The Commercial Chemistry of MDMA: From Research to Patient Access

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Nearly 20 years ago, during our final year of university while studying for our Bachelor's in chemistry, I thought that two fellow students and I were rebels for suggesting that our organic chemistry assignment be on the history, culture, and synthesis of 3,4-Methylenedioxymethamphetamine (MDMA). It was one of the most politicized recreational drugs in the UK at the time, with a broad stigma based on highly publicized events.

Through that project I learned all about MDMA's therapeutic use prior to criminalization; not too long afterward in 2009, the famous quote from psychopharmacologist David Nutt made front-page news in the UK. Dr. Nutt compared the risks of taking ecstasy to those of horse riding, and followed in 2010 with a detailed and comprehensive comparison of legal and illicit drugs in *The Lancet* ("Drug harms in the UK: a multicriteria decision analysis," 2010). It brought into question the science behind the current UK approach to perceived harm and drug scheduling.

However, never did I think that one day I, or anyone else, would be working on the commercial manufacture of MDMA—let alone through a non-profit psychedelic research organization focused on relieving important metal health challenges such as posttraumatic stress disorder (PTSD). But surely as the tutor accepted our idea and we indeed wrote 10,000 words on MDMA, MAPS is currently in the late phase of the first-ever active pharmaceutical ingredient (API) manufacturing campaign which will generate the initial MDMA produced for licensed, prescribed patient access.

MAPS champions transparency and open science, values that align with my own personal principles. Our intention is for our scientific advancements and learnings to be shared widely, not only so they are made publicly available, but also so they can't be privately appropriated. This is quite different from the usual pharmaceutical company approach, and one of the benefits of working within a hybrid, mission-based organization (see the MAPS Policy & Advocacy Department's article in this *Bulletin*) for more information).

An article purely about the current MDMA chemistry data gathered by MAPS and its subsidiary MAPS Public Benefit Corporation (MAPS PBC) could be very long, technical, and for most, dry and uninteresting, so I have therefore chosen to include some of my more personal perspectives on the topic. For those who are eager to know more about the pure chemistry, MAPS will be working to publish more articles on the topic in late 2020.

My father had a Ph.D. in electronics and my mother was a devoted nurse, and I pretty much came out a 50/50 mix of the two. I am strongly analytical with a desire to organize, categorize, and put everything in its rightful and predicable place in a vain attempt to control this very unpredictable world. At the same time, I am emotionally and empathetically driven, feeling that no matter how much we try to draw these lines, we live in a world that transcends any model or equation.

During my A-levels (the UK's version of high school), I made the choice to drop art class and take up chemistry. I had come to really enjoy chemistry during my school years, and eventually it seemed like a better option for me to study than art, which felt too abstract—chemistry is exact and predictable, right? What I learned throughout those years and my subsequent chemistry degree, however, was something different: Science is not exact, and our understanding is constantly evolving. It started to seem like a relentless attempt to place evermore complex sets of round pegs in square holes.

Having said that, it is not as though the results of these human scientific endeavors aren't astounding and necessary, as they include feats of engineering and medicine. The point is that even those feats are imperfect; they are not always fully understood and can carry risks. Just like the building that won awards for structural and architectural brilliance can have unknown faults and fail years later, the drug that is shown to be highly effective in its target indication can bring unknown side effects that surface after licensure.

This background helps me understand why the chemistry of MDMA, a well-known molecule first developed in 1912 and patented by Merck in 1914, is not exact, not yet fully known,

and still requires detailed, stringent analyses and controls.

There are many methods available to synthesize MDMA, some including naturally derived starting materials such as safrole (found in sassafras plants, among others) as was used in the original Merck patent. However, unlike much of the MDMA that has been synthesized in the last decades (up until relatively recently), the synthetic pathway used for the MAPS synthesis of MDMA does not include safrole or related starting materials. Our key starting material is 5-bromo-1,3-benzodioxole, and its precursor, 1,2-methylenedioxybenzene, is likely synthesized in one step from catecho, a bulk commodity chemical made in thousands of tons per year from crude oil. Due to the relatively small quantities currently being made (less than 30 kg per year), the relevant regulatory authority in the country of manufacture has deemed that no environmental impact assessment is needed because this quantity of drug production is considered low-risk and small-scale.

In the context of drug manufacture, the word "commercial" is an important distinction, as it indicates a different standard of production. As we move through the study phases, the requirements for manufacture, analytical testing, and release change and become more stringent for both investigational (unlicensed, clinical-only) active pharmaceutical ingredient (API) and for drug product (the finished dosage form, e.g., capsule or tablet). Good manufacturing practices (GMPs) apply to all, but the level of detail and documentation required increases with exposure and risk. In other words, the regulatory requirements for an investigational drug used in small early-phase trials, manufactured on a small scale without the need for multiple-batch reproducibility, is different than for investigational drugs used for larger, late-phase trials or commercial products (wherein batch sizes can be many orders of magnitude larger and are part of multiple-batch, routine manufacture).

In the last three years, MAPS has been moving through these stages of chemistry development as we transitioned from our early Phase 2 trials to our current Phase 3 trials, and now as we work towards patient access following the first planned approval of MDMA for PTSD in the US.

