Regulatory Frameworks, Licensing Requirements, and Drug Accessibility: Challenges in Puerto Rico Related to Innovative Treatments for Chronic Depression

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Abstract *— This study examined how licensing requirements, certifications, and regulatory frameworks influence drug pricing and access to innovative treatments in Puerto Rico, using TRANQUI-Spray (a fictitious name used for confidentiality purposes), a Risk Evaluation and Mitigation Strategy (REMS)-mandated, controlled-substance nasal spray for treatment-resistant depression as the central case study. The research analyzed how intellectual-property protections and complex approval pathways shape market dynamics, limit competition, and contribute to high medication costs. It also evaluated how FDA and DEA regulations, REMS infrastructure, and clinical certification requirements restrict the availability of novel therapies for chronic diseases. Through a qualitative approach, the study identified structural barriers to equitable access and highlighted opportunities for regulatory simplification, expanded REMS-certified capacity, and improved policy alignment. Findings underscore the need for streamlined processes that reduce administrative burden, support generic entry, and enhance affordability, ultimately promoting better health outcomes and strengthening Puerto Rico's healthcare system.*

Keywords *— Drug Pricing, Patent Regulations, Puerto Rico Healthcare, Treatment-Resistant Depression.*

INTRODUCTION

Healthcare in Puerto Rico faces significant challenges that limit access to affordable, innovative treatments for chronic conditions. This research aims to investigate how regulatory requirements, licensing processes, patents and market access conditions influence the accessibility of innovative treatments and the affordability of drugs in Puerto Rico. The innovative TRANQUI-Spray product was used as the reference case study for this design project. TRANQUI-Spray represents a C-mine nasal spray prescribed for severe depression in adults who have not responded to conventional treatments. It is a derivative of CALMmine and is administered under medical supervision in a certified healthcare center. TRANQUI-Spray is approved for use in adults with specific conditions: Treatment-resistant depression (TRD); For patients who have not responded adequately to at least two other antidepressant medications. It is often prescribed in conjunction with an oral antidepressant. Major depressive disorder (MDD) with acute suicidal ideation or behavior: For this use, it is combined with an oral antidepressant [1].

PROBLEM STATEMENT

The high cost of medications is a pressing issue for patients in Puerto Rico, where many struggle to access essential treatments due to financial constraints. One key factor affecting drug prices is the presence of many regulations, patent laws, licenses, and certifications that protect pharmaceutical companies' intellectual property. While these regulated documents stimulate innovation by enabling companies to recoup their investments, they often lead to higher drug prices, limit market competition, and make healthcare unaffordable for many individuals on the island.

Furthermore, the regulatory framework surrounding the development and approval of novel treatments can significantly impact patient access to

essential medications. This research will specifically evaluate how regulatory processes (specifically, the documentation management process) influence the availability of innovative therapies for chronic diseases, focusing on TRANQUI-Spray, a novel treatment for resistant depression. Understanding these critical issues is essential to balancing innovation with equitable access to healthcare for Puerto Rico's population.

Research Description

This research examined how regulatory requirements, licensing processes, patents laws and market access conditions influence the availability and accessibility of innovative treatments for chronic diseases in Puerto Rico. Using TRANQUI-Spray as the primary case study, the investigation explored how FDA and DEA regulatory frameworks, REMS requirements, certification processes, and market dynamics may affect treatment accessibility, pricing, and patient access for treatment-resistant depression. The study also considered the roles of regulatory and commercialization requirements, as well as regulatory compliance requirements, in shaping the commercialization and distribution of novel pharmaceutical therapies. Through this analysis, the research aimed to provide insight into the relationships among healthcare regulation, market accessibility, and the public health challenges associated with innovative treatments in Puerto Rico.

Research Objectives And Scope

This research aims to analyze the regulatory, licensing, patents, and market-access factors associated with TRANQUI-Spray for the handling of treatment-resistant depression. The study focuses on FDA and DEA regulatory requirements, REMS certification processes, pricing considerations, and operational barriers that may influence treatment accessibility in Puerto Rico and the United States. In addition, the research examines how regulatory and commercialization requirements, as well as healthcare compliance procedures, may affect the commercialization and distribution of innovative pharmaceutical products. Through qualitative regulatory and market analysis supported by expert interviews and secondary regulatory sources, the study seeks to identify factors that may limit or facilitate patient access to innovative therapies.

