SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

FALL 2025

Precision Timed Release and CTx-1301: A New Frontier for CNS Drug Delivery and ADHD Therapeutics

By Hengning Yang

AUTHOR BIOGRAPHY

Hengning (Karl) Yang is a Senior at Saint Andrew's College in Ontario, Canada. After graduating from university, Karl aspires to work in the pharmaceutical field, specifically pharmacology.

ABSTRACT

In a 2021 systematic review study, it is estimated that there are approximately 9.34% of adults who have ADHD, which translates to 366.33 million people worldwide (Song et al., 2021). According to the National Institute of Mental Health, ADHD is characterized by inattention, hyperactivity, and impulsivity (NIMH). To manage ADHD symptoms, several medications such as Ritalin, Concerta, and Adderall have been developed. This review will explore the mechanism of a newly developed drug delivery system known as Precision Timed Release (PTR), focusing on its application to CTx-1301, which is currently undergoing clinical trials and under review by the FDA. PTR is designed to release medication at predetermined times, offering ADHD patients a more controlled and effective treatment. In addition to analyzing how PTR functions within CTx-1301, the review will compare this new technology to the delivery systems currently used in ADHD medications, highlighting both the advantages and limitations of current approaches. Finally, the review will examine the broader Central Nervous System (CNS) medication market to display the potential of the ADHD market and the growing demand for innovative treatments. This market overview will underscore the commercial and therapeutic potential of both PTR and CTx-1301 if both are successful shortly.

Keywords: *Precision Timed Release (PTR), CTx-1301, dexmethylphenidate (DMPH), Attention-Deficit/Hyperactivity Disorder (ADHD), OralogiK™ technology, drug delivery system, treatment-emergent adverse events (TEAEs), abuse-deterrent formulation, Central Nervous System (CNS), patent expiration, once-daily dosing, pharmaceutical innovation.*

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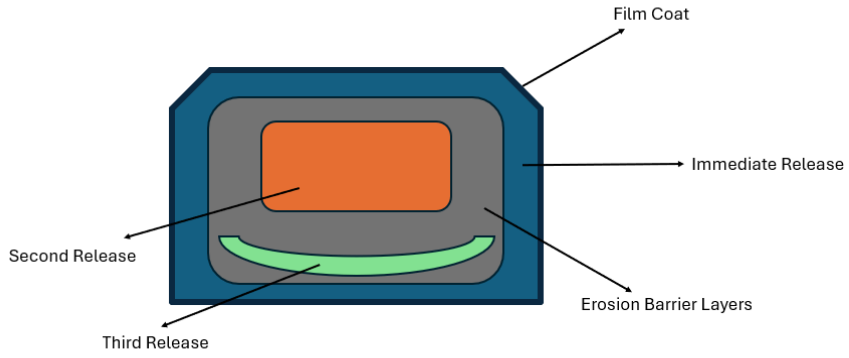
INTRODUCTION

PTR is a drug delivery platform technology that provides patients with controlled drug release at pre-determined times when the drug doses should be released. There is no drug release until the intended release. To achieve this, PTR is incorporated with BDD Pharma's OralogiK™ technology, also known as the Erosion Barrier Layer (EBL) technology, an erodible barrier that is wrapped around the core of the drug-containing core to give a tablet-in-tablet dose form. It is designed to erode at a controlled pace till eventually all drugs in the core are released (Cingulate Technology). BDD Pharma has licensed this technology to Cingulate, allowing them to patent it as a part of PTR.

Figure 1
Diagram of PTR Structure



Note. The film coat (black layer) on the outermost layer helps shield the active pharmaceutical ingredient and extend the shelf life. Immediate release (blue) contains the initial dosage of the drug. Erosion Barrier layers (grey layer) control drug release at pre-determined times. The second (orange layer) and third (green layer) releases provide the last two doses of the drug at pre-determined times.

PTR overcomes common disadvantages of traditional timed-release formulations by providing a more precise and controlled mechanism. They address it by offering a mechanism that is more controlled and precise. The technology includes several innovative features that fix many drug issues using traditional timed-release technology. The technology addresses the problem of requiring patients to take immediate "booster" doses, which could cause insatiable medication levels. PTR fixes it by only requiring the patient to take one pill for the day, and the drug dosage is only released at a pre-defined time for the drug to be more effective and remain more stable (Figure 1). The once-daily dosing also simplifies the medicine regimen, potentially improving a patient's compliance with the doctor's orders (Cingulate). Meanwhile, the adoption of technology provides patients with the choice of taking their drugs, either with or without food, giving the patients more freedom (Cingulate).

