NDA 22-324

REMOXY XRT™
(oxycodone controlled-release) Capsules CII

Advisory Committee Briefing Materials for the Anesthetic Life Support Drugs Advisory Committee Meeting of November 13, 2008

AVAILABLE FOR PUBLIC RELEASE WITHOUT REDACTION

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Attachment 1 Summary of Risk Evaluation Mitigation Strategy

1. INTRODUCTION

1.1. Background

The analgesic action of extracts of the opium poppy plant has been known for millennia. In more recent decades, semi-synthetic opium derivatives, such as oxycodone, have become a standard of care for treating moderate-to-severe pain.

It is also well-known that medicinal opioids such as oxycodone can produce both analgesia and euphoria. The search for euphoric effects can lead to drug-seeking behavior, tolerance and dependence. In particular, rapid increases in plasma levels of oxycodone ('dose-dumping') may lead to overdose, respiratory depression or death.

In recent years, opioid misuse and abuse have become public health problems. A survey in 2006, estimated that 5.2 million persons aged 12 or older had used pain relievers non-medically in the previous month.[1] In 2007, one out of every 20 high school seniors had tried oxycodone in the past year.[2] In 2007, 3.3% of adolescents age 12 to 17 engaged in non-medical use of prescription-type psychotherapeutics.[2] Data from the 2005 Drug Abuse Warning Network (DAWN), the most recent publicly available source, reported 196,225 emergency department visits due to non-medical use of opiates/opioids.[3] Additionally, admission to substance abuse treatment services for primary abuse of opiates has increased from one percent of all admissions in 1996 to four percent in 2006.[4]

The legitimate expansion of the use of time-release oxycodone tablets (OxyContin®) highlights the recent rise in prescription drug abuse. The active drug ingredient in OxyContin is oxycodone (hydrochloride), a U.S. Food and Drug Administration (FDA) approved substance for the relief of moderate to severe pain. Oxycodone, a generic drug in clinical use since the 1930's, is generally considered safe/effective when properly prescribed, dispensed and administered for legitimate medical purposes.

In recent years, however, the *U.S Drug Enforcement Administration* (*DEA*) reports that OxyContin abuse has substantially increased:

> "The introduction in 1996 of OxyContin®, commonly known on the street as OC, OX, Oxy, Oxycotton, Hillbilly heroin, and kicker, led to a marked escalation of its abuse as reported by drug abuse treatment centers, law enforcement personnel, and health care professionals. Although the diversion and abuse of OxyContin® appeared initially in the eastern US, it has now spread to the western US including Alaska and Hawaii. Oxycodone-related adverse health effects increased markedly in recent years." *(Source: www.usdoj.gov/dea)*

Abusers can quickly and easily extract large amounts of oxycodone by simply breaking or crushing OxyContin tablets. Doing so disrupts OxyContin's time release mechanism and allows an abuser to immediately ingest, snort or inject a large dose of oxycodone that was originally

intended to be slowly release over 12 hours. Rapid increases in plasma levels of oxycodone ('dose-dumping') may lead to overdose, respiratory depression or death. The inherent vulnerability of the OxyContin formulation may also lead to accidental overdose by patients who mistakenly cut or crush the tablets.

In order to confront prescription drug abuse, while ensuring that legitimate patients in chronic pain are not penalized, we have developed a novel formulation of twice-daily oxycodone.

1.2. REMOXY XRT™ (Extraction Resistant Technology)

REMOXY XRT™ (hereafter referred to as REMOXY® or PTI-821) is a novel controlled-release oral capsule form of oxycodone in a highly viscous liquid formulation matrix that includes novel excipients. It is specifically formulated to help address issues of abuse and misuse of controlled-release oxycodone.

The REMOXY formulation is designed to resist common methods of chemical or physical challenges but remains a Schedule II substance of the federal Controlled Substances Act of 1970. Approval is being requested for 5 mg, 10 mg, 20 mg, 30 mg and 40 mg dosage strengths for the indication of moderate to severe chronic pain.

Remoxy's capsule dosage form provides therapeutic drug levels of oxycodone on a twice-daily dosing schedule, while resisting 'dose-dumping' effects under common methods of abuse and misuse. Its formulation also resists delivery by unapproved routes of administration, such as injection, snorting or inhalation.

The development program for REMOXY was conducted by Pain Therapeutics, Inc., the Sponsor of the NDA. Upon FDA approval, King Pharmaceuticals, Inc. will have sole responsibility for the commercialization and marketing of REMOXY in the United States and will assume ownership of the NDA.

1.3. Nonclinical Testing Program

The nonclinical testing program for REMOXY was designed to: i) examine the safety profile of oxycodone as formulated in a novel excipient matrix and ii) affirm the safety of novel excipients. The nonclinical program was designed and conducted in accordance with issued FDA guidelines and discussions with FDA. The program included genotoxicity and reproductive toxicity testing and studies in multiple animal species under acute, sub-chronic and chronic dosing conditions.

The nonclinical testing program affirmed the safety of individual excipients in REMOXY as well as the safety of the complete final formulation.

1.4. Clinical Testing Program

REMOXY has been studied in an extensive clinical development program that includes pharmacology studies as well as efficacy and long-term safety studies.

The efficacy of REMOXY has been demonstrated in a multi-center, randomized, placebo-controlled, double-blind study, as agreed with FDA in a Special Protocol Assessment (SPA). In this study, REMOXY demonstrated superior analgesic efficacy when compared to placebo as

measured by AUC for the change in Pain Intensity scores from pre-randomization to end of the 12-week double-blind treatment period (p= 0.007). The long-term clinical safety of REMOXY has been demonstrated in more than 400 patients treated for 6 months and more than 300 patients treated for one year. The overall clinical safety database for REMOXY includes 1,822 unique individuals exposed to the REMOXY final formulation.

A comprehensive Phase I pharmacokinetic program was also completed for REMOXY and included, among other tests, assessment under fed and fasting conditions, assessment at steady-state, confirmation of dose proportionality between dosage strengths, and assessments in both subjects with renal impairment and subjects with hepatic impairment.

1.5. Abuse Resistance Testing

The ability of the REMOXY formulation to resist common methods of abuse has been evaluated in *in vitro* and *in vivo* studies.

Seven *in vitro* studies were performed to evaluate the ability of the REMOXY formulation to resist different challenges, including extraction in beverages and common household liquids, extraction in aqueous buffers, freezing and grinding/crushing followed by solvent extraction, extraction in vegetable oil, extraction following extreme temperatures, injectability and inhalation or smoking. These challenge tests were intended to mimic common oral, injection, snorting or inhalation (smoking) methods of abuse. Results provide *in vitro* evidence for the abuse resistance properties of the REMOXY formulation.

Four *in vivo* abuse resistance studies were conducted to assess REMOXY co-administered with varying strengths of ethanol; when held in the buccal cavity and swallowed; when physically disrupted and administered with 40% ethanol; and when rigorously chewed and then swallowed.

There were no significant effects on the rate or extent of absorption of oxycodone after administration of REMOXY with 4% or 20% ethanol and a minor increase in peak plasma concentration with 40% ethanol. Results from studies investigating chewing, buccal dissolution and physical disruption followed by administration with 40% ethanol resulted in an increase in the rate of oxycodone absorption, but this increase is not associated with defeat of Remoxy's controlled-release characteristics or dose dumping of oxycodone. Various forms of manipulation did not result in immediate peaks in oxycodone plasma concentration, as might be desired by abusers or as might prove dangerous in cases of accidental misuse. These data support the ability of REMOXY to resist rapid extraction or dose-dumping of oxycodone under common methods of formulation abuse.

2. NONCLINICAL DEVELOPMENT

2.1. Background

REMOXY is a novel controlled-release oral capsule form of oxycodone in a highly viscous liquid formulation matrix that includes several novel excipients, one of which is sucrose acetate isobutyrate (SAIB). SAIB has undergone extensive preclinical safety testing for qualification as a food additive; therefore no additional testing was required. Oxycodone is an approved drug product with a safety and efficacy profile that is clinically established and supported by appropriate nonclinical studies. Therefore the focus of the nonclinical program for REMOXY was to: 1) examine the safety profile of oxycodone as formulated in the excipient matrix and 2) affirm the safety of the novel excipients which had not been previously qualified for use in oral pharmaceutical products. A summary of the PTI sponsored nonclinical safety studies is provided in Table 1.

Table 1. Listing of the PTI-Sponsored Nonclinical Testing Program for REMOXY

PTI-Sponsored Toxicity Studies	Novel Excipients	Complete Formulation
Acute:		
Rat	√	–
Dog	√	–
Subchronic:		
Rat (4-week)	√	–
Dog (4-week and 13-week)	√	–
Minipig (13-week)	√	√
Chronic:		
Rat (26-week)	√	–
Dog (39-week)	√	–
Genotoxicity:		
Bacterial Reverse Mutation Assay	–	–
Chromosomal Aberration Assay	√	–
Mouse Micronucleus Assay	√	–
Reproduction/Developmental:		
Fertility/Reproduction		
Rat	√	–
Embryo/Fetal		
Rat	√	–
Rabbit	√	–
Mouse	√	–

In summary, the safety of the novel inactive ingredients were affirmed and the safety of the complete REMOXY oral controlled-release liquid matrix formulation was established in the 13-week oral toxicity study in minipigs.

3. CLINICAL DEVELOPMENT

3.1. Biopharmaceutics

A food effect study indicated that administration with food has a significant effect on the rate and extent of absorption of oxycodone. The rate of absorption is slower and the extent of absorption is higher; REMOXY should therefore be taken with food.

The bioavailability of the 40 mg intended commercial formulation of REMOXY under fed conditions was examined in five studies. All of the studies were conducted in healthy volunteers, at the same site, and used a similar design with the exception of some differences in the sampling schedules. The data indicate that mean plasma concentrations of oxycodone were comparable across studies, as were mean values for C_{max}, T_{max}, and $AUC_{(0–inf)}$. Similar comparability was observed for noroxycodone and oxymorphone, the major metabolites of oxycodone. These data demonstrate consistency in the performance of the REMOXY formulation across multiple panels of subjects.

3.2. Clinical Pharmacology

Studies examining the dose proportionality and steady-state pharmacokinetics were conducted with the intended commercial formulation of REMOXY. The 5 mg, 10 mg, 20 mg and 40 mg strengths of the intended commercial formulation were shown to be dose proportional. Additionally, REMOXY was shown to accumulate to steady-state plasma levels within 24 to 48 hours when multiple doses were administered BID.

A single dose study in normal subjects and subjects with mild, moderate, and severe renal impairment demonstrated that decreased renal function leads to an increase in exposure to oxycodone and noroxycodone but no change in exposure to oxymorphone.

A single dose study in normal subjects and subjects with mild and moderate hepatic impairment (based on Child-Pugh scores) demonstrated that decreased hepatic function leads to an increase in exposure to oxycodone in subjects with moderate impairment but no substantial change in exposure to noroxycodone and oxymorphone.

Maximum and overall systemic exposure to oxycodone, noroxycodone, and oxymorphone were significantly greater for females than for males after the administration of REMOXY. Maximum oxycodone plasma concentrations occurred at later times in females than in males. Although there were differences in exposure, males and females had comparable values for elimination half-life.

3.3. Clinical Efficacy

One multi-center, randomized, double-blind, placebo-controlled Phase III study (Study PTI-821-CO) was conducted to establish the efficacy of REMOXY in subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee. The protocol was submitted to the FDA under the SPA process wherein the FDA agreed that the single trial was acceptable to support the efficacy of REMOXY.

The study consisted of four study periods: washout, open-label titration, double-blind treatment, and taper. During the 4- to 10-day washout period, subjects stopped taking all pain medication other than acetaminophen. Subjects used a daily diary to record their overall pain intensity (PI),

which was scored on an 11-point numerical rating scale where 0 was no pain and 10 was worst pain.

If the mean value of the diary PI score over the last two days of the washout period (baseline PI score) was ≥ 5, diary compliance was ≥ 75%, and the subject continued to meet all study entry criteria, subjects entered a two-week open-label titration period. Prior to entry in the open-label titration period, subjects underwent baseline quality of life assessments using the Short Form 12 Question Health Survey (SF-12) and the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. During the open-label period, subjects' doses were titrated from REMOXY 5 mg twice daily (BID) to 20 mg BID over two weeks.

At the conclusion of the open-label period, subjects who were able to tolerate REMOXY 20 mg BID and whose diary compliance was ≥ 75% were enrolled in the 12-week double-blind, placebo-controlled treatment period.

At the start of the 12-week double-blind treatment period, subjects in the REMOXY treatment group continued dosing with REMOXY 20 mg BID. Subjects were then permitted to titrate up or down to analgesic effect for four weeks. The final dose at the end of Week 4 was fixed for the remaining eight weeks of the double-blind treatment period. Subjects in the placebo group were titrated down from their open-label REMOXY dose over the first two weeks of the double-blind treatment period to prevent the emergence of opioid withdrawal symptoms.

Subjects returned to the clinic at the end of each week for the first four weeks and then every two weeks for the remainder of the double-blind fixed-dose treatment period. Subjects were required to record their overall PI score before bedtime each day. Once per week, subjects were prompted to record scores for Quality of Analgesia and Global Assessment of Study Medication.

At the conclusion of the 12-week double-blind treatment period, subjects were gradually tapered off of study medication in a blinded fashion over a period of 0 to 15 days, depending on the final fixed dose and time on study drug, to prevent the emergence of opioid withdrawal symptoms.

3.3.1. Efficacy Results

The primary efficacy variable was area under the curve (AUC) for the change in PI score from pre-randomization to the end of Week 12 during the double-blind treatment period. This represented a statistically significant greater improvement in PI score for the REMOXY group versus the placebo group (p=0.007).

3.3.1.1. Supportive Efficacy Variables

Supportive efficacy variables included average PI scores by week; quality of analgesia by week; global assessment of study medication by week; SF-12 subscale scores; WOMAC subscale and total scores; and AUC for the change in PI score from baseline. All secondary efficacy variables were analyzed for the entire ITT population.

Compared with subjects receiving placebo, those receiving REMOXY had a statistically significant greater improvement in PI score (p=0.024 at week 12 of double-blind) from pre-randomization at each scheduled evaluation during the double-blind treatment period.

Quality of analgesia was rated significantly better with REMOXY than placebo (p=0.004 at week 12 of double-blind) at all weeks after double-blind Week 1. The lack of significant

treatment differences at double-blind Week 1 was expected since the placebo subjects were still receiving REMOXY (15 mg and 10 mg BID) during double-blind Week 1.

REMOXY was rated significantly better than placebo (p=0.007 at week 12 of double-blind) in the global assessment of study medication at all weeks after double-blind Week 1. The lack of significant treatment group differences at double-blind Week 1 was expected since the placebo subjects were still receiving REMOXY (15 mg and 10 mg BID) during Week 1.

For SF-12, the treatment groups had comparable mean scores at pre-randomization for both the Mental Component Summary (MCS) and the Physical Component Summary (PCS). At the end of double-blind Week 12/early termination visit, a statistically significant (p=0.003) greater improvement in PCS scores from pre-randomization was observed for subjects receiving REMOXY compared to subjects receiving placebo.

For the WOMAC osteoarthritis index, the treatment groups had comparable mean scores at pre-randomization for the subscales and total scores. At the end of double-blind Week 12/early termination visit, a statistically significant (p=0.023) greater improvement in the pain subscale from pre-randomization was observed for the REMOXY group compared to the placebo group. No statistically significant treatment group differences were observed for stiffness or physical function subscales, or the WOMAC total score.

3.3.2. Efficacy Conclusions

Study PTI-821-CO met its primary endpoint in proving statistically significant pain relief with REMOXY when compared to placebo, as evidenced by the AUC for change in PI from pre-randomization to the end of the 12-week double-blind treatment period (p = 0.007).

In addition, statistically significant differences in favor of REMOXY were observed for all secondary endpoints related to pain when compared to placebo. Patients receiving REMOXY had significantly greater reductions in PI scores from pre-randomization compared to the placebo group at each week during the double-blind treatment period. REMOXY was also rated significantly better than placebo at all weeks after double-blind Week 1 for both quality of analgesia and global assessment of study medication; at the end of Week 12 the overall p-values were 0.004 and 0.007, respectively.

REMOXY was also associated with superior improvements in quality of life for subjects in the REMOXY group versus the placebo group, as measured by the end of Week 12 change in the SF-12 Health Survey PCS (p = 0.003). Superior improvements were also noted for the end of Week 12 change in the WOMAC Osteoarthritis Index pain subscale (p = 0.023).

3.4. Clinical Safety

One thousand eight hundred eighty-one (1881) subjects were enrolled in the NDA studies and 1871 subjects received at least one dose of REMOXY during the 5 mg to 40 mg clinical development program. There were a total of 1822 unique subject exposures. At the conclusion of the long-term open-label study (PTI-821-CM), a total of 469 subjects had been dosed for six months and 381 subjects had been dosed for 12 months. The maximum total daily dose of REMOXY ranged from 10 mg to 160 mg, with most subjects (n=469) receiving a 40 mg daily dose at the time of data cut-off for the NDA. Over 100 subjects received a maximum total daily dose of 160 mg.

A total of 495 subjects participated in the Phase I studies. Of these, 490 received at least one dose of REMOXY. Four hundred sixty-two (462) (93.3%) subjects completed the studies and 33 (6.7%) subjects withdrew from the studies. Reasons for discontinuation were adverse events (3.2%), subject request (1.8%), and sponsor request (1.6%).

A total of 558 subjects entered the open-label titration period of the blinded, efficacy study and received at least one dose of REMOXY. Of these subjects, 146 (26.2%) withdrew prior to randomization. A total of 412 subjects were randomized into the double-blind treatment period (207 placebo, 205 REMOXY), and all 412 received at least one dose of blinded study medication. Of the 412 subjects who entered the double-blind treatment period, 145 (35.2%) withdrew before its completion (75 placebo, 70 REMOXY).

A total of 828 subjects were enrolled into the long-term, open label study and 823 received at least one dose of REMOXY. Among the 828 enrolled subjects, 380 (45.9%) completed the study per protocol, 5 were never administered study drug; and 443 (53.5%) withdrew from the study. The most common (≥ 5.0% of subjects) reasons for withdrawal were adverse events (20.9%), other reasons (14.1%), protocol violations (10.3%), and subject request unrelated to study (6.4%).

3.4.1. Long-Term Safety Study PTI-821-CM

Study PTI-821-CM was a multi-center, open-label study designed to evaluate the long-term safety of REMOXY during a 12-month period and the long-term efficacy of REMOXY by assessing PI, the quality of analgesia, and the global assessment of study medication. Subjects with moderate to severe chronic low back pain or moderate to severe chronic pain due to osteoarthritis of the hip or knee were administered REMOXY 5 mg to 80 mg BID.

Subjects who met the study entry criteria were enrolled into the study and began dose titration with study medication. Dose titration was permitted during the entire 12-month study period according to the titration schedule and protocol requirements. Subjects returned to the clinic every two weeks for the first two months and then monthly for the remaining 10 months of the study.

Subjects who were opioid-naïve started at a total daily oxycodone dose of 10 mg administered as REMOXY 5 mg BID. Subjects who were already taking a stable dose of opioid medication prior to study enrollment were started on a REMOXY dose that was equivalent to their total daily opioid dose. A subject's dose could have been increased to the next level if the subject was tolerating the study medication, the PI score was >2, and both the Investigator and the subject agreed that the dose should be increased. Even if a subject was experiencing a PI >2, the subject could have chosen not to increase the dose.

If subjects experienced inadequate pain relief between scheduled clinic visits and they had received the current dose for ≥ three days, they could have returned to the clinic for an unscheduled visit to receive new study medication at an increased dose level. Subjects experiencing unacceptable opioid-related adverse events could have returned to the clinic at any time for an unscheduled visit to receive new study medication at a reduced dose level.

At the conclusion of the study (either early termination or completion of the 12-month study period), the Investigator may have chosen to discontinue study medication, taper the subject off study medication, or switch to another opioid. For five days after the last dose of study medication, subjects were contacted by telephone each day to assess adverse events if they had received study medication for ≥ four weeks. Any subject experiencing symptoms of opioid

withdrawal was encouraged to return to the site for treatment. Subjects were required to return for a post-treatment follow-up visit approximately two to three weeks after the last dose of study medication.

Safety was evaluated by adverse events, clinical laboratory evaluations, opioid toxicity assessments, opioid withdrawal monitoring by telephone, vital signs (blood pressure, respiratory rate, heart rate and temperature), physical examination findings, and ECG results (corrected QT (QTc) interval and overall interpretation).

The most commonly reported AEs during the study (occurring in ≥ 5% of subjects) were constipation, diarrhea, nausea, vomiting, fatigue, influenza, upper respiratory tract infection, dizziness, headache, somnolence, anxiety, depression, insomnia, hyperhidrosis, pruritus, and hypertension. Most of these AEs were mild or moderate in severity and are commonly associated with opioid use. Opioid and non-opioid related AEs occurring in ≥ 5% of subjects are shown in Table 2 and Table 3, respectively.

Table 2. Opioid Related Adverse Events in ≥5% of Subjects

Preferred Term	Remoxy (N = 823) n (%)
Number of Subjects reporting any AE	678 (82.4)
Constipation	257 (31.2)
Nausea	228 (27.7)
Somnolence	137 (16.6)
Vomiting	116 (14.1)
Dizziness	89 (10.8)
Pruritus	75 (9.1)

Table 3. Non-opioid Related Adverse Events in ≥5% of Subjects

Preferred Term	Remoxy (N = 823) n (%)
Number of Subjects reporting any AE	678 (82.4)
Headache	110 (13.4)
Insomnia	101 (12.3)
Diarrhea	97 (11.8)
Fatigue	56 (6.8)
Hypertension	54 (6.6)
Depression	51 (6.2)
Hyperhidrosis	48 (5.8)
Influenza	47 (5.7)
Anxiety	45 (5.5)
Upper Respiratory Tract Infection	43 (5.2)

Of the 823 subjects receiving at least one dose of study medication, 173 (21.0%) discontinued study medication because of AEs. Most frequent events (≥1%) leading to discontinuation were those commonly associated with opioid use.

A total of 50 subjects experienced SAEs, including three deaths. All of the deaths were considered by the investigators to be unlikely related to study medication. Five of the SAEs were considered to be possibly or probably related to study medication (constipation, gait disturbance, intestinal obstruction, overdose).

