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PSYCHEDELICS AND ENTACTOGENS

Challenges Associated with Schedule I Therapeutic Development

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Introduction

Under the Controlled Substances Act (CSA) in the United States, drugs that have the potential to be abused are scheduled into one of five Classes or Schedules (CI-V) as controlled substances. The scheduling method makes a distinction for drugs that have abuse potential and are not approved for medical use (i.e., Schedule I) versus drugs that are approved for medical use and have abuse potential (Schedules II-V). In the classification, the higher the number of the Schedule, the lower the abuse potential of the drug and the less restrictive the conditions regarding its distribution, storage, and prescribing.

Schedule I, or Class I (CI) drugs are currently restricted to research in the U.S., meaning that they are not approved for medical use, and are deemed at highest risk for abuse.

Recent research on psychedelics and entactogens, both of which are Schedule I, is beginning to demonstrate potential therapeutic effects of these drugs for various medical indications. Approvals of such drugs for medical or therapeutic use will inevitably result in the rescheduling of these drugs from their current CI status.

Consult the DEA documents: The Controlled Substances Act and Drug Scheduling

These substances exhibit potential neuroplastic and immunomodulatory effects, and are being investigated for **potential uses** in various psychiatric and neurological disorders that have high unmet needs, such as depression, anxiety, post-traumatic stress disorder, substance use disorder, cluster headache, and migraine. Based on current research on botanically derived and synthetic substances, limited, acute administration with varying dose ranges (low/micro to high) seems to provide benefit. The psychoactive effects and abuse potential are an important consideration, and must be balanced when designing therapeutic applications for the real world.

The abuse potential of these psychoactive substances contributed to their Schedule I classification by the FDA. The CSA outlines the reasons and factors that determine whether a product needs to be controlled.

The 8 factors determining control under the CSA are set out in 21 U.S.C. 81(c) as follows:

1. The drug's actual or relative potential for abuse
2. Scientific evidence of the drug's pharmacological effects
3. The state of current scientific knowledge regarding the drug or substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

As the body of research grows, the understanding of these 8 factors improves. The development of such compounds remains challenging, but increasingly feasible, particularly when sponsors partner with CRO and CDMO facilities that have Schedule I licenses, and a deep knowledge of the regulatory environment to ensure that all study conduct meets the relevant requirements. Experience and expertise to successfully manage the unique challenges and risk/benefit evaluations at both the preclinical and clinical level are essential, as are the appropriately licensed, secure facilities for CDMO formulation. Highly experienced drug development solution companies, such as Altasciences, are integral in conducting preclinical and clinical studies in accordance with regulatory requirements.

Different Scheduling Status for Drugs with Psychedelic Properties

Schedule (C)	Abuse Potential	Accepted Medical Use?	Prescribing Restrictions	Scheduled Drugs
I	High	**No**	Research only	Heroin, marijuana, **DMT (ayahuasca), LSD, MDA, MDMA (ecstasy), ibogaine, mescaline (peyote), psilocin, psilocybin**
II	High	Yes	No telephone Rx; no refills	Opium, oxycodone, opiates, cocaine, **phencyclidine**, morphine, amphetamine, barbiturate types
III	Medium	Yes	Rx; must be rewritten after 5 refills or 6 months	Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), **ketamine, esketamine, LSD precursor (lysergic acid/amide)**, anabolic steroids, testosterone
IV	Low	Yes	Rx; must be rewritten after 5 refills or 6 months; differs from Schedule III in penalties/legal possession	Darvocet, Xanax, Ambien, Lunesta, Valium, other CNS depressants, **lorcaserin** (FDA withdrawal 2020)
V	Lowest	Yes	OTC; may be dispensed without Rx	Lomotil, Phergan, Lyrica, liquid cough suspensions with small amounts of codeine
Unscheduled	No	Yes/No	OTC; may be dispensed without Rx	**2,5-demithoxy-4-iodoamphetamine** (DOI), **dextromethorphan**

Given the growing interest and evidence to support developing these substances to try and reduce high, unmet needs in the neuropsychiatric field, an understanding of the complexities involved is critical to the success of any program.

