

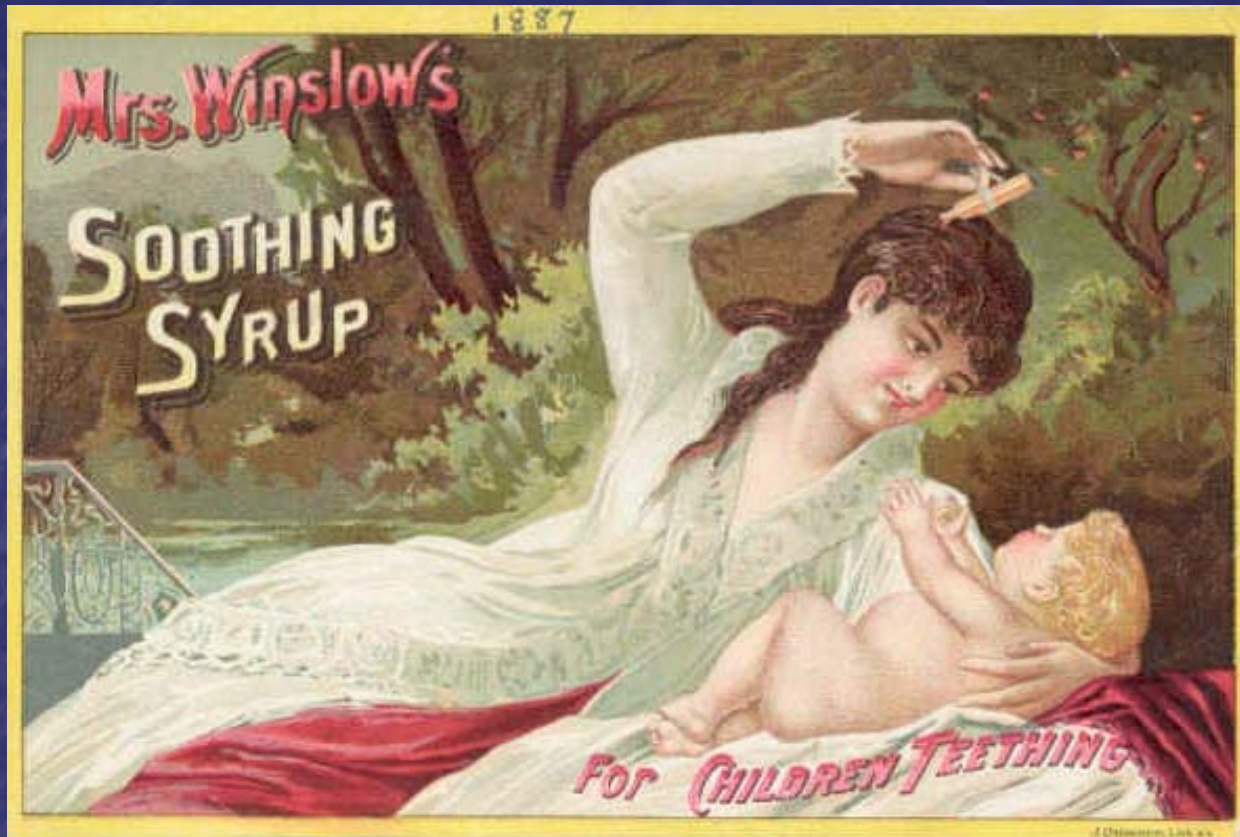
Development of Abuse-Resistant Opioid Formulations

William K. Schmidt, PhD

VP, Clinical Research, Renovis, Inc.

Opioid Risk Management, March 29, 2005

Mrs Winslow's Soothing Syrup



For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle."

Mu Agonist Analgesics

Prototype:



Morphine

Others: Methadone
Meperidine
Fentanyl

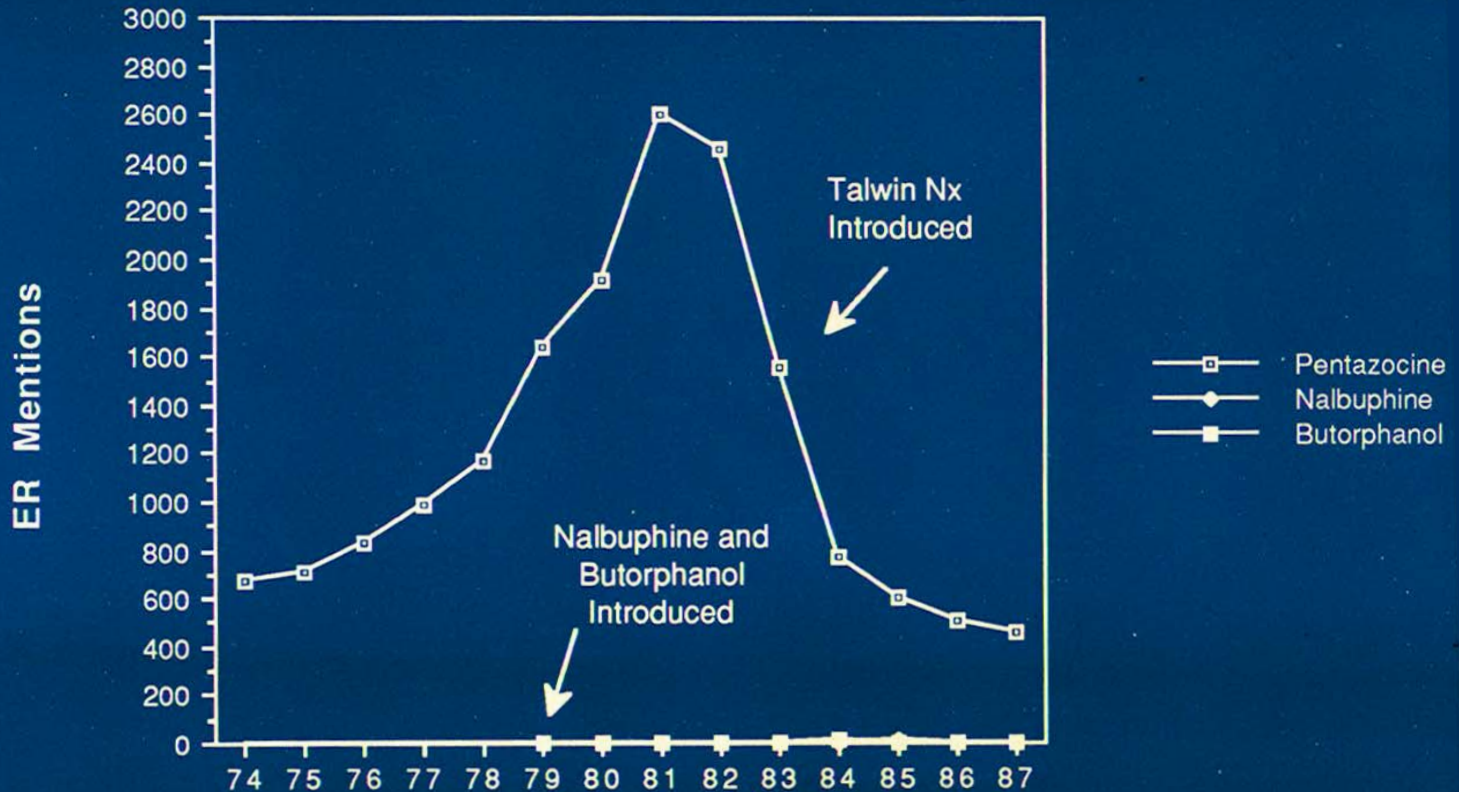
- Strong analgesia
 - Sedation
 - Euphoria
-