REMOXY administered BID for up to 12 months did not have any clinically meaningful effects on vital signs, laboratory safety tests, physical examinations or QTc interval changes during the study.

When compared to the Interim Safety Report, there were no clinically meaningful differences in the type of AEs reported or the AE rates. Additionally, there were no clinically meaningful differences in vital signs, laboratory tests, physical examinations or EKGs.

Based on these results, long-term treatment with REMOXY at doses ranging from 5 mg BID to 80 mg BID was safe and well-tolerated in subjects with moderate to severe chronic low back pain and subjects with moderate to severe chronic pain due to osteoarthritis of the hip or knee.

3.4.2. Safety Conclusions

In summary, REMOXY is safe and well-tolerated. The majority of treatment-emergent adverse events reported by the 1871 subjects receiving at least one dose of REMOXY are those commonly associated with opioid use. Most were mild or moderate in severity, the overall incidence of adverse events tended to decrease over time and no new events emerged as exposure to REMOXY increased to 12 months.

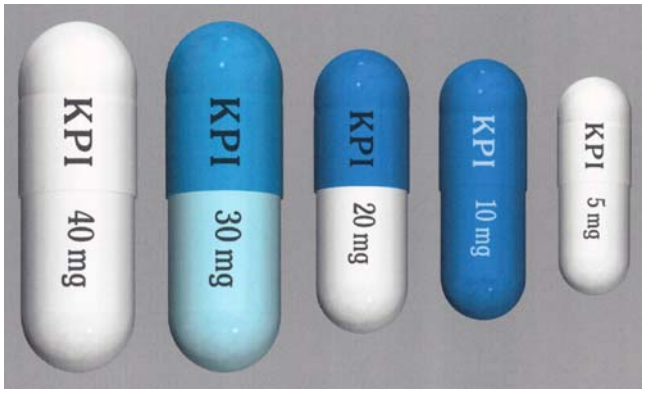
Evaluations of clinical laboratory tests, vital signs, and ECGs revealed no clinically significant results and no trends were noted as REMOXY doses and exposure increased.

4. REMOXY DOSAGE FORM DESIGN

Remoxy is an innovative abuse resistant, controlled-release oral formulation of oxycodone designed to maintain therapeutic levels when a twice-a-day (BID) dosing regimen is followed. Remoxy was developed to resist physical and chemical manipulations that are practiced by drug abusers to defeat the controlled-release mechanism or which alter the formulation to promote delivery by an alternate route of administration such as snorting, injection and smoking. Its novel formulation is a suspension of oxycodone in a high viscosity, hydrophobic fluid matrix.

Five product strengths, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg are planned for REMOXY. A common formulation is used to manufacture all five (5) product strengths which are prepared by adjusting the net weight that is filled into corresponding capsule sizes. The product strengths in the series are differentiated by the size, color and print content on the capsules as illustrated in Figure 1 below.

Figure 1: REMOXY (Oxycodone) Controlled-Release Capsules

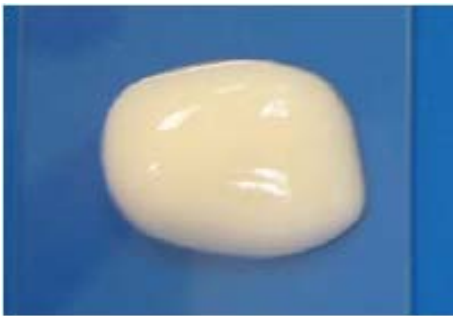


In addition to creating a formulation with abuse resistant features, an objective for REMOXY was to develop a formulation with long acting, consistent pharmacokinetics including minimal peak-to-trough variation in oxycodone plasma concentration at steady state. REMOXY includes a 5 mg strength to facilitate titration in opioid naïve patients.

4.1. Formulation Components

Three novel pharmaceutical excipients are incorporated into REMOXY's formulation in order to achieve the targeted abuse resistance and drug delivery characteristics. The safety of the novel pharmaceutical excipients and REMOXY's formulation has been established in toxicology studies according to current regulatory standards. A photograph of REMOXY's formulation is presented in Figure 2.

Figure 2: REMOXY Formulation (Expressed from the Capsule)



4.2. Abuse Resistance Mechanisms of REMOXY's Formulation.

The routes of abuse of long acting oxycodone formations include oral ingestion, snorting (i.e., nasal insufflation), injection and inhalation. REMOXY's formulation has physical and chemical characteristics that resist each of these modalities. The mechanisms by which abuse resistance is accomplished are discussed below in the context of these four specified routes. The results of *In vitro* tests that were done to assess REMOXY's resistance to an assortment of physical and chemical challenge tests are reported later in this briefing document. Testing was conducted according to instructions that were prespecified in written protocols, and employed reliable quantitative measurement procedures. Comparative *In vitro* testing with OxyContin was included in the studies to provide an additional context for interpretation of the results. Additionally, *in vivo* clinical studies are reported within the briefing document which demonstrate the abuse resistance following physical manipulation of REMOXY. Two of these studies employed methods of manipulation to REMOXY or OxyContin similar to practices employed during *in vitro* testing (i.e., physical disruption of the REMOXY dosage form followed by alcohol extraction, and the influence of mastication of the dosage form prior to ingestion).

4.2.1. Oral Ingestion

REMOXY's controlled-release matrix is not defeated by mechanical forces associated with crushing, chewing or grinding. In contrast, OxyContin is formulated with brittle materials such as polymers that are formed into tablet matrices or applied as coatings that control the rate of drug release. Crushing an OxyContin tablet destroys the polymeric matrix integrity thereby defeating the controlled-release mechanism. The integrity of controlled-release coatings that are commonly employed in tablet and capsule formulations is similarly defeated by the mechanics of crushing or grinding. REMOXY's formulation is neither polymer based nor crystalline and, as such, does not form a brittle or glass-like structure that is susceptible to defeat by crushing. Additionally, even at extreme cold temperature REMOXY's formulation can not be forced into a hardened state. Its hydrophobic fluid matrix remains intact to maintain the controlled-release mechanism. While physical manipulations or disruptions of the formulation may increase the rate of oxycodone release from the matrix, the formulation does not immediately release a significant portion of its dose (i.e., dose dumping).

Test procedures that attempt to extract oxycodone from REMOXY are expected to be among those practices that will be performed by drug abusers and were, therefore, employed during *in vitro* abuse resistance testing. Abuse is often associated with either attempting to dissolve or disperse the narcotic product into a drinkable preparation (i.e., alcoholic, and non alcoholic beverages, cold or hot preparations). REMOXY's high viscosity, hydrophobic formulation is immiscible in aqueous or alcoholic solvents independent of pH, and resists oxycodone extraction

by substantially limiting the extent of solvent penetration. A continuous hydrophobic barrier surrounds the suspended drug particles preventing aqueous solvents from reaching the drug solute. Finally, REMOXY's formulation resists extraction in alcohol by establishing a secondary entrapment network within the formulation.

4.2.2. Snorting (Nasal Insufflation)

Snorting oxycodone is considered to be a more advanced or progressive practice which prevails among experienced abusers. Similar to the practice described for oral abuse, a prerequisite for snorting oxycodone is to crush and grind the dosage form which defeats the controlled-release mechanism and creates a fine particle size that can be drawn within the nasal cavity. REMOXY's formulation resists defeat of the controlled-release mechanism or modification of its high viscosity fluid matrix to a snortable form when challenged by an assortment of physical or chemical challenges.

4.2.3. Injection

Injection of oxycodone is also considered to be a more advanced or progressive practice which prevails among experienced abusers. The ease with which the controlled-release mechanism of existing oxycodone products are defeated and the high solubility of oxycodone hydrochloride in aqueous vehicle facilitate abuse by injection. The resistance to extraction of oxycodone from REMOXY's high viscosity, hydrophobic formulation, poses logistical difficulties for injection abuse.

The sticky and high viscosity characteristics of REMOXY's formulation offer resistance to direct injection. Testing was undertaken to demonstrate the practical difficulties of syringe loading and physical barriers to delivering REMOXY's formulation from a syringe. While laboratory tests provide evidence of REMOXY's abuse resistance to direct injection, introduction of its insoluble formulation by venipuncture is expected to pose a serious safety threat. Additionally, subcutaneous or intramuscular injection of REMOXY's formulation would be expected to depot in the tissues without loss of the controlled-release mechanism.

4.2.4. Inhalation

Inhalation abuse, or smoking oxycodone requires thermodynamic conditions that promote volatilization of the drug into an inhalable vapor state. Inhalation or smoking results in a fast onset of action due to rapid absorption from the nasal mucosa and capillaries within the lungs. The risk of infection including immunodeficiency virus that are transmissible by injection has further increased the popularity of smoking among abusers.[5]

The physical characteristics of the oxycodone molecule relative to the thermodynamic characteristics of the formulation components play an important and practical role affecting the attractiveness of a formulation to be smoked. Results from *in vitro* studies designed to assess the extent of oxycodone recoverable from the vapor of heated REMOXY formulation and compared to the oxycodone recoveries from OxyContin are presented later in this briefing document.

REMOXY's formulation includes components present in substantial abundance relative to the oxycodone dose which limit the amount of drug recoverable in the vapor, and contribute to aversive conditions associated with the vapor, as listed below.

- Lower boiling components of REMOXY's formulation each have inhalation hazards associated with their vapors or gases including toxicity to the respiratory tract and in

some cases to the eyes. (Safety information was referenced from Material Safety Data Sheets for the pure ingredients). Heating for a relatively long time is required to drive off a minor portion of the dose.

- REMOXY's formulation decomposes (resulting in carbonization or charring) at temperatures necessary for oxycodone volatilization which decreases liberation of oxycodone vapor.

5. IN VITRO ABUSE RESISTANCE STUDIES

5.1. Introduction

To evaluate and characterize the abuse resistant features of REMOXY's formulation seven studies that mimic common methods of abuse were undertaken at independent laboratories. The seven studies were designed based upon abuse techniques described in a variety of references including reports by governmental agencies, literature sources on drug abuse and addiction, from consult with expert advisors, or from information available from publicly accessible internet sources. Additionally, *in vitro* studies incorporated input received from the FDA during development.

5.1.1. Objectives and Scope

These studies were conducted with REMOXY 40 mg capsules, which represent the highest proposed commercial strength and thus potentially pose the greatest potential for abuse. As explained earlier, a common formulation is used to manufacture all five (5) product strengths from 5 mg to 40 mg by adjusting the net weight that is filled into corresponding capsule sizes.

In vitro testing included solvent extraction with and without physical challenge and attempting to administer REMOXY via injection or inhalation (smoking). Solvent extractions were performed following physical challenges aimed at defeating the controlled-release matrix such as freezing, crushing/grinding or extreme heating. Solvents used in the extractions included high proof alcohol (ethanol), beverages or common household liquids/preparations, aqueous buffers (pH 1-12), and vegetable oil. Abuse resistance results for REMOXY were compared to data from extraction and vaporization studies performed with commercially available 40 mg OxyContin tablets.

Test Articles

In Vitro Extractability and Volatilization (Inhalation Abuse) Studies

Remoxy Controlled-Release Capsules, 40 mg – three lots;
#E06029, #E06038 and #E07020

OxyContin® Tablets, 40 mg
Lot W28A1 – Purdue Pharma L.P. commercial lot

Injectability Study

PTI-821 Matching Placebo Capsules, lot #2004-12-95

PTI-821 Placebo Controlled-Release Mass, lot #5F010

5.1.2. Testing Laboratories

In vitro tests were conducted at independent testing laboratories.

5.2. Extraction in Beverages and Common Household Liquids / Preparations

5.2.1. Study Design

Extraction of oxycodone from REMOXY capsules or OxyContin tablets by each of four commercial beverages or common household liquids/preparations was experimentally determined. The four solvents were chosen based on their ubiquity and were selected to substantially span the acidic and alkaline pH range. In addition to these solvents being readily accessible to potential abusers, they comprise an assortment of non-toxic drinkable liquids that may be used to facilitate abuse. Samples of REMOXY or OxyContin were prepared for introduction into each solvent by exuding the formulation from the capsules or crushing and grinding the tablets. Closed jars containing REMOXY or OxyContin samples in solvent were agitated for 60 minutes, with interruptions to withdraw samples at 5 minutes, 20 minutes, and at the conclusion of the test (60 minutes).

5.2.2. Results

Extraction results for REMOXY capsules or OxyContin tablets are presented below in Table 4 and Figure 3. Post-extraction photographs are shown in Figure 4 through Figure 8.

REMOXY resisted extraction of oxycodone in all test solvents over the course of 60 minutes with agitation. After five minutes, 1% or less of oxycodone was extracted from the REMOXY formulation in Solvents #1, #3 and #4, as compared to 90% or greater extracted from OxyContin Solvents #1 and #2 and approximately 75% extracted from OxyContin in Solvent #4. The greatest mean extraction (6%, or 2.4 mg) of oxycodone from REMOXY test articles at the 5 minute time point occurred in Solvent #2. In comparison, extraction from OxyContin in Solvent #2 was ten fold higher (60%, or 24 mg). The extraction of oxycodone from REMOXY slightly increased in all liquids over 60 minutes. In comparison, extraction from OxyContin mostly occurred within 5 minutes and remained fairly constant for the remainder of the test, which strongly suggests dose dumping. The highest mean amount of oxycodone extracted from REMOXY (15%, or 6 mg) occurred after 60 minutes of shaking in solvent #3.

REMOXY possesses a hydrophobic, high viscosity liquid matrix that does not erode or disintegrate. This matrix remained intact and resisted rapid extraction or dose dumping under the aggressive conditions of the test. Representative photographs of each dosage form after extraction show that the REMOXY matrix remained intact, whereas crushing of an OxyContin tablet completely destroyed the integrity of its controlled-release brittle polymer matrix and allowed rapid and nearly quantitative extraction of its dose by most aqueous solvents.

These data demonstrate the abuse resistant properties of REMOXY when extracted in several commonly available beverages and household liquids/preparations spanning a wide pH range (pH 2.4 – pH 10.1). Comparison of these data for REMOXY and OxyContin provides evidence of the potential safety advantage of REMOXY at preventing the rapid release of its dose of oxycodone when crushed/ground and extracted.

Table 4 Oxycodone Extracted in Beverages and Common Household Liquids

Solvent	Test Article, Samples Tested		Mean Percent of Oxycodone Dose Extracted (SD)		
			Extraction Time (min)		
			5	20	60
#1	REMOXY	n = 9	1 (0.6)	3 (1.3)	10 (1.4)
	OxyContin	n = 3	91 (4.4)	92 (5.3)	92 (5.5)
#2	REMOXY	n = 9	6 (2.6)	11 (3.2)	15 (3.3)
	OxyContin	n = 3	60 (11.1)	62 (10.3)	62 (9.0)
#3	REMOXY,	n = 9	0 (0.2)	2 (0.6)	10 (1.3)
	OxyContin	n = 3	90 (3.0)	92 (2.5)	92 (2.5)
#4	REMOXY	n = 9	1 (0.5)	2 (0.6)	3 (1.1)
	OxyContin	n = 3	74 (10.7)	78 (5.2)	77 (5.5)

Figure 3 Oxycodone Extracted (% of dose) in Beverages and Common Household Liquids

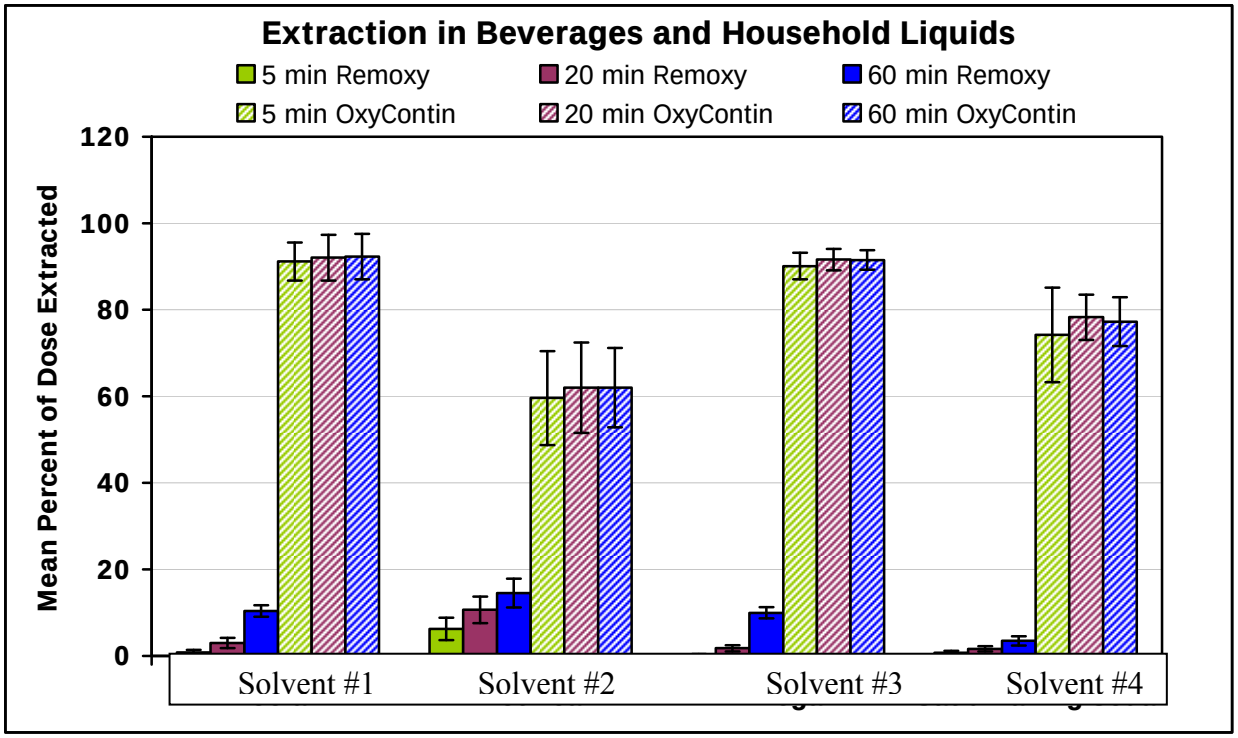


Figure 4 REMOXY Post Extraction in #1

Figure 5 REMOXY Post Extraction in #2

Figure 6 OxyContin Post Extraction in #1

Figure 7 REMOXY Post Extraction in #3

Figure 8 REMOXY Post Extraction in #4

5.3. Extraction in Buffers, pH 1 – pH 12

5.3.1. Study Design

Extraction of oxycodone from REMOXY capsules or OxyContin tablets by each of six aqueous buffers over a range of pH 1 – pH 12 was experimentally determined for three dosage forms from each lot (total of 9 samples). Samples of REMOXY or OxyContin were prepared for introduction into each solvent by exuding the formulation from the capsules or crushing and grinding the tablets. Closed jars containing REMOXY or OxyContin samples were shaken for 60 minutes, with shaking interrupted to withdraw samples at 5 minutes, 20 minutes, and at the conclusion of the test (60 minutes).

Solvent samples taken at each of the extraction times were centrifuged and assayed for oxycodone content by HPLC. Post-extraction photographs of all formulations were taken to provide visual reference of the impact of extraction on each sample.

5.3.2. Results

Extraction results for REMOXY capsules or OxyContin tablets are presented below in Table 5 and Figure 9. Post-extraction photographs are shown in Figure 10 and Figure 11.

REMOXY test articles were seen to resist extraction of oxycodone in all buffers over the course of 60 minutes with agitation. After five minutes, 1% or less of oxycodone was extracted from REMOXY in all solutions as compared to 64% or greater extracted from OxyContin. The greatest mean oxycodone extraction from REMOXY test articles was 12% (4.8 mg) in solvent #1 after 60 minutes as compared to 89% mean oxycodone extraction (35.6 mg) from OxyContin. Extraction of oxycodone from REMOXY in all buffers increased slightly with time; in contrast, virtually complete dose dumping of oxycodone from OxyContin occurred within the first 5 minutes (i.e. 64%-89% or 25.6 mg-35.6 mg, respectively) and remained fairly constant for the remainder of the test. Representative photographs show that the REMOXY matrix did not significantly erode or disintegrate regardless of buffer pH. The ability of the REMOXY formulation to prevent rapid extraction or dose dumping over a wide range of pH values was successfully demonstrated through this extraction study.