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E-ISSN: 2996-8380
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Above all, adopting this technology in psychiatry might improve patients' overall experience of using psychiatric drugs.

In the context of CTx-1301, the PTR technology functions by having one outer Film Coat and two Erosion Barrier Layers with three releases (Figure 1). Respectively, they are the first and the immediate second and third releases (Figure 1). The immediate release provides patients with 35% of a person's required daily dosage, designed to achieve its therapeutic efficacy within 30 minutes (Figure 1). The second release happens three hours after patients take the drug and provides patients with 45% of a person's daily dosage over 90 minutes (Figure 1). The third release, the final release, happens seven hours after patients take the drug and releases 20% of a person's daily dosage within 30 minutes (Figure 1).

The erosion-based mechanism controls the rate of dexmethylphenidate (DMPH) release, the primary substance used to improve attention and impulse; the mechanism allows the drug to be released at a controlled rate and is independent of factors like pH level or Gastrointestinal motility (*Controlled Drug Release & Timed Release Delivery Solutions,* 2022). By adjusting the erosion timing, PTR can ensure drug release after specific delays to create pulsatile release profiles (*Controlled Drug Release & Timed Release Delivery Solutions,* 2022). In short, PTR's mechanism is to physically "time-gate" the release of the active drug.

However, the release of new technology typically comes with many disadvantages. In the context of CTx-1301, dexmethylphenidate safety is still a concern. Like many other methylphenidate-based medications, DMPH can come with side effects such as dizziness, headache, tics, restlessness/akathisia, nausea/vomiting, dry mouth, decreased appetite, weight loss, abdominal pain, tachycardia, and palpitations (MedlinePlus). Even though a study has shown that CTx-1301 has a lower incidence of treatment-emergent adverse events (9%) compared with the placebo (30%) (Biospace, 2024), its relatively small sample size still raises questions of potential concerns that are yet to be addressed. For the patients, the adoption of new technology typically means the drug will not be affordable; the high price of the drug will push patients away to look for alternative medications instead of choosing CTx-1301 if they are not covered by insurance.

CTx-1301 (PTR) COMPARED WITH CURRENT ADHD MEDICATION OPTIONS

It is imperative to note that even though the PTR is currently patent, there is an expiration date around 2036-2037. After this time, the technology will be free in the public domain and can be utilized in other medications. In the context of PTR, it is highly likely for other direct competitors in the ADHD market to adopt the exact or similar approach to their drug delivery technology, and potentially, other medicines could be doing so as well.

