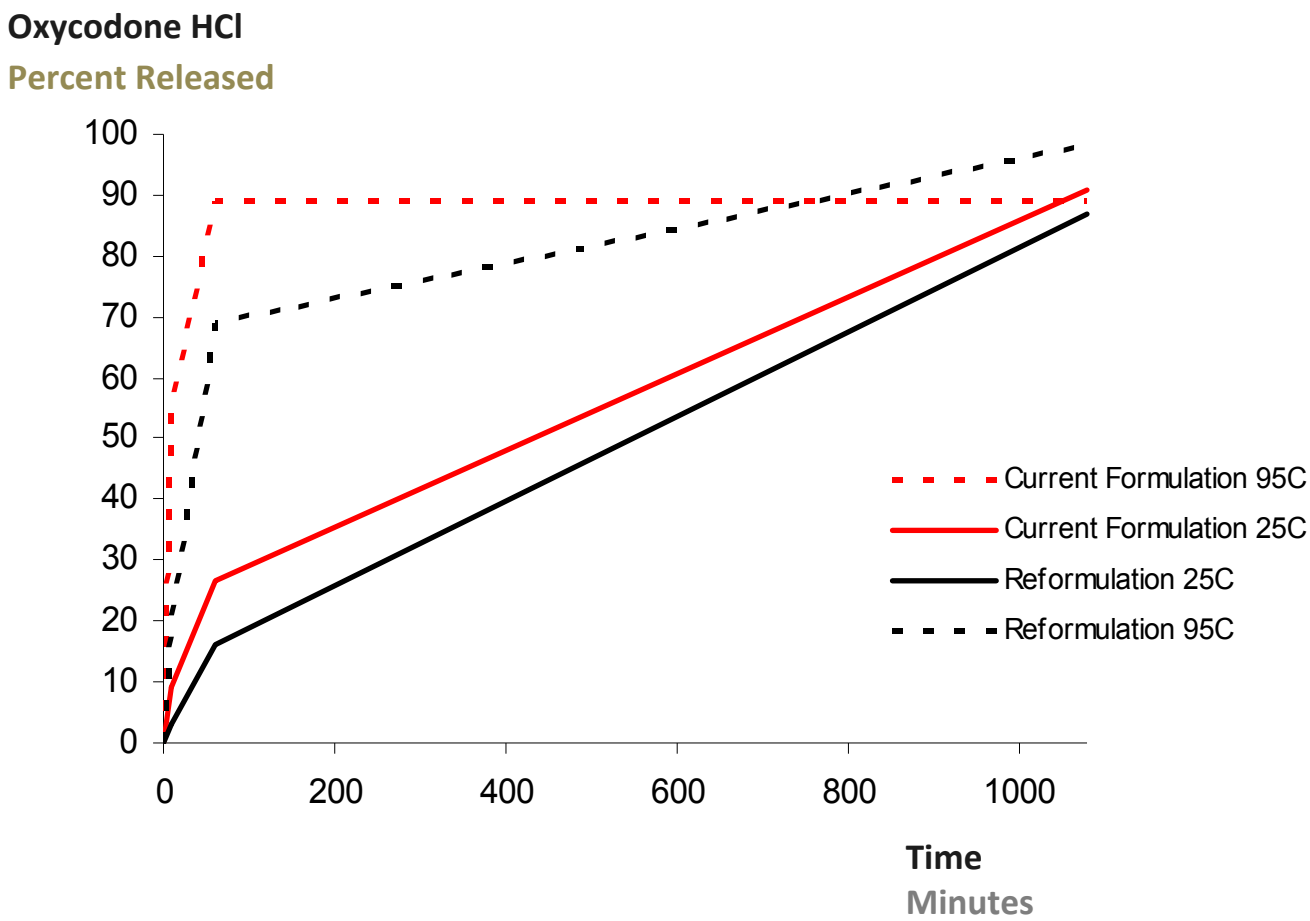
Current formulation vs. reformulation of intact tablets in pH 8 buffer at room temperature and 95°C



Current formulation vs. reformulation of intact tablets in saline (0.9%) at room temperature and 95°C

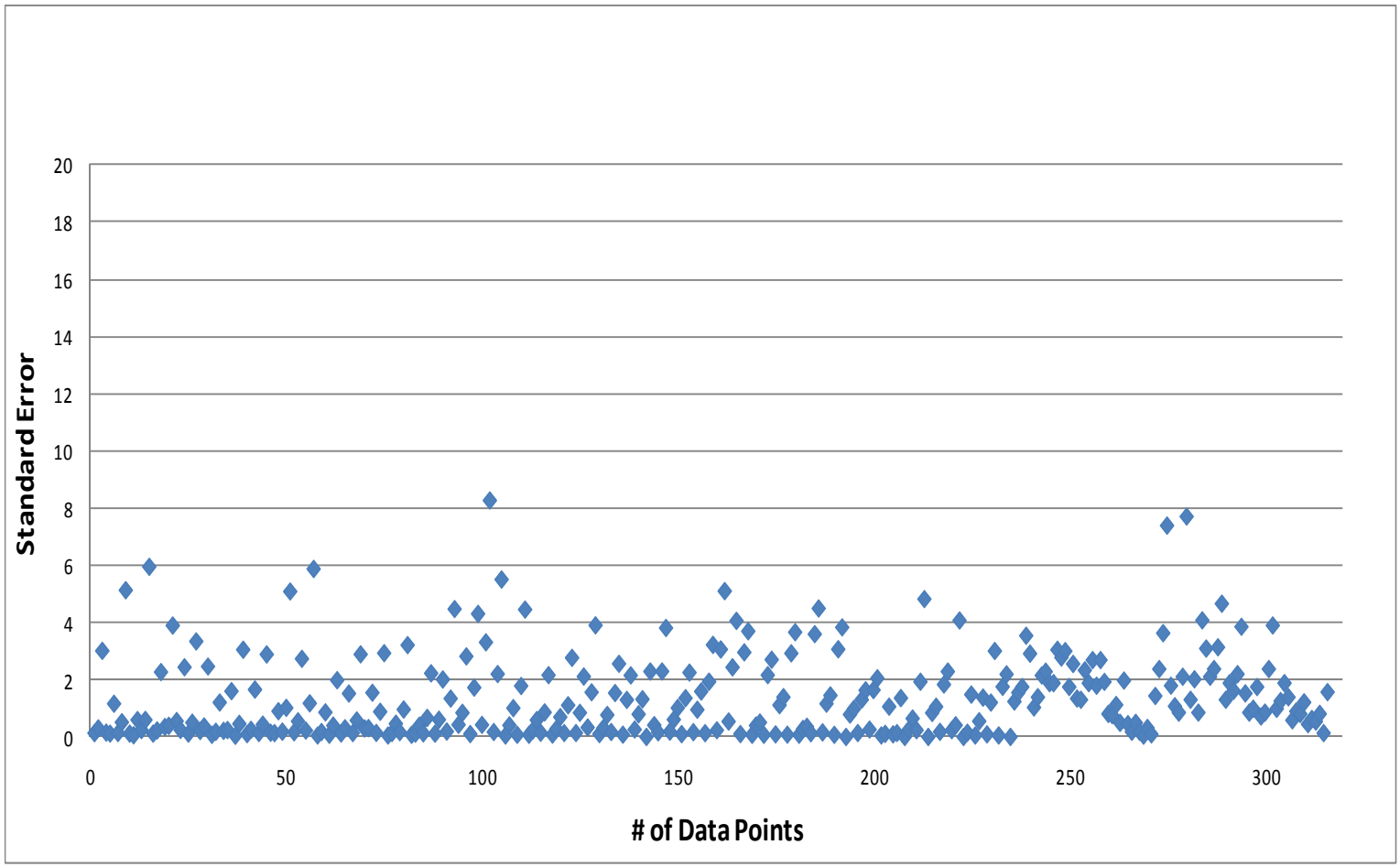


Current formulation vs. reformulation of intact tablets in caffeine-free Coke® at room temperature and 95°C