- Nausea
 - Constipation
 - Respiratory Depression
 - Tolerance / Dependence
 - Addiction Liability
-

- Scheduled narcotic

Formulation Impact on Abuse Liability

DAWN EMERGENCY ROOM
MENTIONS BY YEAR



Talwin NX®: A solution?

Pentazocine--naloxone: another "addiction-proof" drug of abuse.

Pentazocine, in combination with the antihistamine tripeleennamine, was a popular drug of intravenous abuse in many large cities in the late 1970s and early 1980s. To stem the abuse of pentazocine, naloxone was added to the tablet. This would presumably allow oral activity, but naloxone would block the euphoria if the pills were injected. Abuse of pentazocine appears to have diminished, but we have recently treated three addicts who continued to inject pentazocine, despite its naloxone content. Two patients experienced no overall decrease in the drug-induced euphoria. The third patient became acutely psychotic with each injection. Hypotheses are advanced to explain these findings.

Lahmeyer & Craig. Int J Addict. 22:1163-1166, 1987

OxyContin® + Naloxone

International Patent Application To Be Published on Abuse-Resistant Pain Reliever Being Developed by Purdue Pharma

Stamford, CT, August 8, 2001 – Purdue Pharma L.P. expects to receive notification soon of the publication of an international patent application for a pharmaceutical formulation that combines an opioid pain reliever with a “sequestered antagonist” that would work to help prevent the medication from being abused.

OxyContin® + Naloxone

Purdue Pharma Provides Update on Development Of New Abuse-Resistant Pain Medications

FDA Cites Patient Needs As First Priority; New Drug Application Delayed

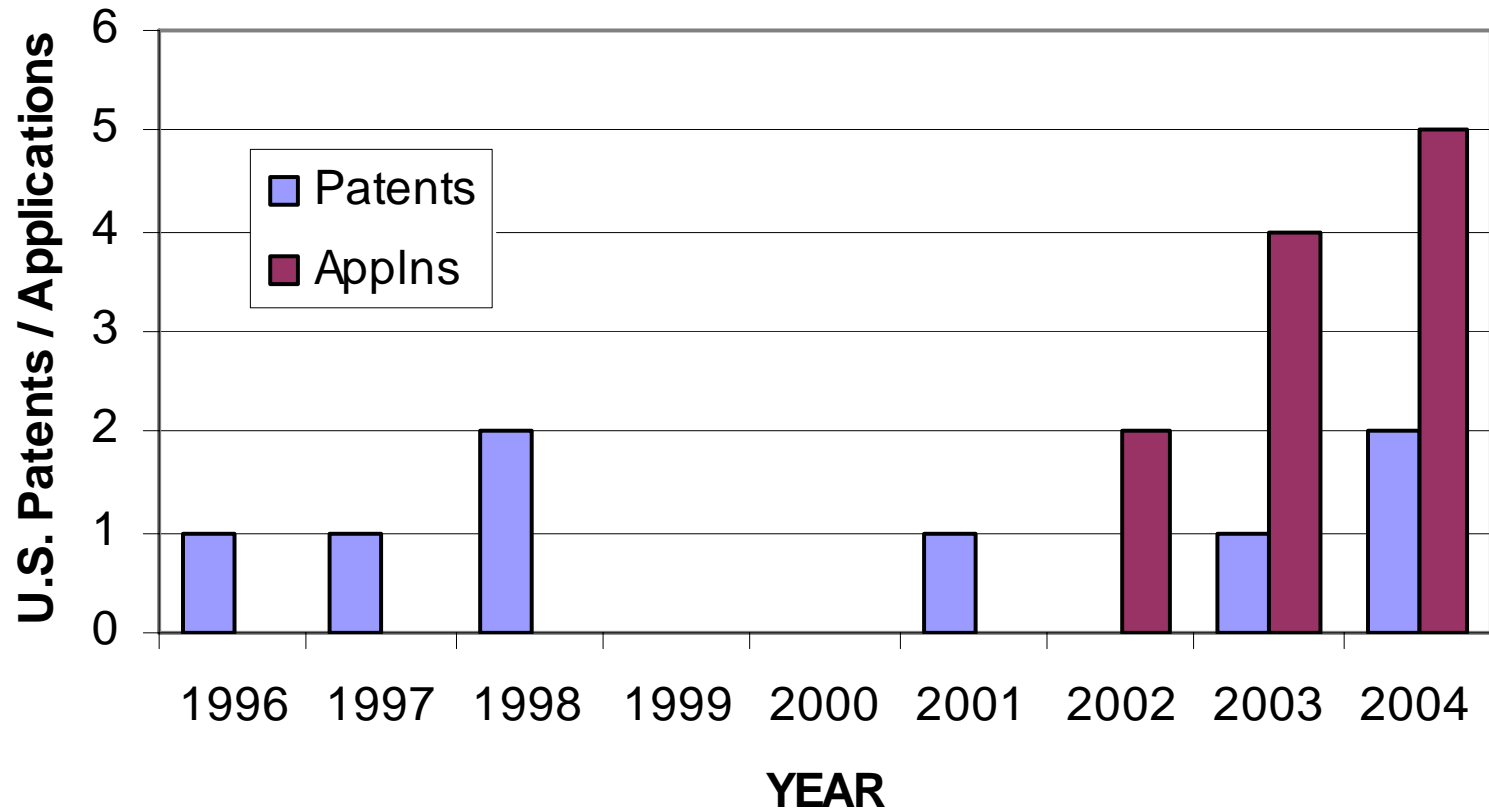
Stamford, CT - (June 18, 2002) - Purdue Pharma L.P. announced today that the company and the U.S. Food & Drug Administration have determined that additional studies would be required to more fully assess the safety and effectiveness of the company's investigative drug combining the opioid analgesic oxycodone with the opioid antagonist naloxone. The NDA for this product was originally projected to be submitted to FDA by end of 2002. These further studies however, will substantially delay the company's NDA submission for its first abuse-resistant product.

