2024

Whitepaper

Regulatory Aspects of Psychedelic Drugs: Current & Future Outlook

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Introduction

Definition of Psychedelic Drugs

Psychedelic drugs, also known as hallucinogens, are a class of substances that alter perception, mood, and cognitive processes. They can induce profound alterations in consciousness, leading to experiences such as hallucinations, altered time perception, and heightened introspection.

Historical Context

Psychedelics have been used for millennia in various cultural and religious contexts. In the mid-20th century, they gained popularity in Western societies, culminating in the counterculture movement of the 1960s. However, due to concerns over misuse and adverse effects, many countries implemented strict regulatory controls, criminalising their possession and use.

Purpose of the Whitepaper

This whitepaper seeks to comprehensively examine the current state of regulation surrounding psychedelic drugs, including recent shifts towards acceptance for therapeutic applications. It also aims to identify potential areas of improvement in regulatory frameworks, considering the evolving scientific understanding and clinical potential of these substances.

Historical Perspective

Early Uses and Traditional Practices

The earliest evidence of psychedelic use can be found in a cave depiction of a 'mushroom man', sprouting mushrooms identified as *Psilocybe mairei*, native to the Tassili-N-Ajjer region of the Sahara Desert, Algeria[1] where the cave is located. The mural is dated to be between 7,000 to 9,000 years old. In fact, some researchers believe rock paintings in Western Australia[2] show the use of psilocybin in Indigenous ceremonies over 10,000 years ago which would predate the African claim. Regardless, it is clear that psychedelic substances like psilocybin mushrooms, peyote, and ayahuasca have been used throughout history for millennia in indigenous cultures for spiritual, healing, and divinatory purposes. These practices often involve structured rituals guided by experienced practitioners.

The Early Science of Psychedelics

In the late 1800s and through to the mid-1960s, scientists started to study psychedelic plants and mushrooms, including their chemical compounds, effects, and potential therapeutic applications. It was during this period that the first synthetic psychedelic active substances such as 3,4-methylenedioxymethamphetamine (MDMA) and lysergic acid diethylamide (LSD) were also synthesised.

Counterculture Movement and Prohibition

The 1960s witnessed a surge of interest in psychedelics in Western societies, partly due to the work of figures like Timothy Leary, psychologist and writer, and Aldous Huxley, writer and philosopher. This led to widespread use and experimentation, contributing to the social and cultural upheavals of the era. However, concerns over adverse effects and the potential for misuse prompted governments to enact strict regulatory measures. In 1966, the public use and sale of peyote, mescaline, LSD, and N,N dimethyltryptamine (DMT) were prohibited in the United States (US). Shortly afterwards in 1970, LSD, DMT, methylenedioxyamphetamine (MDA), psilocybin, psilocin, mescaline, peyote, and cannabis became Schedule I drugs under the United States Controlled Substances Act. In 1971 the world followed suit and the United Nations included psychedelic compounds in the Schedule I classification as part of the Convention on Psychotropic Substances, which made psychedelic compounds internationally illegal. This meant, in terms of the law, psychedelics had no recognised medical value and a high potential for abuse, therefore, formal scientific studies on this class of compounds ceased across the developed nations.

Recent Resurgence of Interest

Since the 1990s, there has been a resurgence of interest in the therapeutic potential of psychedelic drugs. When psychedelics are taken, several processes are believed to be at play in the brain. Psychedelic substances can change how certain mood-related chemicals including serotonin receptors work, potentially reduce inflammation, and increase communication between specific emotional and sensory processing networks. Clinical research has demonstrated promising results in the treatment of various mental health disorders, including depression, anxiety, post-traumatic stress disorder (PTSD), and both drug and alcohol addiction. The health authorities in various countries have acknowledged the current lack of options for patients with specific treatment-resistant mental health disorders. This has spurred a re-evaluation of their legal status and regulatory frameworks, particularly in the European Union (EU) and Canada where regulatory approaches have been more progressive.