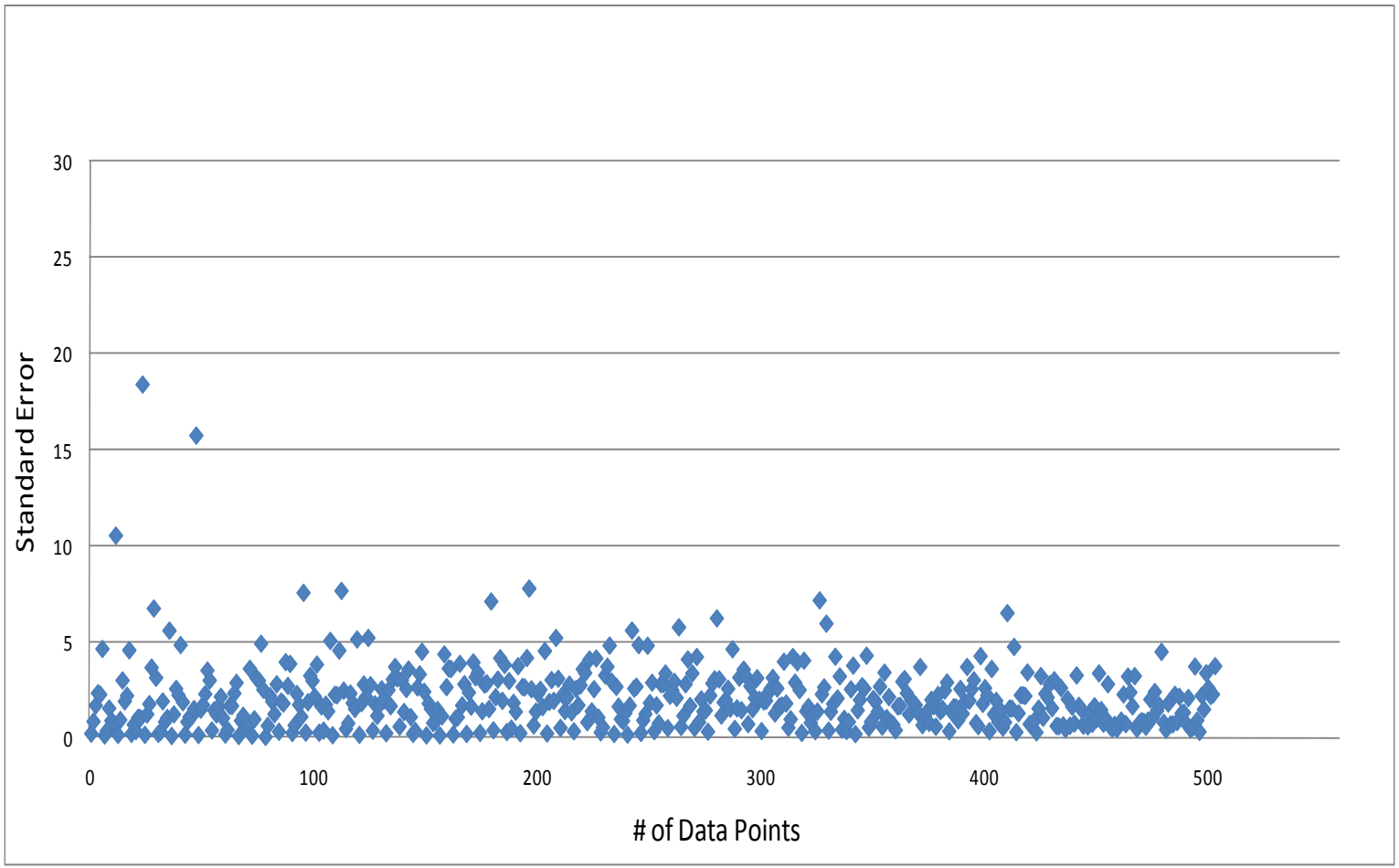


Polyethylene oxide imparts viscosity to small volumes of water

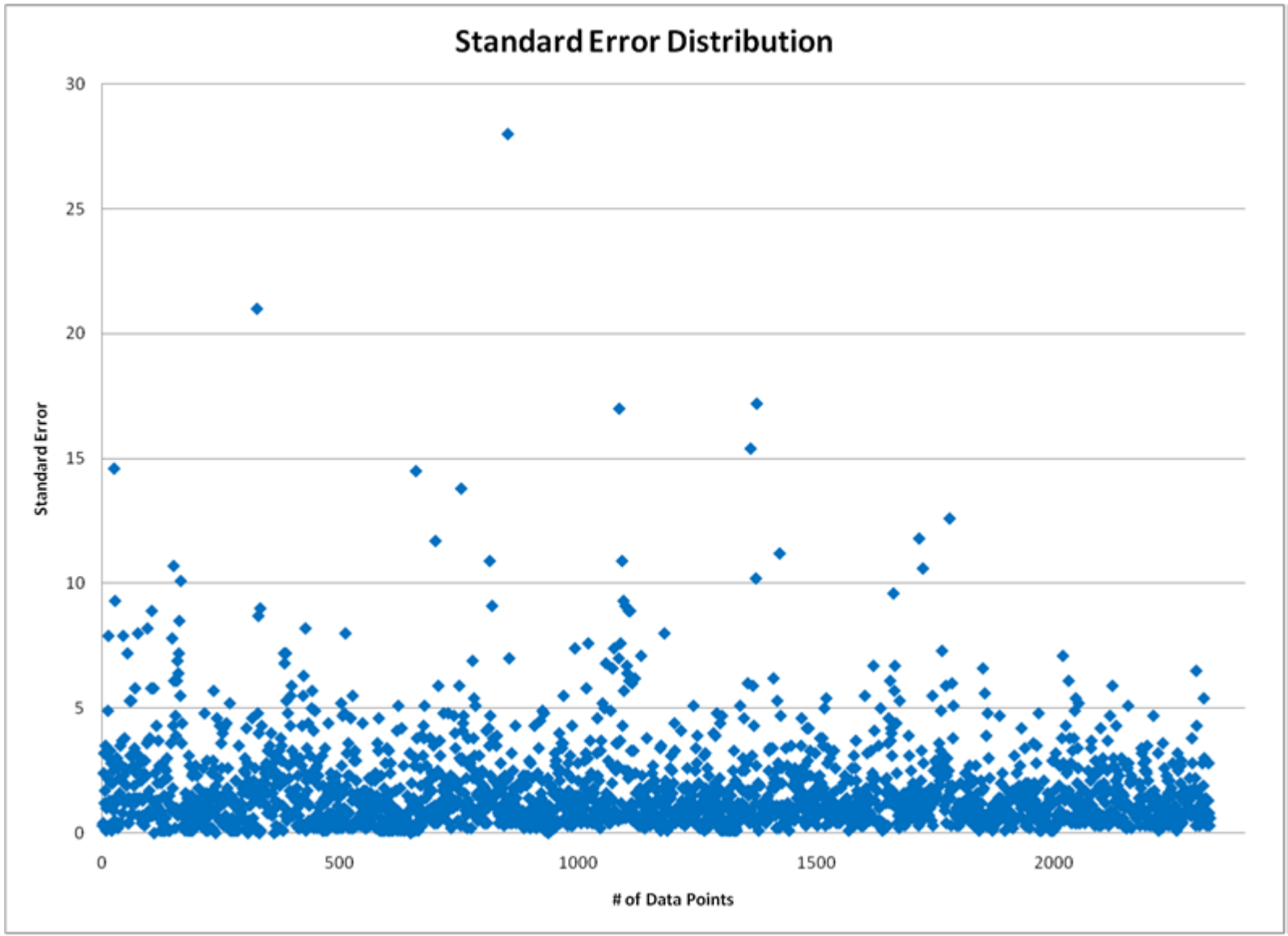
Study 5: Standard error distribution tests for syringability, injectability, and vaporization