Abuse-Resistant Opioid Formulations

Sources of Information

- Medline / PubMed = 0 relevant hits
 - “opioid abuse resistant formulation”
 - “(abuse OR addiction) AND (narcotic OR opioid OR opiate OR morphine OR oxycodone OR hydrocodone OR hydromorphone OR codeine) AND resistant AND (pain OR analgesia OR analgesic)”
 - “(abuse OR addiction) AND resistant AND pain AND formulation)”
- FDA Website = 0 relevant hits
- Delphion Patent Server = 19 relevant hits
- Press Releases / Company web sites

U.S. Patent Office: Patents & Applications



“(abuse OR addiction) AND resistant AND pain”

Approaches to Abuse Resistance

- **Modified release to resist crushing / extraction**

Collegium, Pain Therapeutics (Durect), Roxane, TheraQuest

- **Prodrugs**

New River

- **Agonist & antagonist combinations / aversion**

Acura, Elite, Endo, Purdue, 3M

- **Nasal gel**

Ionix

Acura Pharmaceuticals / Halsey Drug Co.



Aversion™ Technology

The primary business of Acura Pharmaceuticals, Inc. ("the Company") is the research and development of proprietary abuse deterrent formulation technologies (the "Aversion™ Technology") intended to deter the abuse of orally administered opioid analgesic products.

Bioavailability / Bioequivalence comparison to marketed product

- IND filed October 2004 for 1st formulation; Phase I completed
- IND to be filed for 2nd formulation 1Q'05

www.acurapharm.com

Collegium Pharmaceuticals

Collegium Pharmaceutical Signs Agreement with Endo Pharmaceuticals to Develop Abuse Deterrent Pain Products

CUMBERLAND, RI--(BUSINESS WIRE)-December 3, 2003-

Collegium Pharmaceutical, Inc., a closely held specialty pharmaceutical company, today announced that it has entered into a Product Development and Licensing Agreement with Endo Pharmaceuticals Inc. aimed at developing pain products with abuse deterrent properties. Collegium will employ its proprietary technology, **DETERx™**, to derive abuse deterrent formulations of opioids that can deliver the required analgesic effects while diminishing these drugs' potential for abuse. The collaboration provides for an upfront payment to Collegium as well as the potential for additional milestones and royalties contingent upon the successful launch of products incorporating the **DETERx™** technology.

www.collegiumpharma.com

Collegium Pharmaceuticals

Abstract: An abuse-deterrent pharmaceutical composition has been developed to reduce the likelihood of improper administration of drugs, especially drugs such as opioids. **In the preferred embodiment, a drug is modified to increase its lipophilicity.** ... modified drug is homogeneously dispersed within microparticles composed of a material that is either slowly soluble or not soluble in water. ... drug containing microparticles or drug particles are coated with one or more coating layers, where at least one coating is water insoluble and preferably organic solvent insoluble, but enzymatically degradable by enzymes present in the human gastrointestinal tract. ... the drug is slowly released from the composition as the composition is broken down or dissolved gradually within the GI tract by a combination of enzymatic degradation, surfactant action of bile acids, and mechanical erosion.