Current Legal and Regulatory Frameworks

United States

In the United States, the regulatory landscape for psychedelic drugs is evolving. The Controlled Substances Act of 1970 classifies most psychedelics as Schedule I substances, meaning they are considered to have a high potential for abuse and no accepted medical use. However, there have been recent exceptions, such as the Food and

Drug Administration (FDA) breakthrough therapy designations granted to MDMA-assisted therapy for PTSD in 2017 and psilocybin in 2018 for treatment-resistant depression. This recognition expedites their development as prescription medications, highlighting their potential to revolutionize mental healthcare. Furthermore, the FDA has funded psychedelic research with a $35 million grant. Also, in 2019 the FDA approved the use of ketamine, which is approved for treatment-resistant depression. Ketamine is often classified as a dissociative anaesthetic, rather than a classical psychedelic like LSD or psilocybin, however, it does have some psychedelic properties, particularly at higher doses.

European Union

Regulations regarding psychedelic drugs vary among EU member states. The Dutch government, until recently, took a prohibitive stance toward psychedelic research but in early 2022, the country's health minister announced his approval of research into psychedelic therapies and increased funding for mental health research. Some other countries, for example Portugal and Austria, have decriminalised or adopted more lenient approaches towards certain psychedelics. At an EU level, a framework for the regulation of controlled substances, which member states may implement with some flexibility, has been provided.

United Kingdom

The United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) are aware of psychedelics' potential adverse effects. Yet they also recognise that most existing treatments for mental health disorders are only moderately effective. Thus they, too, are taking an evolutionary approach to encourage psychedelic research. Adding to this, the first formal centre for psychedelic research in the world has been launched at Imperial College London. The new £3 million Imperial Centre for Psychedelic Research, builds on over a decade of work in this area by the University.

Canada

Canada has taken progressive steps towards the regulation of psychedelics for therapeutic and research purposes. Health Canada has granted exemptions and licenses for the legal use of substances like psilocybin in specific clinical contexts. One of these is a class exemption which covers certain types of potential Special Access Programme authorizations for psilocybin and MDMA. Psilocybin-assisted therapy has gained recognition as a legitimate treatment option. So much so that in 2023, a research investment of nearly $3 million through the Canadian Institutes of Health Research has been granted to support three clinical trials that will examine psilocybin-assisted psychotherapy as a potential treatment option for alcohol use disorder, treatment-resistant depression, and end-of-life psychological distress in advanced-stage cancer patients.

Australia

The Therapeutic Goods Administration (TGA) in Australia has made changes to increase access to psychedelic therapies for patients. The country has reclassified psilocybin and MDMA since 1st July 2023, to enable prescribing by authorised psychiatrists. These substances have been rescheduled from Schedule 9 of the Poisons Standard, which is prohibited substances, to Schedule 8, which is controlled drugs for use in the treatment of certain mental health conditions.

Other Countries of Note

Brazil has a long history with psychedelic drugs. Today, psilocybin mushrooms are not prohibited for sale, distribution, or use, and no charges have been made in relation to psilocybin in recent years. Additionally, possession of ayahuasca, a plant-based psychedelic extract containing DMT, has been legal in Brazil since 1992, after a series of legal battles regarding the rights of traditional practitioners to possess ayahuasca for religious and ritual use. Given this attention, the potential of ayahuasca within neuroscience is now being investigated and several psychedelics research programmes in Brazil have emerged. Other Latin American countries including Mexico and Peru, and some Indigenous territories have long-standing traditions

involving psychedelic substances, which are legally protected within certain cultural and religious contexts. Additionally, Israel, Jamaica and other countries have explored regulatory frameworks for psychedelic research and therapy.

Research and Clinical Trials

Breakthrough Studies and Therapeutic Potential

Recent clinical studies have shown promising results in the treatment of mental health disorders using psychedelics. Psilocybin-assisted therapy, for example, has demonstrated significant efficacy in alleviating symptoms of depression, anxiety, and addiction. MDMA-assisted therapy has shown promise in treating PTSD whilst DMT is being investigated for the treatment of major depressive disorder. The integration of psychedelics into psychotherapy sessions has yielded profound results, often promoting healing and personal growth.