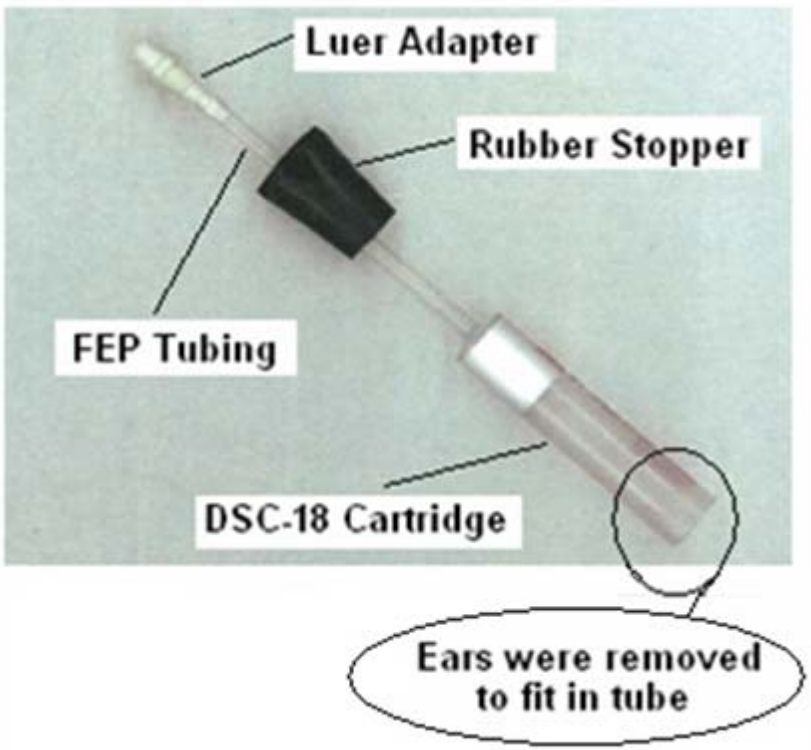
Study 3: Standard error distribution tests for dissolution testing