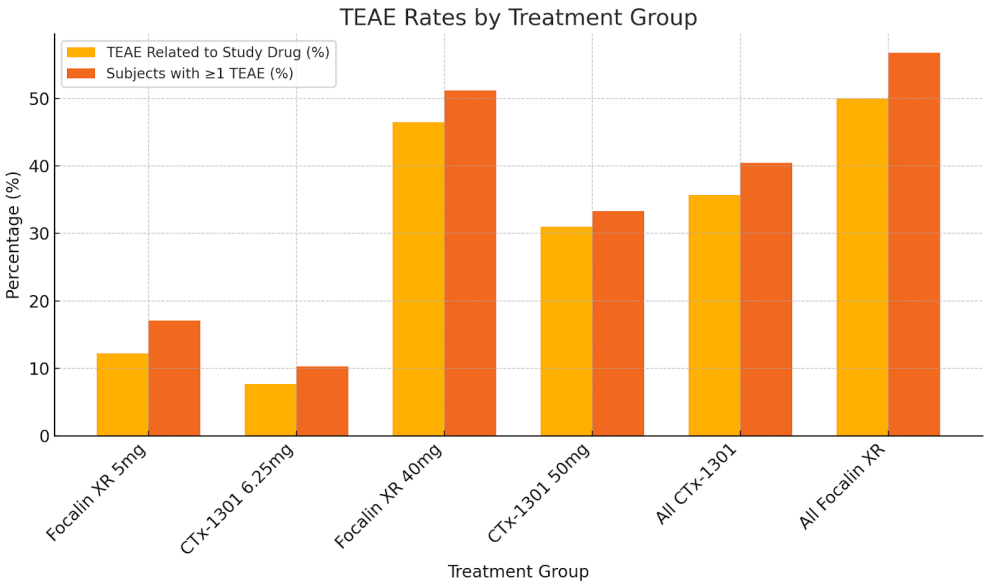
Figure 2

Comparison of Different Doses of Focalin XR and CTx-1301 and Their Respective Treatment-Emergent Adverse Events (TEAE)

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

FALL 2025



Note. The dose of Focalin XR was 5mg and 40 mg, and the dose of CTx-1301 was 6.25mg and 50mg. The yellow bars represent the percentage of TEAEs that CTx-1301 causes, and the orange bars represent the test subjects that experienced one or over 1 TEAEs. Reprinted from "Ctx-1301 comparative bioavailability study," by M. Brams et al., 2019, *Case Medical Research*, https://doi.org/10.31525/ct1-nct04138498. Copyright 2019 by M. Brams.

For example, in Figure 2, compared to traditional stimulant ADHD medication such as Focalin XR, CTx-1301 demonstrated a faster onset of release, a prolonged controlled descent, and an extended therapeutic duration of 4 hours (Brams et al., 2019). The phase ½ clinical trial data above suggest that adopting new delivery technology positively impacts both the speed of immediate release and the duration of the drug. Meanwhile, the clinical study has also found that CTx-1301 has significantly lower treatment-emergent adverse events (TEAE), about 28.6% lower (Brams et al., 2019). Since the adoption of PTR has significantly improved the release of DMPH, it is and more than likely will be adopted by other current medications, such as Ritalin (3-4 hours duration) **(**DailyMed**)**, which requires multiple daily doses, therefore reducing patient compliance; Concerta and Focalin XR both seeing more TEAEs due to their extended release mechanism (Andrade, 2015. Brams et al., 2019).

Additionally, something that no academic research papers have discussed is the potential of how PTR can lower the risk of drug abuse and overdosing. For starters, its controlled release mechanism ensures that even if someone takes more tablets than prescribed, the slow, multi-phased release- immediate, sustained, and delayed, limits the rapid spike of DMPH in the blood levels that the abusers seek for euphoria. Unlike immediate-release, which immediately delivers the dosage in the tablet, making it more prone to abuse. Next, having a drug delivery system without sharp peaks, it has a more consistent dopamine release that can decrease the psychological state

that fuels abuse. Finally, the once-daily intake decreases the frequency of dosing, lowering the opportunities for sharing, selling, or misusing the extra pills, indirectly reducing the amount that can be used.

Beyond ADHD, many other conditions have medications that require multiple daily dosing, and they can potentially see significant improvements by using the PTR release mechanism, an example being medications or drugs with toxicity. Some drugs come with side effects or toxicity due to the rapid increase in plasma level after the initial dosage release, a prime example of this could be the asthma/COPD drug Theophylline. Theophylline is a methylxanthine derived from tea/cocoa, and has been used for over 80 years as a bronchodilator. However, recently it has shifted its role to using it as an anti-inflammatory drug for both asthma and COPD (Barnes, 2013). Theophylline exhibits anti-inflammatory effects at lower concentrations than bronchodilation (Barnes, 2013). At around this concentration, the drug can inhibit phosphodiesterase-4 and activate histone deacetylase-2 to suppress the expression of the inflammatory gene. Though low concentration may lower the side effects of the drug, however, research has suggested that toxic doses of theophylline can be as low as 7.5 mg/kg, with continuous treatment recommending 8 mg/kg twice daily, it is possible for certain patients to experience common adverse effects such as headache, nausea and vomiting, abdominal discomfort and restlessness (Barnes, 2013).