Table 5 Oxycodone Extracted in Aqueous Buffers, pH 1 – 12

Solvent Buffer pH	Test Article, Samples Tested		Mean Percent of Oxycodone Dose Extracted (SD)		
			Extraction Time (min)		
			5	20	60
#1	REMOXY	n = 9	1 (0.4)	4 (0.9)	12 (2.0)
	OxyContin	n = 3	83 (4.9)	88 (5.5)	89 (5.7)
#2	REMOXY	n = 9	1 (0.5)	3 (0.7)	7 (1.3)
	OxyContin	n = 3	86 (2.3)	91 (2.6)	92 (2.6)
#3	REMOXY	n = 9	1 (0.6)	3 (1.0)	7 (2.4)
	OxyContin	n = 3	79 (1.0)	89 (3.5)	90 (4.2)
#4	REMOXY	n = 9	1 (0.5)	2 (0.6)	5 (1.2)
	OxyContin	n = 3	89 (2.6)	90 (1.2)	91 (1.5)
#5	REMOXY	n = 9	0 (0.5)	2 (0.5)	4 (0.8)
	OxyContin	n = 3	82 (1.5)	88 (0.6)	88 (0.6)
#6	REMOXY	n = 9	0 (0.3)	1 (0.2)	3 (0.4)
	OxyContin	n = 3	64 (7.0)	69 (4.0)	72 (3.1)

Figure 9 Mean Oxycodone Extracted (% of dose) in Aqueous Buffers

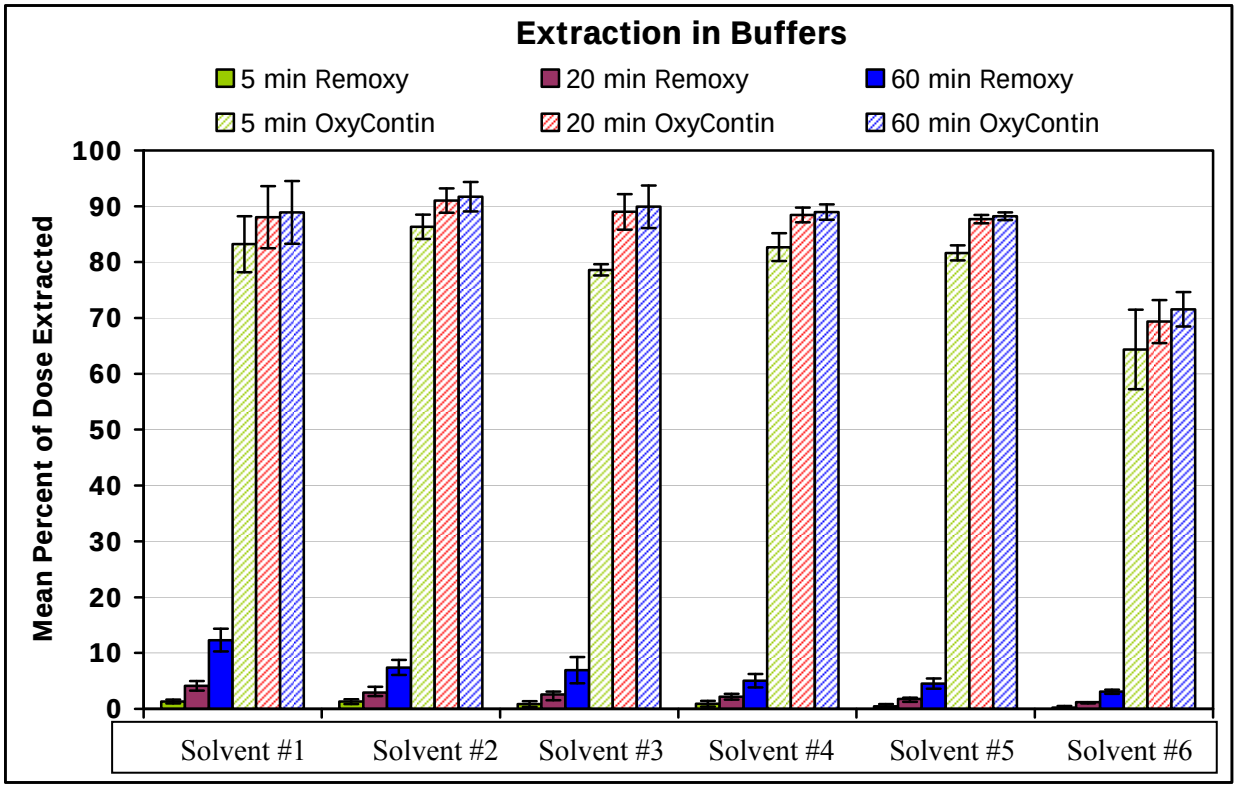


Figure 10 REMOXY Post Extraction in #1

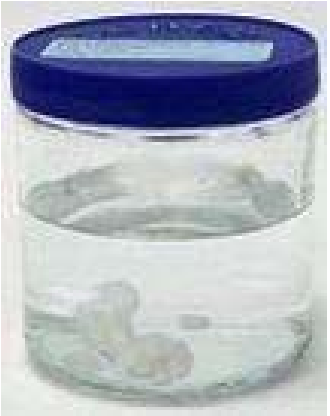


Figure 11 OxyContin Post Extraction in #1

5.4. Physical and Mechanical Stress Followed by Extraction

5.4.1. Study Design

Extraction of oxycodone from REMOXY capsules or OxyContin tablets following physical disruption was experimentally determined. REMOXY capsules were chilled at an extreme cold temperature to promote any tendency for freezing or brittleness of the formulation. Each chilled capsule was then crushed and ground. Each OxyContin tablet was also crushed and ground. Three solvents, including high proof ethanol, were employed for extraction.

Physically disrupted samples of REMOXY capsules or OxyContin tablets were placed into a wide mouth jar containing solvent. Closed jars containing disrupted REMOXY or OxyContin samples were agitated for 60 minutes, with interruptions to withdraw samples at 5 minutes, 20 minutes, and at the conclusion of the test (60 minutes).

Solvent samples taken at each extraction time were assayed for oxycodone content assay by HPLC. Photographs of frozen intact and disrupted REMOXY capsules, as well as post extraction photographs of REMOXY and OxyContin formulations, were taken to provide visual reference of the impact of extraction on each sample.

5.4.2. Results

Extraction results for each lot of REMOXY capsules or OxyContin tablets are presented below in Table 6 and Figure 12 and Figure 13. Post-extraction photographs are shown in Figure 14 through Figure 18.

The REMOXY formulation is a high viscosity liquid which maintains its fluid characteristics even at very low temperatures employed in this study. Figure 14 contrasts a frozen REMOXY capsule with Figure 16, which shows the capsule and formulation after crushing. The gelatin capsule shell fractures as a result of crushing and grinding, but the REMOXY formulation remains a high viscosity liquid which adheres to the film. The formulation is thus not susceptible to techniques that may be used to crush or grind conventional controlled-release solid dosage forms.

Extraction results shown in Table 6 demonstrate that the REMOXY controlled-release matrix resisted rapid release of oxycodone even after chilling, crushing, grinding, and exposure to extraction liquid. The amount of oxycodone extracted after 60 minutes ranged from 18% in solvent #1 to 35% in solvent #4. Cumulative extraction was seen to gradually increase with time in all liquids, with no evidence of rapid release or dose dumping. These data strongly suggest that the REMOXY controlled-release matrix resisted extraction of oxycodone even after aggressive physical disruption. Furthermore, the sticky liquid mass was difficult to handle and was not altered into a physical form that facilitated snorting.

The OxyContin tablet consists of a brittle polymeric controlled-release matrix that is vulnerable to crushing and grinding. Crushing and grinding of OxyContin in this test clearly resulted in defeat of its solid controlled-release matrix into a fine powder. From 78% to 90% of the oxycodone dose was extracted from OxyContin in each of the extraction liquids after only 5 minutes, with slight increase thereafter. This rapid initial release provided evidence that the controlled-release matrix was destroyed by crushing and grinding prior to extraction.

Table 6 Oxycodone Extracted After Physical and Mechanical Stress

Solvent	Test Article, Samples Tested		Mean Percent of Oxycodone Dose Extracted (SD)		
			Extraction Time (min)		
			5	20	60
#1	REMOXY	n = 9	3 (2.4)	9 (3.3)	18 (5.2)
	OxyContin	n = 3	88 (1.7)	89 (2.6)	89 (2.3)
#2	REMOXY	n = 9	11 (2.3)	22 (4.7)	32 (7.0)
	OxyContin	n = 3	90 (2.0)	92 (3.2)	91 (3.1)
#3	REMOXY	n = 9	10 (5.6)	19 (3.2)	30 (2.9)
	OxyContin	n = 3	88 (4.5)	92 (2.5)	92 (2.5)
#4	REMOXY	n = 9	8 (3.0)	20 (5.2)	35 (4.5)
	OxyContin	n = 3	78 (5.1)	88 (2.1)	93 (0.0)

Figure 12 Mean Oxycodone Extracted (% of dose) After Physical Manipulation

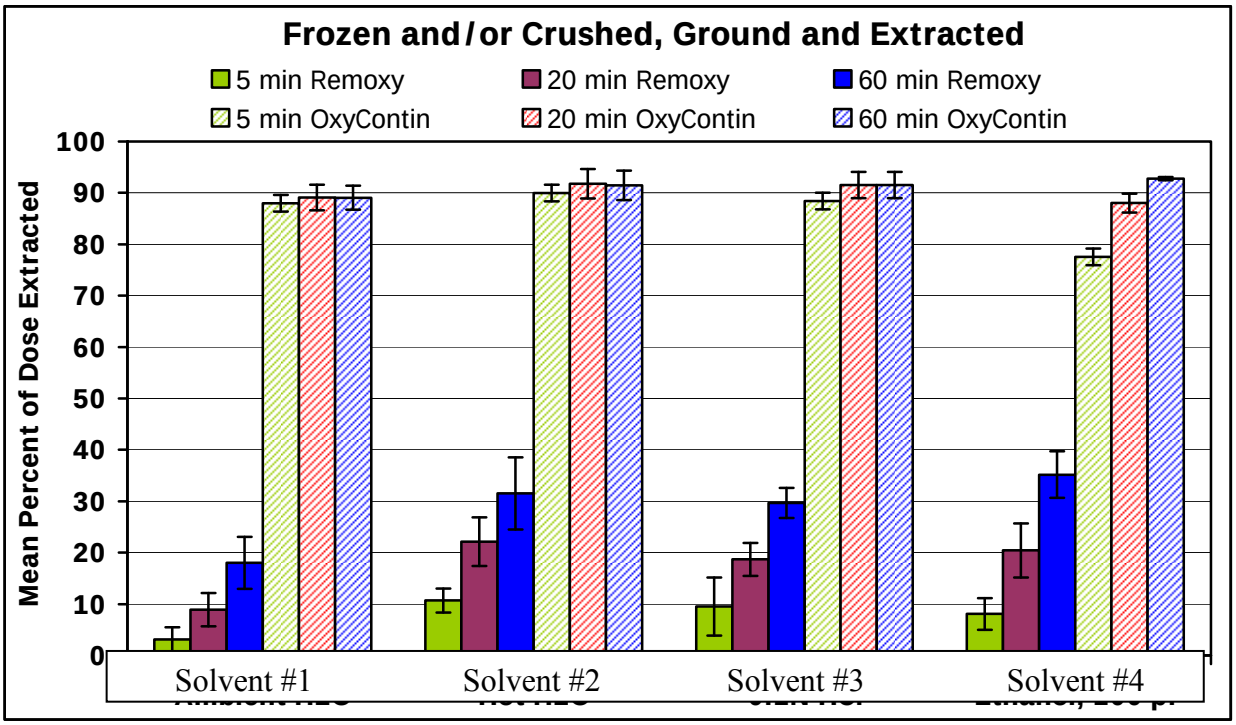


Figure 13 Mean Oxycodone Extracted (% of dose) After Physical Manipulation

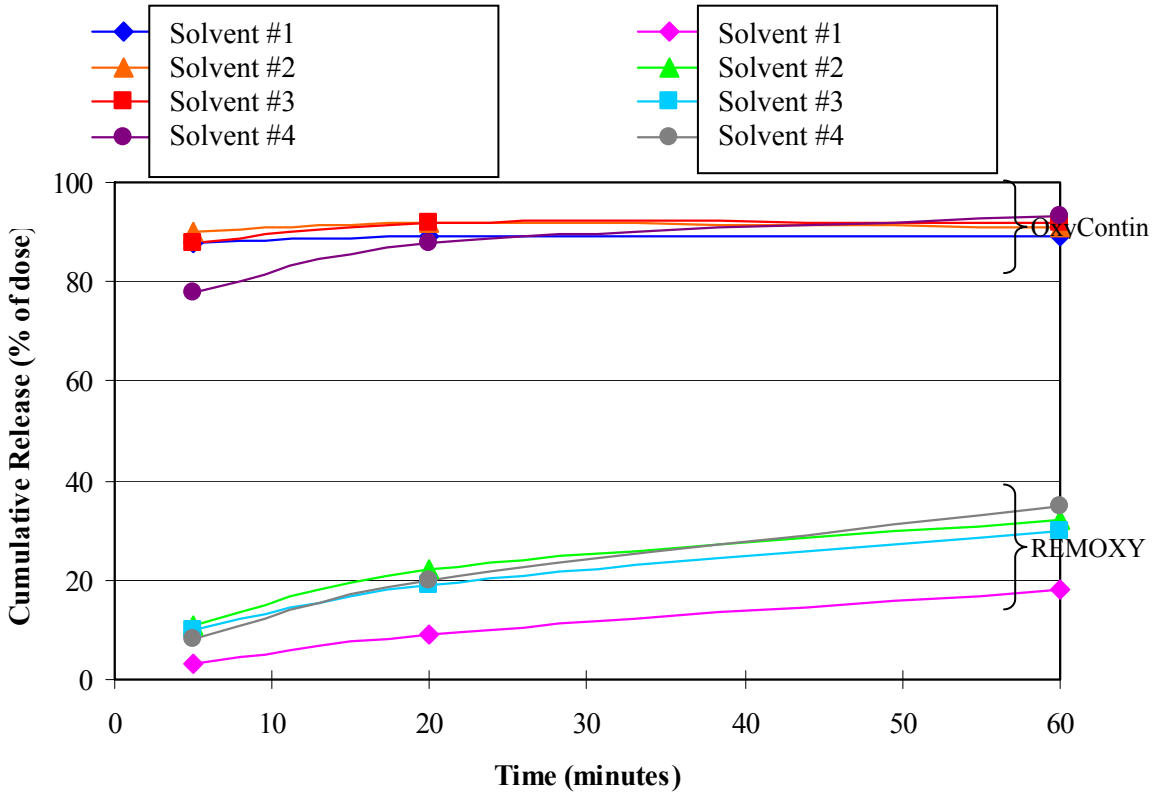


Figure 14 REMOXY After Freezing

Figure 15 REMOXY Crushed/Ground and Post Extraction in Solvent #1

Figure 16 REMOXY Capsule after Crushing

Figure 17 REMOXY Post Extraction

Figure 18 OxyContin Post Extraction in Solvent #1

5.5. Extraction in Vegetable Oil

5.5.1. Study Design

Extraction of oxycodone from REMOXY capsules or OxyContin tablets in vegetable oil was experimentally determined for three dosage forms from each lot. Samples of REMOXY or OxyContin were prepared for introduction into each solvent by exuding the formulation from the capsules or crushing and grinding the tablets. A 10 mL volume of oil was used since routine ingestion of a larger amount would have a laxative effect and was therefore considered impractical. REMOXY or OxyContin samples were agitated for 60 minutes, with interruptions to withdraw samples at 30 minutes and at the conclusion of the test (60 minutes).

Solvent samples taken at each of the extraction times were assayed for oxycodone content by HPLC. Post-extraction photographs of all formulations were taken to provide visual reference of the impact of extraction on each sample.

5.5.2. Results

Results of extraction trials in vegetable oil are summarized in Table 7. Post-extraction photographs REMOXY and OxyContin are shown in Figure 19 and Figure 20, respectively. The integrity of REMOXY's viscous fluid formulation was maintained in vegetable oil, while the crushed and ground OxyContin tablet formed a turbid slurry.

Neither REMOXY nor OxyContin demonstrated significant extraction in vegetable oil. Not more than 1% of oxycodone was extracted from either formulation after 60 minutes. These data suggest that vegetable oil is not a good solvent for oxycodone.

Table 7 Oxycodone Extraction in Vegetable Oil

Solvent	Test Article, Samples Tested		Mean Percent of Oxycodone Dose Extracted (SD)		
			Extraction Time (min)		
			5	20	60
Vegetable Oil	REMOXY	n = 9	0 (0)	0 (0.3)	1 (0.4)
	OxyContin	n = 3	0 (0)	0 (0)	0 (0)

Figure 19 PTI-821 Post Extraction in Vegetable Oil

Figure 20 OxyContin Post Extraction in Vegetable Oil

5.6. Extraction Following Extreme Heating

5.6.1. Study Design

Extraction of oxycodone from REMOXY capsules following extreme heating was experimentally determined. Each capsule was heated and oxycodone extracted from the capsule using test solvents. A volume of test solvent was added to the sample jar containing the heated REMOXY capsule. The closed jar was then agitated for 60 minutes, with interruptions to withdraw samples at 5 minutes, 20 minutes, and at the conclusion of the test (60 minutes).

Solvent samples taken at each of the extraction times were centrifuged and assayed for oxycodone content by HPLC. Post-extraction photographs of the REMOXY formulation were taken to provide visual reference on the impact of extraction on each sample.

5.6.2. Results

Extraction results from heated REMOXY capsules are presented in Table 8 and Figure 21. Post-extraction photographs are shown in Figure 22 and Figure 23. These results show that, after 5 minutes, only 4% (1.6 mg) or less of the oxycodone dose was extracted from the heated REMOXY formulation by any test liquid. After 60 minutes, only 14% - 20% was extracted by any test liquid. These data support the ability of the REMOXY formulation to resist rapid extraction or dose dumping of oxycodone in common liquids following extreme heating.

Table 8 Oxycodone Extraction from REMOXY Following Extreme Heating

Solvent	Test Article, Samples Tested		Mean Percent of Oxycodone Dose Extracted (SD)		
			Extraction Time (min)		
			5	20	60
#1	REMOXY	n = 9	2 (2.2)	7 (3.0)	14 (5.9)
#2	REMOXY	n = 9	4 (4.2)	9 (4.8)	20 (8.3)
#3	REMOXY	n = 9	4 (2.6)	11 (4.6)	20 (6.9)

Figure 21 Oxycodone Extraction Following Heating

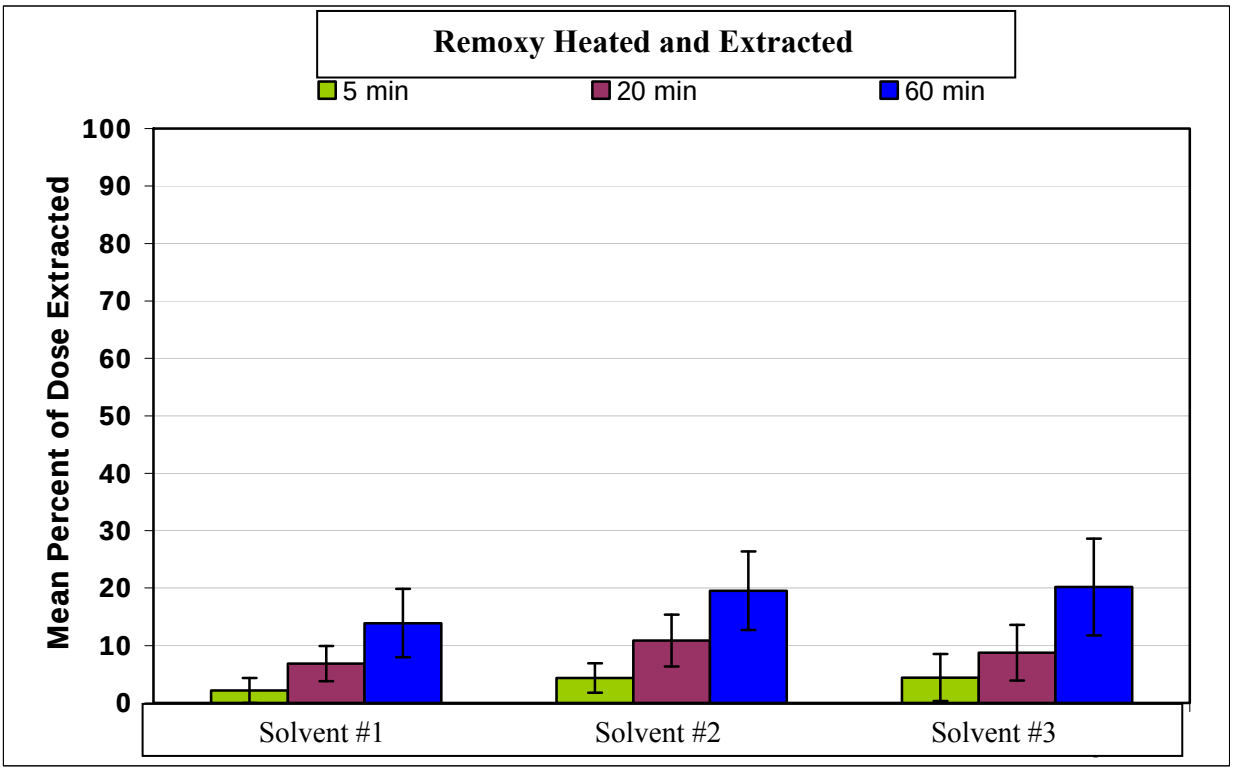


Figure 22 PTI-821 After Heating, Prior to Extraction

Figure 23 PTI-821 Heated Sample, Post Extraction in Solvent #2

5.7. Injection Abuse Resistance Evaluation

This study evaluated the potential for delivery of the REMOXY high viscosity liquid controlled-release matrix by injection. Allahham, et al. define the characteristics of an injectable suspension as syringeability and injectability.[6] Syringeability pertains to the ability of the formulation to be drawn into an empty syringe through a hypodermic needle, while injectability addresses the ability of the suspension to be pushed from a pre-filled syringe through a hypodermic needle. Both characteristics depend on the viscosity and physical characteristics of the formulation.

The high viscosity of the REMOXY formulation should significantly impede both its syringeability and injectability. Studies were thus designed to evaluate the syringeability and injectability of the REMOXY formulation to assess its resistance to abuse by injection.

5.7.1. Study Design

Both syringeability and injectability evaluations were performed using a REMOXY placebo formulation.

Syringeability was assessed in two ways: First, by attempting to draw the formulation through a hypodermic needle; and second, by attempting to load the formulation into the posterior end of a syringe barrel. Both assessments represent practices that may be employed by drug abusers. The mass successfully drawn into or filled into the syringe in each test was quantified and recorded.

Injectability was assessed using pre-loaded Becton Dickinson syringes with needles of various gauges and the plungers depressed by controlled mechanical instrumentation at prescribed speeds.

<u>Failure Modes</u>

The following failure modes were used to assess injectability of REMOXY placebo formulation.

- A Plunger Barrel Failure
- A Force Failure
- A Luer-Lok™ Coupling-Failure

5.7.2. Results

Syringeability (Evaluation of Syringe Loading)

It was not possible to draw the formulation into the syringe using the largest bore needle due to its high viscosity. As a result, evaluations using smaller bore needles were not performed. In attempting to loads the formulation into the posterior end of the syringe barrel, the high viscosity and sticky character of the REMOXY formulation prevented quantitative transfer of the capsule contents into the syringe.

Injectability (Evaluation of Product Delivery from Pre-loaded Syringe)

Table 9 summarizes the results of the injectability study. One or more of the failure modes occurred under all test conditions with three of the four needles. Injectability of REMOXY placebo formulation was only achieved using the largest gauge needle at the slowest speed of

plunger depression. Note that the largest gauge hypodermic needles used in this evaluation are typically used for aspiration biopsy, and are much larger than those on readily available insulin or tuberculin syringes.

Results of both the syringeability and injectability evaluations demonstrate the improbability of load and delivering the REMOXY formulation through common hypodermic needles due to its viscous nature. Based on the results of this study, it is concluded that REMOXY is an unlikely candidate for abuse by injection.