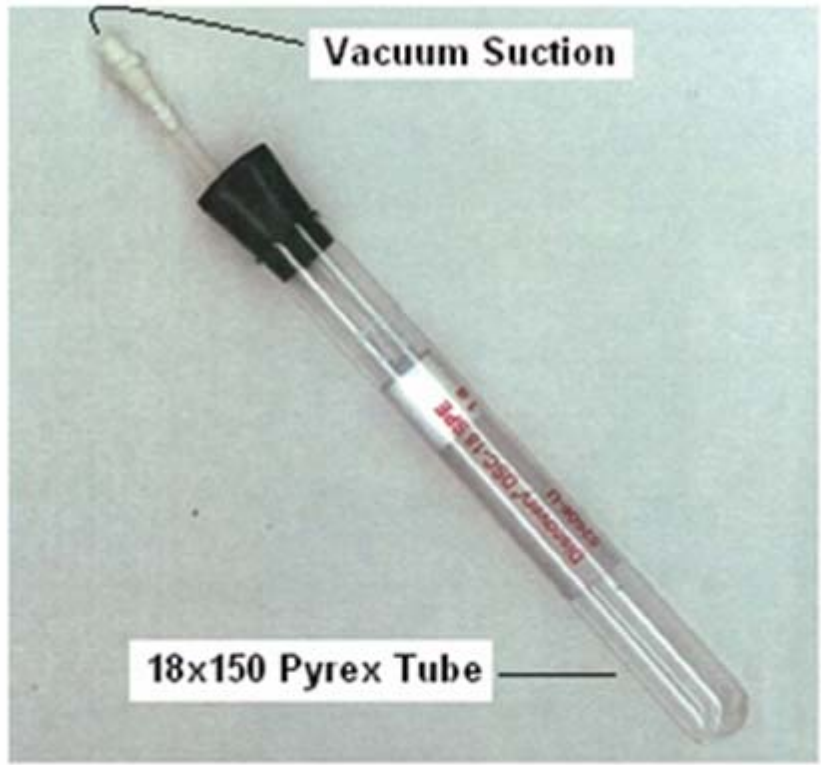


Studies 2, 4: Small Volume Extraction , 95% of standard errors are less than 5

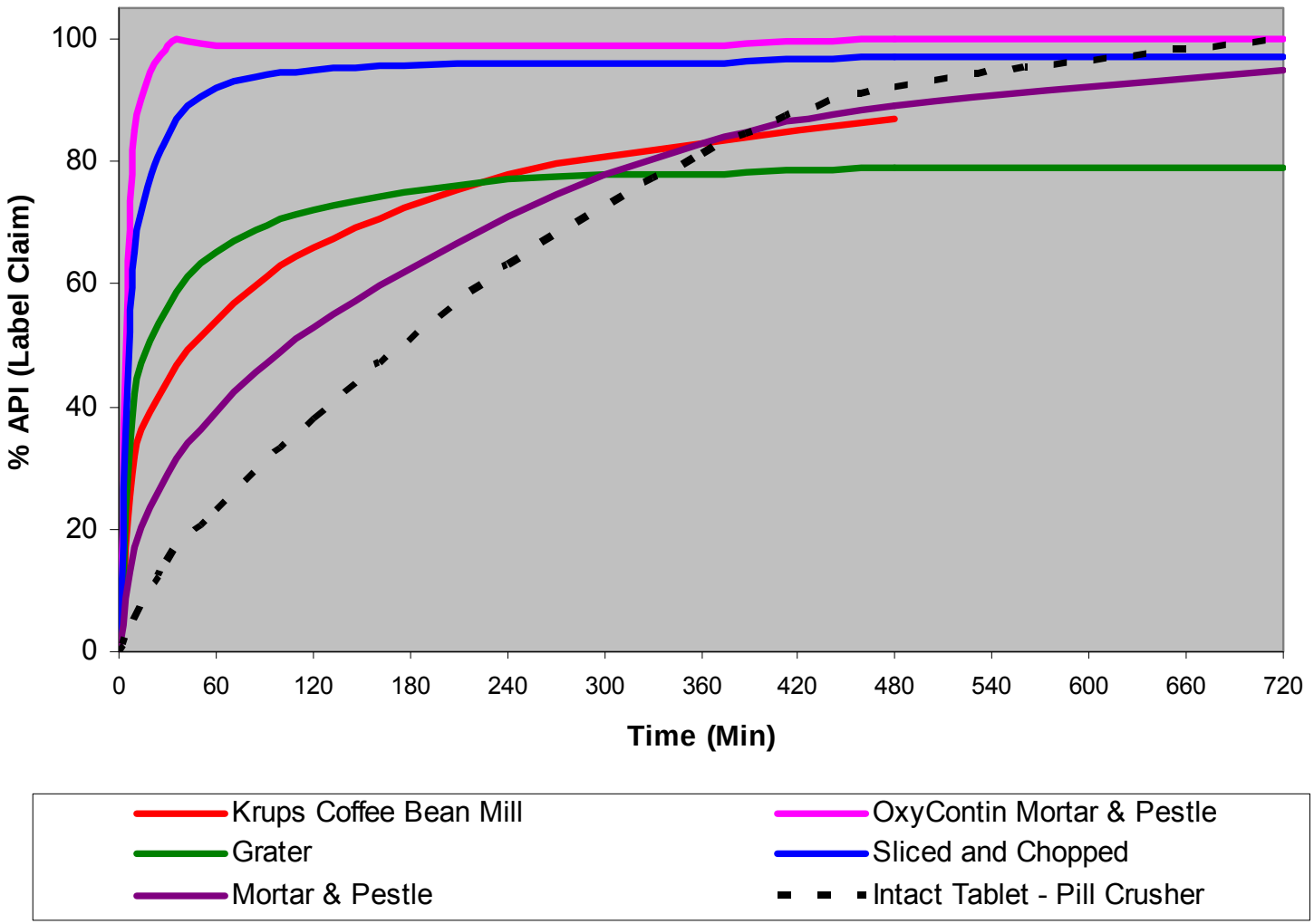


Study 5: Standardized equipment to determine vaporization efficiency





Dissolution profiles for real world tablet manipulations are dependent on particle size



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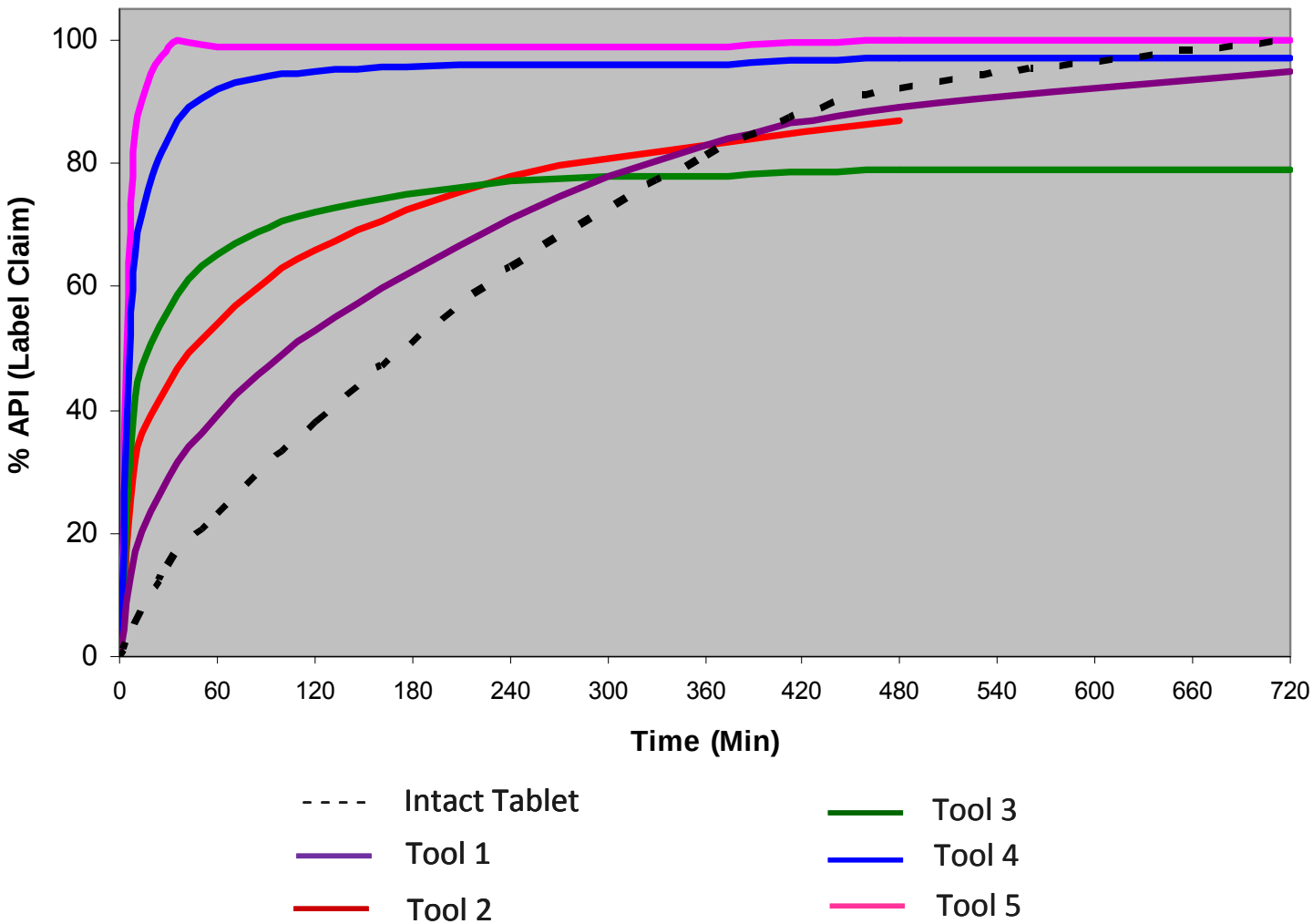
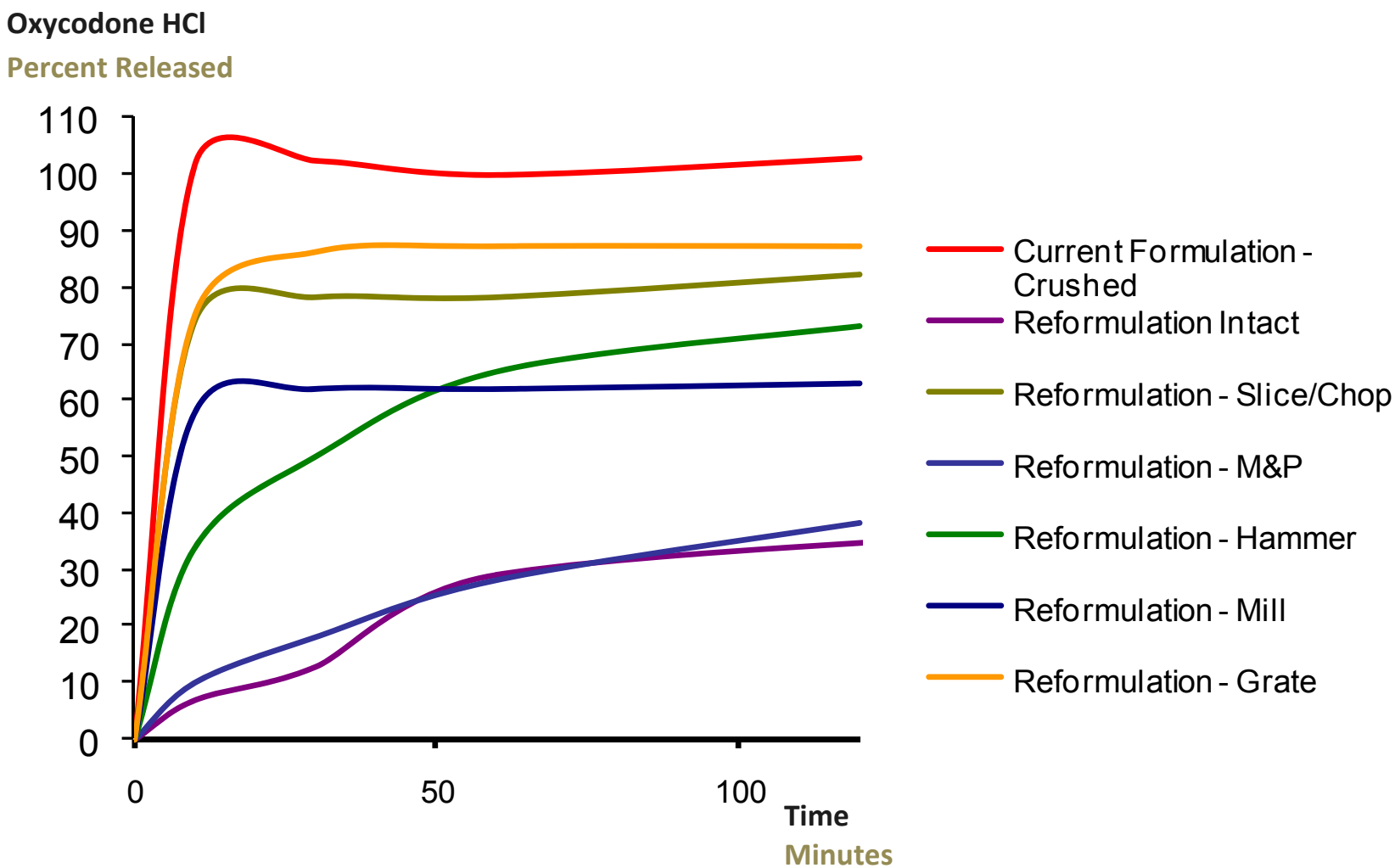