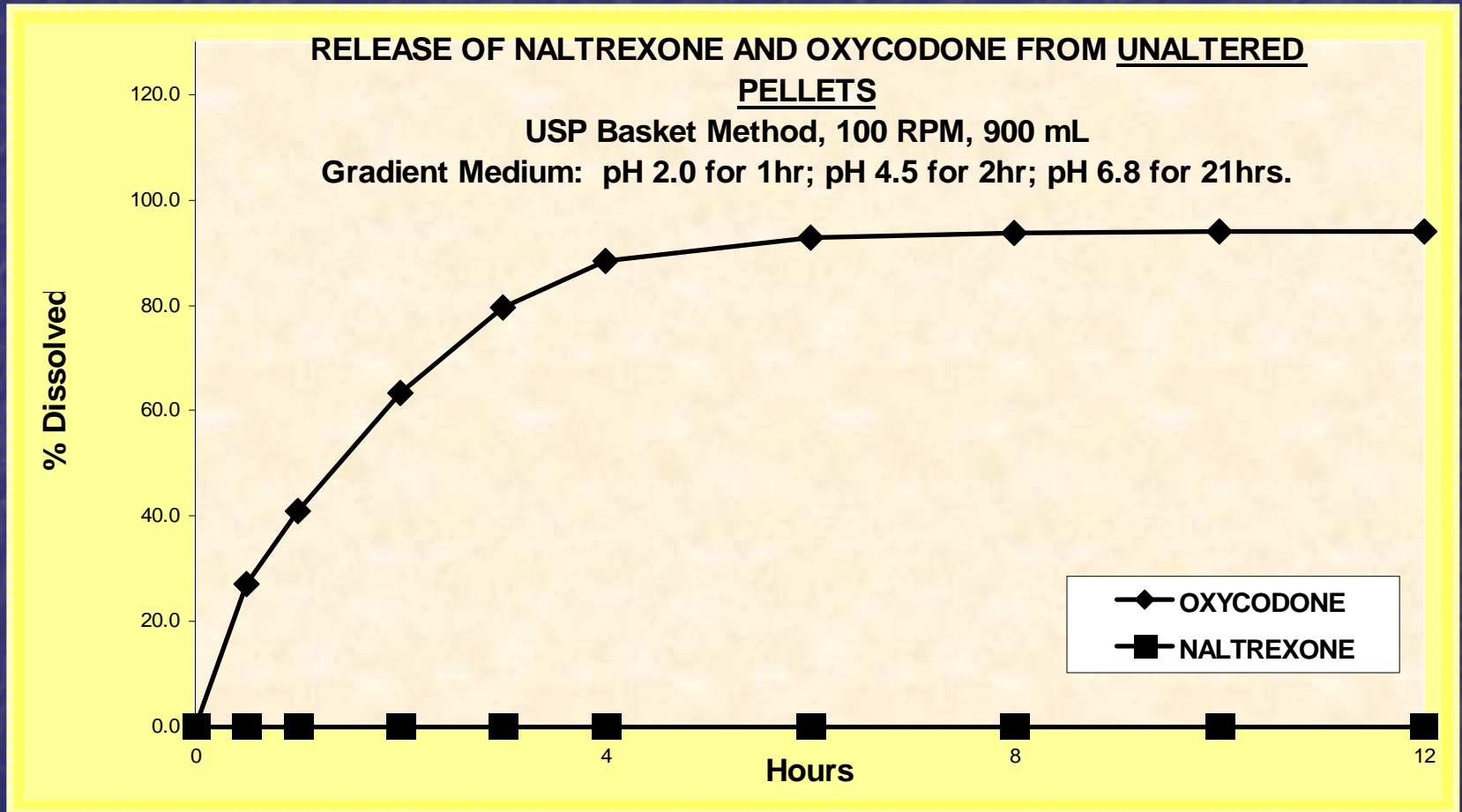
Elite Pharmaceuticals

Abuse Resistance Technology (ART™)

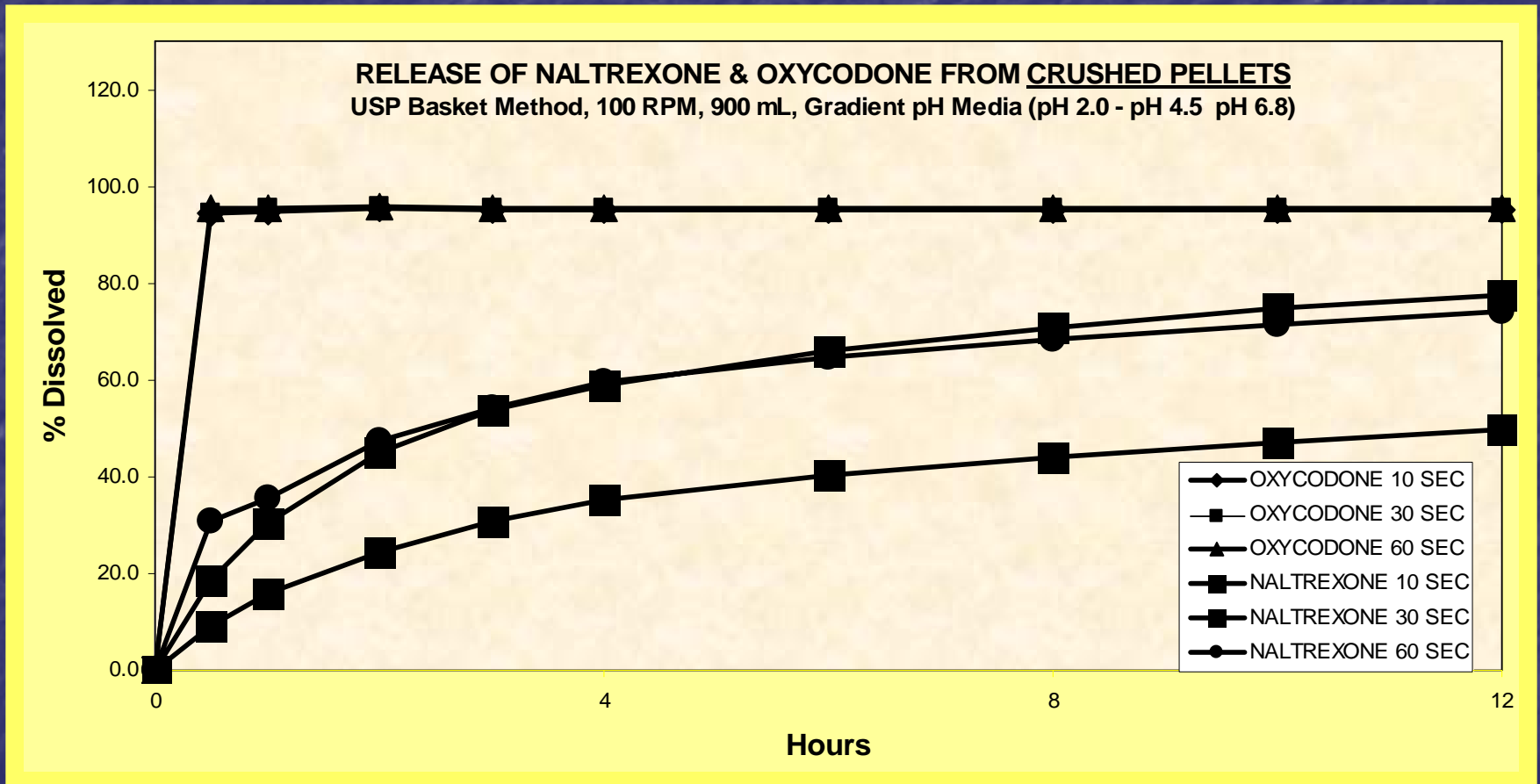
Co-administration of an antagonist with agonist

