Making MDMA a Medicine (I)

Scheduling Process for FDA Drug Approvals

Allison Coker, Ph.D., and
Jack Henningfield, Ph.D.

When a new drug is submitted to the Food and Drug Administration (FDA) in a New Drug Application (NDA) for marketing approval, if the drug has central nervous system activity, it will need to be assessed for abuse potential. For novel products with new chemical entities, that assessment typically includes several studies designed to assess the drug's potential for abuse, conducted in both animal models and human participants. The FDA provides detailed guidance[1] describing their generally recommended study designs for these investigations and the types of data to be collected from them. The data from both the animal and human studies are combined in nonclinical and clinical summaries, then included in the application for approval. The sponsor also must include a summary of data from any earlier research that has been published, as well as potentially relevant public health survey data such as real-world use patterns and recreational use of the substance in the product or substances with similar effects. FDA requests the sponsor to make its own recommendation for scheduling based on this analysis. Sponsors may also include a summary abuse potential analysis and recommendation for consideration based on the eight factors laid out in the Drug Enforcement Administration (DEA) Controlled Substances Act (CSA)[2], because ultimately the new drug will be scheduled based primarily on this Eight-Factor Analysis as required by the CSA. This assessment is largely based on relative comparisons to the abuse and dependence potential of other substances in each schedule. While the sponsor includes its recommendation to the FDA, it is ultimately up to the FDA to assess these abuse potential studies and, with input from the National Institute on Drug Abuse (NIDA), make its scheduling recommendation to the DEA based on the whole of the data. If the FDA approves the drug for market, this approval and the FDA scheduling recommendation will be passed to the DEA, who has 90 days to respond and issue a scheduling of the drug.

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MDMA is different from novel drugs that are brought to market, in that it is not a new chemical entity. For novel drug products, typically all of the research on the drug's effects—including efficacy, safety, and abuse potential—are conducted by the study sponsor under controlled conditions based on the specific studies necessary for that product, including abuse potential studies. In the case of MDMA and other well-studied

psychedelic substances (i.e., psilocybin and LSD), they have been independently studied for decades, with many publications in the literature of both clinical and nonclinical studies which were conducted outside of a sponsor-directed drug development program. In addition, there is substantial real-world and epidemiological data collected on naturalistic use of these drug substances including monitoring in major federal health and substance use surveys since the 1970s.

Notably, once MDMA was added to Schedule I in 1985, research into its potential therapeutic effects became more challenging, and a large portion of laboratory research conducted focused on the abuse potential and purported toxicity of MDMA.[3] This literature includes much of the data investigating the abuse liability of MDMA, with studies conducted with similar, though not identical, designs to the typical FDA-guided sponsor-conducted abuse liability studies. Based on this extensive pre-existing body of evidence, including many NIDA-supported studies, the FDA waived MAPS' requirement as sponsor to conduct dedicated new studies on the abuse potential of MDMA.

Instead, MAPS will summarize the published preclinical and clinical abuse-related studies that have been conducted with MDMA to guide the abuse potential assessment of MDMA, which will follow and be based on the eight factors of the CSA.

The 8 Factors of the CSA

1. Actual or relative potential for abuse
2. Scientific evidence of pharmacological effect
3. The state of current scientific knowledge regarding the drug or other substances
4. History and current pattern of abuse
5. Scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Psychic or psychological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

The eight factors of the CSA that are used to assess abuse potential fall into a couple broad categories. Factor 1 focuses on the actual or relative potential for abuse. This includes preclinical studies which test whether animals find the drug reinforcing, how hard they will work to get more of it, and the degree to which animals will self-administer the drug. Human abuse potential studies similarly assess how much drug-experienced humans "like" a new drug in comparison to a known drug they are experienced with. Factors 2 and 3 assess other lines of scientific evidence relevant to abuse potential, including information around the chemical structure, receptor targets, pharmacology, and pharmacokinetics. This helps to understand how the drug works in the body, the mechanism of action for the intended effects, and other effects that might be involved. Factors 4, 5, and 6 address the public health impact of the drug. This is focused largely on risks but also typically includes the potential public health benefits of the proposed new drug product. Together, they describe the history and patterns of abuse, including the scope, duration, and significance of abuse and the risks to users and public health. Again, because MDMA is not a new drug, we have a lot of public health and epidemiological data about MDMA use. Though these data are confounded by the fact that unregulated substances sold as "Ecstasy" are represented as MDMA, but may contain other adulterants instead of, or in addition to, MDMA[4], the public health and epidemiological data are still significant in assessing these factors. The discussion of potential risks to public health will also importantly discuss potential public health benefits of MDMA. Factor 7 looks at the risk amount of potential "psychic" (a.k.a. "psychological" or "behavioral") dependence associated with use of the drug and withdrawal symptoms that may occur when the drug is discontinued. Factor 8 is based on prior scheduling of drugs with similar chemical structure.

