

Remoxy[®]: A Novel Formulation of Extended-Release Oxycodone Developed Using the ORADUR[®] Technology

Michael Zamloot¹

Wendy Chao²

Ling-Ling Kang²

Julie Ross³

Roger Fu¹

¹*Pain Therapeutics, Inc, San Mateo, CA*

²*Durect Corporation, Cupertino, CA*

³*King Pharmaceuticals, Inc, Cary, NC.*

Julie Ross

King Pharmaceuticals

4000 CentreGreen Way, Suite 300

Cary, NC 27513

Phone: 919-653-7048

E-mail: julie.ross@kingpharm.com

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ABSTRACT

As opioid use for the treatment of acute and chronic pain has increased in the United States, so have the potential problems associated with opioid misuse such as dependence, addiction, overdose, and abuse. Opioid abusers seek fast onset euphoria, and therefore, typically rely on tampering (physical and/or chemical manipulation) to facilitate their preferred route of abuse. ORADUR[®] is a novel, oral, extended-release formulation that was designed to resist the most common methods of tampering and has been incorporated into Remoxy[®], a twice-daily extended-release oral capsule of oxycodone being developed for the treatment of moderate to severe pain in patients

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requiring continuous around-the-clock opioid treatment for an extended period of time. This paper reports several in vitro studies that assessed the specific performance characteristics of Remoxy capsules compared with a typical commercial extended-release oxycodone following physical and chemical challenges including crushing, extraction, injection, and volatilization (inhalation). The results of these studies demonstrated that in all cases, the Remoxy formulation was less vulnerable to tampering or modification to facilitate delivery compared with a commercially available extended-release oxycodone. Although Remoxy cannot eliminate abuse, these data present evidence of its resistance to common tampering practices that may translate to an incremental improvement toward reducing nonmedical use of prescription opioids.

INTRODUCTION

Opioids are one of the most frequently used prescription medications in the United States, with a recent representative survey reporting that over 10 million Americans take opioids in any given week.¹ Although considered an effective treatment for both acute and chronic pain,² the potential for misuse of opioids is a concern, as it can lead to problems including dependence, addiction, overdose, and abuse. For example, the most recent Treatment Episode Data Set from the Substance Abuse and Mental Health Services Administration indicated more than 85,000 admissions to substance-abuse treatment programs per year for prescription opioid abuse.³ Furthermore, in the most recent Drug Abuse Warning Network Report, the number of emergency department (ED) visits for nonmedical use of narcotic pain relievers increased by 111% from an estimated 144,644 visits in 2004 to 305,885 visit in 2008.⁴ Oxycodone was the most frequently involved opioid, accounting for 105,214 ED visits in 2008 – a 152% increase over the reporting period.⁴

Routes of Abuse

Opioid abusers seek fast onset euphoria, and usually rely on the four most prevalent routes of abuse of prescription opioid medications, including oral ingestion (whole or crushed), snorting, injection, and inhalation. Long-acting or extended-release formulations are prone to abuse because they have a much higher content of the active ingredient than immediate-release forms (usually enough to last 12 to 24 hours) and often exclude a co-formulated, non-opioid analgesic ingredient (eg, acetaminophen) that can make snorting or injection less desirable. Tampering, defined as physical and/or chemical manipulation, is often employed to defeat the rate-controlling feature or modify the physical form to facilitate the preferred route of abuse.

Tampering occurs more frequently among experienced abusers than recreational

abusers. However, the rate of tampering among recreational abusers is still high, and cause for concern. In an internet survey of nearly 900 recreational prescription opioid abusers, 74% reported snorting or sniffing OxyContin® (Purdue Pharma LP, Stamford, CT) and 34% reported chewing and swallowing the drug.⁵ Tampering may be associated with accelerated progression along the trajectory of addiction. For example, approximately 17% of abusers were tampering when they first initiated prescription opioid abuse, whereas this increased to 78% by the time they entered treatment.⁶ Additionally, adverse medical consequences are greater with self-administration following tampering than administration by the intended route. In the Researched Abuse, Diversion, and Addiction-Related Surveillance System® Poison Center database, ingestion following tampering was associated with a major outcome or death in 8.6% of cases. Other routes of administration resulted in even higher rates of major outcomes or death. Inhalation was reported in 10.3% of cases, and injection in 16.5% of cases (Richard Dart, personal communication). Tampering has also been associated with dramatically higher rates of injection-related diseases such as acquired immune deficiency syndrome (AIDS) and hepatitis.⁷