Literature Review

Mental health disorders have risen substantially since the COVID-19 pandemic, with depression and anxiety increasing >25% globally in 2020 [2]. This research will encompass a comprehensive analysis of Puerto Rico's existing patent laws and their impact on medication affordability. It will explore how these laws shape market dynamics and the pricing structure of pharmaceutical products. Additionally, the study will evaluate the regulatory processes involved in the development and approval of innovative treatments for chronic diseases, with a specific focus on TRANQUI-Spray for resistant depression. By examining these two critical factors, this research aims to provide insights that inform policy recommendations and initiatives to enhance access to affordable healthcare for patients with chronic conditions in Puerto Rico.

In 2019, the U.S. Food and Drug Administration approved C-mine, the S-enantiomer of CALMmine, marketed as TRANQUI-Spray for adults with treatment-resistant depression and for major depressive disorder with suicidal ideation [2]. Its effectiveness has been replicated in numerous studies across diverse patient groups [2]. However, despite this evidence and the urgent need for new treatments, broader adoption has been slowed by the intensive monitoring required during and after dosing under the drug’s FDA-mandated REMS [2], [3].

The Food and Drug Administration Amendments Act of 2007 empowered the FDA to require REMS programs to ensure a drug’s benefits outweigh its risks [2], [3]. REMS go beyond standard labeling, targeting specific safety concerns

and mandating actions to reduce their likelihood or severity [2], [3]. TRANQUI-Spray's REMS addresses risks of abuse and misuse, as well as adverse effects such as physiological changes, dissociation, and sedation [2], [3]. It mandates provider training and certification, and in-clinic observation by a healthcare professional for at least two hours post-dose [2], [3]. Before discharge, clinicians must confirm that blood pressure is within an acceptable range and that dissociative symptoms have resolved [2], [3].

Other consciousness-altering therapeutics (e.g., classic psychedelics, MDMA) show promise but will likely require similar intensive monitoring, posing infrastructure barriers to widespread adoption [2]. Passive, continuous physiological monitoring, now feasible with modern sensors and consumer-grade devices, has improved outcomes in other areas of medicine and could reduce the burden of these treatments [2]. MindMed developed MSMS, a smartphone/smartwatch-based system to monitor patients during consciousness-altering sessions passively; this proof-of-concept study (MSMS-001) tests its feasibility during TRANQUI-Spray care [2]. During research, the TRANQUI-Spray treatment for any patient, the standard REMS care continued: vitals at ~40 and ~120 min post-dose; CADSS and MOASS at ~120 min; extended observation if needed; recording ended at release [2], [3]. Passive monitoring could reduce the monitoring burden associated with REMS-like requirements, potentially improving scalability and access for consciousness-altering treatments [2], [3]. According to Lee and Sprague, "Since its establishment in 1906, the FDA has been at the center of several national controversies. The agency has been criticized by consumers, pharmaceutical companies, and governmental and nongovernmental bodies alike for being too strict, not strict enough, or unfairly biased in its approvals and regulations" [4]. By emphasizing the public health impact of chronic diseases, especially mental health conditions such as depression, this research will underscore the need to expand access to innovative and affordable treatments, ultimately improving patient outcomes, well-being, and quality of life. Previous studies have highlighted the importance of improving regulatory guidelines, approval processes, market exclusivity policies, and innovation assessment frameworks to enhance healthcare accessibility and affordability. Prior research suggests that effective policy reforms in drug pricing and regulation may improve health outcomes, reduce financial burdens, encourage the use of generic medications, and expand healthcare access, benefiting individuals and supporting Puerto Rico's broader economic recovery and growth.

METHODOLOGY

This section describes the seven steps applied in the methodology.