- With unaltered dosage form, antagonist is not released
- If crushed, antagonist is released and absorbed

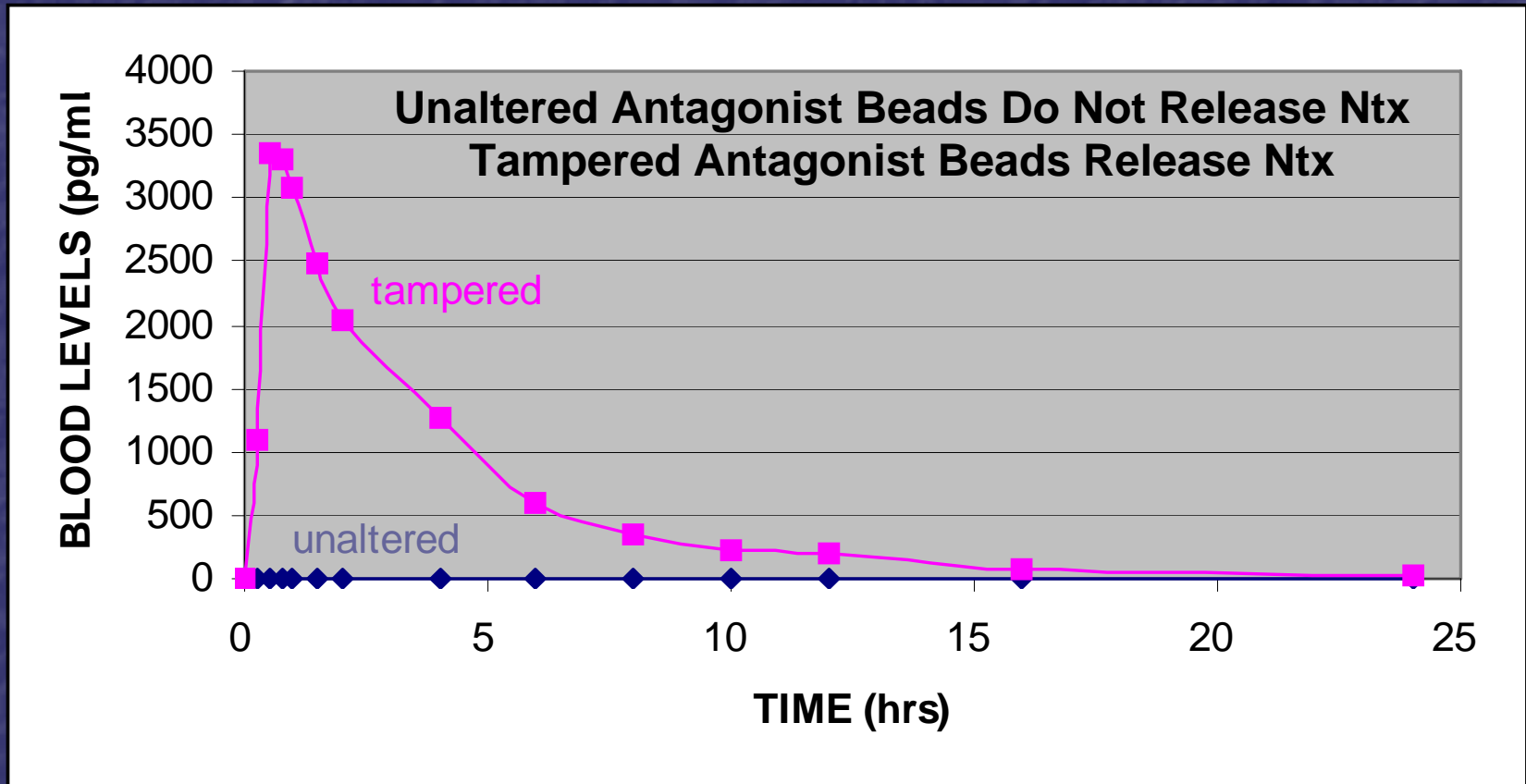
Elite Pharmaceuticals



Elite Pharmaceuticals



Elite Pharmaceuticals



Endo Pharmaceuticals

US20030065002A1	Abuse-resistant controlled-release opioid dosage form	2003-04-03
US20030064122A1	Abuse resistant pharmaceutical composition containing capsaicin	2003-04-03
US20030004177A1	Abuse-resistant opioid dosage form	2003-01-02

Technologies:

- 1. Agonist & Antagonist:** “ ... combination containing an opioid antagonist such as **naloxone** at a level that needed to suppress the euphoric effect of the opioid, if the combination were crushed to break the controlled release properties causing the opioid and opioid antagonist to be released as a immediate release product as a single dose ... ”
- 2. Aversion:** “Aside from the effective pharmaceutical ingredient(s) the composition includes an amount of **capsaicin** which serves as a deterrent to the intranasal, intravenous, or oral abuse of the composition. Such a composition deters abusers from crushing prescription pharmaceutical tablets for abusive snorting, injection, or ingestion.... ”

Ionix Pharmaceuticals

Product Pipeline



IONIX AND RECKITT BENCKISER HEALTHCARE FORM STRATEGIC ALLIANCE TO DEVELOP AND MARKET ANALGESIC PRODUCTS

Cambridge, UK. February 28, 2005: Ionix Pharmaceuticals, a specialist in the discovery and development of analgesic drugs, today announced that it has formed a multi-product strategic alliance with Reckitt Benckiser Healthcare, a subsidiary of the global health and household products company.