A study in 1990 has already suggested that once-daily formulation is better than the traditional twice-daily formulation. The once-daily formulation can peak during 2-6 AM, when asthma symptoms and airway obstruction often peak in patients, having 36% higher theophylline levels overnight compared to average levels. In contrast, twice-daily formulations only see a 3% increase compared to average levels (D'Alonzo et al., 1990). Furthermore, patients on the once-daily formulation also reported comparable daytime lung function, more stable airflow, and fewer symptoms that affect patients' quality of life (D'Alonzo et al., 1990). However, there are several potential shortcomings of once-daily formulations: greater fluctuation in serum levels, more adverse events during inpatient testing, and greater variability in serum concentration (D'Alonzo et al., 1990). By adopting PTR, theoretically, it addresses all the issues above through its erosion-based, tablet-in-tablet design that delivers the drug in precisely timed pulses rather than a single large dose. The multi-phase release mechanism smooths the plasma level and reduces the fluctuation, also minimizing the risk of adverse events that come with the fluctuation at various periods. Additionally, PTR's pH-independent erosion layers make its release profile more predictable and consistent across individuals, regardless of food intake, posture, or GI motility. This predictability helps stabilize therapeutic drug levels and enhances both safety and performance.

Another more recent study published in 2010 confirmed similar results. This specific study compared the two different doses of once-daily formulation of Indacetorl and twice-daily formulations of Formoterol used for COPD treatment (Dahl et al., 2010). The 52-week study divided 1732 participants with moderate to severe COPD into four equal groups: Indacaterol 300 μg once daily, Indacaterol 600 μg once daily, Formoterol 12 μg twice daily, and placebo group. The results of the study indicate that after 12 weeks of treatment, both once-daily Indacetrol doses outperform the twice-daily Formoterol by increasing the trough of Forced Expiratory Volume in one second (FEV1) by 100 mL, and the results remain significant after 52 weeks (Dahl et

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al., 2010). The difference is measured during the morning, when COPD patients describe it as the time that they experience the worst symptoms (Dahl et al., 2010).

CNS MARKET OVERVIEW

As of 2024, the CNS (Central Nervous System) market continues to grow, propelled by the rising international burden of psychiatric and neurological disorders. The global market is roughly $140 billion, with North America leading due to its health infrastructure and aging populations (*Central Nervous System Therapeutics Market Report, 2030*). The Asia-Pacific region comes behind North America, led by China and India, and is projected to grow fastest at an 11% compound annual growth rate (*Central Nervous System Therapeutics Market Report, 2030*). However, with such high market value, the CNS therapeutics market continues to be acknowledged as a high-risk and high-reward sector within pharmaceutical development. Recent estimates indicate that the total cost of developing a drug often takes billions of dollars and typically takes 12-15 years to fully develop the drug when taking into account time and failures. With these presented challenges, though there is a clear societal and clinical need for CNS drugs, few effective ones are reaching the market, which is primarily contributed to by the extended development timelines and high failure rates in late-stage trials, often failing in Phase II or Phase III due to the complex human biology (Wegener & Rujescu, 2013).

An example of a highly successful and profitable CNS drug would be Ocrevus, also known as Ocrelizumab, which generated over $6.7 billion in sales for Roche in 2024 (Zacks Equity Research, 2025). Though the research and development cost of Ocrevus was never disclosed, a study published in 2020 suggested that "the estimated median capitalized research and development cost per product was $1.1 billion, counting expenditures on failed trials" (Wouters et al., 2020). Also, considering the complexity of the research, we can estimate that in the case of Ocrevus, it will be in the multi-billion range, showing the significant risk that comes when investing in the research and the development of the drug. Ocrevus is an immunotherapy designed to target and reduce the B-cell-mediated activity in primary progressive multiple sclerosis (Montalban et al., 2017). According to Montalban et al, multiple sclerosis is described as "a disease in which progression consists mainly of gradual worsening of neurologic disability from symptom onset, although relapses may occur," and more specifically, primary progressive multiple sclerosis is is a chronic form of MS where neurological function declines steadily from the beginning, without the ups and downs seen in other types. It is thought to be driven by immune-related damage, particularly involving B cells. (Montalban et al., 2017). Before Ocrevus, there was no disease-modifying treatment available for the patients due to the failure of previous clinical trials, which makes the invention of Ocrevus much more significant. The start of the Ocrevus research and development can be traced back to 1986, when Stephen Hauser initiated the lab work at Harvard in 1986 and later continued the work at UCSF in 1992, developing an improved animal model that more closely mirrors multiple sclerosis in humans (Bai, 2017). Later, Hauser decided on a clinical approach to tackle multiple sclerosis by confirming that transferring B cells with antibodies and T cells causes multiple sclerosis-like disease in animals (Bai, 2017). However, in 2001, when Hauser petitioned the NIH to trial rituximab (a cancer drug that targets CD20 B cells) in multiple sclerosis, the NIH declined its request and suggested that Hauser focus on T-cell therapies instead (Bai, 2017). Therefore, later on, he turned to Genentech to initiate a pilot rituximab trial in multiple sclerosis,