- **Research Design**: The study used a qualitative research approach supported by regulatory, market, and documentary analysis, together with expert interviews and secondary data sources. This design enabled a comprehensive understanding of the multiple factors influencing medication costs and access to innovative treatments in Puerto Rico**.**
- **Literature Review**: A detailed review of academic research, legal databases, government publications, and case studies was conducted to examine the economic effects of patent protections, the relationship between regulation and pharmaceutical pricing, the development of innovative treatments such as TRANQUI-Spray, and broader issues of healthcare access and affordability on the island.
- **Data Collection**: Quantitative data included information on patent laws, licensing structures, certification requirements, and TRANQUI-Spray pricing from pharmaceutical databases, insurers, and pharmacies. Qualitative data were gathered through semi-structured interviews with healthcare providers, policy experts, legal professionals, and regulatory specialists to understand

perceptions of regulatory barriers, pricing, and access.

- **Data Analysis**: Regulatory, pricing, and market-access information were analyzed through comparative and descriptive analysis to identify patterns related to treatment accessibility, licensing requirements, and regulatory barriers.
- **Comparative Framework**: A comparison with other jurisdictions, particularly the mainland United States, was developed to contextualize Puerto Rico's regulatory environment and assess how differences in patent laws, licensing requirements, and regulatory processes influence drug pricing and treatment availability.
- **Policy Recommendations**: Findings from both data streams informed policy recommendations aimed at improving access to TRANQUI-Spray and other essential medications. These recommendations will be communicated through executive summaries, stakeholder presentations, and comprehensive reports designed to support regulatory and legislative decision-making.
- **Ethical Considerations and Recommendations**: The study adhered to ethical standards regarding informed consent, confidentiality, and voluntary participation, with Institutional Review Board approval sought from the Polytechnic University of Puerto Rico. Limitations such as data availability, potential interview bias, and generalizability were acknowledged. Ethical rigor ensured that the research could meaningfully guide improvements in drug pricing policy and access to innovative treatments.

MARKET AND REGULATORY ANALYSIS

This section presents a market and regulatory analysis of TRANQUI-Spray, integrating expert interview findings with the regulatory requirements governing combination and parenteral products. The analysis also examines the regulatory framework, patents, licenses, and other compliance requirements that influence product approval, distribution, and public accessibility.

Qualitative Data: Expert Interviews

As part of the information-gathering process, multiple meetings and interviews were conducted with key personnel from the TRANQUI-Spray manufacturer and the pharmaceutical industry in Puerto Rico. Also, additional information was obtained from regulatory agency websites and official TRANQUI-Spray sources. Below are the key findings obtained from three expert interviews.

The first interview was conducted with a *Senior Compliance Specialist* (*Regulations*). The following questions were asked: How would you classify the TRANQUI-Spray Product to determine which regulations apply? What are the regulations for a combination drug? What is the process, or what documents are necessary, for the approval of a parenteral product?

According to the interviewee, the pharmaceutical industry in Puerto Rico is divided into two entities: synthetics and biotherapeutics. The biotherapeutic products or parenteral products correspond to TRANQUI-Spray, a parenteral product and a combination product. This product is regulated by the FDA and the DEA under CFR 210/211 for Combination Products, CFR 610 for Sterility Testing, and CFR 600-800 for Biologics. We can find the process and the list of documents (guidance) on the websites of the FDA, ICH, eCTD, and the DEA. More details in the Market and Regulatory Analysis section.

The second interview was conducted with the *Medical Affairs Associate Director (Market Division)*. The following questions were asked: What could be the contraindications that may affect the accessibility of TRANQUI-Spray to the public? What permits or licenses must a treatment center obtain to administer TRANQUI-Spray? What is that process like?

Refer to details in the Market and Regulatory Analysis section for a regulatory-focused

explanation of contraindications that limit public access to TRANQUI-Spray (CALMmine) and the permits, licenses, and certifications a treatment center must obtain to administer it, based strictly on FDA labeling, REMS requirements, and DEA rules. For testimony, refer to the conclusion section.

The third interview was conducted with a *Biotherapeutics QA Senior Manager*. The following questions were asked: What is the range of pricing of TRANQUI-Spray in the U.S. and Puerto Rico? Why are there different prices in the U.S. vs Puerto Rico? How many people can access this treatment in the U.S. vs Puerto Rico?

The response indicated that pricing varies; they depend on the dosage to be administered to the patient, the country where it will be distributed, and the availability of a certified center to receive TRANQUI-Spray treatment. More information is available in the Results (about pricing section).