Ionix Pharmaceuticals

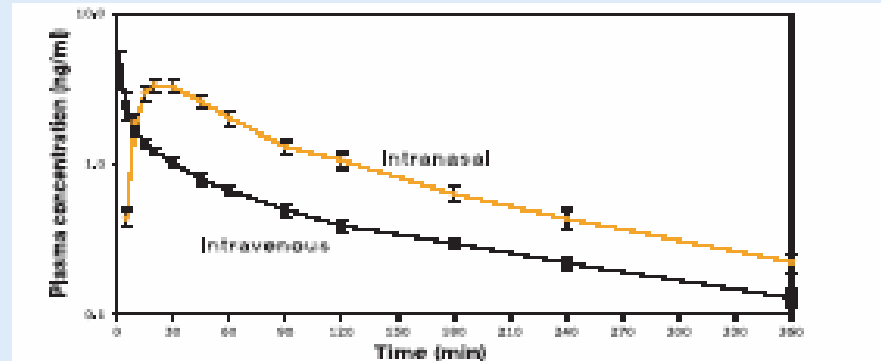


Figure 2: PK Plot for Intranasal Buprenorphine: Pectin

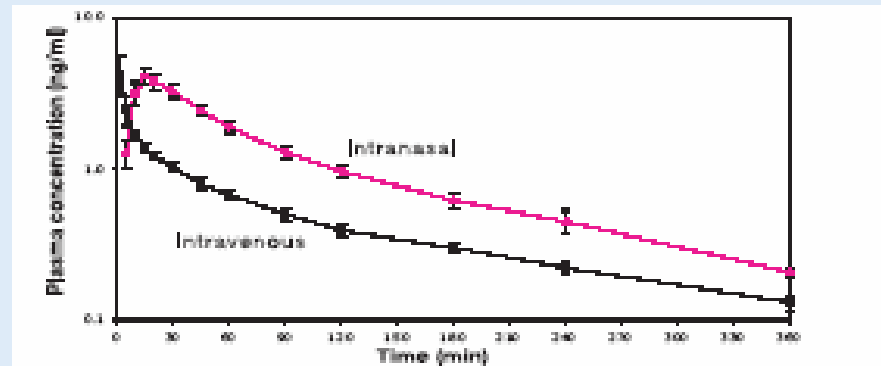
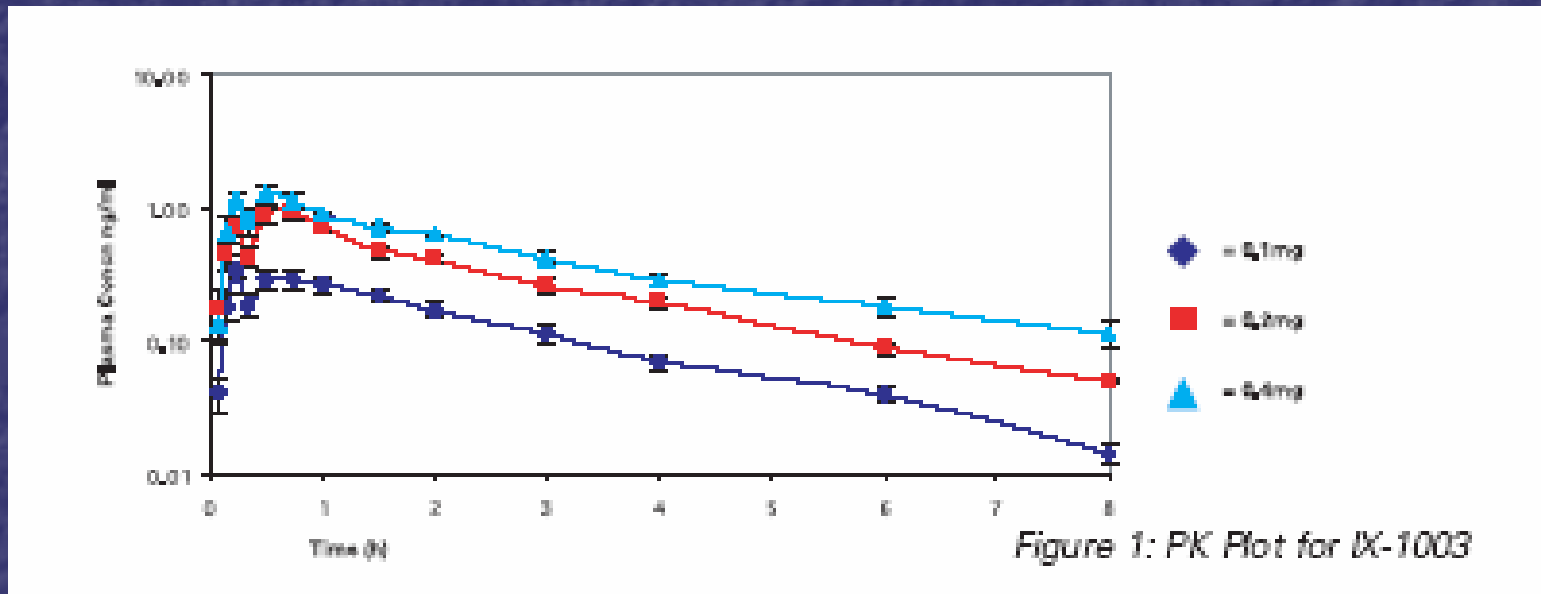


Figure 3: PK Plot for Intranasal Buprenorphine: Chitosan/HPMC

4th Congress of European Federation of IASP Chapters (EFIC), September 2003

Ionix Pharmaceuticals



American Pain Society,
May 2004

New River Pharmaceuticals

We believe our proprietary Carrierwave™ technology can be applied in various ways to improve existing drugs. We refer to our Carrierwave™ compounds as **Conditionally Bioreversible Derivatives (CBDs)**. We create a **new molecule**—a derivative—made of the active pharmaceutical ingredient of a drug such as an amphetamine or opioid, bound to an adjuvant. The bond essentially locks up the active until the bond is broken, or bioreversed, which can only happen under certain conditions.