ORADUR Technology and Remoxy

New formulations and drug-delivery technologies have been developed to address the growing problem of nonmedical use of prescription opioids. ORADUR is a novel, oral, extended-release formulation comprised of a viscoelastic fluid matrix that is filled into a capsule.⁸ It was designed to deter the most common methods of tampering that would lead to a rapid release of the entire opioid content, including crushing and swallowing or crushing for subsequent snorting, extraction, injection, or volatilization (ie, to promote smoking or inhalation).

In its native state, the ORADUR formulation, as filled in the capsule, has

predominantly viscous properties analogous to a thick honey, and remains as such even at subzero temperatures, thereby rendering freeze-fracture of the matrix virtually impossible (Figure 1). In an aqueous medium or in the gastrointestinal tract, the fluid matrix transforms from the viscous state to a matrix, with predominantly elastic properties that control the rate of drug release and resists rapid extraction. Furthermore, the high viscosity of the ORADUR matrix deters direct injection and also serves as a significant barrier to prevent volatilization (inhalation) of an incorporated drug at elevated temperatures.

The high viscosity and sticky properties of the formulated matrix aid in the resistance to various modes of tampering. Furthermore, the high viscosity of the ORADUR fluid matrix (approximately 60,000 centipoise [cP]) deters direct injection and also serves as a significant barrier to volatilization (inhalation) of the incorporated drug at elevated temperatures. By comparison, fluids such as molasses (8640 cP) and honey (1760 cP)⁹ are approximately 7 and 34 times less viscous than the Remoxy matrix.

Remoxy[®] (King Pharmaceuticals, Inc., Bristol, TN) is a twice-daily (BID) extended-release oral capsule of oxycodone being developed for the treatment of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time. Remoxy is formulated with the ORADUR technology, which combines the desired extended drug release profile with novel and patented physico-chemical formulation properties that resist common methods of tampering intended to result in the rapid release of oxycodone. This paper presents the results of several in vitro studies that assessed the specific tamper-resistance characteristics of Remoxy capsules following physical and chemical challenges.

METHODS

Information from public sources, includ-

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ing scientific journals, media coverage, and regulatory reports (ie, US Food and Drug Administration, National Institute on Drug Abuse, Substance Abuse and Mental Health Services Administration, Drug Enforcement Agency [DEA]), scientific advice of experts (including prescribing physicians, addictionologists, law enforcement professionals, and ex-DEA staff), and information from abusers that is available from internet blogs was instructive in establishing protocols for in vitro testing. This resource information provided a comprehensive understanding of the demographics among the population of nonmedical users of opioids, the prevalence and preferred routes of abuse by opioid ingredient, and the adaptive methods used to defeat the rate-controlling mechanisms or modify the product to facilitate an alternate route of administration.

The resistance of Remoxy to tampering was determined through multiple in vitro studies that assessed the extent of oxycodone extraction from the formulation, or the potential of modifying the formulation for injection, snorting, or volatilization. The tests were designed to simulate common methods of drug abuse and incorporated adaptive procedures that were influenced by the material properties of the formulation. An assortment of routinely available household resources were used during testing in an attempt to promote extraction under the conditions of various thermal (extreme heat and cold), mechanical, and chemical challenges. Extraction and volatilization studies were conducted with three lots of Remoxy 40-mg capsules, and one commercial lot of OxyContin 40-mg tablets as a comparator. A matching placebo formulation was used to assess the potential to inject the high viscosity fluid formulation of Remoxy (placebo formulation is a rheologically equivalent surrogate in injectability testing and avoids compliance practices required when working with controlled substances).

Although a general description of the test procedures is included below, specific

details are limited to avoid providing a step-wise set of instructions that could be used by potential abusers.