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which showed impressive and immediate reduction in new inflammatory activity after a single dose (Bai, 2017). In 2008, though, a pivotal study was published on rituximab in multiple sclerosis, giving the concept widespread validation, fueling the interest in B-cell depletion as a therapeutic approach (Sorensen & Blinkenberg, 2015). In 2010, Genentech developed Ocrevus (a humanized anti-CD20 monoclonal antibody) to refine safety and efficacy profiles over rituximab, and later reported the Phase II results for Ocrevus, marking its first signal of efficacy in treating multiple sclerosis (Kappos et al., 2011). In 2015, Genentech presented interim results of three Phase III clinical trials (Hughes, 2015), and soon after, in 2016, the FDA granted breakthrough therapy designation for primary progressive multiple sclerosis. Later in the year, Publication of two primary Phase III trials—OPERA I & II—in The New England Journal of Medicine produces results that shows Ocrevus reduces MS relapse rates by 47%, disability progression by 43%, and MRI lesions by 95%, compared to interferon beta-1a, indicating major success (Hauser et al., 2017). Therefore, in 2017, the FDA approved Ocrevus as the first therapy approval for both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) (Bai, 2017).

An example of a failed CNS drug with flashes of early potential above will be Aducanumab, a drug used for Alzheimer's disease treatment. A 2015 report by FierceBiotech reported that Biogen, the company that developed Aducanumab, will be committing 2.5 billion dollars to the whole research and development process, which by all means is considered an extremely high-stakes gamble (Carroll, 2015). According to the Neurimmune website, the biopharmaceutical company that has discovered Aducanumab licensed it to Biogen in 2007 under a collaborative development and license agreement. The early-stage study in 2015 reported amyloid plaque reduction (Biogen, 2015). Therefore, the company began two pivotal trials–EMERGE and ENGAGE–launched in mid-2015; however, both trials were halted based on futility analysis of data pooled from the first approximately 50% of enrolled patients, indicating that both trials are unlikely to meet their endpoints (Budd Haeberlein et al., 2022). However, Biogen later revisited the complete dataset and claimed that the high-dose arm in EMERGE showed approximately 23% slower cognitive decline, prompting them to move forward with a regulatory filing despite ENGAGE remaining negative (Park, 2019). Therefore, based on those findings, Biogen began pursuing FDA approval (Park, 2019). In June 2021, after reviewing the clinical data presented by Biogen, Aducanumab was granted accelerated approval to treat early Alzheimer's disease based on amyloid plaque reduction as a surrogate endpoint, even though one of the key Phase III trials failed and the cognitive benefit was uncertain (Tampi et al., 2021). Afterwards, Biogen launched the drug at $56,000/year, sparking controversy, and many healthcare systems opted not to prescribe Aduhelm, citing insufficient benefit relative to cost and risk (Tradeoffs, 2024). As a result, Biogen discontinued the drug's development and commercialization in 2024 (Biogen, 2024).

THE GLOBAL CNS PATENT OVERVIEW

When mentioning the business aspect of pharmacology, it is essential to discuss the patent and how different pharma companies leverage it to generate more profit from the drug it has developed. However, what exactly is a patent? According to the World Intellectual Property Organization, "A patent is an exclusive right granted for an invention. Patents benefit inventors by providing them with legal protection of their inventions."

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(WIPO) However, it is also important to note that for all patents, the exclusive right only lasts for a specific period, typically lasting about 20 years in the United States and the EU (USPTO, 2025; EPO), and after the designated time, the invention covered by the patent can be freely used, reproduced, and selled by anyone without the permission of the owner of the patent. Therefore, currently in the market, many CNS blockbuster drugs are entering the end of their patent and their monopoly of the market.