Regulatory Aspects

Psychedelic materials derived from plants or fungi are considered by the European Medicines Agency (EMA) as herbal products whilst in the US, these substances are considered as botanicals. Development of psychedelics should comply with the respective guidance concerning these types of products. However, it should be noted that from a US perspective, psychedelic compounds derived from plants or fungi which have been genetically modified; produced by fermentation of yeast, bacteria, or plant cells; or highly purified from naturally occurring sources are not considered botanicals and should be treated in the same manner as psychedelic materials with a fully synthetic origin by consulting FDA guidance in order to ensure compliance with the Current Good Manufacturing Practice (CGMP).

The EMA is set to hold a multi-stakeholder workshop on medical psychedelics in April 2024 to establish regulatory guidelines for the development and therapeutic use of psychedelic substances in Europe.

Non-Clinical

Whilst psychedelics have been intertwined with humanity for millennia, regulatory agencies must evaluate the safety of psychedelic compounds the same way they assess any other drug. That means researchers must be prepared to follow the same requirements and deliver the same preclinical data as with other drug classifications; there is no waiver just because the compounds being studied are taken from nature or because there are decades-old, published data for select compounds. However, it may be reasonable for clinical studies with certain psychedelic drugs to be initiated in the absence of the typical animal toxicology testing when extensive human exposure and information are available from previously conducted clinical studies and no serious safety concerns were identified. Also, EMA guidance, Guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products, does make provision for the use of documented experience gathered during the long-standing use for the basis of the non-clinical assessment of traditional and well-established herbal medicinal products. However, it in no way relaxes the requirements of proof of safety, especially with regard to reproductive and developmental toxicology, genotoxicity and carcinogenicity.

Quality

Quality aspects also need to follow regulatory guidance and manufacturers are required to have a specific licence to be able to produce psychedelic drugs (either the plants, the extractions, or the active pharmaceutical ingredients (APIs)). Adherence to Good Agricultural and Collection Practices (GACP), Good Manufacturing Practice (GMP) and strict quality controls is required. Sponsors should develop formulations dependent on the desired routes of administration, and delivery system. The stability of the API (or biomass extract) as well as the finished product should be demonstrated, to establish the shelf life of the product.

Synthetic psychedelic active substances and their corresponding drug products also need to meet exacting quality requirements and numerous guidelines are provided by regulatory bodies, to ensure that the manufacture of the drug substances, through to stability of the final drug products including all steps in between, provide products of upmost quality.

Clinical

The design of clinical studies to evaluate the safety and efficacy of these products presents unique challenges. Psychedelic drugs can cause intense perceptual disturbances and alterations in consciousness that can last for several minutes to several hours depending on the route of administration. Clinical study designs may incorporate a psychological or behavioural intervention and researchers hypothesize that psychedelic drugs may have both rapid-onset and long-term benefits after only one or a few doses. These and other unusual characteristics should be considered when designing clinical studies so that the results of those studies can be interpretable allowing treatments to be approved by health authorities.

Regulatory Pathways for Research

Regulatory bodies like the FDA in the U.S. and the EMA have established pathways for conducting clinical trials on psychedelics. These pathways involve rigorous protocols for safety, efficacy, and ethical considerations. Researchers must adhere to strict guidelines to obtain approval for studies involving these substances. However, researchers must also be aware of the rapidly changing regulatory landscape and be able to pivot quickly to optimise their clinical trial strategies. For example, in 2021, a type of fast-track status known as the Innovation Passport Designation was granted by MHRA for DMT-assisted therapy for major depressive disorder. Given the potential therapeutical benefits of psychedelics in life threatening and serious debilitating mental health diseases, there are several expedited pathways opening up for this class of drugs. These include:

- ***Accelerated assessment:*** This EU pathway enables faster approval for therapies expected to be of major public health interest, particularly from the point of view of therapeutic innovation.
- ***Authorisation under exceptional circumstances:*** This EU pathway permits ongoing safety monitoring and risk/benefit assessments after the therapeutic goes to market. It is reserved for instances when very little data exists, nor can it be gathered—such as with exceptionally rare diseases.
- ***Adaptive pathways:*** This EU pathway is typically used when sponsors want to broaden a therapeutic's indications, but regulators require more data.
- ***Conditional marketing authorisation:*** This EU pathway offers short-term approval when the need for immediate drug access outweighs the risk of having limited data and it is anticipated that it will eventually be possible to provide comprehensive proof of safety and efficacy.
- ***PRIME (Priority Medicines):*** PRIME enables early and enhanced scientific and regulatory support from agencies, including the EMA and Health Technology Assessment (HTA) organisations.
- ***Breakthrough therapy designation:*** This US pathway offers early-phase benefits, including greater FDA collaboration. Sponsors must show that the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.
- ***Fast track designation:*** This US pathway most often comes into play at the investigational new drug (IND) stage of drug development.
- ***Accelerated approval:*** This US pathway is usually leveraged at later stages in drug development and permits sponsors to use surrogate endpoints to get faster FDA approval. However, they must still conduct Phase IV confirmatory trials.
- ***Priority review:*** This US pathway reduces the application review period by several months.
- ***Innovative Licensing and Access Pathway:*** The UK's MHRA launched its Innovative Licensing and Access Pathway (ILAP) in January 2021 with the aim of providing early and enhanced scientific and regulatory support, accelerating the time to market, facilitating patient access to medicines.

Challenges and Controversies

Safety Concerns

While psychedelics have shown promise in clinical trials, there are safety concerns, particularly regarding the potential for adverse psychological reactions in vulnerable individuals. It is imperative that research protocols include comprehensive screening, preparation, and integration processes to minimise risks. In addition, there is a high potential for abuse of psychedelics. For general information on how to conduct an abuse potential evaluation the FDA have issued a guidance for industry Assessment of Abuse Potential of Drugs.

Public Perception and Stigma

Public perception of psychedelics remains a significant barrier to broader acceptance and legalisation. Misconceptions and stigma surrounding these substances persist, stemming from historical association with counterculture movements and misconceptions about their safety and potential benefits. It is, therefore, necessary for education and communication between researchers, clinicians, patients, and the general public to reduce stigma and promote mutual scientific understanding of the potential risks and benefits of psychedelic therapies.

Integration with Existing Mental Health Treatments

Integrating psychedelic-assisted therapy into mainstream mental health care poses challenges. Establishing protocols for training therapists, ensuring accessibility, and integrating these therapies with existing treatment modalities will be essential for widespread adoption.

Practicalities of Handling Controlled Drugs

Controlled drugs are managed and used in a variety of settings by health and social care practitioners and by people who have prescribed them. They are closely regulated because they are susceptible to misuse and can cause harm. To ensure that they are managed and used safely, legal frameworks for governing their use have been put into effect. Developers must establish and develop processes for handling, storage, transporting, distribution, disposal, and destruction of controlled drugs to satisfy these legal obligations.

Emerging Trends

Compassionate Use and Expanded Access Programmes

Certain countries currently permit compassionate use with MDMA, and psilocybin and in addition, Switzerland allows access to LSD-assisted psychotherapy. In the US, expanded access programmes, allowing patients with serious and treatment-resistant conditions to access psychedelic therapies under medical supervision, are also becoming available. These programmes provide a bridge to broader acceptance and can inform future regulatory decisions. Moreover, these programmes can raise awareness of psychedelics in a clinical setting and help reduce negative public perception and stigma.

Decriminalisation Efforts

Several countries, states and cities in the US have pursued decriminalisation of psychedelic substances, aiming to reduce criminal penalties for possession and use. These efforts reflect a growing recognition of the potential benefits of decriminalisation, such as redirecting resources towards harm reduction and treatment programmes.