Small volume extraction in water after real world manipulations (80 mg)



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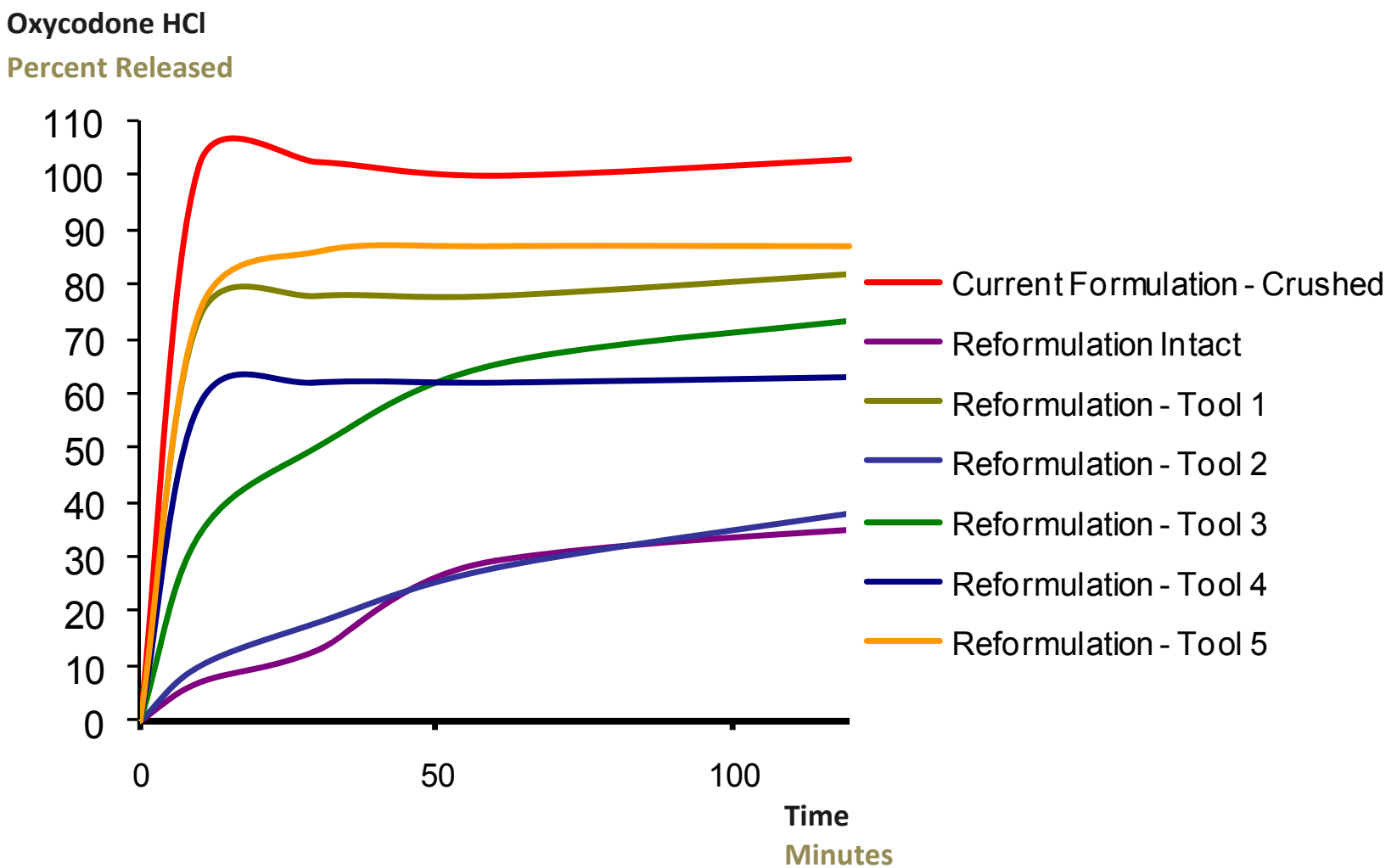
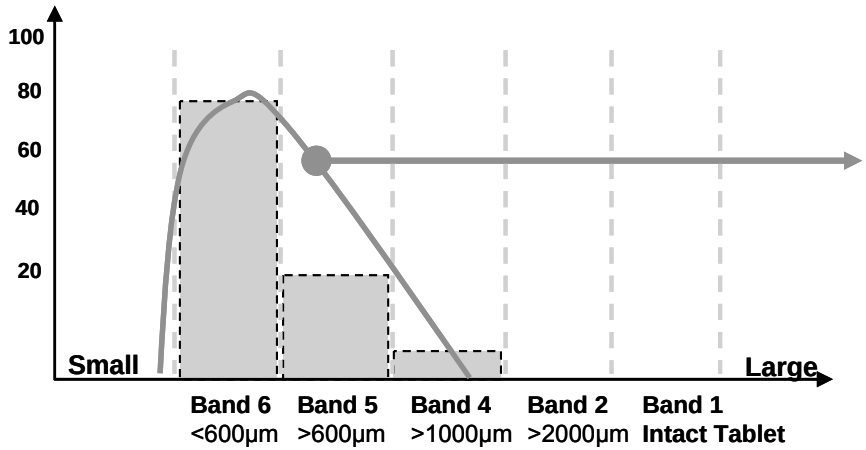
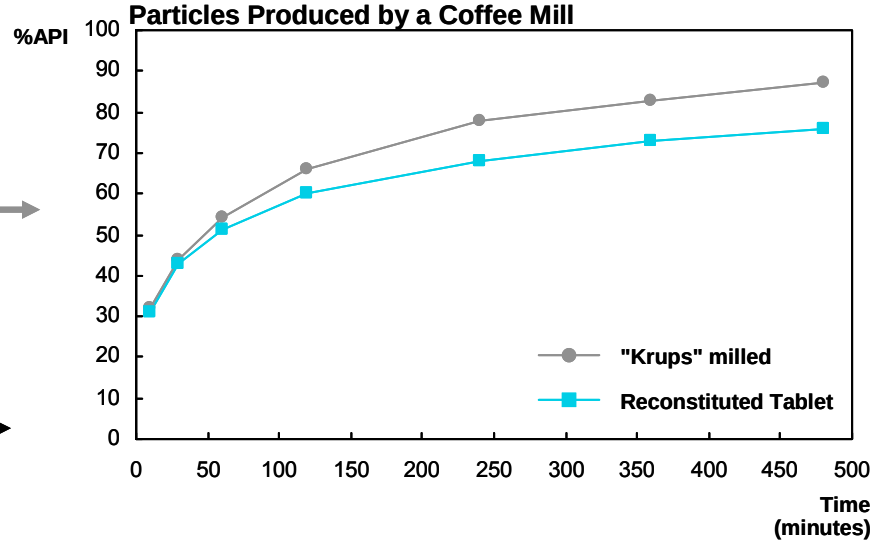