Table 9 Injectability Evaluation of REMOXY Placebo

	Needle #1 Plunger Speed (mm/min)			Needle #2 Plunger Speed (mm/min)		
No.	A	B	C	A	B	C
		Temperature 1			Temperature 1	
1	PASS	FAIL	FAIL	FAIL	FAIL	FAIL
2	PASS	FAIL	FAIL	FAIL	FAIL	FAIL
3	PASS	FAIL	FAIL	FAIL	FAIL	FAIL
		Temperature 2			Temperature 2	
1	PASS	PASS	FAIL	FAIL	FAIL	FAIL
2	PASS	FAIL	FAIL	FAIL	FAIL	FAIL
3	PASS	PASS	FAIL	FAIL	FAIL	FAIL

	Needle #3 Plunger Speed (mm/min)			Needle #4 Plunger Speed (mm/min)		
No.	A	B	C	A	B	C
		Temperature 1			Temperature 1	
1	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL
2	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL
3	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL
		Temperature 2			Temperature 2	
1	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL
2	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL
3	FAIL	FAIL	FAIL	FAIL	FAIL	FAIL

Fail = force failure, plunger barrel failure or Luer-Lok™ coupling failure

Pass = majority of placebo delivered through needle

5.8. Volatilization (Inhalation) Evaluation

5.8.1. Study Design

A volatilization study was conducted to evaluate the potential for abuse of REMOXY by inhalation. A volatilization system was designed to control the temperature applied to the sample. Samples of Remoxy or OxyContin were prepared for introduction to the sample dish by exuding the formulation from the capsules or crushing and grinding the tablets. .

Optimum conditions (heating temperatures and times) that were experimentally determined to maximize volatilization of oxycodone from each dosage form were used in this study. Oxycodone samples recovered from vapor were analyzed using HPLC. Experiments were videotaped, and photographs were taken at the completion of the study.

5.8.2. Results

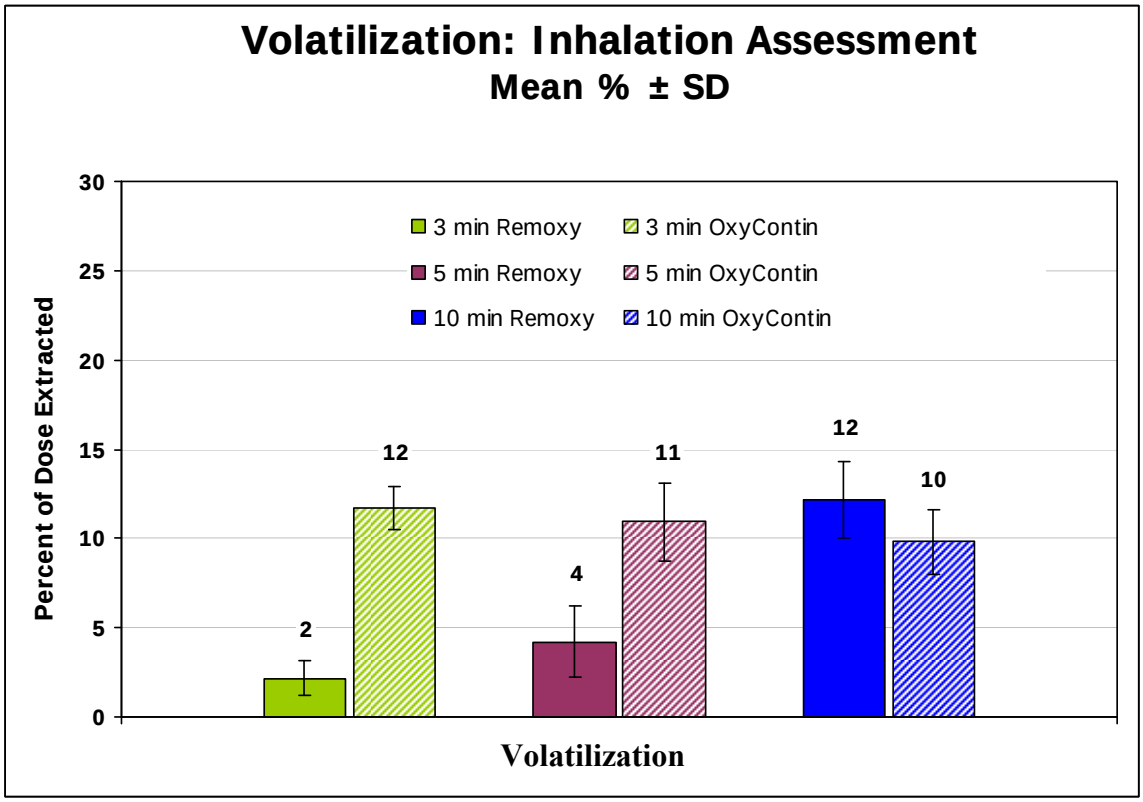
Results of volatilization studies on REMOXY capsules and OxyContin tablets are provided in Table 10 and shown graphically in Figure 24. These data show that the REMOXY formulation limits the vaporization rate of oxycodone at elevated temperatures. Volatilization of OxyContin tablets resulted in 12% of its dose being liberated in 3 minutes while volatilization of REMOXY during the same thermal exposure time resulted in an average oxycodone release of 2% of the dose. Rapid liberation of drug vapor upon heating is known to facilitate abuse by inhalation or smoking. Additionally, vaporization of oxycodone from REMOXY was accompanied by liberation of a greater mass of noxious vapors from its formulation components. An approximately equal amount of oxycodone was volatilized from OxyContin and REMOXY during the 10 minute test.

The slower rate of oxycodone volatilization and the accompanying liberation of noxious vapors offer evidence that Remoxy's formulation does not facilitate abuse by inhalation, and may offer resistance to this mode of abuse.

Table 10 Average Oxycodone Recoveries Following Volatilization

Sample ID	Oxycodone Recovered (% of dose (SD))		
	3 Min	5 Min	10 Min
REMOXY	2 (0.8)	4 (2.1)	12 (2.1)
OxyContin	12 (2)	11 (2)	10 (2)

Figure 24 Volatilization of Oxycodone from REMOXY and OxyContin



5.9. Conclusions

Seven *in vitro* studies were performed to gauge the ability of the REMOXY formulation to resist different abuse practices, including extraction in common beverages and household liquids, extraction in aqueous buffers, freezing and grinding/crushing followed by solvent extraction, extraction in vegetable oil, extraction following extreme temperatures, injectability, and inhalation or smoking. Studies were conducted with three (3) registration lots of REMOXY 40 mg capsules. All studies except for the heating challenge and the injectability evaluation were also conducted with a commercial lot of OxyContin 40 mg tablets as a comparator. Injectability studies were conducted using a REMOXY placebo formulation only.

REMOXY and OxyContin test articles were extracted in beverages and common household liquids over a 60 minute time period. Cumulative extraction, expressed as a percent of the dosage strength, from the REMOXY formulation increased with increasing temperature but did not exceed 15% after 60 minutes in any liquid. Photographic evidence shows that the REMOXY matrix did not significantly erode or disintegrate after 60 minutes extraction in any of the test liquids. The REMOXY formulation thus retarded drug release by extraction. In contrast, oxycodone release from OxyContin was very rapid and substantial, with from 60% to 91% of the dose being extracted after only 5 minutes.

REMOXY and OxyContin test articles were also extracted in aqueous buffer solutions ranging from pH 1 to pH 12. The greatest cumulative amount of oxycodone extracted was 12% after 60 minutes. In contrast, release from OxyContin was again very rapid and substantial, ranging from 64% to 89% of the dose being extracted after only 5 minutes. The REMOXY formulation thus retarded release during extraction, while OxyContin exhibited rapid release or dose dumping.

REMOXY test articles were chilled crushed and ground, and extracted in a variety of solvents, while OxyContin test articles were crushed, ground, and extracted without initial chilling. REMOXY's high viscosity fluid formulation did not harden after storage at low temperature. Thus, the REMOXY formulation cannot be frozen to facilitate crushing and grinding which is associated with abuse by snorting. Traditional controlled-release solid dosage formulations such as OxyContin, however, can be easily crushed and ground at room temperature to potentially facilitate their abuse by snorting. Physical manipulation of the REMOXY formulation prior to extraction increased the cumulative release of oxycodone from 12% after 60 minutes (Study 2) to 30% after 60 minutes. Maximum release of oxycodone from the manipulated REMOXY formulation was 35% after 60 minutes. The REMOXY formulation thus retarded release during extraction. In contrast, crushed and ground OxyContin tablets displayed almost complete release in all liquids after only 5 minutes, ranging from 78% to 90%. The REMOXY formulation was thus seen to resist rapid release or dose dumping even after aggressive physical manipulation. While physical manipulations or disruptions of the REMOXY's formulation may increase the rate of oxycodone release from the matrix, the formulation does not immediately release a significant portion of its dose (i.e., dose dumping). In models of physical manipulation involving crushing and/or grinding, increased rate of oxycodone release is not associated with failure of the controlled-release mechanism.

REMOXY and OxyContin test articles were also extracted in vegetable oil. Both formulations, however, exhibited only 1% oxycodone extracted over a 60 minute time period. The REMOXY controlled-release matrix was observed to remain intact in vegetable oil. Although vegetable oil

is a poor solvent for oxycodone and showed very little extraction into the solution phase, it is likely that oxycodone from OxyContin was present as an immediate release suspension since the same crushing and grinding procedure was shown to defeat its controlled-release matrix during several procedures in this study.

To evaluate the impact of elevated temperature on integrity of the REMOXY controlled-release matrix, test articles were heated prior to extraction. Extraction from heated REMOXY formulations did not exceed 20% after 60 minutes in any liquid. The REMOXY formulation thus retarded release even after being subjected to extreme heating.

The REMOXY placebo formulation was evaluated for its ability to be drawn into or delivered by a syringe. The formulation could not be drawn into the largest size needle used in the test, due to its high viscosity. Also, the viscous property of the formulation significantly impeded its ability to be pushed through needles of different gauges. Injection was only achieved using the largest gauge needle tested under the low and medium injection rates. Results of the injectability study reasonably support that the REMOXY formulation may not be easily administered by injection.

REMOXY and OxyContin test articles were volatilized for 10 minutes with recovery and quantitation of vaporized oxycodone. The amount of vaporized oxycodone recovered from the REMOXY formulation increased from 2% at 3 minutes to 12% at 10 minutes, while the OxyContin quickly liberated 12% of its dose within 3 minutes with little change thereafter (10% after 10 minutes). Based on a review of safety information available for several components of REMOXY's formulation the smoke and vapor produced by heating is expected to be irritating to the respiratory and GI tracts, and eyes.

In conclusion, results of these *in vitro* studies demonstrate the abuse resistant properties of the novel REMOXY controlled-release formulation. The REMOXY formulation successfully resisted dose dumping or rapid extraction when physically manipulated or chemically challenged, and resisted manipulations performed in an attempt to modify the formulation to facilitate alternate routes of delivery such as snorting, injection or inhalation.

6. IN VIVO ABUSE RESISTANCE STUDIES

Human drug-liking studies have demonstrated that reward increases with the rate of rise in drug blood levels; the faster influx of drug into the blood, the better the rush or high.[7; 8] A study to determine which properties of prescription opioids make them more attractive for the purposes of getting high supported the speed of onset as a key factor.[9]

Abusers manipulate controlled-release (CR) opioid formulations to dose dump (rapidly release) the active ingredient and increase the rate of rise to achieve a high. Common methods of CR opioid abuse are chewing, crushing and extracting and then orally ingesting, snorting, or injecting the drug to achieve a high.[10] Inexperienced casual abusers may chew or crush CR opioids and mix these manipulated drugs with alcohol or marijuana.[10] As casual abusers generally have no drug tolerance, dose dumping of the active ingredient poses a significant health risk and may even lead to an accidental and possibly fatal overdose.

A phase I study, conducted in five healthy male volunteers was sponsored by PTI to investigate the extent of dose dumping that occurs after physical manipulation of the currently available extended-release formulation of oxycodone, OxyContin®.

In this study, Protocol 20-041, the lowest OxyContin dose (10 mg) was chosen to optimize safety for the volunteers. Considering the worst case scenario, crushing may fully destroy the controlled-release mechanism and cause it to be quickly absorbed like an immediate release formulation.

This study provided data on the pharmacokinetics of crushed OxyContin (10 mg), simulating a common abuse method, in a controlled and safe clinical setting. The pharmacokinetics of a crushed OxyContin 10 mg tablet with water or alcohol were compared to an OxyContin 10 mg tablet swallowed whole and to a 10 mg dose of an immediate release formulation of oxycodone (2 × 5 mg).

Crushing of OxyContin with water or alcohol significantly increased the rate and extent of absorption of oxycodone (Figure 25). The mean C_{max} increased from 6.82 ng/mL to 21.8 and 21.0 ng/mL for OxyContin crushed with water or alcohol, respectively (Table 10). This C_{max} was very similar to that after the oxycodone IR tablets at 18.9 ng/mL. Similarly, T_{max} decreased from 1.91 hr to 0.90 and 0.95 hr after crushing with water or alcohol, respectively (Table 10). These T_{max} values were shorter than the T_{max} after the IR tablets at 1.35 hr.

Figure 25 Mean (± SEM) Plasma Concentrations Of Oxycodone (0-3 hours) After Oral Administration of Single 10 mg Doses of OxyContin Swallowed Whole, Crushed With Water, Or Crushed With Alcohol, And A Single 2 × 5 mg Dose Of An Oxycodone IR Tablet Swallowed Whole

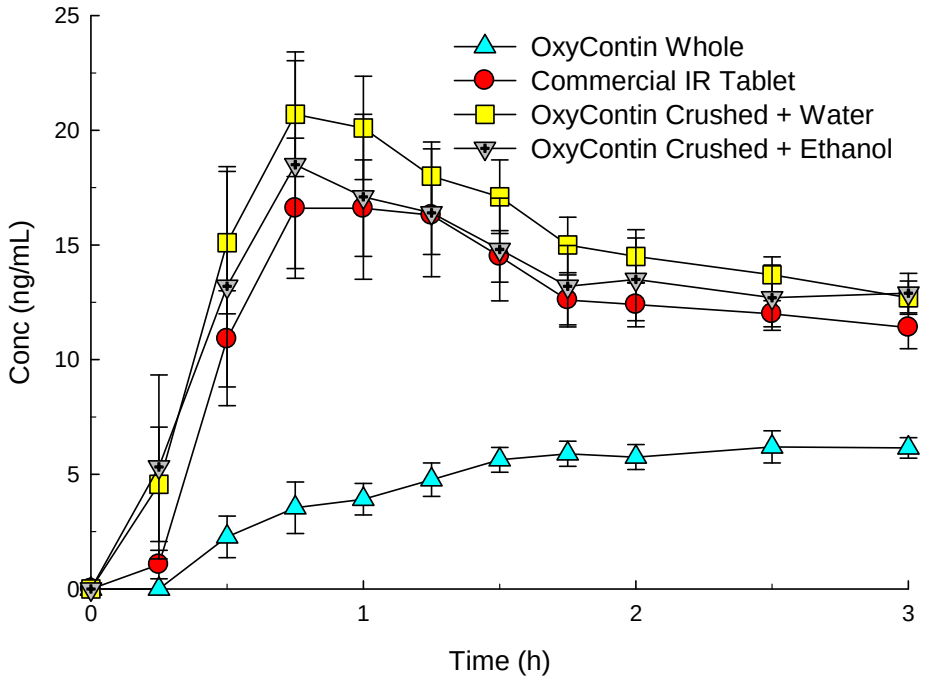


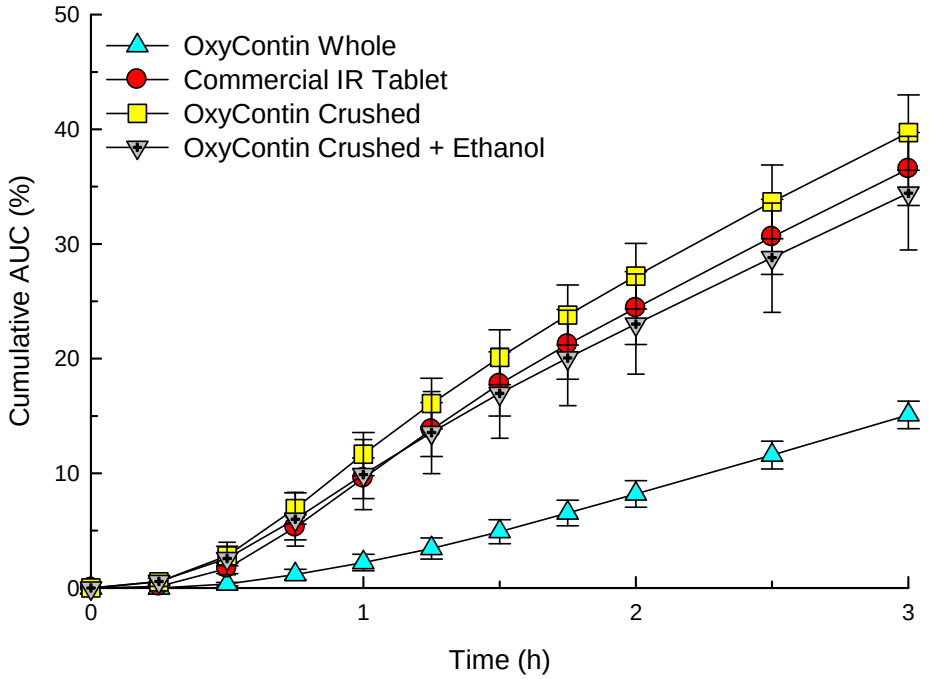
Table 10 Pharmacokinetic Parameters of Oxycodone after Oral Administration of OxyContin 10 mg Tablet, Oxycodone IR 2 x 5 mg Tablets, OxyContin 10 mg Tablet-Crushed with Water, and OxyContin 10 mg Tablet-Crushed with Alcohol

Parameter	OxyContin 10 mg Whole		Oxycodone IR 2 × 5 mg Whole	
	Mean	SD	Mean	SD
T_{max} (hr)	1.91	0.90	1.35	0.95
C_{max} (ng/mL)	6.82	1.26	18.9	4.86
Parameter	**OxyContin 10 mg Crushed with Water**		**OxyContin 10 mg Crushed with Alcohol**	
	Mean	SD	Mean	SD
T_{max} (hr)	0.90	0.22	0.95	0.41
C_{max} (ng/mL)	21.8	5.84	21.0	8.24

The total AUC is a metric that represents the total amount of drug absorbed. The AUC to a specific time, i.e. the cumulative AUC, represents the amount of drug absorbed to that time. Cumulative percent AUC represents the fraction of total absorption that has occurred to that time

and allows one to look at the rate of increase in exposure. This automatically corrects for differences in bioavailability and allows for a true comparison among treatments and/or formulations. The rapid rate of absorption and the loss of controlled-release mechanism after physical manipulation of OxyContin is also evident from Figure 26 showing that the rate of absorption significantly increased.

Figure 26 Cumulative Percent (Mean ± SEM) Of The Total Area Under The Oxycodone Plasma Concentration vs. Time Curve After Oral Administration Of OxyContin 10 mg Tablet, Oxycodone IR 2 x 5 mg Tablets, OxyContin 10 mg Tablet-Crushed with Water, and OxyContin 10 mg Tablet-Crushed with Alcohol



The Abuse Quotient, or AQ, represents a method to express the attractiveness for abuse of a formulation.[11] The AQ takes into account the observation that increasing C_{max} and decreasing T_{max} increases the attractiveness of a drug for abuse. Represented as a formula, AQ= C_{max} / T_{max}. In this study, the AQ was 3.57 for OxyContin taken intact and 14.0 for Roxicodone IR Tablet. After crushing OxyContin with water or ethanol, the AQ increased to 24.2 and 22.2, respectively, suggesting that the attractiveness of OxyContin for abuse was greatly increased after physical manipulation. AQ is a dose dependent metric as C_{max} varies with dose. For ease of comparison of the data from this study to data in subsequent *in vivo* studies with REMOXY with dose levels of 40 mg, the equivalent Abuse Quotient after dose adjustment would be 14.3 for OxyContin taken intact and 56.0 for Roxicodone IR Tablet. After crushing OxyContin with water or ethanol, the dose adjusted AQ would increase to 96.8 and 88.8, respectively.

The data gained from this study support that OxyContin's popularity among abusers may be largely attributable to the ease of disruption of the controlled-release mechanism.

To investigate similar challenges to REMOXY's formulation, several "abuse resistance" studies were conducted. These *in vivo* abuse-resistant studies are summarized in detail in the following sections.

6.1. PTI-821-CZ: A Phase I, Single-Center, Four-Way Crossover, Active-Controlled Pharmacokinetic Study to Determine the Absorption of REMOXY Following Physical Disruption and Subsequent Administration with 40% Ethanol in Healthy Volunteers

6.1.1. Introduction

Crushing and extracting CR opioid formulations in alcohol is a common way abusers defeat the CR mechanism to increase the rate of rise in blood levels and to achieve a high.

6.1.2. Objective

The objective of this study was to assess the effect of physical disruption (crushing and extraction with 40% alcohol) of the controlled-release mechanism on the rate and extent of absorption of oxycodone from REMOXY capsules in comparison with oral doses of oxycodone solution and OxyContin.

6.1.3. Methods

This was a single center, randomized, four-period, five-treatment, 10-sequence incomplete block crossover study. Subjects were to receive four separate single-dose administrations of study medication, one treatment per period, according to the randomization schedule.

The treatments were:

Treatment A:	REMOXY 40mg capsule (whole)
Treatment B:	REMOXY 40mg capsule (crushed, extracted with 40% ethanol)
Treatment C:	OxyContin 40mg tablet (whole)
Treatment D:	OxyContin 40mg tablet (crushed, extracted with 40% ethanol)
Treatment E:	Oxycodone oral solution 40mg

Fifty (50) subjects enrolled into the study and 49 were included in the PK analysis.

REMOXY was administered with food, while the oxycodone oral solution was administered under fasting conditions; the latter as a benchmark for the most rapid absorption of oxycodone. Subjects were pretreated with naltrexone.

6.1.4. Results

Disruption of the REMOXY formulation by crushing and extracting with 40% ethanol resulted in an increase in peak exposure and in a decrease in the time to peak exposure relative to REMOXY taken whole, however plasma concentration profiles displayed a broad plateau with typical characteristics of an extended-release formulation, suggesting that the controlled-release mechanism of the formulation was not defeated. Disruption of OxyContin by crushing and

extraction with 40% alcohol led to an almost complete loss of the controlled-release characteristics of the formulation as indicated by a rapid rate of rise in oxycodone plasma concentrations which was similar to that of an oral solution of oxycodone.