Research Site Requirements Associated with Development of Schedule I Drugs for Therapeutic Use

The FDA plays a critical role in the drug scheduling and approval process; however, they do not provide the authorization or oversight of the logistics for working with controlled substances. Those aspects are handled by the Drug Enforcement Agency (DEA), who have jurisdiction over the licenses to ship, handle, store, and otherwise work with controlled substances. Sponsors are responsible for obtaining a license to store and ship the active pharmaceutical ingredient (API). Once that API is shipped out, site authorization must be requested by the site that is receiving the substance, as they will be required to demonstrate that the appropriate security and controls are in place. The **DEA process** is outlined on their website, and they provide a **searchable portal** that contains all their guidance documents. Canada and the E.U. also schedule and control drugs, and the specific requirements will be considered if a sponsor plans to file for approval in these geographic locations.

Abuse, misuse, and diversion are the main concerns for regulatory bodies. License submissions will include information on the measures in place at each site to mitigate any such risks. Study protocols must address these concerns, and all products received at any site must be accounted for to ensure that no amount was diverted or lost.

Once a site receives a CI license for a particular substance, that license is permanent, although subject to audit and revocation if conditions are not met. Relevant conditions that sites must demonstrate include highly secure, locked storage capacity with limited, controlled access, and standard operating procedures for the safe handling, dispensing, and administration of the controlled substance.

Each new controlled substance that the site intends to work with will be added to the existing license. In 2018, the DEA issued a press release affirming their support for Schedule I research and their desire to speed up the licensing process. On average, DEA review for addition to an existing license is typically four to twelve weeks, while delays for a site that is applying for the first time can exceed six to twelve months.

Sites must also consider state and local legal requirements, which differ and may be product- specific. This can affect timelines, transport, and site abilities to conduct work. For example, Kansas Board of Pharmacy registration is required for a CI license in that state. California requires state notification for CI and CII research, in addition to DEA licensing.

IND- and IRB-approved protocols are required for submission of each project. DEA requirements for clinical protocol content include:

- Investigator information, affiliation, and qualifications
- Research project details, including purpose of the research, controlled substances used and the amounts, number and species of research subjects, location, security, and provisions
- Authority and approvals, including details on funded grants, if any

Access the DEA application forms for a complete listing of conditions and requirements.

Required Preclinical Studies

In addition to safety pharmacology and toxicity studies for psychedelic compounds, abuse potential and dependence evaluation is necessary as part of the final proof of concept. Novel psychedelic drugs for medical use will have to undergo rigorous preclinical assessments to determine the abuse and/or dependence risks that they carry. Based on current evidence, the abuse risks posed by psychedelics are no greater or more onerous than those associated with CII opiates or stimulants. The potential therapeutic benefit and the capacity to properly assess and develop mitigation strategies adds to the argument in support of further research on such compounds.

Information from scientific literature and Altasciences' own research indicate that psychedelic drugs pose specific technical challenges for evaluation of their preclinical abuse/dependence potential, which explores three distinct aspects of risk:

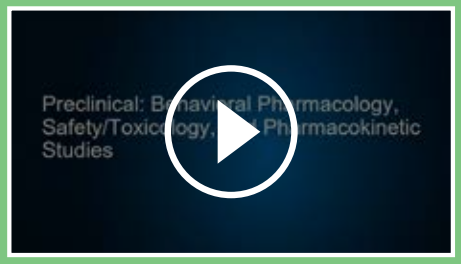
- Drug discrimination: to assess whether the psychoactive effects of the new chemical entity (NCE) are identical or similar to those of known substances of abuse.
- Intravenous self-administration: to determine if the experience produced by taking the drug candidate is rewarding or reinforcing, and if it leads to drug-seeking behavior. This is evaluated in the intravenous self-administration (IVSA) test.
- Physical dependence (withdrawal symptoms): to evaluate if, after repeated administration, the NCE produces physical dependence once administration is stopped.