Regulatory Framework for TRANQUI-Spray

This section presents the regulatory framework governing TRANQUI-Spray as a combination and parenteral product in the United States and Puerto Rico. It also discusses the interactions between FDA and DEA regulatory requirements, as well as patents, licenses, and other regulations that influence the product's approval, distribution, and administration.

FDA Regulations for Combination and Parenteral Products

In the United States and Puerto Rico, products that combine two or more types of medical products (such as drug-device combinations) are regulated primarily by the Food and Drug Administration (FDA). Below is a summary of the key regulations and guidelines related for combination products:

- **Definition and Overview**: A Combination Product is a product composed of two or more regulated components (e.g., drug, device, biological product) [5].
- **Regulatory Framework**: The main regulatory framework comes under Title 21 of the Code of Federal Regulations (*21 CFR*): Part *3* - Covers the classification and regulation of combination products. Part *4* - Addresses the good manufacturing practice requirements for combination products [5].
- **Designation Process**: The FDA has procedures for designating the primary mode of action (*PMOA*) for a combination product, determining which center will regulate it (*CDER* for drugs, *CDRH* for devices, or *CBER* for biologics) [5].
- **Pre-market Requirements**: Pre-market Approval (*PMA*), required for Class III combination products. New Drug Application (*NDA*) or Abbreviated NDA, required for drug components. The *510(k)* submission, required for certain device components to demonstrate substantial equivalence [5].
- **Post-market Regulations:** Manufacturers must report adverse events to the FDA. Also, must comply with labeling regulations applicable to the primary mode of action.
- **Good Manufacturing Practices (*GMP*)**: Is about the *Quality Systems Regulation* (*QSR*), where device components must comply with QSR. Also, the Current Good Manufacturing Practice (*CGMP*), in which the drug components must adhere to CGMP [5].
- **Safety and Effectiveness**: If the combination product requires clinical data to demonstrate safety and effectiveness, appropriate *clinical trials* must be conducted.
- **Special Considerations / Risk Assessment:** Combination products might involve unique risk considerations that need to be addressed through specific studies. To support this, the FDA provides guidance documents for specific types of combination products (e.g., drug-device combinations).
- **Puerto Rico Regulations:** Puerto Rico follows the federal laws and regulations set by the FDA, with additional local regulatory requirements enforced by the Puerto Rico

Department of Health, specifically the Food and Drug Administration of Puerto Rico.

Guidance Documents for Parenteral Products

FDA publishes guidance documents to assist in the development and regulation of combination products, outlining expectations for QA, regulatory affairs, and CMC review during NDA, ANDA, or BLA submissions, with emphasis on sterility, aseptic processing, and container-closure controls.

For parenteral products guidance, the FDA requires documents submission materials to be filed in *eCTD* format using the Common Technical Document (*CTD*) structure [5] which is divided into 5 CTD Modules.

- **Module 1: Administrative & Labeling Documents (region-specific, U.S. FDA)** Required documents include: FDA Form 356h (application form), cover letter, application type (NDA, ANDA, or BLA), establishment information (FEI, DUNS), debarment certification, financial disclosure forms, patent certifications (ANDA/NDA) if applicable, facilities and manufacturing sites, environmental assessment or categorical exclusion, proposed labeling (prescribing information, container labels, carton labels) and REMS (if required) [6].
- **Module 2: Quality Overall Summary (QOS)** is the high-level summary of sterility, formulation, manufacturing, controls, and stability data. The nonclinical & clinical overviews **(**summarized justification of): safety, pharmacology, clinical performance [6].
- **Module 3: Quality (CMC)** is the *most critical component* of the submission for parenteral products, as it establishes product quality, safety, and manufacturing consistency. It includes three major sections: drug substance, drug product, and manufacturing process. The *Drug Substance* section details the active pharmaceutical ingredient (API), including information on the manufacturer, the manufacturing process, analytical specifications, impurity profiles, reference standards, and stability data [6]. The *Drug Product* section focuses on the parenteral formulation, the composition of the product, excipients, and pharmaceutical development data such as compatibility studies, hold-time studies, microbiological rationale, and validated analytical methods including sterility testing, endotoxin testing, particulate matter analysis, pH, osmolarity, assay, and impurity assessments. It also includes risk evaluations related to aseptic processing and final product specifications. The *Manufacturing Process* section describes the batch formula, aseptic operations, sterilization, validation, media-fill studies, and the container closure system. It also requires regional documentation such as GMP certificates, facility registrations, sterility validation, environmental monitoring, cleanroom classification, and aseptic operator qualifications, ensuring compliance with FDA regulations under 21 CFR Parts 210, 211, and 610.12.
- **Module 4: Nonclinical Study Reports** include: toxicology (including local tolerance for injectables), pharmacology, safety studies [6].
- **Module 5: Clinical Study Reports** required unless waived (some ANDAs): Phase I–III clinical study reports, bioequivalence (for ANDA injectables), safety and efficacy data [6].