The Tmax after REMOXY crushed and extracted with ethanol was significantly greater than and twice as long as that of OxyContin.

The fact that the controlled release characteristics of REMOXY were maintained after crushing REMOXY and extracting with 40% ethanol is further illustrated by a comparison of early exposure, AUC_{0-2} (Figure 27). Although crushing and extracting resulted in somewhat higher mean values for AUC_{0-2} for REMOXY, they were significantly below those for the solution and OxyContin. By comparison, the mean values for these AUCs for OxyContin are essentially the same as those for the solution.

Figure 28Figure 28 shows that based on the cumulative percent of total AUC, the rate of exposure for REMOXY after crushing and extracting it with 40% ethanol remains substantially lower than that for OxyContin crushed and extracted or for an oxycodone oral solution. This is particularly evident during the initial hours after drug administration.

In this study, the AQ was 8.5 for REMOXY taken intact and 26.5 for REMOXY crushed and extracted. However, the AQ for OxyContin taken whole was only slightly lower than that for REMOXY crushed and extracted (20.2), while the values for OxyContin crushed and extracted and the oral solution were 59.7 and 94.3, respectively. The fact that the AQ for REMOXY crushed and extracted is significantly lower than those for OxyContin crushed and extracted or the oral solution suggests that the REMOXY crushed formulation is less attractive for abuse than either OxyContin crushed and extracted or than an oral solution of oxycodone.

Figure 27 Mean (± SEM) Areas Under The Curve To 2 Hours After Oral Administration Of Single 40 mg Doses Of REMOXY Whole Or Crushed And Extracted With 40% Ethanol And OxyContin Swallowed Whole Or Crushed And Extracted With 40% Ethanol Or A Single 40 mg Dose Of Oxycodone Solution (PTI-821-CZ)

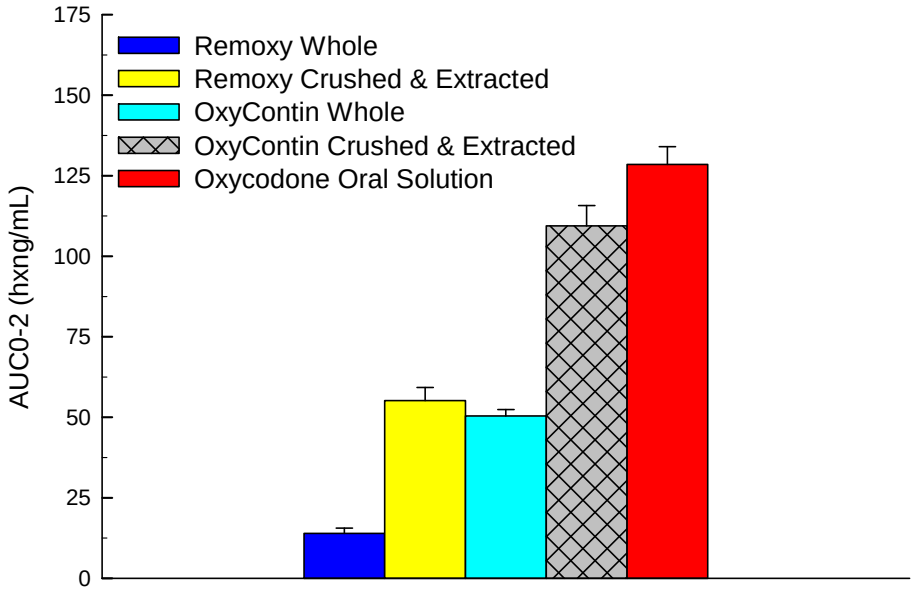
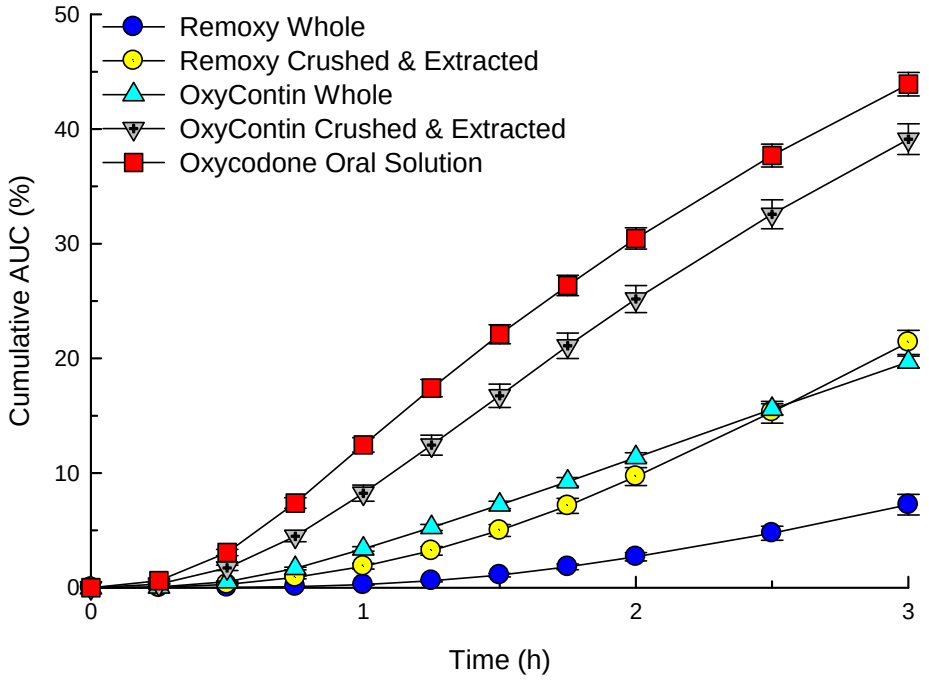


Figure 28 Cumulative Percent (Mean ± SEM) Of The Total Area Under The Oxycodone Plasma Concentration vs. Time Curve After Oral Administration Of Single 40 mg Doses Of REMOXY Whole or Crushed and Extracted With 40% Ethanol, And OxyContin Swallowed Whole Or Crushed And Extracted With 40% Ethanol, And A Single 40 mg Dose Of Oxycodone Solution (PTI-821-CZ)



6.1.5. Conclusion

Crushing of REMOXY followed by extraction with 40% ethanol resulted in an increase in C_{max} and a decrease in T_{max}. However, T_{max} after REMOXY when disrupted remained greater than T_{max} after OxyContin when taken intact. Furthermore, plasma concentration profiles retained a broad plateau indicating there was no dose dumping and that the controlled-release mechanism of the formulation was retained. T_{max} after disruption of the formulation remained approximately 3-fold longer than after an oral solution and approximately two-fold longer than after OxyContin when disrupted. Although the rate of absorption was increased after disruption of REMOXY, it remained well below that for OxyContin and for the comparator immediate release solution.

6.2. PTI-821-C04: A Phase I, Single-Center, Three-Way Crossover, Active-Controlled Pharmacokinetic Study to Determine the Effect of Mastication on the Absorption of REMOXY in Healthy Volunteers

6.2.1. Introduction

Chewing or crushing CR opioid formulations is a common way abusers defeat the CR mechanism to increase the rate of rise in blood levels and to achieve a high.

6.2.2. Objective

The objective of this study (PTI-821-C04) was to assess the effect of rigorous mastication on the rate and extent of absorption of oxycodone from REMOXY capsules in comparison with REMOXY capsules swallowed whole (both under fed conditions) and an oxycodone immediate release solution under fasted conditions.

6.2.3. Methods

This was a single center, randomized, three-period, three-treatment, six-sequence crossover study. Forty-eight (48) subjects were enrolled and 44 subjects were entered in the PK analysis. The treatments were:

Treatment A:	REMOXY 40 mg capsule (whole)
Treatment B:	REMOXY 40 mg capsule masticated rigorously for 3 min and swallowed
Treatment C:	Oxycodone oral solution 40 mg

REMOXY was administered with food, while the oxycodone oral solution was administered under fasting conditions. Subjects were pretreated with naltrexone.

6.2.4. Results

Plasma concentrations of oxycodone after rigorous chewing of REMOXY were increased relative to REMOXY taken whole but profiles displayed a broad plateau with typical characteristics of an extended-release formulation, suggesting that the controlled-release mechanism of the formulation was not defeated.

Early exposure (AUC_{0-2}) to oxycodone after chewing of REMOXY was much lower than after an oral solution (Figure 29), supporting the premise that the controlled release of drug from the formulation was maintained. Figure 30 shows that, based on cumulative percent AUC, mastication does increase the rate of exposure compared to swallowing REMOXY whole, but that this rate remains substantially lower than for oxycodone oral solution. This is particularly evident during the initial hours after drug administration.

The AQ for REMOXY taken intact in this study was 7.3, while the AQ for REMOXY chewed was 30.8. However, the AQ for the comparator oral solution was 95.3, suggesting that REMOXY chewed would offer less appeal for abuse than an oral solution of oxycodone.

Figure 29 Mean (± SEM) Areas Under The Curve To 2 Hours After Oral Administration Of Single 40 mg Doses Of REMOXY Whole Or After Chewing Or A Single 40 mg Dose Of Oxycodone Solution (PTI-821-C04)

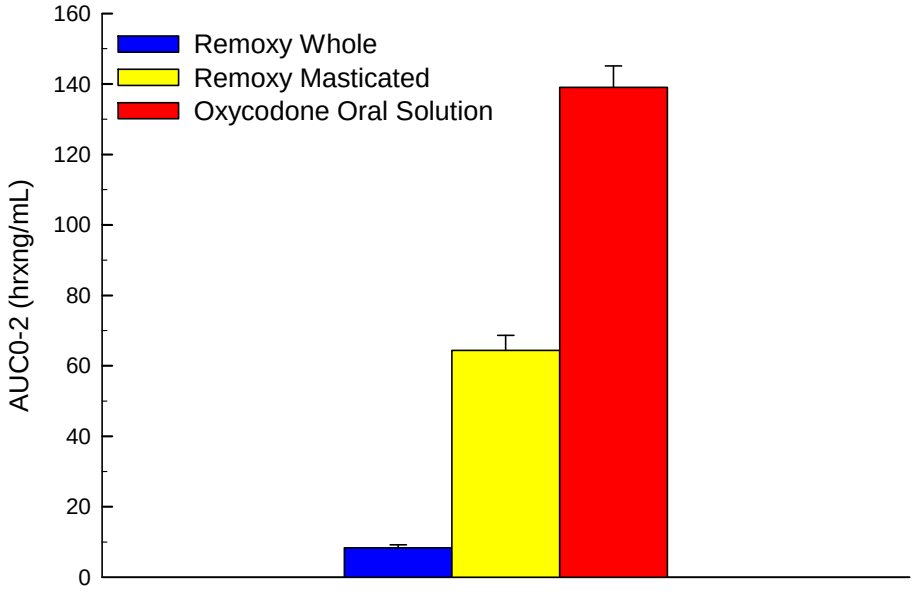
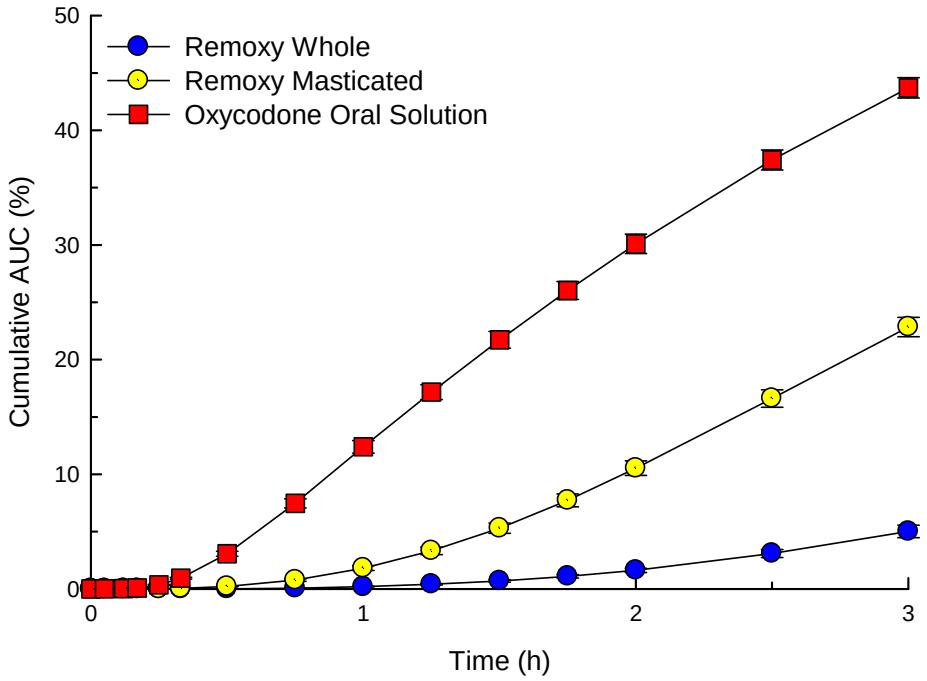


Figure 30 Cumulative Percent (Mean ± SEM) Of The Total Area Under The Oxycodone Plasma Concentration vs. Time Curve After Oral Administration Of Single 40 mg Doses Of REMOXY Whole Or After Chewing Or A Single 40 mg Dose Of Oxycodone Solution (PTI-821-C04)



6.2.5. Conclusion

A decrease in T_{max} and an increase in C_{max} were observed after rigorous chewing of REMOXY. However, the data indicated that the controlled-release mechanism of the REMOXY formulation was not defeated, as was evident from the lack of dose dumping and plasma concentration profiles which retained a broad plateau, from a T_{max} which remained approximately 2.5-fold longer than after an oral oxycodone solution, and a C_{max} which was lower than after an oral solution. The data taken together demonstrate that although mastication of REMOXY does increase the rate of absorption of oxycodone and peak exposure compared to REMOXY swallowed whole, it does not approach that observed with an immediate release oxycodone oral solution.

6.3. PTI-821-CU: A Phase I, Single-Center, Three-Way Crossover, Active-Controlled Pharmacokinetic Study to Determine the Buccal Absorption of REMOXY in Healthy Volunteers

6.3.1. Introduction

The buccal route of drug administration provides an alternative for oral administration. It offers the potential for rapid delivery of drug to the systemic circulation and in most cases bypasses degradation by first-pass hepatic metabolism.[12, 13] After buccal administration of an oral oxycodone solution in children, the estimated bioavailability ranged from 0.22-0.84 relative to intravenous administration of the same dose with a large degree of variability in rate and extent of absorption.[14; 15]

6.3.2. Objective

The objective of this study (PTI-821-CU) was to compare the absorption of oxycodone from REMOXY administered by dissolving in the buccal cavity followed by swallowing with an oral dose of REMOXY administered intact and an oral dose of immediate-release oxycodone solution.

6.3.3. Methods

This was a single center, randomized, three-treatment, three-sequence crossover study. Forty-eight (48) subjects were enrolled in this study; 42 subjects were included in the PK analysis. The treatments were:

Treatment A:	REMOXY 40 mg capsule (whole)
Treatment B:	REMOXY 40 mg capsule placed in buccal cavity for 10 min and swallowed
Treatment C:	Oxycodone oral solution 40 mg

Subjects received a single 40 mg dose of REMOXY either whole or held in the buccal cavity for 10 minutes followed by swallowing under fed conditions or a single 40 mg dose of oxycodone solution under fasted conditions. Subjects were pretreated with naltrexone.

6.3.4. Results

Plasma concentrations of oxycodone after holding REMOXY in the buccal cavity for 10 minutes prior to swallowing were increased relative to REMOXY taken whole, but profiles displayed a broad plateau with typical characteristics of an extended-release formulation, suggesting that there was no rapid transmucosal absorption.

The maintenance of the controlled release and the lack of dose dumping after buccal administration when compared to an oral solution was further evident from a comparison of the AUC to 2 hours (Figure 31). While the AUC after buccal administration was higher than after swallowing an intact capsule during the initial hours after drug administration, it was well below that for the oral solution (Figure 31). In addition, Figure 32 indicates that, based on cumulative percent AUC, administration of REMOXY in the buccal cavity does increase the rate of exposure compared to swallowing REMOXY whole, but that this rate remains substantially lower than for oxycodone oral solution. This is particularly evident during the initial hours after drug administration.

Total extent of exposure was not affected by holding REMOXY in the buccal cavity.

The AQ for REMOXY administered intact in this study was 7.5, while the AQ for REMOXY after holding in the buccal cavity was 24.6. However, the AQ for the comparator oral solution was much greater at 75.4, suggesting that REMOXY held in the buccal cavity prior to swallowing would offer less attractiveness for abuse than an oral solution of oxycodone.

Figure 31 Mean (± SEM) Areas Under The Curve To 2 Hours After Oral Administration Of Single 40 mg Doses Of REMOXY Whole Or Dissolved In The Buccal Cavity And A Single 40 mg Dose Of Oxycodone Solution (PTI-821-CU)

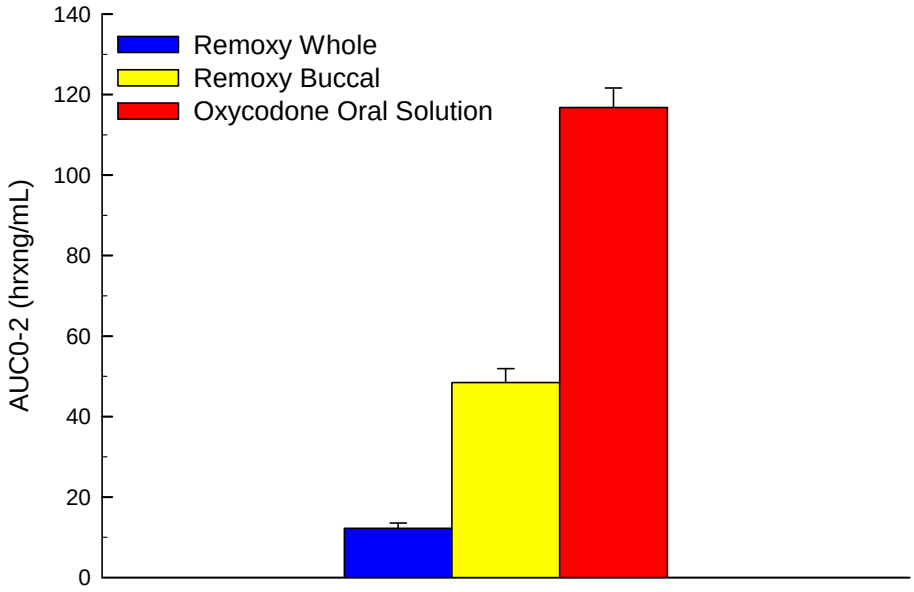
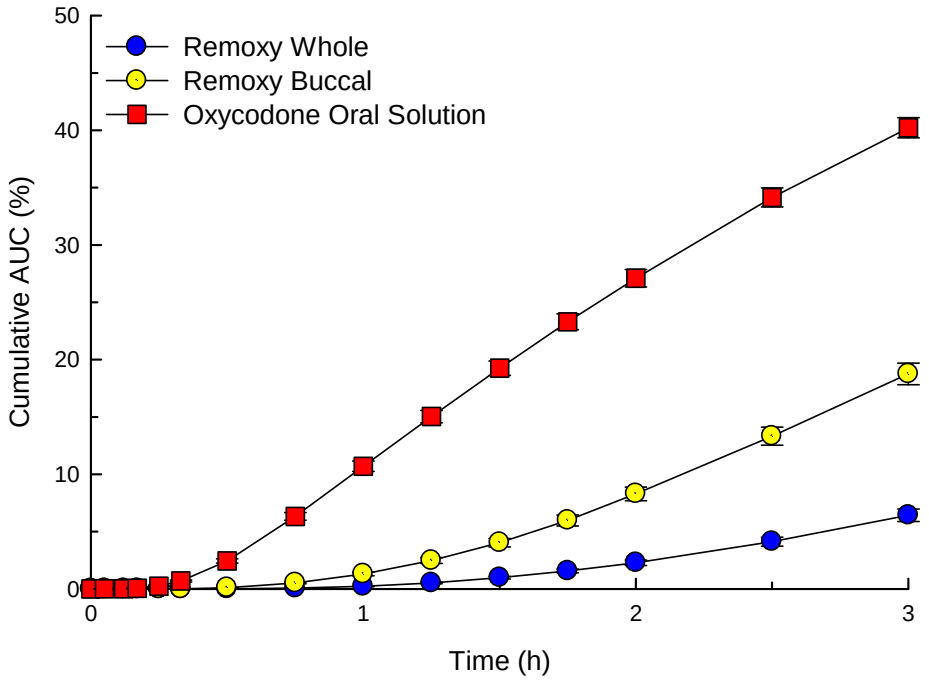


Figure 32 Cumulative Percent (Mean ± SEM) Of The Total Area Under The Oxycodone Plasma Concentration vs. Time Curve After Oral Administration Of Single 40 mg Doses of REMOXY Whole Or Dissolved In The Buccal Cavity And A Single 40 mg Dose Of Oxycodone Solution (PTI-821-CU)



6.3.5. Conclusion

Results from this study show that buccal administration of REMOXY resulted in an increase in the rate of oxycodone exposure, but one that was much lower than after an oxycodone oral solution. Maximum plasma concentrations remained significantly below those for an oral solution and peak plasma concentrations occurred at a T_{max} which was approximately 2.5-fold greater than that for the solution. The data show that dissolving REMOXY in the buccal cavity does not result in rapid transmucosal absorption of oxycodone or in a defeat of the controlled-release mechanism of the formulation.

6.4. PTI-821-CS: A Phase I, Single-Center, Four-Way Crossover, Pharmacokinetic Study to Determine the Absorption of REMOXY When Administered with Ethanol in Healthy Volunteers

6.4.1. Introduction

Co-ingestion of alcohol with extended-release drug products can alter the PK and bioavailability of these drugs.[16] Additionally, the adverse effects of opioids may be enhanced by alcohol.[17] Dose-dumping, which is the unintended, rapid release of a significant portion of the active ingredient from an extended-release drug product, can pose a significant health risk. FDA has

raised concerns that the co-ingestion of alcohol with extended-release opioid formulations could compromise their extended release mechanisms leading to dose-dumping and thus to significant health risks.[18]

Such alcohol-induced dose-dumping was recently observed after ingestion of an extended release hydromorphone formulation (Palladone®). Due to the magnitude of the increase in maximal plasma concentrations (a six-fold average increase in C_{max} after co-ingestion with 40% ethanol relative to after water, with a 16-fold increase for one individual subject), FDA concluded that the overall risk-benefit ratio was no longer favorable due to the potentially fatal interaction with alcohol and the product was withdrawn from the market in 2005.[18]

Various other extended-release formulations containing an opioid have also reported that co-ingestion with alcohol significantly increases peak exposure (C_{max}) as shown in

Table 12.[19,20,16, 21]

6.4.2. Objective

The objective of the PTI-sponsored study (PTI-821-CS) was to assess the effect of alcohol on the rate and extent of absorption of oxycodone from REMOXY capsules when administered under fed conditions.