The preclinical assessment of abuse risk includes a chemical structure analysis, and in vitro screening of:

- Dopamine receptors
- Serotonin (5-HT) receptors – including 5-HT2A, 5-HT2B and 5-HT2C
- Gamma-Aminobutyric (GABA)/benzodiazepine receptors
- Opioid receptors
- Nicotine receptors
- N-methyl-D-Aspartate (NMDA) receptors
- Ion channel complexes
- Transporters sites – including 5-HT and DA

Additionally, the results of behavioral screening using the **Irwin functional observation battery** will inform future decisions for the drug development pathway.

For a deeper analysis of the preclinical processes, watch as Dr. Sharon Cheetham, Director, In Vivo Pharmacology at Sygnature Discovery, explains with a supporting case study (15 minutes).



Formulation, Manufacturing and Analytical Considerations

Before any research can be conducted, the active pharmaceutical ingredient (API) has to be formulated and produced in an appropriate dosage form. Choosing a manufacturing partner that already has a CI license will reduce timelines, and ensure that the site has the expertise and experience to work with controlled substances. Once a license is in place for a particular substance, it remains in place as long as the site is in good standing with the DEA. Future projects will therefore be able to start quickly, with less logistical challenge.

The storage and handling requirements maintained by a Schedule I-licensed CDMO are rigorous, with CI material stored in a locked vault dedicated for this purpose, with secure, controlled, and limited access. Detailed records for vault access must be maintained, and be available for audit.

Processing of CI substances requires dedicated handling areas, staffed by knowledgeable and well-trained operators. Mitigation of potential exposure to the drug material should include appropriate PPE, powerful air filtration systems to minimize airborne particles, and thorough and rigorous cleaning procedures.

Formulation expertise for Schedule I substances is another critical element for successful development. Psychedelics are often dosed at very low levels; for example, a dose of LSD is typically in the area of 25 to 200 micrograms. Ensuring the accuracy and reproducibility of low dose tablets can present a significant challenge; liquid-filled capsules (LFCs), where the drug is dissolved in an appropriate medium and then filled with great precision into hard-shell capsules, are an excellent alternative. The use of LFCs also protects operators, physicians, and patients from accidental contact with the controlled substance.

Schedule I narcotics are subject to **annual production quotas** and require accurate inventory control to ensure there is no diversion of the controlled drug substance. The quantity of each Schedule I narcotic used in the formulation process, including accounting for all process loss, and in-process and finished product release testing, must be equal to the initial quantity of the Schedule I narcotic received.

A CDMO facility with the expertise to manage these demands will contribute to a more efficient and effective drug development pathway.

Required Clinical Studies

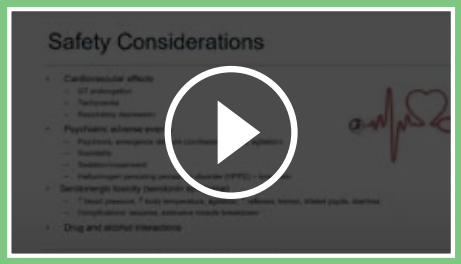
As with other NCEs entering clinical development, novel psychedelics need to be assessed for safety, pharmacokinetics, and efficacy. Given the drug class and associated risks, abuse/dependence evaluation is a central part of any drug development program.

Given the known serious safety concerns around psychedelic substances, extremely thorough, robust, and precise safety monitoring must be an integral part of the protocol, and the recruitment needs to carefully screen subjects for eligibility.

Clinical Safety Considerations

Cardiovascular effects, such as QT prolongation, tachycardia, and respiratory depression will be assessed. Psychiatric adverse events, including psychosis, emergence delirium (confusional states, agitation), suicidality, sedation, and functional/cognitive impairment will need to be closely evaluated. Drug-related mood changes, such as aggression and confusion, must all be closely monitored, from both an impairment and enhancement perspective. Specific measurement scales and questionnaires are used, and may need to be customized and adjusted according to the specifics of the trial. A potential longer-term effect, hallucinogen persisting perception disorder (HPPD), should also be assessed as part of the drug development program.