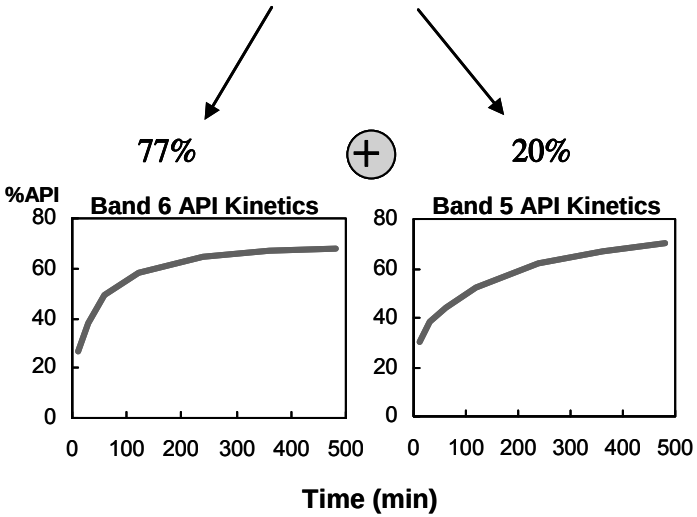
Reconstitution of "real world" manipulation profiles from component particle bands

Distribution of particles after reduction via a "Krups" Coffee Mill



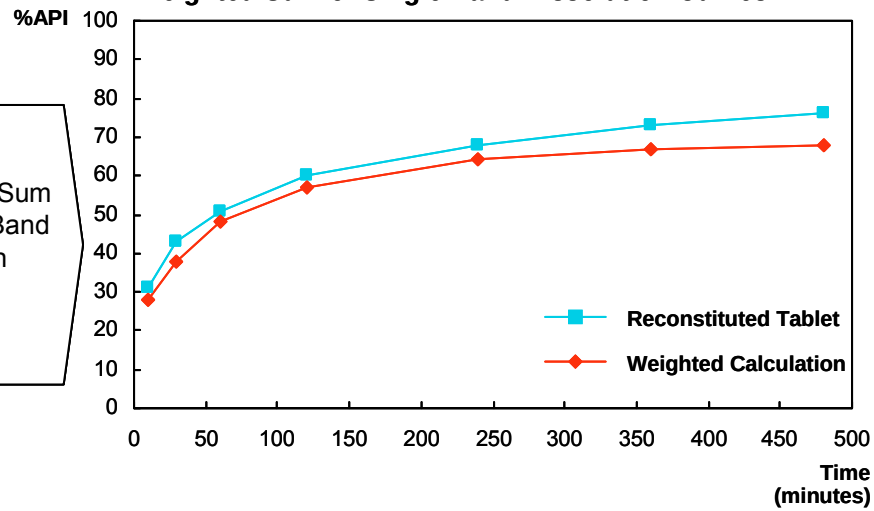
New OCR API Kinetics in SGF Using Whole Tablet Particles Produced by a Coffee Mill