Controlled Substances Act Scheduling Assessment

Abuse Potential	No Approved Medical Use	Approved Medical Use
High	I	II
Medium		III
Low		IV
Lowest		V

MDMA was determined in 1985 to have sufficient abuse potential to warrant inclusion in the CSA. Critically, the only schedule a drug may be placed in if it does not have an "approved medical use" is Schedule I, regardless of the actual or relative degree of abuse potential.[5] There is a common misconception that Schedule I explicitly indicates an exceptionally high abuse potential compared to other substances, but this is

[1] FDA guidance 2017 on abuse potential assessment
[2] Section 201 (c), [21 U.S.C. § 811 (c)] of the Controlled Substances Act.
[3] Belouin and Henningfield, 2018
[4] Drugsdata.org, 2020 data
[5] Drugs of Abuse | A DEA Resource Guide: 2020 EDITION [https://www.dea.gov/documents/2020/2020-04/2020-04-13/drugs-abuse]

Allison Coker, Ph.D., is the Associate Director of Regulatory Affairs at MAPS Public Benefit Corporation (MAPS PBC) where she guides regulatory strategy to develop and deliver innovative products to marketing approval in alignment with global business strategy across the MAPS and MAPS PBC clinical development programs. She earned a bachelor's degree in Neuroscience and Behavioral Biology from Emory University and a doctorate in Neuroscience from the University of California, San Francisco (UCSF). She applies her multidisciplinary background in behavioral pharmacology studying motivation, addiction, and stress and training across diverse research methodologies in both preclinical and clinical research settings to developing novel treatment strategies for PTSD and alcohol and substance use disorders.

Jack Henningfield, Ph.D., is the Vice President, Research, Health Policy, and Abuse Liability at PinneyAssociates, Inc., where he provides scientific and regulatory consulting support for abuse potential assessments and eight factor analyses new CNS-active drugs and nondrug products and regulatory pathways for psychedelics, cannabinoids, and CNS-active dietary supplements. He has been involved in animal and human abuse potential assessment research since the 1970s, and contributed to abuse potential assessments and drug scheduling recommendations at NIDA for 16 years in collaboration with FDA and DEA. Since 1978, he has been a member of The Johns Hopkins University School of Medicine faculty in the Department of Psychiatry and Behavioral Sciences. He has contributed to numerous reports on abuse potential assessment and drug scheduling as a member of various expert committees and in his service at NIDA and with the World Health Organization.

not always the case (e.g. cannabis's inclusion in Schedule I). What often follows from this misconception is that in rescheduling a drug out of Schedule I, that Schedule II is the clear placement. However, the decision of the appropriate Schedule for a newly approved drug should be based on the abuse potential for that drug as evaluated through the assessment described above; there is no presumption of the level abuse liability to be drawn from prior Schedule I inclusion, because its distinguishing factor is the absence of approved medical use. Unlike Schedule I, determination of placement in Schedules II – V is based on a relative comparison of abuse liability to other scheduled drugs and the likelihood of abuse or dependence. In Factor 1, we can compare the degree to which animals will self-administer the considered drug with the animal self-administration studies for other drugs with known schedules, such as cocaine, amphetamine, or opioids. In Factors 4, 5, and 6, we can compare the relative public health risks of MDMA to those of other scheduled drugs. These comparisons inform the appropriate schedule and restrictions that should accompany the newly approved drug, and ultimately its placement in the CSA.

Following the development of the literature-based abuse potential summary, MAPS' application to the FDA will follow a similar process to other drugs that have effects on the central nervous system. The FDA will inform the DEA that the drug has been approved and provides its recommendations for how the drug should be scheduled. By law, CSA Schedule I drugs must be rescheduled or descheduled when approved. The DEA will have 90 days (according the 2015-2016 Improving Transparency in Medical Therapies Act) to issue an "interim final schedule" that allows the drug to be officially approved and marketed. The schedule assigned for a newly approved drug impacts the distribution, control, and access to the drug. These are significant considerations for MAPS as we continue to work towards pharmaceutical development of MDMA and supporting the accessibility of a potential future treatment modality.