



The FDA and Psychedelic Drug Development: Working Together to Make Medicines

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THE MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC Studies (MAPS), the Usona Institute, and Compass Pathways are each pursuing U.S. Food and Drug Administration (FDA) approval of an investigational psychedelic medicine. One of the biggest objections to the FDA regulation of psychedelic medicines is the medicalization of a tool that people believe they learned to use successfully without government regulation, interference, or control. (MDMA was legal prior to being assigned Schedule 1 status.) The purpose of this article is to provide my perspective that FDA involvement is beneficial to increasing acceptance of psychedelic medicines as mainstream therapies.

Psychedelics are unusual in that the vast majority of new medicines do not reach humans until there is extensive knowledge about mechanism of action, chemical contaminants produced during synthesis, drug distribution, and animal safety and efficacy. Try to view the FDA as a vehicle to address the gaps in scientific knowledge resulting from human use of these agents prior to pursuing the conventional drug development path. Further, as MDMA is a synthetic chemical (and is not derived from plants or fungus), the Federal Food, Drug, and Cosmetic Act, which governs how FDA operates, requires that specific scientific knowledge be ascertained before the compound can be made available to the public as a medicine.

The FDA is a public health agency, under Health & Human Services (HHS), along with the Public Health Service (PHS), National Institutes of Health (NIH), and Centers for Disease Control (CDC). Thus, the FDA is responsible for protecting the American public from unscrupulous or untested drugs that may cause significant harm to patients if misused. In my view, the FDA takes its public health mission seriously.

However, despite the fact that psychedelic compounds are regulated by the Drug Enforcement Administration (DEA) under Schedule 1 of the Controlled Substances Act, the FDA reviews psychedelics the same as other investigational psychiatric drugs. FDA is required to base its decisions on the scientific data submitted by the research sponsor (pharmaceutical company); if FDA provides a negative response, it is often the case that the sponsor failed to provide adequate scientific data to support its arguments.

Pharmaceutical companies (or sponsors) submit their Investigational New Drug (IND) Applications to the Center for Drug Evaluation & Research (CDER) at FDA. Note the use of the word drug: FDA refers to new chemical entities as drugs, because in the FDA's vocabulary they are chemicals intended to treat disease; but the psychedelic community often refers to psychedelics as medicines.

Prior to establishing a drug or medicine is both safe and effective, the FDA labels new chemical entities as "investigational." Therefore, the adjective "investigational" should be used prior to FDA approval. Thus in 2020, MDMA and psilocybin are investigational medicines.

Throughout the development process, the sponsor performs studies and submits data to FDA for review. The FDA website provides guidances and guidelines for the

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entire investigational drug development process. It is customary for all sponsors (even large pharmaceutical companies) to have multiple meetings with FDA prior to submission of the New Drug Application. The relationship that each company has with the FDA varies widely.

I believe that it is always best to maintain a friendly, mutually respectful relationship with any regulatory body. Both the FDA and research sponsors can learn much from each other. The FDA has analyzed the data from thousands of investigational medicines and knows much more than they can share publicly. What may initially seem to be a conservative FDA position or response may in reality result in improved patient safety or efficacy, and perhaps even save a sponsor time and money.

At the time of this writing, both MDMA and psilocybin have been granted Breakthrough Therapy Designation by the FDA, signifying FDA's agreement that MDMA and psilocybin may offer substantial benefits over existing therapies for some serious or life-threatening conditions. By granting this designation (which not every drug gets), the FDA is demonstrating its commitment to facilitating the development of new therapeutics that may improve the health status of Americans, as demonstrated by the granting of this designation to three out of three investigational psychedelic medicines currently in development.

After the sponsor submits volumes of data and reports to FDA over many years, what does the FDA do exactly? It is the FDA's job to review everything that is submitted and reanalyze the most important datasets. FDA may even discard some data that it believes are problematic or unreliable, so FDA's final calculations often differ from what the sponsor submits. The final work product of FDA is the new drug labeling. It is that large document with very fine print that includes warnings, clinical trial effectiveness, side effects, whether pregnant women can use the medicine, dosing instructions, storage conditions, etc. Every word on the label is chosen carefully and negotiated by the sponsor and the FDA, as the label forms the basis of all allowable promotional efforts post-approval.

I strongly support moving psychedelic medicines forward through the FDA because:

1. FDA approval would validate the efficacy of psychedelic-assisted psychotherapy for select psychiatric disorders. Rightly or wrongly, the FDA is acknowledged by many to be the world's premier health regulatory agency. It has strict standards and an FDA approval is a huge accomplishment (even for a large pharmaceutical company).

2. Secondary indications for the medicine are facilitated by the first FDA approval. The first clinical indication (e.g., PTSD for MDMA; depression for psilocybin) involves the most effort, time and money; secondary indications can be faster and less expensive, especially if the dosing regimen, protocol, and for-

mulation remain unchanged.

3. The FDA requires the same formal safety reporting of all psychiatry medicines. Because all psychiatry drugs are developed with the same requirements, it is then easier for prescribing psychiatrists to determine the relative safety of psychedelic medicines for their specific patients, since they were not included in their medical education (such as specific adverse events, percentage occurrence, severity, contraindications).

4. The FDA is a good teacher. Teams in new, small pharmaceutical companies learn a lot about the drug development process through every step with FDA. Drug development cannot be taught at a university—it is an apprenticeship. Unsuccessful experiences with regulators often result in the biggest learnings (which is true for failures in life as well).