Our compounds are designed to confer overdose protection by restricting the release of the active pharmaceutical ingredient from the CBD at greater than therapeutically prescribed amounts. Our CBDs are also designed to be less prone to abuse and addiction by limiting the "rush" or "high" available from the active pharmaceutical ingredient released by the CBD and limiting the ability of abusers to obtain greater doses of the active ingredient through alternative routes of administration or extraction techniques. As a result of these characteristics, we believe that our CBDs may be subject to fewer restrictions by the DEA on their manufacture, distribution, prescribing and dispensing.

www.nrpharma.com

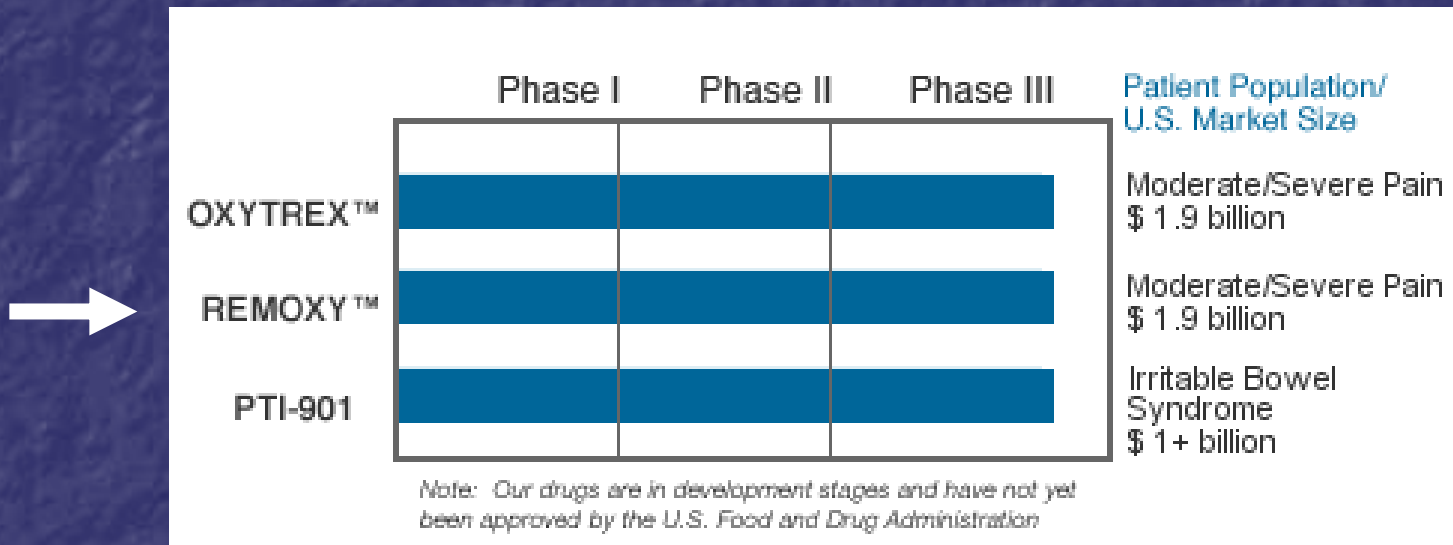
New River Pharmaceuticals



NEW RIVER
PHARMACEUTICALS

- Anticipate filing the Investigational New Drug Application (IND) on NRP290, a conditionally bioreversible derivative of hydrocodone, in 2Q 2005
- Pursuing partnering discussions on NRP369, a conditionally bioreversible derivative of oxycodone
- Anticipate filing the IND on NRP369 by 4Q 2005

Pain Therapeutics / Durect Corporation



Study Results Confirm Remoxy(TM) is Significantly Less Abusable Than Oxycontin(R)

- Goal is to Prevent Drug Abuse, Patient Misuse and Accidental Overdose

SOUTH SAN FRANCISCO, Calif., Dec. 6 /PRNewswire-FirstCall/ -- Pain Therapeutics, Inc. (Nasdaq: PTIE), a biopharmaceutical company, today announced clinical results that demonstrate Remoxy is significantly less abusable than Oxycontin.

Pain Therapeutics / Durect Corporation

Oxycodone using ORADUR™

Market Opportunity: Remoxy™

- Oral, long-acting oxycodone formulated with patented ORADUR™ gel-cap product licensed to Pain Therapeutics, Inc.
- Several abuse-deterrent properties
- Remoxy™'s crushed mass does not fracture
- Remoxy™'s long-acting SABER™ matrix is preserved



Pain Therapeutics / Durect Corporation

Oxycodone using ORADUR™

Anti-Abuse Results: Chew Studies (N = 5)

	Remoxy™	OxyContin®	Difference	p - value ¹
	<u>AUC(hr*ng/ml)</u>	<u>AUC(hr*ng/ml)</u>		
30 Minutes	0.6	1.6	+267%	0.04
60 Minutes	3.1	5.4	+174%	0.02
120 Minutes	10.7	14.7	+137%	0.01

Anti-Abuse Crushing Results (N = 5)

	Remoxy™		OxyContin®	
	<u>AUC(hr*ng/ml)</u>		<u>AUC(hr*ng/ml)</u>	
	<u>Water</u>	<u>Alcohol</u>	<u>Water</u>	<u>Alcohol</u>
60 Minutes	3.2	2.4	12.6	11.4
120 Minutes	8.0	8.4	29.5	26.3

Durect Corporation (used with permission)

Roxane Laboratories

US20030118641A1: Abuse-resistant sustained-release opioid formulation

Assignee: **Roxane Laboratories, Inc.**, Columbus, OH

Published / Filed: 2003-06-26 / 2002-10-03

What is claimed is:

1. A method for reducing the abuse potential of an oral dosage form of an opioid extractable by a solvent selected from the group consisting of: 70% isopropyl alcohol, 100 proof vodka, white vinegar, 88° C. water, 3% hydrogen, 0.01 N HCl, or 50% aqueous ethanol, said method comprising combining a therapeutically effective amount of the opioid compound, or a salt thereof, between 30 and 65% of a matrix-forming polymer and between 5 and 15% ionic exchange resin.

Press releases, Elan, 25 Oct 2001 & aaiPharma, 2 Dec 2003:
aaiPharma acquired Roxicodone from Elan, which had previously acquired it from Roxane Laboratories (Boehringer Ingelheim).

TheraQuest Biosciences

TheraQuest to Present Results on Three Analgesics at the American Pain Society Meeting in Boston

Blue Bell, PA – February 8, 2005 – PRNewswire – TheraQuest Biosciences, a development stage pain management company today announced that it is will be presenting positive results on three acute and chronic pain products (TQ-1011, TQ-1015 and TQ-1016) at the 24th Annual Scientific Meeting of the American Pain Society in Boston, March 30 to April 1, 2005.