Watch as Dr. Beatrice Setnik, Chief Scientific Officer at Altasciences, presents a detailed review of the clinical trial requirements, including a case study (20 minutes).



Serotonergic toxicity (serotonin syndrome) is another important consideration. Testing for increased blood pressure, elevated body temperature, agitation, highly sensitive reflexes, tremor, dilated pupils, and diarrhea must be part of the safety assessment. Complications such as seizures and extensive muscle breakdown are another important consideration, as are drug and alcohol interactions.

Clinical Safety Guidelines

First-in-human trials typically include healthy normal subjects to enable safety evaluations and characterization of drug effects without the confounders of patient pathology. Due to the nature of the pharmacological effects of psychedelics, a healthy population with prior psychedelic experience may be more appropriate. Informed consent, which is always a central element of novel therapeutic studies, must prepare subjects for potential perceptual changes and other risks inherent in the research.

Inclusion/exclusion (IE) criteria must be well-defined, and subject screening precise. Vulnerable populations to be excluded are defined as those with:

- Current, past, or familial (1° or 2° relatives) history of meeting DSM-IV criteria for schizophrenia or other psychotic disorders (unless substance-induced or due to a medical condition), or bipolar I or II disorder
- Elevations in blood pressure
- Use of concomitant medications (e.g., haloperidol, SSRIs, MOAs)
- Use of dietary supplements (e.g., 5-HTP, St. John's Wort)

After meeting the IE criteria, additional screening per session must further exclude those who exhibit pre-session negative mood, anxiety or depression. Subjects continuing should be carefully guided through any of the subjective effects they may experience.

Clinical Trial Setting

The set and setting for clinical study of hallucinogenic drugs is vital, as we must consider the subjective experience as well as the PK/PD effects of the investigational substance. The clinical pharmacology unit staff should be highly experienced with the administration of different types of CNS-active drugs, and additionally be well-trained on the specific attributes of the substance of study, and what the anticipated effects may be.

A safe, comfortable, and enriched environment with appropriate safety equipment is key. For example, EEG and telemetry equipment to monitor vital signs, and crash carts with anti-anxiety and antipsychotic treatments must be close at hand. Staff and facilitators should be trained for the management and safety oversight of subjects during their participation in the study. Trials that include patients and cognitive therapy will require additional training to provide therapeutic interventional support throughout the study.

The physical facilities should include all beds at ground level (no bunk beds), areas for privacy and desensitization during "bad trips", with eye shades, headphones, and screens for subject use. The facility and its pharmacy must be entirely secure, for the safe handling of the CI substance, and for the security of subjects and staff. Qualified clinical staff must handle medical monitoring and management of any adverse events and negative effects, to mitigate any potential negative experiences or outcomes.