Extraction

The in vitro extraction assessment consisted of five studies:

- Extraction in beverages and common household liquids
- Extraction in aqueous buffers (pH 1–12)
- Physical and mechanical stress followed by solvent extraction
- Extraction in cooking oil
- Extraction following extreme heating.

In general, for each extraction study, the exuded Remoxy formulation or crushed and ground OxyContin tablets were placed into a closed jar containing the extraction vehicle and agitated for a period of time. Samples were taken at 5, 20, and 60 minutes (at 30 and 60 minutes for extraction in cooking oil), centrifuged, and assayed for oxycodone using high performance liquid chromatography (HPLC). The procedure employed for the physical and mechanical stress test included Remoxy samples being crushed and subjected to a grinding process after prolonged holding at extreme cold temperature, before extraction.

Extractions were performed in an assortment of solvents including aqueous, organic, or a mixture of the two. For extraction in beverages and common household liquids, four readily available aqueous or organic liquids were examined that spanned a pH range of 2.5 to 10.1. Extractions were also assessed in six aqueous buffers prepared from inorganic acid or alkali that spanned a pH range of 1 to 12. The extraction studies also included solvents that were introduced to samples at room temperature or were preheated.

Injection

The injection potential of Remoxy formulation matrix was evaluated using a matching

placebo formulation with the same rheological characteristics as Remoxy. The ability of the high-viscosity fluid formulation to be drawn into a syringe and the ability to deliver the formulation (injectability) through various bore hypodermic needles (18, 21, 25, and 27 gauge) were evaluated. An adaptive technique that involved squeezing the placebo formulation from a cut capsule into the posterior end of the barrel was also evaluated.

The mass of the room temperature placebo formulation transferred into a syringe was measured to assess each loading technique. Injectability was evaluated using placebo-filled syringes prepared in the laboratory and fitted with various gauge needles (18–27 gauge). Samples were equilibrated to 25°C or 37°C for testing, which was performed using an Instron® Load Frame instrument (Instron Corporation, Norwood, MA) operated at published parenteral injection rates of 150 to 950 mm/min. An injection was considered successful (pass) if >80% of the prefilled mass was delivered. Several failure modes were identified, including a plunger barrel failure (internal pressure causing the syringe barrel to flex and fluid to bypass the plunger), a force failure (force needed to deliver the formulation was greater than the average “pinch” forces reported for the strongest age group of healthy males), or a Luer-Lok™ coupling failure (excessive internal pressure within the syringe causes the needle to separate from the syringe).

Volatilization (Inhalation)

The experimentally determined optimum heating temperature and time to maximize recovery of oxycodone from Remoxy capsules or OxyContin tablets were used for the volatilization study. Samples of Remoxy were exuded from the capsule and OxyContin tablets were crushed before introduction into the sample containers. Samples were uniformly heated using a heat distribution block that was instrumented to provide a

Table 1. Mean (SD) Percentage Oxycodone Extracted From Remoxy Samples (n=9 per solvent) Following Extreme Heating

	5 Minutes	20 Minutes	60 Minutes
Solvent 1	2 (2.2)	7 (3.0)	14 (5.9)
Solvent 2	4 (4.2)	9 (4.8)	20 (8.3)
Solvent 3	4 (2.6)	11 (4.6)	20 (6.9)

continuous display and record of the temperature. The vapor from the heated samples was cooled and condensed, and oxycodone was recovered and quantified using HPLC.

RESULTS

Extraction

In vitro extraction data demonstrated that the Remoxy formulation does not permit the rapid extraction of oxycodone in a set of common household solvents or aqueous buffers of varying pH. On average, 1% or less of the oxycodone in prepared samples of Remoxy was extracted after 5 minutes in Solvents 1, 3, and 4, and 6% was extracted in Solvent 2 (Figure 2). This is compared with $\geq 90\%$ of oxycodone, on average, extracted from prepared samples of OxyContin at the same timepoint in Solvents 1 and 3, 74% in Solvent 4, and 60% in Solvent 2 (Figure 2). A slight increase in the mean percentage of oxycodone extracted from Re-

moxy (range, 3%–15%) was observed at 60 minutes, but still remained lower than that extracted from OxyContin, for which values remained relatively steady throughout the time course (Figure 2). Similar results were seen in the study of extraction in aqueous buffers, with $\leq 1\%$ of oxycodone, on average,

extracted from Remoxy samples after 5 minutes for all six buffers compared with mean values of 64% to 89% for OxyContin samples (Figure 3). Extraction was negligible ($\leq 1\%$) from both Remoxy and OxyContin in cooking oil.