Additional expectations for parenteral products (frequently requested during FDA review) are Pre-Approval Inspection (PAI) readiness, Continued Process Verification (CPV), Data integrity & ALCOA+ compliance, and the Lifecycle CMC change strategy [6].

Interaction Between FDA and DEA Regulatory Requirements

Combination products are regulated under FDA rules (21 CFR Part 4), while the DEA regulates controlled substances, including parenteral controlled drugs, under the Controlled Substances Act (CSA). These are two different but

overlapping regulatory frameworks [7]. Parenteral controlled substances (e.g., injectable Schedule II opioids, benzodiazepines, C-mine molecules, etc.) fall under the Controlled Substances Act (CSA) and DEA regulations. Key requirements include:

- **Scheduling (21 U.S.C. §§ 811–812)**: The DEA assigns the drug to Schedule I–V based on abuse potential and medical use; also, parenteral forms of Schedule II drugs (e.g., morphine, fentanyl) are tightly controlled.
- **Registration Requirements (21 CFR Part 1301):** Any entity that manufactures, distributes, dispenses, imports, or exports a controlled parenteral drug must be DEA-registered.
- **Security Controls (21 CFR §§ 1301.71–1301.76):** Secure storage (safes, vaults, restricted access), alarm systems, and employee screening.
- **Recordkeeping & Inventory (21 CFR Part 1304):** Detailed logs of receipt, dispensing, wastage, and disposal; biennial inventory of all controlled substances.
- **Labeling & Packaging (21 CFR Part 1302):** Must include the controlled substance symbol (e.g., "C-II, C-mine"); tamper-evident packaging for parenteral products.
- **Ordering & Transfer (DEA Form 222 for Schedule II)**: Schedule II parenteral drugs require a DEA Form 222 for purchase or transfer.
- **Disposal (21 CFR Part 1317)**: Reverse distributors must handle destruction; witnessed wastage for parenteral doses in clinical settings. But *how do DEA and FDA Regulations Interact?* If a product is both A controlled substance and a combination product (e.g., an injectable controlled drug in an autoinjector). Both frameworks apply simultaneously, as shown in Figure 1.

Patents Laws, Licenses, and Other Regulations

TRANQUI-Spray remains expensive and limited in Puerto Rico primarily due to seven extensive patent protections and regulatory exclusivities (US11883526, US11311500, US10869844, US11173134, US11446260, US8785500, US9592207) that prevent generic competition until at least 2028 and possibly 2040 [8]. These protections allow monopoly pricing, with monthly treatment costs often exceeding USD $4,700-6,800 and remaining comparable or higher in Puerto Rico due to logistical constraints (refer Figure 2). Patent-driven costs interact with FDA-REMS requirements, which restrict administration to certified centers with specialized infrastructure. Puerto Rico has only two centers, certified in San Juan and Caguas, while insurers impose stringent prior authorization requirements. Together, these factors significantly restrict access for patients with treatment-resistant depression.