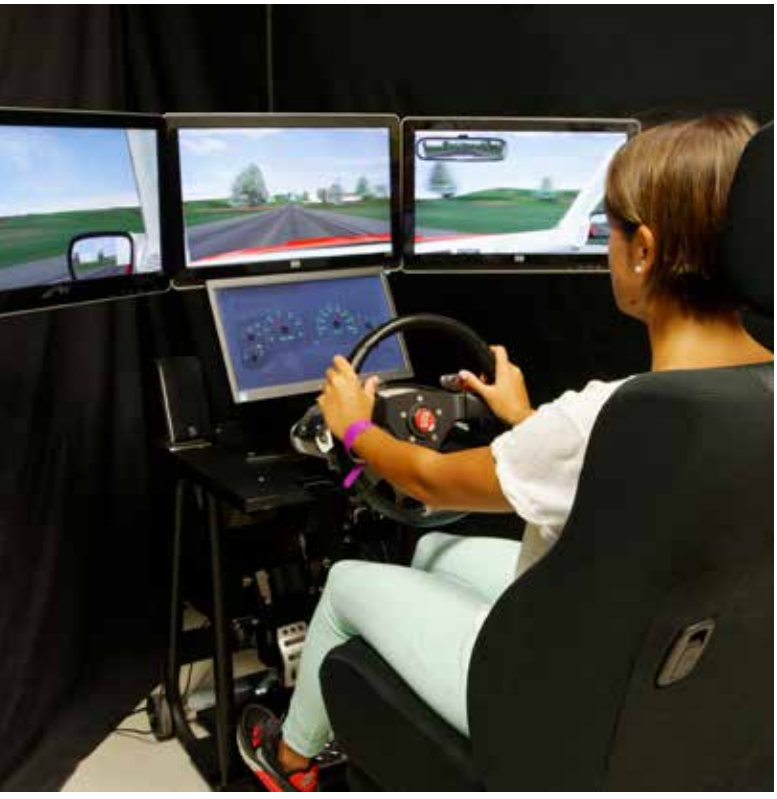
Given the strict controls in place for clinical development in this area, trial conduct and data capture that meets regulatory requirements (ICH, GCP) is pivotal, to ensure that the resulting data is complete, and unbiased. Randomization of subjects and treatment blinding mitigates responder bias.

Specialized Clinical Assessments

Human Abuse Potential

Human abuse potential assessment, or HAP, evaluates the 'likeability' of a drug substance in a face-valid population, and will always be required for Schedule I controlled substance research. These studies are pivotal data sources for evaluating abuse potential and in supporting scheduling status of a drug. HAP studies are single-dose, double-blind crossover studies, in non-dependent recreational drug users.

HAP studies are placebo- and active-controlled with the scheduled controls including opioids, stimulants, depressants, sedative/hypnotics, cannabinoids, and/or other psychedelics. They involve a pharmacological challenge to ensure non-dependence and sensitivity to the active control. Subjective and objective measures are then used to evaluate drug effects, cognition, and effects of the drug on motor skills.



Driving

Dedicated driving studies with higher face validity than more general tests of CNS function may be needed. Per the FDA guidance, these studies can be conducted with actual motor vehicles or driving simulators. We recommend simulators for safety reasons as well as for cost and time savings.

Different driving test scenarios need to be used to assess somnolence and executive functions (such as impulsivity or risk-taking). Testing is conducted in a time frame during which the investigational drug and active comparators are expected to reach maximum exposure levels in the human body. Such testing must be consistently administered to subjects who require sufficient practice and acclimatization to the driving conditions. Baseline assessments are important and serve as a basis for post dose comparisons. Highly trained staff are required to ensure consistent administration of the tests and in maintenance of the testing environment.

Why Work with Altasciences?

For novel CNS-active Schedule I drugs, tremendous benefit can be achieved by engaging with a drug development partner that has Schedule I licenses across every stage of early phase development. Integration across preclinical, clinical, bioanalytical, and formulation/manufacturing phases ensures complete continuity, data transfer, information sharing, and efficient, active timeline management. At Altasciences' CNS Center for Excellence, you have a team of well-recognized experts to ensure that your psychedelic research and studies are conducted with the rigor and efficiency needed to meet regulatory requirements, and fulfill your drug development goals.

ALTASCIENCES' RESOURCES

Webinars

- The Many Facets of Early Phase Evaluation of Psychedelics in Psychiatry
- The Brain on Drugs: Strategic Use of Cognitive Measures and Biomarkers in Early Phase CNS Drug Studies
- To Control or be Controlled, Navigating the Abuse Potential Evaluation of CNS-Active Drugs for EU and U.S. Submissions
- Assessing Cognition and Driving Ability in Clinical Pharmacology Studies

Specialty Services

- Abuse Potential Studies
- Substance Abuse Studies
- Psychiatric Drug Studies
- Cannabis Studies

Blog

- Clinical Applications of Psychadelics, Dissociatives, and Other Schedule I Drugs

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.