6.4.3. Methods

This was a single center, randomized, four-treatment, four-sequence crossover study. Thirty-seven (37) subjects were enrolled in this study. The treatments were:

Treatment A:	REMOXY 40 mg capsule + 240 ml water
Treatment B:	REMOXY 40 mg capsule + 240 ml 4% ethanol "Low Proof"
Treatment C:	REMOXY 40 mg capsule + 240 ml 20% ethanol "Medium Proof"
Treatment D:	REMOXY 40 mg capsule + 240 ml 40% ethanol "High Proof"

All treatments were followed by 240 mL water. Subjects were pretreated with naltrexone.

Thirty-six (36) subjects completed Treatment A (REMOXY + water) and Treatment B (REMOXY + 4% ethanol) for PK analysis. Twenty-eight subjects completed Treatment C (REMOXY + 20% ethanol). Eighteen (18) subjects completed Treatment D (REMOXY + 40% ethanol) for PK analysis.

6.4.4. Results

Mean plasma concentration profiles after REMOXY co-ingested with water or ethanol from 4% to 40% were similar across all treatment groups and displayed a typical controlled-release pattern, indicating there was no dose-dumping.

Mean plasma concentrations after co-ingestion with ethanol were comparable to those after ingestion with water as were the mean values for C_{max} and AUC_{last} (Table 11). Comparison of C_{max} and AUC_{last} between each ethanol treatment and water demonstrated no effect after 4% ethanol, a small decrease in C_{max} after 20% ethanol and a 10% increase in C_{max} after 40% ethanol suggesting a minor increase in exposure after co-ingestion with 40% ethanol.

Table 11 Pharmacokinetic Parameters For Oxycodone After Oral Administration Of Single 40 mg Doses Of REMOXY With Water, 4% Ethanol, 20% Ethanol, And 40% Ethanol To Healthy Volunteers (PTI-821-CS)

Parameter	REMOXY + Water		REMOXY + 4% Ethanol		REMOXY + 20% Ethanol		REMOXY + 40% Ethanol	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max} (ng/mL)	45.30	23.10	45.00	20.60	39.00	16.10	49.70	27.20
AUC_{0-2} (hr*ng/mL)	21.01	24.54	18.12	21.77	14.84	11.31	29.98	29.39
AUC_{last} (hr*ng/mL)	471.30	154.60	471.80	147.50	496.30	153.60	537.70	191.50

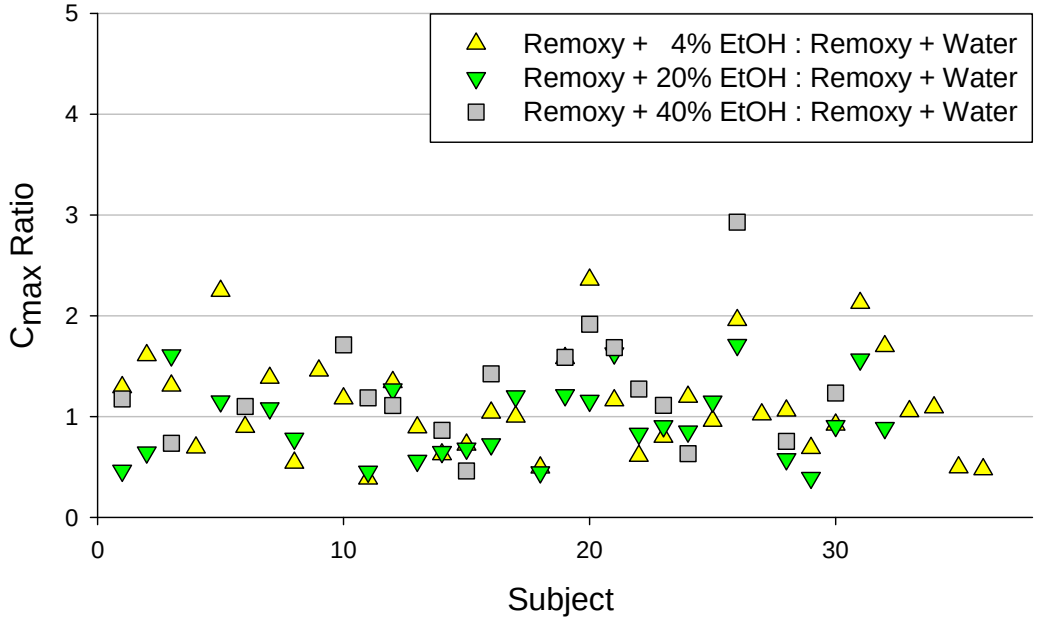
Table 12 Effect of Alcohol on Extended-Release Opioid Formulations

	Increase in C_{max} Relative to Drug Co-ingested With Water			Range of C_{max} Ratios (at 40% Ethanol)	Percent Change in T_{max} at 40% Ethanol
	4% Ethanol	20% Ethanol	40% Ethanol		
REMOXY®	-1.01	-1.14	1.1	0.46−2.93	+3
Palladone™	1	2	6	1−16	-
OPANA ER®	1.07	1.31	1.7	up to 3.7	-25
OROS® Hydromorphone	1.17	1.31	1.28	-	-25
EMBEDA™ ALO-01 Morphine Sulfate	No change	No change	2	-	-55
Kadian® Morphine Sulfate	-	-	1.03	0.43-4.54	No change

C_{max} ratios for co-ingestion of REMOXY with alcohol relative to water were calculated and summarized for individual subjects (Figure 33) and ranged from 0.38 to 2.36 for co-ingestion of REMOXY with 4% ethanol relative to water; three subjects showed a ratio greater than 2. Individual C_{max} ratios ranged from 0.39 to 1.71 for co-ingestion with 20% ethanol relative to water, and 0.46 to 2.93 for co-ingestion with 40% ethanol relative to water. For the latter treatment, there was only one subject with a ratio greater than 2.00; the ratios for the remainder of the subjects ranged from 0.46 to 1.92.

Table 12 shows the effect of alcohol on C_{max} and T_{max} of various extended release opioid formulations.

Figure 33 C_{max} Ratios of REMOXY + Ethanol vs. REMOXY + Water for Each Subject After Oral Administration Of Single 40 mg Doses Of REMOXY With Water, 4% Ethanol, 20% Ethanol, And 40% Ethanol To Healthy Volunteers (Study PTI-821-CS)



6.4.5. Conclusion

After co-ingestion of REMOXY with ethanol from 4-40% the plasma concentration profiles were similar to those after ingestion with water and continued to display typical controlled release properties, consistent with maintenance of the controlled-release characteristics of the formulation and without any evidence of dose dumping. There were no significant effects on the rate or extent of absorption of oxycodone after administration of REMOXY with 4% or 20% ethanol and overall exposure was not affected. There was a minor increase in C_{max} (10%) and exposure after co-ingestion with 40% ethanol. T_{max} was not affected by co-ingestion of REMOXY with ethanol from 4-40%.

6.5. Conclusions from *in vivo* abuse-resistance studies

Four robust *in vivo* studies have shown that under certain physical and chemical challenges the controlled-release formulation of REMOXY is not defeated and that these challenges do not result in a rapid release or dose dumping of oxycodone. Moreover, after mechanical and/or chemical manipulation, the rate of rise of oxycodone plasma concentrations from REMOXY is less and the T_{max} is longer than after an oral oxycodone solution or OxyContin. The attraction of drugs such as oxycodone for abuse purposes requires an effect that is both rapid and intense. The Abuse Quotient (AQ), a measure of attractiveness of a formulation for abuse, for REMOXY after physical and/or mechanical manipulation remained far below that of OxyContin when manipulated in a similar manner, or after an immediate release oral solution of oxycodone. The

combined data from these studies suggest that REMOXY after certain physical and chemical challenges may offer less appeal for abuse than its comparators.

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Attachment 1

Summary of Risk Evaluation Mitigation Strategy

REMOXY XRT™
(oxycodone controlled-release) Capsules CII

United States Food and Drug Administration

Joint Meeting

Anesthetic and Life Support Drugs
Advisory Committee
and

Drug Safety and Risk Management
Advisory Committee

Meeting Date: November 13, 2008

Document Date: October 8, 2008

AVAILABLE FOR PUBLIC DISCLOSURE

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1. RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR REMOXY XRT

1.1 INTRODUCTION

REMOXY XRT is a potent analgesic and even with appropriate pain management may lead to unintended but well recognized adverse consequences including overdose, misuse, abuse and diversion (see Table 1 for definitions). Therefore, to assure the safe use of REMOXY XRT, a Risk Evaluation and Mitigation Strategy or REMS will be implemented.

Table 1. Definitions of Misuse, Abuse and Diversion[1]

TERM	DEFINITION
Misuse	Use of a medication (for a medical purpose) other than as directed, whether willful or unintentional, and whether harm results or not.
Abuse	Intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness (e.g., getting high).
Diversion	Intentional removal of a medication from legitimate distribution and dispensing channels.

Prescription opioid abuse is a complex, multi-dimensional issue existing both within and outside of the healthcare system and involving children. Patient misuse or individual casual abuse is typically the entry point into this pathway with opioids being supplied from various sources. Behaviors that can lead to addiction are thought to come from a combination of increase in frequency of use and the intensity of the euphoria achieved. The intensity of euphoria is influenced by the route of administration. Snorting, smoking or injecting opioids are ways abusers and addicts get high drug concentrations quickly into the brain and are therefore particularly dangerous behaviors. Modifying these behaviors is important to mitigate serious outcomes. REMOXY XRT, by being difficult to snort, smoke or inject has the potential to do this.

For the vast majority of patients with moderate to severe chronic pain, opioids are effective analgesics and are safe and well tolerated. In addition, abuse deterrent products could contribute to the overall benefits of opioids. Balanced against this are the risk of overdose, misuse, abuse and diversion as well as a potential for lowered vigilance in patient management perhaps associated with the availability of a medication perceived to have abuse deterrence features.

Responsible pain management is promoted by many professional pain societies and practiced by pain specialists. A Universal Precautions approach within this setting borrows from successful practices in infectious diseases by coupling pain management to risk management. This approach allows for risk assessment and stratification to occur based on the application of simple tools in the doctor's office. Entering into a treatment agreement with patients, tracking prescriptions and diligent monitoring with documentation is anticipated to help improve patient selection, patient management and risk mitigation for patients with chronic pain. Encouraging more opioid prescribers and

in particular primary care including family practitioners to apply these straightforward and sensible practices as part of care-giving, could have a significant impact.

Opioids remain the mainstay of treatment for the control of most moderate to severe chronic pain conditions as demonstrated by increases in the utilization of both immediate-release and extended-release products.[2,3,4] However, non-medical use of pain relievers has also increased over time. A survey in 2006 estimated that 5.2 million persons aged 12 or older had used pain relievers non-medically in the previous month.[5] Prescription opioid abuse among adolescents is also a concern. In 2007, one out of every 20 high school senior has tried oxycodone at least once in the past year.[6] In 2007, 3.3% of adolescents age 12 to 17 engaged in non-medical use of prescription-type psychotherapeutics.[5] Unintentional overdose may require emergency intervention and can result in death. Data from the 2005 Drug Abuse Warning Network (DAWN), the most recently publicly available source, reported 196,225 emergency department visits due to non-medical use of opiates/opioids.[7] Additionally, admission to substance abuse treatment services for primary abuse of opioids has also increased from one percent of all admissions in 1996 to four percent in 2006.[8]

Extended-release (ER) formulations have been abused by circumvention of the intended mechanism of delivery by tampering with the controlled-release mechanism in order to extract the active ingredient and to prepare it for other routes of administration [e.g., smoke, snort or intravenous (IV) injection]. One study by Hays et al. suggests that abusers move from oral to snorting and IV use in a short period of time.[9] This is an area where REMOXY XRT could be expected to have a significant impact by making it difficult for abusers to extract oxycodone for the purpose of snorting or IV administration.

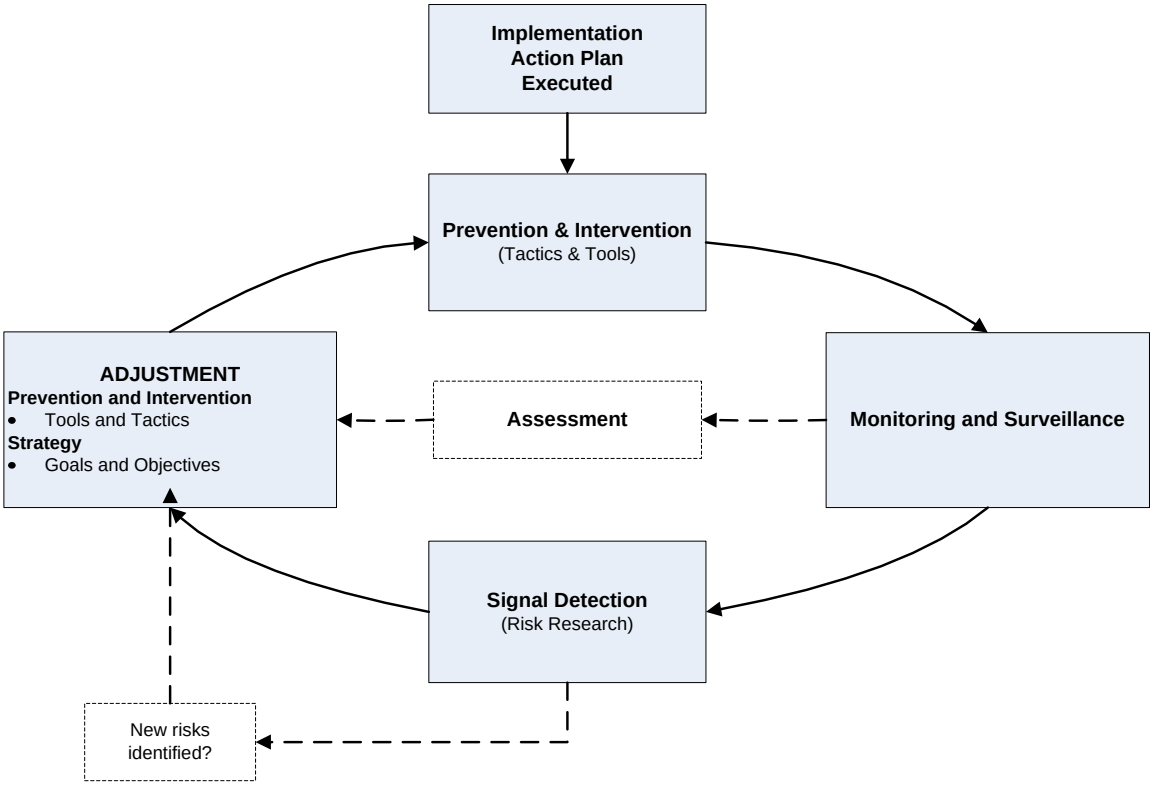
Prescription opioid diversion can occur in many ways including legitimate as well as illegal sale of prescriptions, theft or forgery. However, recent data indicate that greater than 50% of people using opioids non-medically obtained these medicines from family or friends. Therefore, patients with legitimate opioid prescriptions kept at home can have a significant impact simply by properly securing and disposing unused medications.

Prescription drug abuse is a multifaceted problem that requires multifaceted solutions. With REMOXY XRT, we have developed a formulation that specifically aims to address one aspect of the problem, tampering, and this has the potential of deterring abuse. However, the risk for misuse, oral abuse and diversion exists with REMOXY XRT even with new technology. We are committed to implementing strategies that specifically aim to reduce such risks by implementing this REMS.

1.2 REMS OVERVIEW

The overall goal of the REMS is to optimize the benefit-risk balance for REMOXY XRT. The benefits of REMOXY XRT should outweigh the negative health consequences typically associated with opioid therapy including the potential for overdose, misuse, abuse and diversion. The REMS Overview below (Figure 1) describes the process that will be instituted once this medicine is approved in order to achieve a balance of optimal pain control and mitigate overdose, misuse, abuse and diversion.

Figure 1. REMS Overview



1.3 RISKS, GOALS AND OBJECTIVES

The Goals and associated Objectives have been designed specifically to mitigate the following risks potentially associated with REMOXY XRT:

- Risks associated with appropriate medical use
- Risks resulting from non-medical use
- Risks resulting from the potential for lowered vigilance in treatment practices

1.3.1 RISKS ASSOCIATED WITH APPROPRIATE MEDICAL USE

The specific risks associated with appropriate medical use include:

- Adverse reactions, including drug/drug or drug/alcohol interactions, occurring in the setting of appropriate pain management using REMOXY XRT
- Misuse of REMOXY XRT by patients

1.3.1.1 GOAL: To optimize the safe and effective use of REMOXY XRT as a controlled-release opioid for the treatment of chronic moderate to severe pain

Specific objectives intended to meet this Goal:

- Educate healthcare professionals on the risks associated with REMOXY XRT therapy, including drug/drug and drug/alcohol interactions, medication errors, errors of dosing due to conversion from other opioids and patient misuse
- Educate healthcare professionals on the appropriate use of REMOXY XRT as part of the management of chronic moderate to severe pain together with ways to monitor patients and mitigate risks
- Educate patients on the risks, including drug/drug and drug/alcohol interactions, taking extra doses and use of the medication other than as directed, associated with the treatment of chronic moderate to severe pain with REMOXY XRT
- Ensure that company representatives thoroughly understand the risks associated with REMOXY XRT therapy, including drug/drug and drug/alcohol interactions, medication errors, errors of dosing and patient misuse, the appropriate use of REMOXY XRT and have the skills to communicate these issues appropriately and effectively to healthcare professionals
- Monitor adverse reactions in patients receiving REMOXY XRT

1.3.2 RISKS RESULTING FROM NON-MEDICAL USE

The specific risks resulting from non-medical use include:

- Overdose of REMOXY XRT in the opioid naïve population seeking euphorigenic effects
- Overdose of REMOXY XRT in the opioid tolerant population seeking euphorigenic effects or to satisfy drug craving in opioid-addicted individuals
- Overdose of REMOXY XRT in combination with CNS depressants including alcohol

- Abuse of REMOXY XRT
- Diversion of REMOXY XRT

1.3.2.1 GOAL: To prevent opioid overdose with REMOXY XRT

Specific objectives intended to meet this Goal:

- Increase public awareness of the issue of teen abuse and diversion of prescription drugs
- Promote the understanding among parents, adolescents and young adults of the serious risks associated with prescription opioid abuse
- Educate healthcare professionals on the issue of overdose of prescription opioids in adolescents and young adults and the importance of engaging their patients in the mitigation of this risk
- Educate patients on the risks of overdose with prescription opioids as well their role in protecting family and friends from accidental or unintended exposure to their medication
- Prevent accidental ingestion of REMOXY XRT by children
- Decrease the amount of unsecured as well as unused controlled substances available in patient households
- Monitor rates of overdose of REMOXY XRT

1.3.2.2 GOAL: To prevent the abuse and diversion of REMOXY XRT

Specific objectives intended to meet this Goal:

- Educate healthcare professionals on the risks of REMOXY XRT abuse and diversion, the importance of engaging their patients in the mitigation of these risks and ways to assess patients and mitigate risks
- Educate patients on the risks associated with and their role in preventing abuse and diversion of REMOXY XRT
- Increase community awareness of the issue of opioid abuse and diversion of prescription opioids
- Educate parents, adolescents and young adults about the dangerous issue of prescription opioid abuse and diversion
- Prevent diversion from the supply chain
- Monitor the abuse and diversion rates of REMOXY XRT

1.3.3 RISKS RESULTING FROM THE POTENTIAL FOR LOWERED VIGILANCE IN TREATMENT PRACTICES

The specific risks resulting from the potential for lowered vigilance include:

- Perception that responsible pain management practices may not apply to the treatment of moderate to severe chronic pain with REMOXY XRT
- Patients taking fewer precautions with the use of REMOXY XRT when securing and disposing their medication in an appropriate way

1.3.3.1 GOAL: To ensure that health care professionals and patients remain vigilant against the possibility of misuse, abuse and diversion when REMOXY XRT is prescribed and dispensed according to the conditions of labeling

Specific objectives intended to meet this Goal:

- Inform healthcare professionals that the potential for misuse, abuse and diversion of REMOXY XRT remains
- Provide education on the use of a universal precautions approach as a means to assess, stratify and mitigate these risks
- Ensure patients have a clear understanding of the risks of misuse, abuse and diversion with REMOXY XRT as well their role in protecting family and friends from accidental or unintended exposure to their medication.
- Ensure that company representatives thoroughly understand the risks of misuse, abuse and diversion with REMOXY XRT and have the skills to communicate these risks effectively to healthcare professionals
- Monitor the misuse, abuse and diversion rates of REMOXY XRT

1.4 PROPOSED REMS ELEMENTS

Within the paradigm of routine clinical practice, there are several opportunities where interventions can be implemented to mitigate risks associated with REMOXY XRT: point of prescribing, point of dispensing, patient use, patient storage, patient disposal and supply chain. To assure safe use of REMOXY XRT, the REMS is designed to take advantage of these key opportunities and address the defined goals and objectives and thereby mitigate the risks associated with REMOXY XRT. Such elements communicate key messages regarding optimal and appropriate product use to healthcare professionals and patients and provide guidance on appropriate medical situations and patient populations in which to prescribe and dispense REMOXY XRT. The elements can also address the issue of diversion from the supply chain by engaging prescribers, pharmacists and patients with legitimate prescriptions.

The proposed REMS is an interrelated, multi-dimensional set of strategies, tactics and tools that, from the time of launch, will help mitigate risks associated with REMOXY XRT while maximizing its benefits. Effective implementation of the REMS requires initial introduction of prevention and intervention tools and tactics followed by continuous cyclical monitoring and surveillance, signal detection, adjustments and implementation of revised prevention and intervention tools and tactics as needed.