While the extent of oxycodone extracted from Remoxy showed a slight increase resulting from physical and mechanical manipulation, only a minor portion of the dose was extracted compared with the majority of the OxyContin dose being extracted after 5 minutes (Figure 4). Extraction of Remoxy samples in four test solvents following freezing and crushing gradually increased to between 18% and 35% over the 60 minutes time course (Figure 4). This is compared with 78% to 90% of oxycodone extracted from OxyContin at 5 minutes, with slight increases thereafter (Figure 4).

Table 2. Summary of the Injectability Evaluation of Remoxy

	18 Gauge Needle			21 Gauge Needle			25 Gauge Needle			27 Gauge Needle		
	Plunger Speed (mm/min)			Plunger Speed (mm/min)			Plunger Speed (mm/min)			Plunger Speed (mm/min)		
	150	550	950	150	550	950	150	550	950	150	550	950
25°C												
Attempt 1	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Attempt 2	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Attempt 3	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
37°C												
Attempt 1	Pass	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Attempt 2	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail
Attempt 3	Pass	Pass	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail	Fail

Extraction results following extreme heating demonstrated that 20% or less of the overall dose of oxycodone was extracted from the Remoxy capsule at 60 minutes (Table 1; OxyContin was not assessed in the extreme heat study).

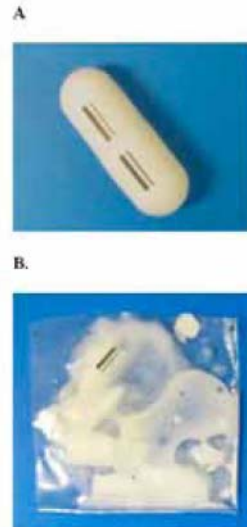
Injection

It was demonstrated that because of the high viscosity of the Remoxy formulation, it could not be drawn into a syringe using the largest bore needle evaluated (18 gauge). Consequently, additional evaluations using smaller bore needles were not performed. On average, about 54% (range, 28%–64%) of the formulation was transferred to the syringe following an improvised method of squeezing the contents from the capsule into the barrel. The results of the injectability evaluations are summarized in Table 2. In general, one or more failure modes occurred under all test conditions for all but the 18 gauge needle. Remoxy placebo formulation was delivered through an 18 gauge needle at both temperatures at the slowest plunger rate (150 mm/min), and in 2 of the 3 37°C samples tested at the mid-range injection rate (550 mm/min).

Volatilization

The rate of oxycodone liberated from heated Remoxy samples was slower and included noxious vapors from co-formulated ingredients as compared with the rapidly liberated oxycodone vapor from OxyContin. After 10 minutes of heating Remoxy or OxyContin samples, the formulation residue was charred and ceased to liberate vapor. The volatilization of oxycodone from OxyContin occurred within about 30 seconds of initiating heating and finished within 3 minutes resulting in an average recovery of 12% (Figure 5). Beyond 3 minutes of heating, condensed oxycodone showed slight thermal degradation in the apparatus as evidenced by a 2% reduction in the portion of dose recovered. Throughout the course of heating Remoxy, a heavy vapor from the formulation excipients accompanied the oxycodone

Figure 1. An intact ORADUR capsule (1A) and freeze fracture resistance of capsule following a crushing action (1B).



done vapor. After 5 minutes of continuous heating, approximately 4% of the dose, on average, was recovered from the vapor of the heated samples. A maximum of 12% of the dose was recovered from vapor after 10 minutes of continuous heating.