Despite evidence supporting new treatments, their broader adoption has been hindered by the extensive monitoring required during and after dosing, as outlined in the FDA-mandated REMS for the drug. The FDA Amendments Act of 2007 granted the agency the authority to require REMS programs to ensure that the benefits of a drug outweigh its risks, as shown in Figure 1. REMS programs go beyond typical labeling requirements by addressing specific safety concerns and implementing measures to minimize the likelihood and severity of potential risks. In the case of TRANQUI-Spray, the REMS focuses on issues related to abuse and misuse, as well as adverse effects like physiological changes, dissociation, and sedation. It also means that providers undergo training and certification, and in which patients are observed in a clinical setting for at least two hours after dosing. Before patients can be discharged, healthcare professionals must verify that their blood pressure is stable and that any dissociative symptoms have subsided. Below is a regulatory-focused explanation of the contraindications that limit public access to TRANQUI-Spray (CALMmine), based strictly on FDA labeling, REMS requirements, and DEA regulations. These steps also describe the permits, licenses, and certifications that treatment centers must obtain to administer the medication.

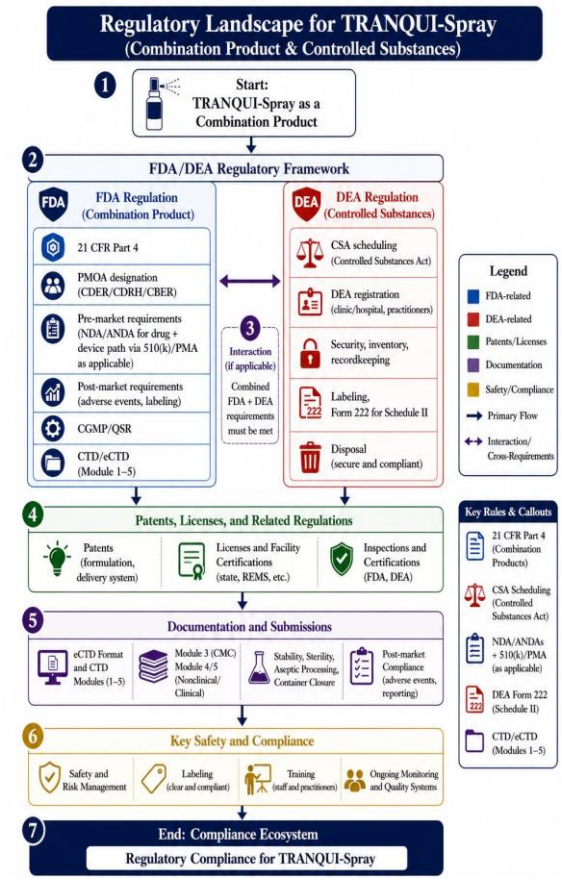

Figure 1

Flowchart of Regulatory Landscape, Patents, Laws, and Certification for TRANQUI-Spray (Summary Process)

Contraindications That Affect Public Access to TRANQUI-Spray

Accessibility is limited not only by insurance or clinics, but primarily by medical contraindications and regulatory safety controls mandated by the FDA. There are absolute contraindications (FDA-Labeled) in which patients cannot receive TRANQUI-Spray under any circumstances, which directly limits the eligible patient population. These include aneurysmal vascular disease (including thoracic, abdominal, intracranial, or peripheral vessels, or arteriovenous malformation); history of intracerebral hemorrhage; hypersensitivity to CALMmine, C-mine, or excipients. These contraindications are associated with TRANQUI-Spray's known transient increases in blood pressure and dissociative effects, which can precipitate catastrophic outcomes in high-risk patients.

In addition, other major warnings and precautions create practical barriers to real-world access, even when they do not constitute absolute contraindications. These include cardiovascular or cerebrovascular disease (BP elevation risk); history of substance use disorders (Schedule III abuse potential); psychosis or bipolar disorder without mood stabilization (may worsen dissociation); pregnancy and breastfeeding (embryo-fetal toxicity risk); and concurrent use of CNS depressants, psychostimulants, or MAOIs.

Further access limitations arise from age and setting restrictions. TRANQUI-Spray is not approved for pediatric patients under 18 years of age and cannot be used outside a certified healthcare facility (no home administration).

Access is further impacted as providers often exclude patients conservatively due to liability, REMS audits, and payer scrutiny, narrowing the pool further than labeling alone suggests**.**

Permits, Licenses & Certifications Required to Administer TRANQUI-Spray

TRANQUI-Spray is one of the most tightly controlled outpatient medication in the United States, requiring compliances with FDA, REMS, DEA, and state requirements simultaneously.