The elements of the REMS include:

- **Prevention and Intervention**
  - Education
  - Supply Chain Security
- **Monitoring and Surveillance**
  - Passive Surveillance
  - Active Surveillance

  - Surveys
- **Signal Detection**
  - Monitoring and Surveillance Evaluations
  - Research to further define potential serious risks and identify any new unanticipated serious risks
  - REMS Evaluation
- **Adjustment**
  - Prevention and Intervention
    - Targeted Interventions Derived from Risk Assessments
    - Tools and Tactics
  - Strategy
    - Goals and Objectives

These elements are described in detail below. Appendix 1 summarizes how these elements will be applied to the Risks, REMS Goals and REMS Objectives as presented in Section 1.3. Inadequate performance of the elements to assure safe use on the mitigation of risks and/or the identification of new risks will prompt timely adjustments of the goals, objectives and/or tactics and tools as appropriate in an ongoing process.

1.4.1 PREVENTION AND INTERVENTION TOOLS AND TACTICS

1.4.1.1 Education

Upon the introduction of REMOXY XRT into clinical practice, a collection of tools and educational strategies will be directed at healthcare professionals in order to meet goals and objectives of the REMS. Educational tools and programs advising patients on appropriate usage, storage, and disposal of REMOXY XRT, risks of overdose, misuse, abuse and diversion, and opioid-related side effects will be disseminated through various mechanisms. These educational initiatives will be targeted toward the approximately 60,000 primary care and pain specialist physicians and the 2-3 million chronic pain patients. Community initiatives targeting parents, adolescents and young adults regarding the risks and dangers associated with prescription opioid overdose and abuse will be implemented. Furthermore, training for sales representatives and medical science liaisons will be tailored to complement health care professional, patient and adolescent initiatives.

A cornerstone to many of the educational initiatives aimed at healthcare providers will include information on responsible pain management including Universal Precautions as they apply to pain management.[10]

Upon product approval, information will be communicated to a wide audience of health care providers and relevant institutions. The purpose of this communication will be to alert the respective audience of the REMS for REMOXY XRT and their specific roles relative to these risk mitigation strategies and will emphasize the key safety messages for REMOXY XRT and highlight the risks and the associated goals of the REMS. A summary of the elements to assure safe use will also be provided along with instructions

on where to obtain additional information. The Full Prescribing Information (FPI) and the Medication Guide (MG) will be attached to each communication.

The communications will be sent to physicians (pain specialists and primary care physicians), pharmacists, Federal and local agencies, law enforcement communities, medical associations, pharmacy associations, state medical and pharmacy boards and pharmaceutical compendia.

Healthcare Professional Education

One key goal is to responsibly market REMOXY XRT to ensure patients receive REMOXY XRT for effective and safe treatment of their moderate to severe chronic pain while mitigating the inherent risk of overdose, misuse, abuse and diversion associated with opioid analgesics. A critical component of the REMS includes educating health care professionals on the appropriate use of REMOXY XRT and risks associated with its use.

We will employ or sponsor a range of communications opportunities to educate physicians, physician assistants, nurse practitioners and pharmacists, including the following:

- **Scheduled II product classification** – restrictions placed on the prescribing and dispensing of Schedule II products provide the healthcare community tools to control diversion and mitigate the risk of abuse by patients
- **Full Prescribing Information (FPI)** – highlights important safety risks and provides the information necessary for the effective use of REMOXY XRT
- **Medication Guide (MG)** – highlights important safety risks including possible side effects and provides the information on how to take and properly store and dispose of REMOXY XRT
- **Dear Healthcare Professional Letter** – mailed to approximately 60,000 primary care and pain specialist physicians designed to convey and reinforce the risks of overdose, the importance of appropriate use, the misuse potential and potential for drug diversion of REMOXY XRT
- **Company-Sponsored Medical Education** – disseminating educational information to the health care practitioners related to safety and mitigation of the risks of opioids including a summary of the Universal Precautions approach to managing chronic pain patients
- **Independent Continuing Medical Education (CME)** – to enhance the understanding of appropriate use of opioids and the risk of overdose, misuse, abuse and diversions through various forums
- **Peer Direct – PV Update** – to provide disease awareness and education to healthcare professionals in multiple media formats to ensure that physicians can access programs in a format they prefer at a time that is suitable for them to learn
- **PainEDU website** – a free, unbranded, targeted internet-based educational initiative with reminder system tools to address the issues of adverse events, opioid misuse, abuse and diversion through the use of case-based learning, roundtable discussions, 'ask the expert' modules, and downloadable tools such as the Screener and Opioid Assessment for Patients in Pain, revised (SOAPP-R), the

Current Opioid Misuse Measure (COMM), and a step-by-step guide to managing chronic pain patients on opioids

- **REMOXY XRT website** – for distributing updated Full Prescribing Information and Medication Guides and will also include Frequently Asked Questions about REMOXY XRT, Healthcare Provider information, details on how to report adverse events or request additional information, and information regarding the REMS including Universal Precautions
- **Dear Pharmacist Letter** – sent to pharmacists and designed to convey and reinforce the risks of overdose, the importance of appropriate use, the misuse potential and potential for drug diversion of REMOXY XRT
- **Independent Continuing Pharmacy Education (CPE)** – to enhance the understanding of appropriate use of opioids and the risk of overdose, misuse, abuse and diversions through various forums

Patient Education

In order to properly address risks associated with REMOXY XRT, development and dissemination of patient education materials are essential. The following identifies the educational tools and strategies developed for patients for safe use and to mitigate misuse, abuse and diversion associated with REMOXY XRT use.

- **Medication Guide** – highlights important safety risks including possible side effects and provides information on how to take and properly store and dispose of REMOXY XRT
- **PainACTION website** – a free, unbranded, consumer-oriented internet-based educational and reminder system website that provides chronic pain patients with educational materials covering issues such as risk of addiction, proper storage and disposal of medication, communicating effectively with your doctor and the importance of avoiding co-ingestion with alcohol and other specific drugs
- **REMOXY XRT website** – for distributing Medication Guides and will also include Frequently Asked Questions about REMOXY XRT, Patient/Caregiver information and details on how to report adverse events or request additional information

Public Education

In addition to patient education, public education is important in preventing risks associated with REMOXY XRT abuse. With the rise of prescription opioid abuse among adolescents, initiatives that target adolescents and young adults are important in informing them of the dangers and consequences of prescription opioid overdose and abuse. The following highlights such initiatives that we are sponsoring.

- **myStudentBody: Drugs** – a comprehensive suite of college prevention and intervention educational programs targeted towards college students designed to educate young adults on the serious risks associated with prescription opioid abuse and diversion and increasing community awareness of these issues
- **Time to Talk Online Community** – an online community, resource and toolkit to help parents connect and talk with their kids about alcohol and drugs, and

Podcast Series, which will feature special guests addressing critical issues parents and teens are facing today when it comes to drug and alcohol abuse and addiction

Company Education

Responsible marketing and risk management education is especially important for REMOXY XRT. The sales force and Medical Science Liaisons (MSLs) are the main vectors for information to the healthcare community and others on the safety, effectiveness and potential risks of REMOXY XRT. Education is the main method for ensuring proper understanding of prescribing and other information. To that end, we have set out a comprehensive educational program for sales representatives and MSLs.

- **Sales Representative and Medical Science Liaison Training** – to ensure that all sales representatives and medical science liaisons are trained on the REMOXY XRT REMS and understand the goals, objectives and elements to assure safe use so that they can communicate these issues effectively to healthcare professionals

1.4.1.2 Supply Chain Security

Standard Operating Procedures (SOPs) are in place at our Distribution Center to ensure that all products are handled in a safe and secure manner. We are committed to ensuring the safe and effective handling of controlled substances by abiding by these SOPs. All employees involved in the receipt, shipment or handling of controlled substances, including handling of raw materials or monitoring of finished products, have received documented training on the SOPs that affect their area.

We will comply with the regulations governing manufacturers of controlled substances set forth in 21 CFR 1301.76. Additionally, to promote communication and information sharing with the Drug Enforcement Agency (DEA), we have identified a DEA Liaison. Our DEA Liaison is in regular contact with the DEA and stays abreast of any new requirements for the handling of regulated drugs. The liaison will also be a resource to the DEA and other law enforcement entities to obtain information about REMOXY XRT in order to get a better understanding of the product and potential risks.

We have instituted additional elements to monitor and assure the supply chain for REMOXY XRT including the following:

- **Prescription Drug Disposal Information Clearinghouse Website** – to provide education information regarding opioid (and non-opioid) drug disposal issues; connect the currently fragmented take-back community by creating a centralized location for information; and inform interested parties on the issues related to take-back programs, drug disposal and proper opioid management
- **NADDI Listserv** – listserv postings from this organization will be monitored for information related to burglary or pharmacy robberies to identify signals or patterns regarding diversion of REMOXY XRT and issues pertaining to physicians involved in possible diversion or inappropriate prescribing of opioids
- **DEA Website** – this site will be monitored for notices of denial, suspension or revocation of physician DEA Certificate of Registrations
- **Reporting of Suspicious Activities** – representatives will be instructed on how to identify suspicious activities which may raise concern regarding the

appropriateness of the prescribing of pain medications by particular healthcare professionals and how to forward those concerns for evaluation

1.4.2 MONITORING AND SURVEILLANCE

A number of passive and active surveillance systems will be implemented to assess the occurrence of adverse events and risk of overdose, misuse, abuse and diversion associated with REMOXY XRT. Additionally, the potential for lowered vigilance with regard to REMOXY XRT will be monitored through active surveillance such as media and the internet. Finally, several surveys will be conducted to test the understanding of key educational messages of the REMS directed to healthcare professionals, patients, the community and company representatives. These assessments will be used to tailor interventions to the specific signal identified and to guide any future modifications to the REMS.

1.4.2.1 Passive Surveillance Systems

The passive surveillance systems described below will commence immediately upon the availability of REMOXY XRT and will be conducted by our Drug Safety and Pharmacovigilance department in conjunction with our Risk Management Team.

Spontaneous Adverse Event Reports

Spontaneous adverse event reports meeting the criteria for expedited reporting to the FDA, as defined in 21 CFR § 314.80, will be submitted within 15 calendar days. All other reportable adverse events will be submitted to the FDA in the Periodic Adverse Drug Experience Report (PADER). We will participate in the MedWatch to Manufacturer program to obtain reports submitted directly to the FDA and will include these as part of the evaluation in PADERs.

In addition to those reports meeting the criteria for expedited reporting, the following adverse events of interest and significant safety experiences will be considered reportable and will be submitted to the FDA within 15 calendar days regardless of expectedness or meeting the definition of an adverse event:

- Deaths due to REMOXY XRT abuse
- In-patient or out-patient admission to a drug abuse treatment center due to REMOXY XRT addiction
- Overdose due to REMOXY XRT abuse

These additional expedited reporting criteria will apply to reports received from both spontaneous sources as well as reports identified in the literature.

In addition to a summary and evaluation of expedited 15-day reports and significant new safety information, the PADER will also include an evaluation of reports of misuse and abuse.

Scientific Literature

The MEDLINE database will be reviewed on a continual basis to identify reports of adverse events in the world-wide scientific literature pertaining to REMOXY XRT. Articles describing adverse events meeting the criteria for expedited reporting to the agency, as defined in 21 CFR § 314.80, will be submitted to the agency within 15 calendar days. In addition, adverse events of interest and significant safety experiences (as defined under the *Spontaneous Adverse Event Reports* section above) will be considered reportable and will be submitted to the FDA within 15 calendar days regardless of expectedness or classification as an adverse event.

1.4.2.2 Active Surveillance Systems

The process of monitoring and reporting real-time postmarketing surveillance of REMOXY XRT abuse will be accomplished by the collection of accounts of REMOXY XRT abuse from substance abuse treatment centers, internet, media and emergency room visits.

NAVIPPRO (National Addictions Vigilance Intervention & Prevention Program) Surveillance

NAVIPPRO (National Addictions Vigilance Intervention & Prevention Program) Surveillance is a risk management system designed to monitor non-medical use of prescription drugs in the United States, and allow for in-depth analysis of abuse, including product-specific rates of abuse, locations of abuse "hot spots" that may be candidates for prevention efforts, changes in the rate of abuse over time, and demographic analysis among English and Spanish-speaking populations of prescription drug abusers.

NAVIPPRO examines multiple data sources for indicators of prescription opioid abuse including a proprietary survey of patients entering substance abuse treatment (ASI-MV Connect), governmental data (FDA's AERS, DEA's news bulletins, DAWN drug related emergency room visit data) and media (news reports, legislative activity and law enforcement, internet monitoring). Incorporating multiple active and passive, quantitative and qualitative data sources ensures that all channels that may present information regarding prescription abuse are proactively monitored. These various independent and complimentary streams of information will be incorporated into a quarterly report which will provide a timely, yet comprehensive and detailed perspective of trends in drug abuse on a product specific level.

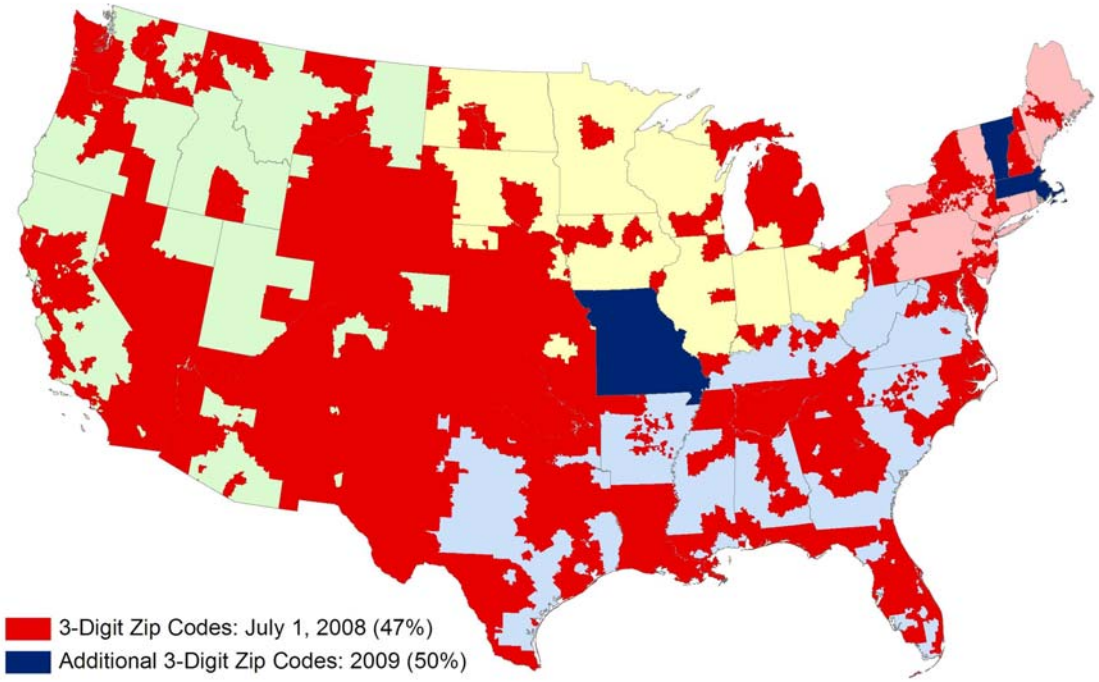
ASI-MV Connect

The NAVIPPRO program will aggregate and utilize Addiction Severity Index-Multimedia Version (ASI-MV) data as one component in the comprehensive and integrated surveillance of non-medical use of prescription opioids including REMOXY XRT. It is capable of calculating rates of non-medical use among patients in this population and obtains product specific information of patients' drug abuse habits. The Addiction Severity Index or ASI is a semi-structured interview for substance abuse patients that is administered by a clinician in a treatment setting.[11] The ASI-MV Connect is an interactive program that allows for client self-administration of the ASI assessment.

Using statistical methods, ASI-MV Connect will provide real-time access to product-specific, medically relevant data on current rates and trends in prescription drug abuse.

Currently, 317 substance abuse treatment centers are part of the ASI-MV Connect system. The area covered as depicted by the patient's home 3 digit zip code is included in Figure 2 below. Inflexxion will continue to recruit substance abuse treatment centers with the goal of having 450 sites activated by December 2009.

Figure 2. ASI-MV® Connect Network: Patient Home 3 Digit Zip Code



We will review and evaluate quarterly reports for national and regional abuse rates for REMOXY XRT compared to the entire opioid class (all opioids evaluated by ASI-MV Connect) aggregated as a group and three other comparators. Geo-spatial representation of the cases of abuse for REMOXY XRT will also be included in the quarterly reports. Product-specific abuse rates within the population of adults presenting for substance abuse treatment have been examined and defined in several ways.

Based on geospatial surveillance reports, interventions can be disseminated into specific areas where issues of misuse, abuse and diversion are detected. Effectiveness of the intervention can be monitored through active surveillance.

Additionally, details on specific routes of administration for non-medical purposes as well as the source of products for REMOXY XRT and comparators will be analyzed and reported on a quarterly basis. Demographic analysis of abusers will be presented in quarterly reports.

Internet

Internet monitoring of substance and recreational drug abuse message boards is designed to provide a temporally sensitive "snapshot" of user opinions and knowledge regarding opioid abuse, particularly actions and information regarding the use and abuse of REMOXY XRT. Selected message boards will be monitored for REMOXY XRT mentions to capture any new posts, including the verbatim body of the text, time of post, message board where the post was found, screen name of the poster and the title of the thread from which the post was drawn.

Quarterly reports will provide quantitative descriptions of the number of messages or posts related to REMOXY XRT as well as qualitative assessment of the content of these posts (e.g., whether a message encourages or discourages abuse of the product in question). Posts will be categorized by specific topic area (e.g., route of administration, extraction techniques, procurement/sources, comparison with other drugs/products, etc.).

Media Reports

The media will be monitored for report mentions of REMOXY XRT misuse, abuse and diversion. Summaries of relevant abstracts from leading media outlets and federal legislative activity of REMOXY XRT and other key words will be gathered and evaluated. Monitoring will include the use of Google News RSS Feed: Google News™ searches over 4,500 news sources from around the world on a continuous basis.

DAWN Live!, FDA-AERS and NCSBeta

NAVIPPRO will also investigate and interrogate data from the following external data sources:

- *Drug Abuse Warning Network (DAWN) Live!* is a national public health surveillance system operated by the Substance Abuse and Mental Health Services Administration (SAMHSA) that monitors drug-related visits to emergency departments. *DAWN Live!* will be reviewed for REMOXY XRT reports on a quarterly basis.
- *Food and Drug Administration Adverse Event Reporting System (FDA-AERS)* is an external, computerized database designed to support the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. Proportional reporting rates (PRR) and empirical Bayes geometric means (EBGMs) for REMOXY XRT and three comparators will be calculated quarterly.
- *American Association of Poison Control Center's New Core System Database (NCSBeta)* is an external, comprehensive poisoning surveillance database. NCSBeta will be reviewed for REMOXY XRT mentions and findings will be reported on an annual basis.

As a multi-faceted monitoring system, NAVIPPRO will provide a comprehensive and timely report on abuse, diversion and accidental overdose of REMOXY XRT and will enable the monitoring of the effectiveness of targeted risk mitigation tools and interventions implemented as part of the REMS. Quarterly reports will integrate both active and passive, quantitative and qualitative analyses. The quantitative analyses

examine several different data sources such as abuse-related adverse events in FDA AERS, emergency department visits related to prescription opioid abuse via DAWN and product specific abuse rates via survey of patients entering substance abuse treatment. Qualitative analyses incorporates research such as monitoring of drug-related internet chat sites, reports of drug abuse in the media, legislation on the topic, law enforcement bulletins and scholarly research on substance abuse. The use of various data sources complements each other. An indication of a rise in abuse of a particular product found in one data source may then be examined and verified via other sources.

NAVIPPRO is currently operational and quarterly reports will be prepared once REMOXY XRT has been approved and is available.

1.4.2.3 Surveys

An assessment of patient understanding regarding the safe use of REMOXY XRT will be made by administering surveys to patients. The survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment before it is administered to patients in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size, how the sample will be determined (selection criteria), the expected number of patients to be surveyed, how the participants will be recruited, how and when the surveys will be administered, and an explanation of controls used to minimize bias.

To assess the understanding of physicians' recall after visits by sales representatives, a Message Recall Study will be conducted within 6 months of product launch. Specifically, this study will seek to evaluate the content of the REMS messages communicated to physicians and assess physician responses to these messages.

Lastly, as part of the NAVIPPRO Surveillance risk management system, an internet survey will be conducted of college students on an annual basis to assess which prescription opioids are being abused, how these products are being abused and where these products are being obtained.

1.4.3 SIGNAL DETECTION AND EVALUATION

The effectiveness of the elements to assure safe use employed to mitigate the risks of overdose, misuse, abuse and diversion will be evaluated through monitoring and surveillance. These evaluations may suggest that the elements have no impact on a particular risk or a particular risk has increased. Additionally, risks may change or a new risk may be identified through monitoring and surveillance or risk research. Additional research on prescription opioid abuse will be conducted and these data will be used to modify the educational element of the REMS and further refine subsequent research efforts. Our Risk Management Team and Medicines Safety Board will assess the overall effectiveness of the REMS on mitigating risks with REMOXY XRT and recommend changes as appropriate.

1.4.3.1 Monitoring and Surveillance Evaluations

Data collected through monitoring and surveillance will be evaluated on a periodic basis and reported to the FDA. Table 2 below outlines the evaluations that will be reviewed.

Table 2. Monitoring and Surveillance Evaluations

Monitoring & Surveillance Element	Monitoring
Spontaneous Adverse Event Reports	
• All Postmarketing AE Reports • Serious/Unexpected AEs • Deaths due to REMOXY XRT abuse • In-patient or out-patient admission to a drug abuse treatment center due to REMOXY XRT addiction • Overdose due to REMOXY XRT abuse • Scientific Literature	• Reports of unexpected AEs • Change in frequency of known AEs • Change in seriousness or specificity of known AEs • Identification or change in risk factors for known AEs
NAVIPPRO	
Addiction Severity Index-Multimedia Version (ASI-MV) data	• Standardized rate of REMOXY XRT abuse per 100 patients assessed • Standardized abuse trends for REMOXY XRT • Standardized abuse trends for REMOXY XRT and comparison drugs calculated as cases of reported abuse per 100 patients assessed • Statistical Process Control (SPC) is used to analyze the average variability of abuse with REMOXY XRT and calculates whether future observations are within or outside of normal limits.
Drug Abuse Warning Network (DAWN) Live!	• Drug related ED admissions for REMOXY XRT by quarter for trends over time in drug use, misuse, abuse and consequences • Drug related ED admissions for REMOXY XRT by quarter subdivided by age, patient disposition, route of administration
Food and Drug Administration Adverse Event Reporting System (FDA-AERS)	• Proportional Reporting Rate (PRR) and Empirical Bayes geometric mean (EBGM) for reports of Overdose with REMOXY XRT over time • PRR and EBGM for reports of Drug Abuse with REMOXY XRT over time
American Association of Poison Control Center's New Core System Database (NCSBeta)	• Calls to poison control related to poisoning involving oxycodone. Results will include date of call and location by 3-digit zip code of call. These data will be merged with prescription data from REMOXY XRT for evaluation.