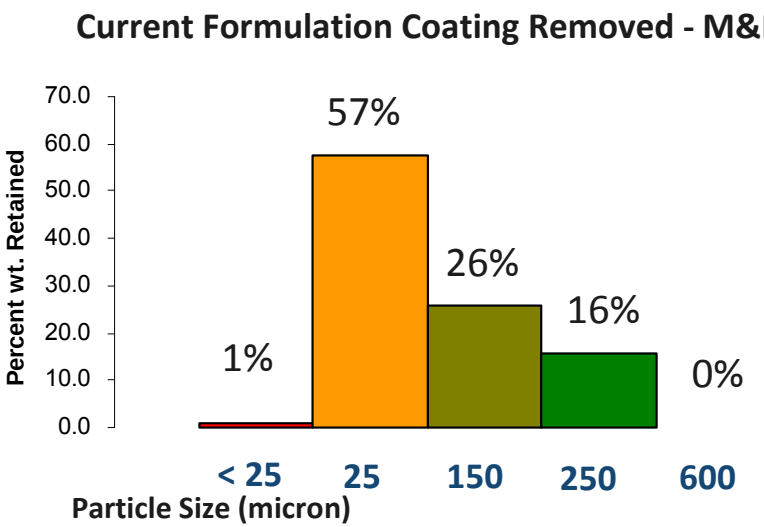


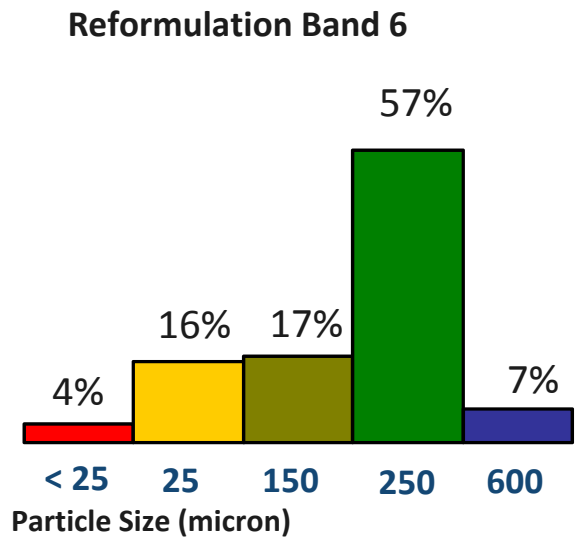
Weighted Sum of Single Band Dissolution Curves

Reconstituted New OCR API Kinetics in SGF Using Weighted Sum of Single Band Dissolution Curves

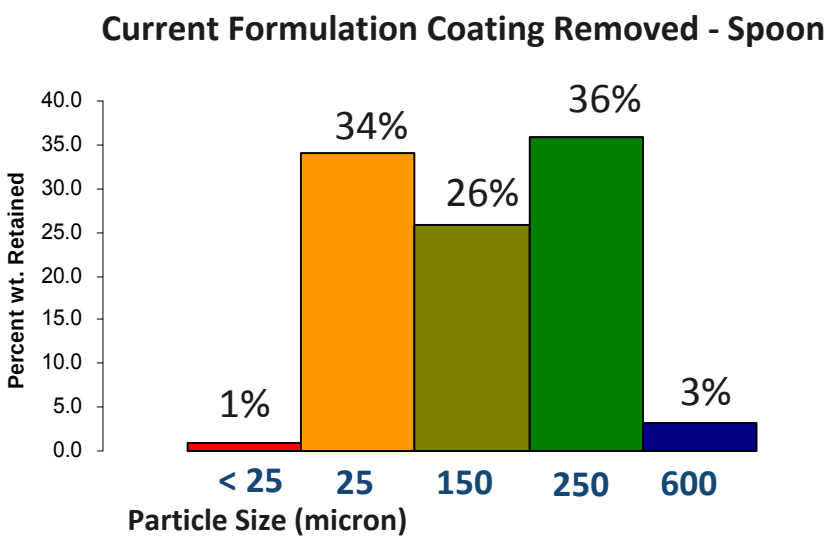


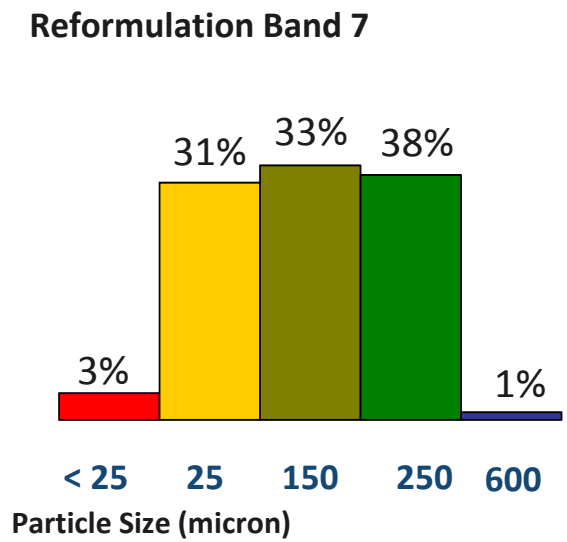
Study 1: Comparison of particle sizes achieved with the reformulation (band 6) and OxyContin (mortar and pestle)





Study 1: Comparison of particle sizes achieved with physical manipulation of current formulation and reformulation band 7





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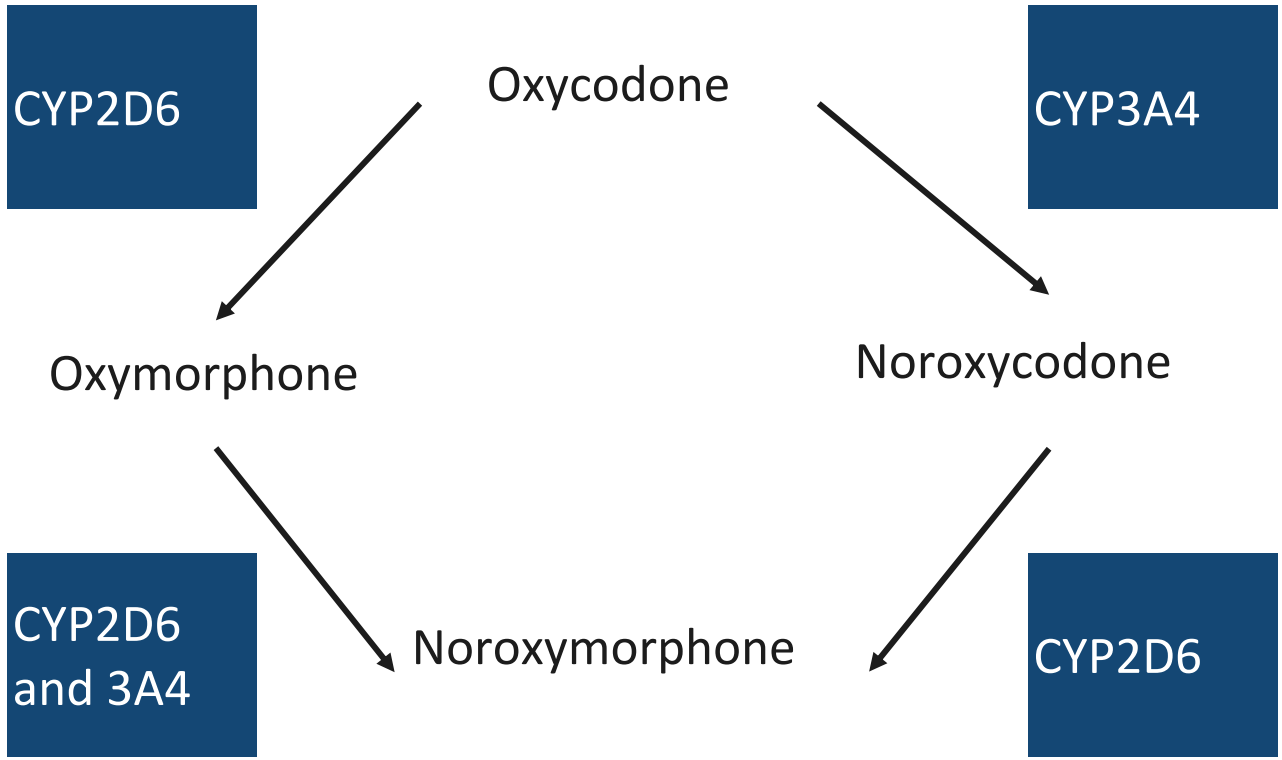
2. Value of CR opioids and oxycodone
3. Bioequivalence
4. PEO (properties, toxicity)
5. *In vitro* studies (design, data, statistics, interpretation)
6. ***In vivo* studies (PK and likability)**
7. Anticipated impact of reformulation on abuse
8. Risk mitigation (epidemiology, current actions and plans, REMS)
9. Commercial (label, marketing, “switch” timeline)