Under the FDA REMS requirements every treatment center must be certified, enroll as a REMS-certified healthcare setting, designate an authorized representative, maintain staff training and documentation, enforce 2-hour post-dose monitoring, submit patient monitoring forms, and never dispense the drug for home use. Without REMS certification, facilities cannot order or administer TRANQUI-Spray**.**

And because TRANQUI-Spray (CALMmine) is classified as a Schedule III controlled substance under the U.S. Controlled Substances Act, DEA registration (Form 224) is also required for clinics, hospitals and practitioners administering the drug, along with secure storage, controlled access, and strict inventory and recordkeeping.

Additionally, a pharmacy or distributor certification may also be required. TRANQUI-

Spray can be obtained via Buy-and-Bill (clinic purchases the drug) or a REMS-certified specialty pharmacy. Either pathway requires pharmacy or distributor REMS certification, chain-of-custody accountability, state licensing, and local requirements (Critical Gatekeeper).

States may require additional approvals before DEA or REMS use, such as clinic or facility licensure, mental health or substance use program licensing, controlled substance facility registration, and PDMP reporting enrollment. For example, in Florida, U.S., substance-use or psychiatric facilities may require licensure under Chapter 397 [9]. And centers must also demonstrate operational readiness, including dedicated observation space, pulse oximetry and BP monitoring, emergency response protocols, and staff competency documentation.

What the Certification Process Looks Like

The certification process includes six steps: a) clinic readiness (space, staff, protocols); b) DEA registration; c) application for TRANQUI-Spray REMS certification; d) securing REMS-certified drug supply; e) patient enrollment in REMS; f) maintaining audit-ready documentation. The typical timeline is 4 to 12 weeks, depending on state and DEA processing.

Why is Access Limited?

TRANQUI-Spray access is constrained by narrow medical eligibility, mandatory REMS structure, DEA-controlled-substance regulations, and state-level facility licensing requirements. Together, these create a high-barrier, clinic-based access model, even for FDA-approved patients.

Moreover, pricing further limits access. Figure 2 presents a side-by-side breakdown of the typical cost of TRANQUI-Spray (CALMmine) treatment in the United States (mainland) and Puerto Rico, based on 2025– 2026 pricing data, FDA-mandated treatment structure, and real-world clinic billing practices. These figures are estimates, as final costs depend on dose, insurance, clinic fees, and payer rules.

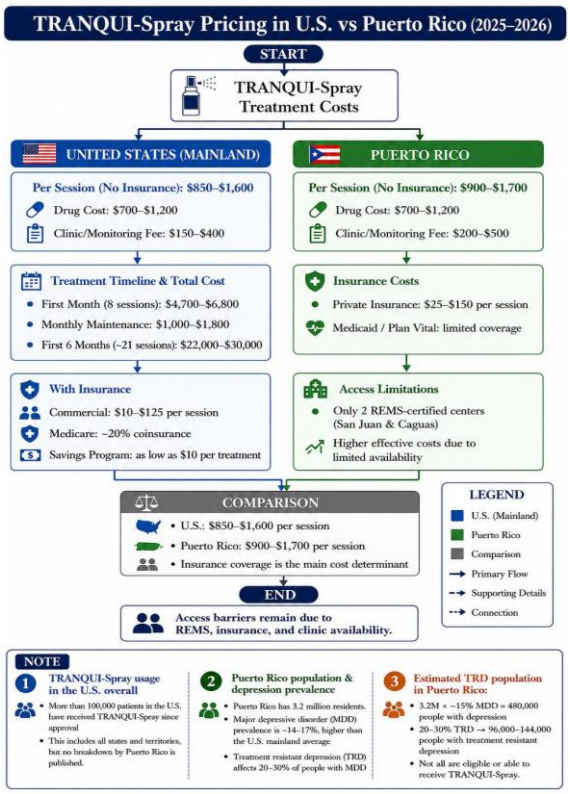

Figure 2
TRANQUI-Spray Pricing in U.S. vs Puerto Rico (2025-2026)

It is important to note that Puerto Rico is legally part of the U.S., so TRANQUI-Spray has the same FDA approval, is subject to the same REMS programs, and has similar drug prices. However, access and pricing differ due to fewer REMS-certified centers, differences in insurance reimbursement (Medicaid/Plan Vital), and more hospital-based administration.