Table 2 Monitoring and Surveillance Evaluations

NAVIPPRO (continued)	
Internet	Posts from internet bulletin boards, chat sites and weblogs will be monitored for the following: • Trends for REMOXY XRT posts per month • Total number of posts per month for REMOXY XRT on each message board • Total number of unique threads with mention of REMOXY XRT on each message board Posts will be categorized into the following topic areas: • Route of administration • Extraction techniques • Procurement/sources • Comparison with other drugs/products • General posts o Abuse-related o Non-abuse related o Quote Content of individual posts related to the following routes of administration: • Injection • Inhaled/sniffed/snorted • Chewing
Media Reports	Media reports identifying reports of misuse, abuse or diversion involving REMOXY XRT

1.4.3.2 Risk Research

REMOXY XRT has extraction resistant properties. However, extraction resistance is an untested surrogate for abuse deterrence. Estimation of real-world abuse of REMOXY XRT can only be quantified prospectively post-approval in the setting of an implemented REMS. Many systems and databases exist which provide signals of prescription opioid abuse, however, there is, as yet, no consensus on the definitions of the term abuse and related terms, and on how to link any specific definition with a specific dataset, or group of datasets, to measure the phenomenon of interest. Although we anticipate that NAVIPPRO will provide a detailed dataset for monitoring and surveillance, we also recognize that additional research is warranted. Additional research will be conducted in order to better understand the complexity of prescription opioid abuse, the impact that REMOXY XRT may have, including whether new and unintended risks arise and how other tools and methodologies may impact this problem. The goals of the risk research program are to:

1. Determine whether REMOXY XRT is associated with less non-medical use than other controlled-release oxycodone products, particularly with respect to route of abuse
2. Determine the effect that the application of Universal Precautions, involving risk assessment, stratification and related clinical tools may have to better:
    a. Identify patients who are abusing or diverting prescription opioids or at high risk of doing so

b. Manage patients who are identified as at risk of abusing or diverting prescription opioids

c. Inform patients of the risks of substance misuse and abuse

Epidemiology Study

Epidemiology Studies will be conducted to describe and quantify the degree of abuse of REMOXY XRT when prescribed in a clinical setting. The study will focus on routes of abuse and will include the use of specific measurable health events (e.g., non-medical use, abuse) and routes of administration and will account for other factors such as product availability. The program will include an assessment prior to and following the market introduction of REMOXY XRT.

Research to be Conducted Prior to REMOXY XRT Launch

Specific databases will be explored to gain an understanding of the current prevalence of prescription opioid abuse (including by route of abuse) and misuse before REMOXY XRT is launched. Three databases will be utilized for this information: ASI-MV Connect, *DAWN Live!*, and NCSBeta. These three databases are also monitored as part of the NAVIPPRO Surveillance risk management system (see Section 1.4.2.2).

NAVIPPRO is one of the surveillance systems that we are using in the active monitoring and surveillance program for REMOXY XRT. The ASI-MV Connect data will provide a baseline assessment of the prevalence of prescription opioid abuse by product and route of abuse. *DAWN Live!* and the NCSBeta will provide a baseline assessment of abuse and misuse of prescription opioids. This baseline information will be used to measure the impact of REMOXY XRT using the same databases as will be interrogated post-launch.

Studies to be Conducted After REMOXY XRT Launch

An epidemiology research program aiming to evaluate the abuse of REMOXY XRT relative to a comparator, particularly with respect to route of abuse, will be implemented post launch. The model that will be used is DETER (Dynamic Evaluation & Timely Estimate of Rx Opioid Routes of Administration and Abuse Deterrence). DETER involves three components to gather data on a different aspect of route of abuse and these three components have a theoretical relationship with one another. The three components include ADAMM (Abuse Deterrent Adjusted Measurement Model), ROAM (Rx Opioid Attractiveness Measure), and iPOST (Internet-based Prescription Opioid Surveillance Technology).

ADAMM uses a multilevel, conditional logistic regression model to compare the odds ratios of two drug formulations (abuse deterrent formulation vs. a comparator) for rates of abuse. Factors such as product availability are included in the analysis. ADAMM will be the prime component that will be used to determine whether REMOXY XRT is associated with less non-medical use than other controlled-release oxycodone products. ROAM is an online survey of abusers used to measure the attractiveness of REMOXY XRT relative to other prescription opioids. iPOST involves internet monitoring to track route of abuse and extraction information and will provide a signal of potential new routes of abuse or extraction.

Data from the program will not only be used to gauge the public health impact of REMOXY XRT but importantly will be used to focus on and strengthen relevant REMS tools and tactics.

Universal Precautions Studies

A universal precautions approach to responsible pain management as an adjunct to opioid prescribing among primary care providers is currently being evaluated in a clinical trial (ACCESS 2008). This study will be followed with an additional study specifically designed to determine clinician and patient views of the various tools that may be employed, the risk assessment, stratification and intervention strategies that may be employed, and the impact such an approach may have on the overall management of the patient with chronic moderate-severe pain requiring the use of an opioid. We intend to continue updating the educational elements of the REMS with the knowledge gained from these studies.

Study 1: ACCESS 2008 (Ongoing)

Using specific tools, this study is evaluating the following outcomes in patients with chronic moderate to severe pain treated with a long acting morphine in a primary care setting:

- Potential risk for misuse and abuse
- Monitored aberrant behaviors and interventions
- Pain management recommendations based upon abuse risk stratification
- Level of compliance with a universal precautions approach

Study 2

This study will use the information learned from ACCESS 2008 in order to test specific hypotheses relative to the Universal Precautions approach, in the context of REMOXY XRT prescribing in a clinical setting.

Study 1 (ACCESS 2008) is currently ongoing and results will be available within six months of the launch of REMOXY XRT. Study 2 will be implemented within one year of the launch of REMOXY XRT.

1.4.3.3 REMS Evaluation

The Risk Management Team (RMT) will monitor and evaluate risks associated with REMOXY XRT and assess the effectiveness of the REMS in achieving its goals and objectives on a periodic basis. The performance of each element of safe use will be reviewed. Acceptability of each element by consumers and healthcare professionals will be considered. Additionally, surveillance reports will also be examined and assessed as described in our Company procedures. When a pattern of REMOXY XRT abuse is detected or a signal is identified, the issue will be further evaluated by the RMT to determine if the data are valid or invalid. The RMT may also decide to validate the findings via clinical studies or surveys of the population. Compliance with key REMS processes and procedures by Company personnel will also be assessed. All findings will be reported in the REMOXY XRT REMS assessment reports.

Risk Management Team (RMT)

The RMT is comprised of representatives from multiple functional areas within our organization. The mission of the RMT is to coordinate and review the REMS for REMOXY XRT.

The RMT will ensure commitments to FDA are fulfilled and periodically assess and provide recommendations to the Medicines Safety Board (see below) regarding the REMS components as well as safety issues for REMOXY XRT. The RMT shall meet, in person, electronically, or otherwise, as often as necessary to fulfill its mission but no less than quarterly.

In addition, the RMT will also review data from passive and active surveillance to assess safety signals related to REMOXY XRT. The RMT may initiate field investigations as needed to investigate and/or evaluate signals. These investigations may include telephone interviews and/or on-site visits with the primary reporter and/or a HCP knowledgeable of the patient/case for adverse events, administrators of addiction treatment centers, law enforcement personnel, community leaders or school officials. The RMT will escalate findings and recommended interventions to the Medicines Safety Board (MSB) for their approval.

Medicines Safety Board (MSB)

The MSB reviews aggregate safety information for the Company's development and marketed products and is charged with providing guidance, direction and/or approval regarding potential human safety issues. This group is chaired by the Chief Science Officer and its members include the heads of Drug Safety and Pharmacovigilance, Clinical Development, Medical Affairs, Regulatory Affairs, Legal and Quality. The MSB will review and approve all interventions needed to address signals identified for REMOXY XRT.

1.4.4 ADJUSTMENT

The overall goal of the REMS is to optimize the benefit-risk balance for REMOXY XRT. We will monitor the effectiveness of the REMS on meeting this goal. If a pattern of REMOXY XRT abuse is detected or a signal is identified, we are committed to implementing targeted interventions and/or adjusting the REMS.

1.4.4.1 Prevention and Intervention

Interventions and adjustments to the tools and tactics contained in the REMS will be implemented to address signals identified through signal detection and evaluation. Immediate and appropriate responses will vary depending upon the circumstances. Success of the intervention or adjustment to the tools and tactics will be monitored through active and passive surveillance.

Targeted Interventions Derived from Risk Assessments

After verification of a change in risk, responses such as direct education or communication to a specific population or key stakeholder such as law enforcement or clinicians may be implemented. Targeted interventions will be tailored to the specific signal identified. In addition to customizing the intervention, follow-up measures, which may include passive and active surveillance, will be identified to assess the effectiveness of the targeted intervention. By intervening when a signal is detected, strategies to address potential REMOXY XRT abuse and diversion issues can be implemented to mitigate further misuse, abuse and diversion of REMOXY XRT.

Examples of interventions that may be implemented in the field to address misuse, abuse and diversion of REMOXY XRT include, but are not limited to:

- **Local Community Intervention** – contact local political, community or law enforcement personnel to tailor an intervention to address the issue
- **Dear HCP Letters** – to provide educational information regarding newly identified or unmitigated risks
- **Peer Direct – PV Update** – targeted educational pushes to provide educational information regarding newly identified or unmitigated risks
- **myStudentBody: Drugs** – covers topics such as the dangers of mixing prescription opioids and alcohol, consequences on the misuse of prescription opioids, and identifying dependence
- **painACTION** – includes courses and articles on not sharing medications with others and proper storage of medication to reduce unintended access to prescription opioids

Tools and Tactics

In addition to targeted interventions, the tools and tactics may be adjusted to respond to signals including updates to the Full Prescribing Information or Medication Guide. If signals regarding diversion are identified, we will develop internal interventions or work with local law enforcement, political or community personnel to determine an appropriate

adjustment to address supply chain security. Additionally, usage rates of the individual educational initiatives (e.g., PainEDU, PainACTION, etc.) will be evaluated to determine continued use or the need or modification of the tool. Finally, surveys will be conducted to assess healthcare professionals' and patients' understanding of the risks of overdose, misuse, abuse and diversion of REMOXY XRT. Effectiveness of the adjustment will be monitored through active surveillance.

1.4.4.2 Strategy

Goals and Objectives

In addition to adjustments to the prevention and intervention tools and tactics as described, we may identify a further need to add or modify a REMS Goal or Objective. We will modify the Goals and Objectives in an expeditious manner with appropriate coordination with the FDA.

1.4.5 IMPLEMENTATION

We are prepared to commence activities as described in the *Proposed REMS Elements* immediately upon the availability of REMOXY XRT. See Appendix 2 for further information regarding the Implementation Plan for the REMS Elements.

The timetable for submission of the assessments of the REMS includes the following:

1st FDAAA assessment:	18 months from NDA approval
2nd FDAAA assessment:	3 years from NDA approval
3rd FDAAA assessment:	7 years from NDA approval

Each assessment will include a summary of the reporting period above as well as a cumulative summary and will be submitted within 60 days of the close of the reporting period.

1.5 CONCLUSION

The overall goal of this REMS is to optimize the benefit-risk balance for REMOXY XRT. The benefits of REMOXY XRT need to outweigh the associated negative health consequences of overdose and diversion activities associated with its misuse, abuse and diversion. We are committed to ensuring that the risks of REMOXY XRT are monitored and addressed accordingly.

1.6 REFERENCES

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Appendix 1. Summary of Elements to Assure Safe Use of REMOXY XRT

Risk	REMS Goal	REMS Objective	Elements to Assure Safe Use
Adverse reactions, including drug/drug or drug/alcohol interactions, occurring in the setting of appropriate pain management using REMOXY XRT Misuse of REMOXY XRT by patients	To optimize the safe and effective use of REMOXY XRT as a controlled-release opioid for the treatment of chronic moderate to severe pain	Educate healthcare professionals on the risks associated with REMOXY XRT therapy, including drug/drug and drug/alcohol interactions, medication errors, errors of dosing due to conversion from other opioids and patient misuse Educate healthcare professionals on the appropriate use of REMOXY XRT as part of the management of chronic moderate to severe pain together with ways to monitor patients and mitigate risks	Product Scheduling Full Prescribing Information Medication Guide Dear HCP Letter to Physicians Company-Sponsored Medical Education Independent Continuing Medical Education (CME) Peer Direct – PV Update PainEDU website REMOXY XRT website Dear HCP Letter to Pharmacists Independent Continuing Pharmacy Education (CPE)
		Educate patients on the risks, including drug/drug and drug/alcohol interactions, taking extra doses and use of the medication other than as directed, associated with the treatment of chronic moderate to severe pain with REMOXY XRT as a long acting opioid	Medication Guide PainACTION website REMOXY XRT website
		Ensure that company representatives thoroughly understand the risks associated with REMOXY XRT therapy, including drug/drug and drug/alcohol interactions, medication errors, errors of dosing and patient misuse, the appropriate use of REMOXY XRT and have the skills to communicate these issues appropriately and effectively to healthcare professionals	Sales Representative Training MSL Training
		Monitor adverse reactions in patients receiving REMOXY XRT	Spontaneous AE Reports Scientific Literature

Summary of Elements to Assure Safe Use of REMOXY XRT (continued)

Risk	REMS Goal	REMS Objective	Elements to Assure Safe Use
Overdose of REMOXY XRT in the opioid naïve population seeking euphorigenic effects	To prevent opioid overdose with REMOXY XRT	Increase public awareness of the issue of teen abuse and diversion of prescription drugs	MyStudentBody: Drugs Time to Talk Online
Overdose of REMOXY XRT in the opioid tolerant population seeking euphorigenic effects or to satisfy drug craving in opioid-addicted individuals		Promote the understanding among parents, adolescents and young adults of the serious risks associated with prescription opioid abuse	MyStudentBody: Drugs Time to Talk Online
Overdose of REMOXY XRT in combination with CNS depressants including alcohol		Educate healthcare professionals on the issue of overdose of prescription opioids in adolescents and young adults and the importance of engaging their patients in the mitigation of this risk	Full Prescribing Information Medication Guide Dear HCP Letter to Physicians Company-Sponsored Medical Education Independent CME Peer Direct – PV Update PainEDU website REMOXY XRT website Dear HCP Letter to Pharmacists Independent CPE
		Educate patients on the risks of overdose with prescription opioids as well their role in protecting family and friends from accidental or unintended exposure to their medication	Medication Guide PainACTION website REMOXY XRT website

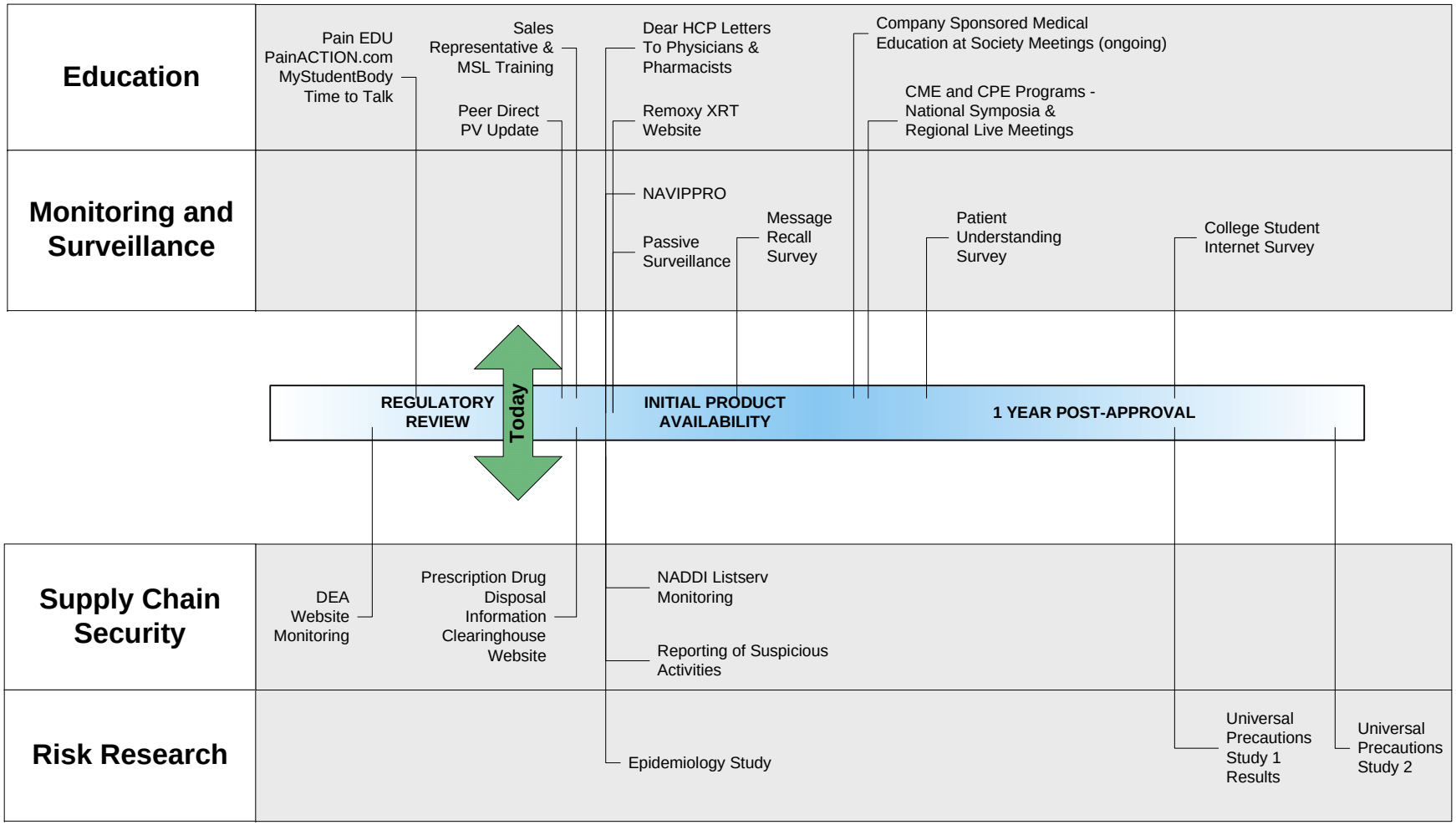
Summary of Elements to Assure Safe Use of REMOXY XRT (continued)

Risk	REMS Goal	REMS Objective	Elements to Assure Safe Use
		Prevent accidental ingestion of REMOXY XRT by children	Medication Guide PainACTION website REMOXY XRT website Prescription Drug Disposal Information Clearinghouse website
		Decrease the amount of unsecured as well as unused controlled substances available in patient households	Medication Guide Prescription Drug Disposal Information Clearinghouse website
		Monitor rates of overdose of REMOXY XRT	Spontaneous AE Reports Scientific Literature NAVIPPRO Media Reports Internet
Abuse and Diversion of REMOXY XRT	To prevent the abuse and diversion of REMOXY XRT	Educate healthcare professionals on the risks of REMOXY XRT abuse and diversion, the importance of engaging their patients in the mitigation of these risks and ways to assess patients and mitigate risks	Full Prescribing Information Medication Guide Company-Sponsored Medical Education Independent CME Peer Direct – PV Update PainEDU website REMOXY XRT website Independent CPE

Summary of Elements to Assure Safe Use of REMOXY XRT (continued)

Risk	REMS Goal	REMS Objective	Elements to Assure Safe Use
		Educate patients on the risks associated with and their role in preventing abuse and diversion of REMOXY XRT	Medication Guide PainACTION website REMOXY XRT website
		Increase community awareness of the issue of opioid abuse and diversion of prescription opioids	MyStudentBody: Drugs Time to Talk
		Educate parents, adolescents and young adults about the dangerous issue of prescription opioid abuse and diversion	MyStudentBody: Drugs Time to Talk
		Prevent diversion from the supply chain	Prescription Drug Disposal Information Clearinghouse website Supply chain SOPs Basic Flow of Materials Process DEA Liaison DEA Form 106 NADDI listserv and DEA website Reporting of Suspicious Activities
		Monitor the abuse and diversion rates of REMOXY XRT	Spontaneous AE Reports Scientific Literature NAVIPPRO Media Reports Internet

Summary of Elements to Assure Safe Use of REMOXY XRT (continued)

Risk	REMS Goal	REMS Objective	Elements to Assure Safe Use
Perception that responsible pain management practices may not apply to the treatment of moderate to severe chronic pain with REMOXY XRT	To ensure that health care professionals and patients remain vigilant against the possibility of misuse, abuse and diversion when REMOXY XRT is prescribed and dispensed according to the conditions of labeling	Inform healthcare professionals that the potential for misuse, abuse and diversion of REMOXY XRT remains Provide education on the use of a universal precautions approach as a means to assess, stratify and mitigate these risks	Full Prescribing Information Medication Guide Company-Sponsored Medical Education Independent CME Peer Direct – PV Update PainEDU website REMOXY XRT website Independent CPE
Patients taking fewer precautions with the use of REMOXY XRT when securing and disposing their medication in an appropriate way		Ensure patients have a clear understanding of the risks of misuse, abuse and diversion with REMOXY XRT as well their role in protecting family and friends from accidental or unintended exposure to their medication	Medication Guide PainACTION website REMOXY XRT website
		Ensure that company representatives thoroughly understand the risks of misuse, abuse and diversion with REMOXY XRT and have the skills to communicate these risks effectively to healthcare professionals	Sales Rep Training MSL Training
		Monitor the misuse, abuse and diversion rates of REMOXY XRT	Spontaneous AE Reports Scientific Literature NAVIPPRO Media Reports Internet

Appendix 2. Implementation Plan