DISCUSSION

The results of these in vitro studies demonstrate the tamper-resistant properties of Remoxy subjected to common methods of physical/mechanical and chemical challenges, and in all cases, the data indicate that the formulation is less vulnerable to tampering or modification to facilitate delivery compared with a commercially available extended-release oxycodone product. The Remoxy formulation limited the extraction of oxycodone in common household solvents and aqueous buffers with a maximum extraction of 15% and 12% at the end of the sampling period, respectively. In contrast, the release of oxycodone from OxyContin was rapid and substantial with 60% to 91% released at 5 minutes in common household solvents and 64% to 89% released at 5 minutes in a range of aqueous buffers.

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Figure 2. Mean (SD) percentage of oxycodone extracted from Remoxy ($n=9$ per solvent) and OxyContin ($n=3$ per solvent) samples in typical household solvents.

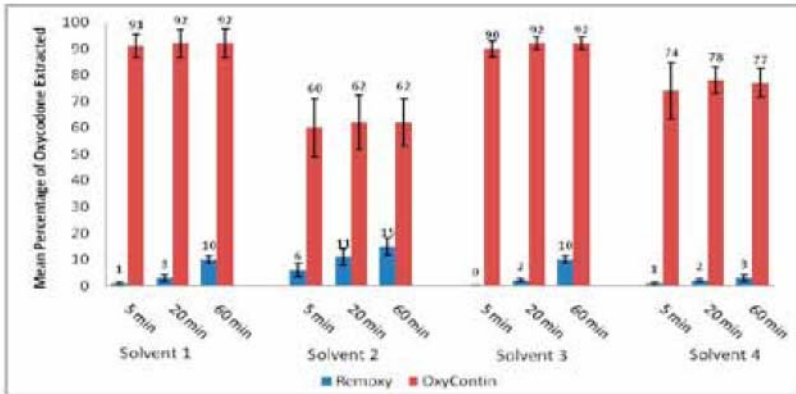


Figure 3. Mean (SD) percentage of oxycodone extracted from Remoxy ($n=9$ per buffer) and OxyContin ($n=3$ per buffer) samples in aqueous buffers.

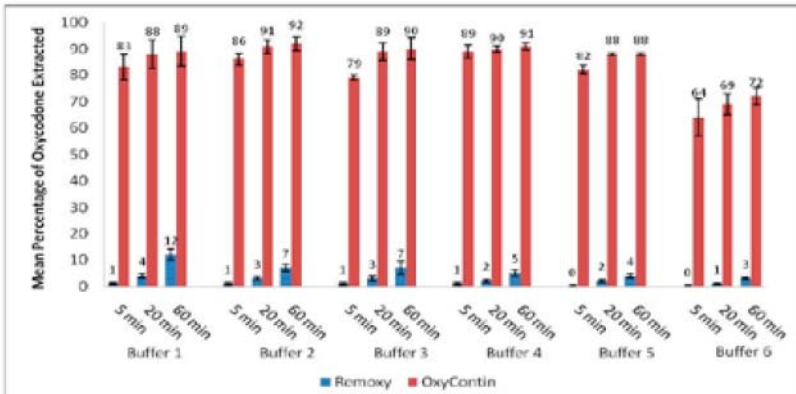
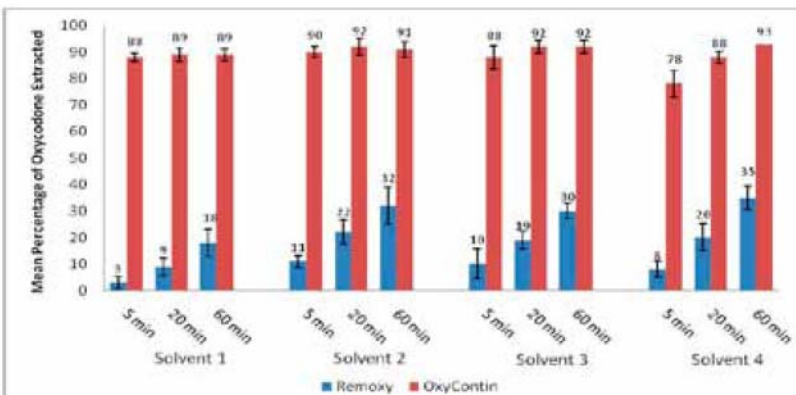


Figure 4. Mean (SD) percentage of oxycodone extracted from Remoxy ($n=9$ per solvent; samples were frozen before being crushed) and OxyContin ($n=3$ per solvent) samples in solvents following crushing.