5. FDA approval facilitates insurance coverage. Americans expect insurance to cover part of the cost of treatments, therapists need to be compensated, and pharmaceutical companies need to be able to support these efforts. More people will have access to MDMA- and psilocybin-assisted psychotherapy when insurance companies cover a large portion of the treatment cost.

6. FDA approval expedites physician and psychotherapist education. Today, many people ask their physicians or therapists about therapeutic options. Fifty years of Schedule 1 designation has taught society that psychedelic drugs offer no benefit and may produce harm. FDA approval would provide an expedited path for physician, psychotherapist, and healthcare provider re-education by the sponsor through continuing education.

7. FDA approval would allow for the possibility of direct-to-consumer advertising and education. Direct education of the public offers an efficient (though costly) way to reach large numbers of individuals who otherwise might not learn about the availability of new medicines for their conditions. All promotional content is derived from studies performed and submitted by the sponsor and approved by FDA. Note: The ability to promote a new medicine to the public can be restricted by FDA if the medicine has significant safety issues.

8. FDA approval would achieve the goal of making psychedelic medicines legal, albeit available only through a prescription.

9. The quality of a new medicine would be assured after FDA approval. A major focus of regulatory agencies is the quality of medicines. Western regulatory agencies (e.g., the FDA, the European Medicines Agency, and Health Canada) set high manufacturing standards so that patients know that these dosage forms provide the dose indicated, release the medicine in a predictable and reproducible way, have few contaminants, and have known stability.

10. MDMA and psilocybin are being developed for use

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with psychotherapy administered by trained psychotherapists. The psychedelic research community recognizes the need for individuals using psychedelics to be accompanied by guides, sitters, or therapists. In the future, as the total number of patients using psychedelics increases, sponsors may work with the FDA to expand or modify the approach to include group therapy, for example. Any such changes would require FDA approval of clinical trials and positive outcomes in the trials.

11. FDA approval often leads to expedited global regulatory approvals. Together, the sponsor's NDA and the FDA's approval documents provide the core materials to support subsequent submissions and regulatory approvals around the world. Every regulatory agency asks for the regulatory approval history in other countries and an FDA approval is a valuable and strategic early asset.

12. Rescheduling of psychedelic medicines, although the purview of the DEA, will require FDA approval. Because Schedule 1 classification states these chemicals have "no currently accepted medical use and a high potential for abuse [harm]," it is incumbent on the sponsor to prove efficacy and safety before rescheduling may occur. FDA approval would be based upon the demonstration of at least some human efficacy and reasonable safety in select conditions (risk-benefit assessment).

13. FDA approval would likely open up new research avenues and NIH funding. FDA approval, accompanied by rescheduling, would enable academics and research institutes access to quality medicine for research purposes and potential funding from traditional U.S. government sources. Scientific and clinical research by others would result in publications and potential media reporting, expanding knowledge of these modalities.

14. The FDA approval process is a partnership between the sponsor and the U.S. government. Subsequent relationships with other government agencies such as the Department of Defense (DoD) or Veterans Administration (VA) system are thereby facilitated.

15. The FDA provides a path that allows for some medicines to convert from prescription-only status to over-the-counter (OTC) status. This has been accomplished for some antihistamines and vaginal antifungals, for example. Note: One of the requirements for these medicines is that a healthcare provider is not required for safe and effective use of the medicine; psychedelic medicines will require trained psychotherapists. Nevertheless, the FDA's prescription-to-OTC switch pathway demonstrates that the FDA is open to demedicalization of some products over time.

There are some down sides of the FDA path to legal access, such as that this path requires about a decade, costs tens or hundreds of millions of dollars, and requires tremendous effort by a large interdisciplinary team of experienced professionals. One could argue that the FDA path also elevates the cost of access. The specific business model and corporate structure of each company (MAPS is a non-profit) have significant impact on final drug pricing and therefore access, unless specific access

programs are developed.

The goals of a pharmaceutical company developing psychedelic medicines for psychiatric disorders are to:

- Provide patients with new, safe and effective, high quality treatment options
- Provide new therapeutics to assist psychotherapists in the treatment of patients
- Offer prescribers new, safe, and effective treatment options
- Provide insurance companies the data they need to justify paying for new therapies
- Produce the evidence necessary to reschedule psychedelic medicines
- Create legal pathways for use of psychedelic medicines

The FDA path of new drug development is long, challenging, and expensive, but an FDA approval assists a pharmaceutical company in achieving all of these goals.

Just as landmark buildings and bridges are legacies of architects, a few medicines become legacies of pharmaceutical scientists and professionals. Think of the Empire State Building or the Golden Gate Bridge. Buildings, bridges, and medicines each require considerable time, money, technical expertise, and regulatory engagement. The finest buildings provide comfort and protection with elegance, for decades or centuries. Likewise, medicines that are strategically developed with thoughtful consideration and anticipation of future use can be highly valued and enduring. Consider penicillin, insulin, or the polio vaccine. The intention and hope of the psychedelic community is for the investigational psychedelic medicines currently under development to eventually offer a similar legacy of benefit to humanity. The FDA is a pivotal member of, and key contributor to, our community's efforts to build a bridge for psychedelic medicines to cross into mainstream medicine.

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