International Cooperation and Harmonisation

Multilateral Agreements and Organisations

Collaboration between countries and international organisations is crucial for establishing consistent and evidence-based regulatory frameworks. Forums such as the three United Nations treaties that together form the international law

framework of the global drug control regime: the Single Convention on Narcotic Drugs, the Convention on Psychotropic Substances, and the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances establish internationally applicable control measures with the aim of ensuring that psychoactive substances are available for medical and scientific purposes, while preventing them from being diverted into illegal channels. The treaties also include general provisions on the distribution and use of psychoactive substances.

Standardisation of Research Protocols

Standardising research protocols and methodologies will be essential for generating robust data on the safety and efficacy of psychedelic therapies. This will facilitate comparisons across studies and enhance the credibility of research findings.

Industry and Market Considerations

Investment Trends

The burgeoning psychedelics industry has attracted significant investment. Companies focused on psychedelics research, therapy, and related technologies have emerged, indicating a growing belief in the potential commercial viability of these treatments. Governments and research institutions worldwide are investing significantly in psychedelics research, recognising the urgency of addressing the global mental health crisis. The previously mentioned grants issued by the FDA and Canadian Institutes of Health Research are testament to the potential seen in this class of medication.

Market Projections

In 2022 the psychedelic drugs market was estimated to be around three billion USD. projections suggest that as regulatory barriers are overcome and therapies gain wider acceptance, the market for psychedelic-assisted treatments could expand exponentially. Experts are predicting the market to grow to over 12 billion USD by 2035.

Intellectual Property and Licensing

As the psychedelics industry develops, issues surrounding intellectual property and licensing will become increasingly important. Companies and researchers will seek to protect their innovations, which may include novel therapeutic protocols, drug formulations, and delivery mechanisms.

Ethical Considerations

Informed Consent and Participant Safety

Ensuring informed consent and participant safety are paramount in psychedelic research and therapy. Comprehensive informed consent processes, thorough participant screening, and robust safety protocols are essential to uphold ethical standards.

Equity in Access and Research Opportunities

Equitable access to psychedelic therapies and research opportunities is a critical consideration. Efforts must be made to ensure that these treatments are accessible to diverse populations and that research is conducted with inclusivity and cultural sensitivity whilst maintaining access for traditional use.

Responsible Marketing and Distribution Practices

As psychedelic therapies become more widely available, responsible marketing and distribution practices will be crucial. Ethical guidelines must be established to prevent over-hype and misinformation, ensuring that patients and healthcare providers have accurate information about the benefits and risks of these treatments.

Future Directions

Potential Legislative Changes

Continued research and evolving societal attitudes may lead to legislative changes regarding the regulation of psychedelic substances. Efforts to reschedule or reclassify these substances to facilitate research and therapeutic applications are anticipated.

Forecasted Regulatory Shifts

Regulatory bodies are likely to adapt their frameworks based on emerging evidence and evolving clinical practices. This may include streamlined approval processes for research and expanded access programmes, as well as potential re-evaluations of scheduling classifications.

Policy Recommendations

Based on the findings outlined in this whitepaper, it is recommended that policymakers consider a balanced approach that prioritises safety, research, and therapeutic potential. Collaborative efforts between regulators, researchers, healthcare professionals, patient organisations and industry stakeholders will be crucial in shaping effective and responsible regulatory frameworks for psychedelic drugs.

Conclusion

The regulatory landscape for psychedelic drugs is evolving, reflecting a growing recognition of their therapeutic potential. This whitepaper has provided a comprehensive overview of the historical context, current regulatory frameworks, emerging trends, and potential future directions for the regulation of psychedelic drugs. We hope that this document serves as a valuable resource for researchers, healthcare professionals, and industry stakeholders as they navigate this dynamic field.

Expert Guidance in Psychedelic Drug Development

DLRC has extensive expertise working with psychedelics, including the support of INDs, Clinical Trials Applications (CTAs), scientific advice meetings, acting as legal representative, and support for the local import/export considerations of controlled drugs. With this vast experience, we are your perfect partner to support your psychedelic drug product development programmes. Please contact us for further information.

References

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