An example can be brivaracetam, an FDA-approved antiepileptic drug indicated as adjunctive therapy for partial-onset seizures in adults and adolescents 16 years or older, where its primary purpose is to Reduces the frequency of partial-onset seizures in patients who are not fully controlled on one or two existing antiepileptic drugs (Khaleghi & Nemec, 2017). Brivaracetam's patent is anticipated to expire on February 21, 2026; however, the company was able to leverage a patent strategy called a multi-layered pharmaceutical patenting approach. This patenting approach is designed to protect the core molecule early, then extend market exclusivity through secondary patents. In this case, the secondary patent protects specific compositions, improved methods of administration, or combinations (Google Patent). The last patent is filed to delay generic competition beyond the initial patent cliff. The overall patenting strategy is to help the company that developed the drug, UCB, extend protection around brivaracetam's formulation and use, even after the core compound patent expires.

After a company files a patent and establishes a monopoly in its specific market, it must advertise and market its drug to potential customers, patients, doctors, or hospitals to generate profit. There are various strategies to advertise the drug, and one of the most common strategies for companies trying to sell the CNS drug is directly advertising to the consumers or patients. An strong example of a CNS drug that had a strong emphasis of advertising to the patients or the consumer of the drug is Abilify, or known as aripiprazole is used for the treatment of Schizophrenia, which it does so by balancing the dopamine activity in the brian through reducing dopamine in areas with overactivity, and preserves dopamine in areas with underactivity (Ribeiro et al., 2018). Abilify focused on advertising the drug's function to help with depression rather than schizophrenia, to reduce the stigma, and reach a broader audience base. In an Abilify TV advertisement, it can be seen that a middle-aged woman is struggling with everyday symptoms, and showing how the woman, after taking Abilify, was able to experience an improvement in life quality and not letting depression define who she was (Abilify, 2010).

CONCLUSION

With the current information and details that are available online, it can be said that the PTR and CTx-1301 could be the representation of an evolution in the future of drug delivery system and ADHD medication respectively, with showing promises in a variety of categories, whether being a longer therapeutic window, less adverse events, or the potential to battle with drug abuse etc. However, some potential concerns regarding DMPH, being the stimulant used for CTx-1301, remain relevant as DMPH comes with side effects such as dizziness, headache, tics, restlessness/akathisia, nausea/vomiting, dry mouth, decreased appetite, weight loss, abdominal pain, tachycardia, and palpitations, though addressed by PTR but not completely resolved.

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However, despite these potential benefits, there are still concerns regarding the scalability and affordability of this delivery technology, especially for the millions of patients in the United States without health insurance coverage. Additionally, the small sample size presented in the clinical trials does not provide a definite answer of CTx-1301 being a better option than other ADHD treatments with mature technology, such as Concerta, Focalin XR, and Ritalin. To increase the sample size of the clinical study, Cingulate could start another phase 3 study that invites participants from its phase 1 or 2 studies to participate. Not only would it improve the sample size, but it would also help Cingulate to expand data on CTx-1301's long-term safety and stability. Additionally, one of the significant concerns of CTx-1301 will be its affordability for all the patients; it will establish its monopoly over the market, making it impossible for consumers to find alternatives, therefore restricting the affordability of the medication.

Looking ahead, the expiration of the PTR patent around 2036-2037 opens a future with tons of opportunity for pharmaceutical companies, as they might adopt this technology (if Cingulate and BDD Pharma do not leverage any patent strategies to prolong this). This not only opens an opportunity for ADHD medications, but also for other CNS drugs with a need for a prolonged release, such as Invega Sustenna for Schizophrenia, Vyvanse for eating disorders, and Xtampza ER for chronic pain. These applications could reduce toxicity, simplify regimens, and improve therapeutic consistency. Still, the broader adoption of PTR will depend on post-market studies, cost-benefit analysis, and policy incentives.

In conclusion, while PTR presents itself as a delivery technology as a step forward in precision pharma, its future success highly depends on the phase 3 clinical trials of CTx-1301 since it is currently the only drug known to market that adopts this specific technology. Furthermore, factors such as affordability and thoughtful integration into both the therapeutic and commercial ecosystems will affect the future success of the technology.

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E-ISSN: 2996-8380
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