In both locations, patients may still face additional barriers, even when insured, such as REMS-mandated observation cost, limited certified centers (especially in PR), transportation challenges due to post treatment restriction on driving, and prior authorization delays (2–4 weeks typical).

Why are exact numbers unavailable?

No agency publishes Puerto Rico-specific TRANQUI-Spray usage because REMS data is not publicly available. The manufacturer (Industrial Pharmaceutical) reports only national totals. Puerto Rico's Department of Health does not track psychiatric medication usage separately, and

insurance claims databases (e.g., Komodo, Optum) rarely include Puerto Rico [3].

CONCLUSIONS

The research highlights how regulatory requirements, licensing, certifications, and market-access conditions influence the availability and accessibility of innovative treatments such as TRANQUI-Spray in Puerto Rico. By reviewing REMS, FDA and DEA regulatory pathways, and operational requirements for controlled-substance combination products, the study identified key factors affecting treatment accessibility, pricing, and healthcare delivery. The findings suggested that administrative complexity, limited numbers of REMS-certified treatment centers, and restrictive compliance requirements may contribute to barriers to patient access and service availability.

The study also emphasized the importance of improving coordination among federal and local regulatory agencies, streamlining documentation processes, and expanding certified treatment infrastructure to improve healthcare accessibility. As noted by Interviewer #2, "These regulatory protections, reinforced by patents and intellectual property laws, support pharmaceutical innovation but simultaneously reduce market competition and keep prices elevated, placing a disproportionate financial strain on Puerto Rican patients who already face fewer REMS-certified clinics and more restrictive insurance coverage."

Although this research provided insight into the regulatory and market conditions affecting access to TRANQUI-Spray, it was limited by the lack of publicly available Puerto Rico-specific utilization data and the limited number of certified treatment centers on the island. The analysis also identified opportunities to improve regulatory efficiency through risk-based inspection approaches, modernizing digital submission systems, and reducing unnecessary procedural duplication. Overall, the study suggested that targeted regulatory and policy improvements may enhance healthcare accessibility, reduce operational barriers, and support a more equitable and sustainable pharmaceutical landscape in Puerto Rico.

REFERENCES

[1] Janssen Research & Development, LLC. (2025). *Assessment of Feasibility of Using Clinician-Directed Cognitive Behavior Therapy Supplemented by a Digital Application in Conjunction With Esketamine (SPRAVATO®) in Participants With Treatment-Resistant Depression* [Online]. Available: https://trialsearch.who.int/Trial2.aspx?TrialID=NCT05268497.

[2] T. M. Solomon, et al., "Evaluating passive physiological data collection during Spravato treatment," in *Frontiers in Digital Health,* vol. 5, 2023. Available: https://doi.org/10.3389/fdgth.2023.1281529.

[3] Janssen Pharmaceutical, Inc. (2025). *What is the Spravato REMS (Risk Evaluation and Mitigation Strategy)?* [Online]. Available: https://www.spravatorems.com/.

[4] M. Lee and N. Sprague. (2024). *FDA Approvals and Regulations: Overview* [Online]. Available: https://www.ebsco.com/research-starters/law/fda-approvals-and-regulations-overview.

[5] U. S. Food and Drug Administration. (2024). *Combination Products: Therapeutic and diagnostic products that combine drugs, devices, and/or biological products* [Online]. Available: https://www.fda.gov/combination-products.

[6] U. S. Food and Drug Administration. (2026). *Electronic Common Technical Document (eCTD)* [Online]. Available: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

[7] DrugPatentWatch. (2026). *SPRAVATO Drug Patent Profile* [Online]. Available: https://www.drugpatentwatch.com/p/tradename/SPRAVATO.

[8] U. S. Dep. of Justice. (2023). *Drug Enforcement Administration, Practitioner's Manual: An Information Outline of the Controlled Substances Act* [Online]. Available: https://deadiversion.usdoj.gov/ GDP/%28DEA-DC-071%29%28EO-DEA226%29_Practitioner's_Manual_%28final%29.pdf.

[9] Florida Department of Children and Families. (2026). *Substance Use Disorder Licensing and Regulation, Florida DCF* [Online]. Available: https://www.myflfamilies.com/services/licensing/samh/.