Oxycodone metabolism



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Reformulation will improve the overall safety profile of OxyContin

		Likely improvement in safety?
Non-abuse	Patients - use as directed	(no change)
	Patients - medication error	✓
	Children - poisoning	✓
Abuse	Occasional intact abusers	(no change)
	Experimenters	✓
	Recreational abusers	✓
	Sophisticated abusers	✓
	Addicts	✓

Post-marketing Safety Experience: Tampering of OxyContin® Tablets

A search of the Purdue Pharma safety database from 12-Dec-1995 (OxyContin NDA approval) thru 31-Aug-2009 for cases involving overdose, intentional drug misuse, drug abuse, or maladministration / medication error associated with tampering of OxyContin® tablets identified 1,460 cases (1,401 originated in the US)

- **85%** of the cases involved drug abuse related terms
- **15%** of the cases involved maladministration / medication error related terms

1 The data was obtained from Purdue's post-marketing safety surveillance database. The typical limitations of a spontaneous surveillance system apply.

Drug Abuse Related Cases (n=1,238)

- Reports involving drug abuse related terms included the following Preferred Terms (PTs):
  Drug abuse (n=660)
  Drug abuser (n=327)
  Substance abuse (n=213)
  Intentional drug misuse (n=84)
  Drug detoxification (n=4)
  ** Cases may have more than one PT per case*

- The methods of tampering included: crushing (n=424), chewing (n=128), splitting (n=26), breaking (n=16), grinding (n=13), melting (n=10), dissolving (n=7), cutting (n=5), and cooking (n=4)

- The methods of administration in the cases of abuse included: snorting (n=586), injecting (n=382), and smoking (n=30)

- 1,228 of the 1,238 drug abuse cases associated with tampering of OxyContin® tablets were Serious, including 187 cases that were associated with a fatal outcome.

1 The data was obtained from Purdue's post-marketing safety surveillance database. The typical limitations of a spontaneous surveillance system apply.

Medication Error Related Cases (n=222)

- Reports involving medication or maladministration errors not associated with drug abuse (n=222) included the following PTs:

  Accidental drug intake by child (n=6)
  Incorrect route of drug administration (n=6)
  Accidental overdose (n=19)
  Medication error (n=25)
  Accidental exposure (n=19)
  Wrong technique in drug usage process (n=84)
  Drug administration error (n=89)
  ** Cases may have more than one PT per case*

- The methods of tampering included: crushing (n=68), chewing (n=61), splitting (n=45), breaking (n=22), cutting (n=17), dissolving (n=8), grinding (n=1), and melting (n=1)

- 70 of the 222 cases were Serious, including 21 cases that involved hospitalization and 19 cases that were associated with a fatal outcome

1 The data was obtained from Purdue's post-marketing safety surveillance database. The typical limitations of a spontaneous surveillance system apply.

Purdue programs & partnerships

- Building Community Partnerships
- Working with Law Enforcement (including federal, state and local officials)
- Anti-diversion Tools for HCPs
- Monitoring activities
- Supply Chain Security
- Developing New Formulations
- Educating Healthcare Professionals

Developing evidence to empirically support less patient misuse or less abuse/diversion is challenging (1/2)

Challenge #1: Uncertain endpoints

Potential endpoint	Problem
• Patient overdose with or without elevated blood levels?	uncommon and only rarely are blood levels collected.
• ED overdose with elevated blood levels?	uncommon but more likely to have blood levels.
• Less reports of diversion through multiple systems?	Relies upon reporting that may be influenced by many factors.

Developing evidence to empirically support less patient misuse or less abuse/diversion is challenging (2/2)

Challenge #2: Difficult to define study design

Potential endpoint	Problem
• How big a change would be enough to conclude it was working?	Small changes from non-randomized study are less compelling than if derived from randomized controlled trials. Interpretation is much less certain.
• Could we rely on secular change or would a concurrent control group be enough?	Secular changes rarely provide compelling data unless very large in scope. Picking concurrent control would be very challenging.
• Would a case control study of ED overdoses provide compelling evidence?	Picking the controls would still be a challenge since controls are supposed to reflect the background odds of exposure. Other hospitalized cases where hospitalization is clearly unrelated to opiate abuse would give the background odds of exposure

Growing industry momentum to develop opioid formulations more robust to tablet manipulations

"…And drug manufacturers should modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected"

CDC Congressional Testimony (March 12, 2008)
United States Senate Subcommittee on Crime & Drugs Committee on the Judiciary and the Caucus on International Narcotics Control

"Trends in Unintentional Drug Overdose Deaths"

Statement of **Leonard J. Paulozzi,** M.D., M.P.H.

- Medical Epidemiologist
- Division of Unintentional Injury Prevention
- National Center for Injury Prevention & Control
- Centers for Disease Control and Prevention
- U.S. Department of Health and Human Services

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Tight supply chain management will allow us to minimize the time both products are simultaneously available at wholesaler level to 6-8 weeks

	API allocation	Manufacturing	Wholesale	Retail	Patients
Challenges	• DEA allocation of oxycodone API separate from OxyContin's allotment is needed (annual allocation)	• 4 month lead time needed to manufacture launch quantities of new OCR	• 3 majors = 89% 2008 OxyContin sales (have average 22-28 days on hand) • 3 majors plus 2 largest regional wholesalers account for 94% of OxyContin sales	• 4 major chains = 44 % OxyContin Rx volume (estimate) • Regional chains, independents, food and mass retailers (without Walmart) account for 56% • ~170,000 doctors prescribe OxyContin • 45,000 pharmacies order OxyContin	• ~900,000 patients fill up to 8.4 million Oxycodone-ER prescriptions per year • Currently 82% of this is OxyContin (expected to rise to ~100%)
Purdue Plan to speed replacement	• Ask Agency to communicate likelihood of new OCR approval to DEA to support request for new OCR allotment API	• Manufacture new OCR at risk during FDA review period (Purdue will destroy if new OCR is not approved)	• Contact major wholesalers prior to launch to explain plan to reduce OxyContin inventory by half before new OCR shipments begin	• Contact national / regional chains and independent buying groups (90% of all retailers) to explain plan to reduce OxyContin inventory before new OCR shipments begin	• Prepare "Dear Patient" communication for physicians and pharmacists to use in explaining product replacement