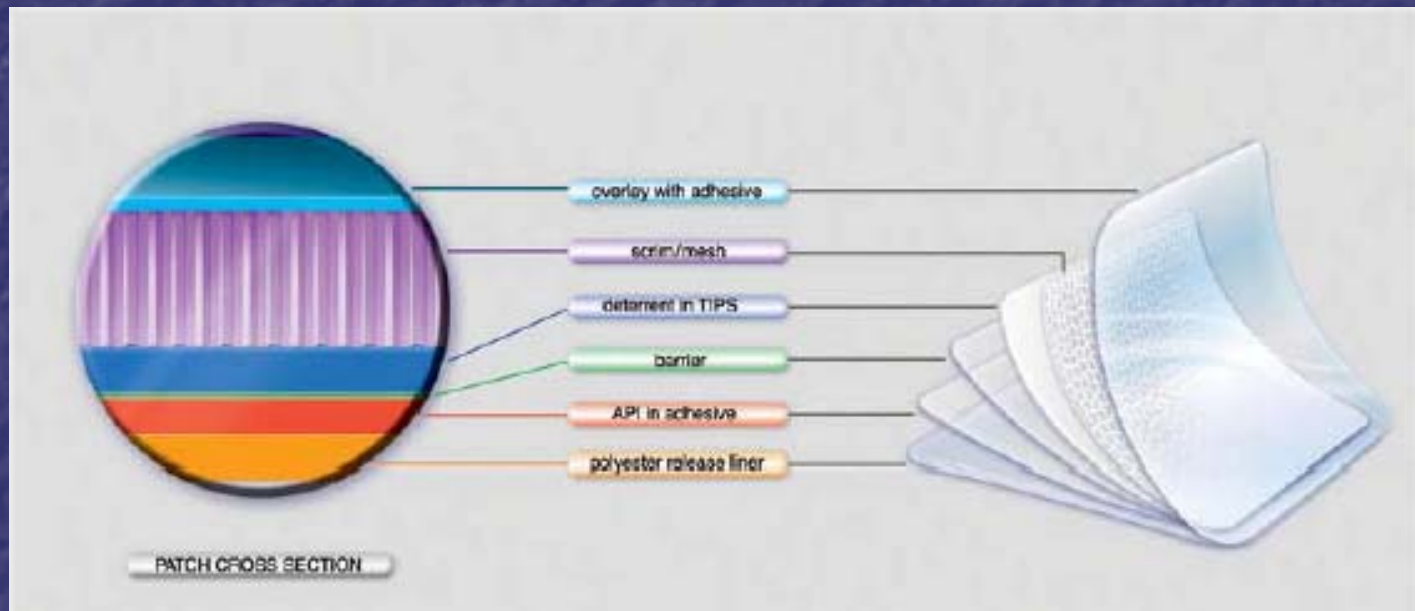
TQ-1015 is a unique once a day sustained release opioid analgesic in a proprietary, abuse deterrent drug delivery system. It cannot be crushed for inhalation or obtaining rapid euphoria. It is also be exceedingly difficult for I.V. abusers to extract the active drug from the formulation using common solvents. TQ-1015 is significantly more potent than current therapies and it has a lower side effect profile than other opioids. The target population includes patients with moderate to severe chronic cancer and non-cancer pain. TQ-1015 will compete in the same market segment as MS Contin®, OxyContin®, Duragesic® and Palladone™. Results from nonclinical studies in mechanical allodynia and thermal hyperalgesia will be presented.

Abuse Deterrent Once-Daily Tramadol: TQ-1017 (orphan drug status)

www.theraquestinc.com

3M Drug Delivery Systems

Approaches to Engineering-Out Abuse Potential in Transdermal Patches



- Multilaminate design: API and deterrent are separated by a barrier
- Deterrent is released if the patch is cut or placed into extraction fluids
- Scrim increases rate of extraction by increasing flow into and out of the patch

3M Drug Delivery Systems

Prototype Comparisons:

Prototype	Mode of Abuse/Potential for Abuse						Potential for Release of Deterrent (Counter-measure)
	Buccal	Bulk Extraction	Surface Extraction	Mechanical Separation	API Removal by Healthcare Worker	Residual API After Use	
	Casual, Accidental	Chronic	Chronic	Chronic	Chronic	Casual, Accidental	
Option A: TIPS w/Scrim	++	+++	-	++	+++	+	--
Option B: TIPS w/Perforations	+++	+++	+++	++	+++	-	---
Option C: Modified TIPS w/Scrim	-	+	-	++	+++	+	++
Adhesive Multilaminate	+	++	-	++	+++	+	+

Purdue Pharma (Euro-Celtique)

ISSUED U.S. PATENTS

US6696088	Tamper-resistant oral opioid agonist formulations	2004-02-24
US6696066	Opioid agonist/antagonist combinations	2004-02-24
US6627635	Method of preventing abuse of opioid dosage forms	2003-09-30
US6326027	Controlled release formulation	2001-12-04
US6228863	Method of preventing abuse of opioid dosage forms	2001-05-08

- Oral and transdermal formulations
- Opioid antagonist used to provide abuse deterrence and tamper resistance

Questions to Ponder: *How* to reduce abuse liability using formulation technology

1. Abuse by crushing tablets / capsules; injection usage
 - Prevent extraction of active opioid ingredients?
 - Mask agonist effects; prevent overdose?
 - Initiate withdrawal in opioid dependent subjects?
2. Pharmacokinetics
 - Avoid initial hedonic rush?
3. Post-marketing surveillance
 - Reduced ER / ME reports?
 - Reduced diversion / street value?
 - Reduced misuse by medical personnel?

Questions to Ponder: *How* to reduce abuse liability using formulation technology

4. What's required for "reduced abuse liability" label claim?
 - Bioequivalence to existing product?
 - Short-term evaluation of therapeutic efficacy?
 - Long-term studies in susceptible populations?
5. What are the standards for:
 - Tampering, extraction, product failure rate?
6. Will abuse-resistant products receive lower DEA scheduling?
7. When the first product is approved:
 - Will all other products in class be required to show similar reduced abuse liability OR be removed?