Furthermore, extraction of oxycodone from Remoxy following freezing, crushing, and grinding resulted in a maximum recovery of 35% of the oxycodone dose at 60 minutes compared with the extraction recovery of 78% to 90% of the oxycodone dose from crushed and ground OxyContin at 5 minutes. Similar results with Remoxy were observed following extreme heating, with 20% of the oxycodone dose extracted at the final sampling time point.

Remoxy was also compared with OxyContin in volatilization studies which, based on quantitative and qualitative assessments, showed Remoxy to have a slower rate of oxycodone volatilization and coliberation with noxious excipient vapors, suggesting that Remoxy is an unlikely candidate for inhalation abuse. For abuse by inhalation, rapid liberation of a pure drug vapor is desirable, which when accompanied with a high conversion recovery of solid drug to vapor (ie, sublimation) can lead to a greater prevalence of inhalation abuse. Subjective factors such as taste, odor, or irritancy to the respiratory tract and lungs may affect desirability of smoking as a preferred route of abuse.

Injection of the Remoxy formulation was also assessed. Because of its high viscosity, the formulation could not be drawn into a syringe, and more than 40% was wasted when an improvised method was followed. Additionally, injection of Remoxy could only be achieved using the largest bore hypodermic needle at low (25°C and 37°C samples) and medium (37°C samples only) plunger speed. Of note, this hypodermic needle gauge (18 gauge) is typically used for aspiration biopsy, and is much larger than syringes with 27- and 28-gauge needles that are typically distributed nationally through needle exchange programs. Injection abuse with commercial long-acting oxycodone includes a prerequisite procedure whereby the controlled release feature of the

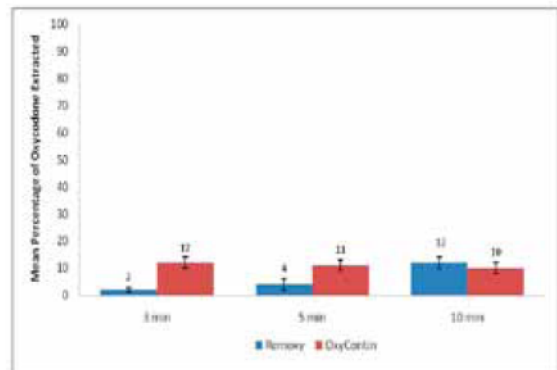
dosage form is defeated and its full dose is dissolved in a small volume of aqueous vehicle for injection. Extraction studies have shown that Remoxy did not rapidly release its oxycodone dose following a broad set of physical and chemical manipulations. Therefore, should a motivated abuser inject Remoxy, the intact formulation matrix would slowly release the drug and not offer the rapid blood level that is associated with a drug “high.” Additionally, injection of the intact highly viscous fluid matrix would likely lead to serious adverse effects. In consideration of the extraction resistance, and difficulties associated with loading and injecting Remoxy, it is not expected to be a candidate for injection abuse.

An oral extended-release opioid that reliably delivers medication within the human gastrointestinal tract while resisting physical/mechanical and chemical influences appears to be a dichotomy. Although Remoxy cannot eliminate abuse, data presented herein offer evidence of its resistance to common tampering practices that may translate to an incremental improvement toward reducing nonmedical use of prescription opioids.

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Figure 5. Mean (SD) percentage of oxycodone recovered from vapor of Remoxy (n=3 per timepoint) and OxyContin (n=3 per timepoint) in the volatilization evaluation.



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Conflict of Interest/Disclosure

Information: J. Ross is an employee of King Pharmaceuticals, the company that is commercializing Remoxy, M. Zamloot and R. Fu are employees of Pain Therapeutics, Inc., the company that developed Remoxy, and W. Chao and L. Kang are employees of Durect Corporation, the company that developed the ORADUR technology.

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