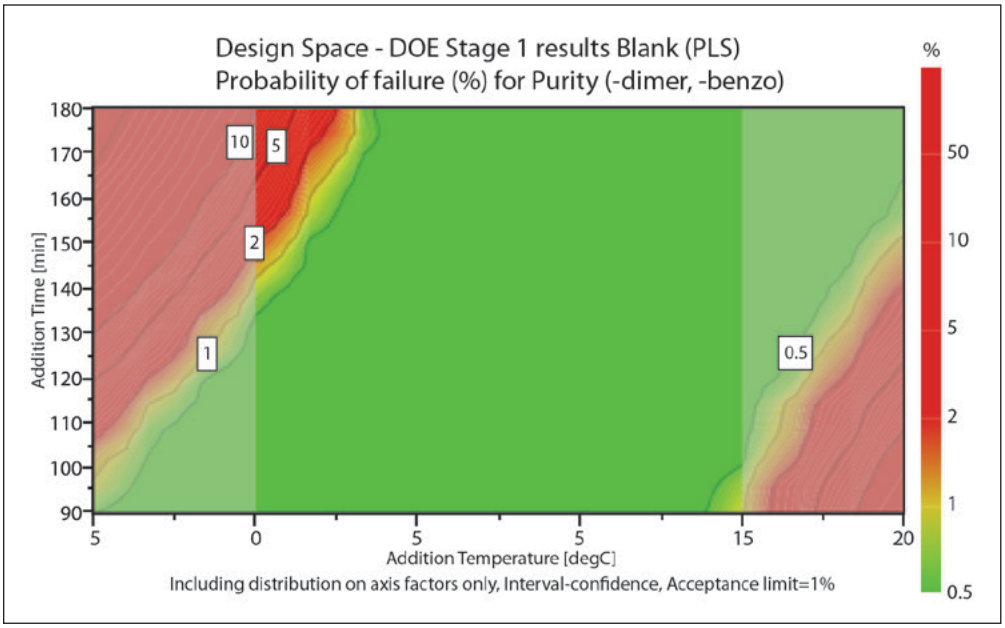
This year, a contract manufacturing organization (CMO) overseen by MAPS PBC is on track to manufacture 16-20 kilograms of commercial MDMA to provide Chemistry, Manufacturing, and Controls (CMC) documentation and data for the eventual MDMA-PTSD New Drug Application (NDA), and to provide the actual active ingredient that will be used for the initial supply chain.

At the same time, development work for the manufacture of the first-ever commercial MDMA "drug product" batches will begin. As with the "active ingredient" above, this campaign will provide CMC data for the NDA and be used for the first fully packaged and labelled drug (i.e., the finished capsules) which will be provided to patients outside of clinical trials after approval. These campaigns will produce the most comprehensive, thorough, and detailed data to date for MDMA API and drug product (as required for a commercial drug).

The path for a molecule, therefore, from early-phase API and drug product to a commercial product, is an iterative one. It involves increased levels of understanding around the synthesis, potential impurities, isomers, crystalline forms, and physical properties—all of which need to be controlled and understood to the fullest, as they can have an effect the safety and pharmacology of the drug.

The chemistry of MDMA is not a given, and requires expert development to get to the commercial standard we need to ensure patient access and safety at scale. However, it should not be expected that we will stop learning about the chemistry of this compound; changes in manufacturing process, scale, and product formulation can bring with them new challenges and lessons.

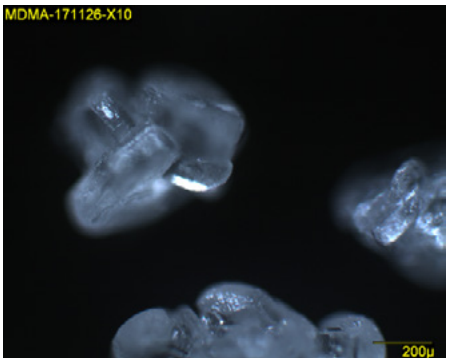
Since the first late-phase GMP API campaign carried out by the MAPS CMO, there has been much development work



Example of Experimental Design Space – Stage 1 MDMA Synthesis

around the four-stage chemical synthesis which forms the basis of the manufacturing process. The chemical purity of the API used by MAPS in any clinical trial has always been extremely high, >99.9%, and that standard has been maintained through scale-up. The focus of the development work on the planned commercial synthetic route has been to support batch reproducibility at a higher scale, validation through intermediate parameters, and ease of stage reaction processing and optimized yield—put more simply, making the reaction easier and cleaner with a higher output of material for the same inputs.

This activity has been carried out through multiple ascending-scale reaction experiments for each of the stages, culminating in 15 experiments for each of the intermediate reactions, to define what is called a "design space" that gives the parameters offering the desired purity and yield.



MDMA Crystals via Microscopy

However, even with this appropriately thorough approach from small-scale to large-scale development, the design space that was defined for Stage 2 of the reaction was shown to not completely predict the outcome. The model that was produced was just a model, and one that produced an unexpected result. More experiments were then completed to understand the issues that related broadly to the larger-scale equipment and the different agitation levels required to get the purity needed for intermediate stages of the synthesis.

Another significant lesson from the last 12 months of API development work was the discovery of two new polymorphic forms of MDMA, never seen previously in the literature. A polymorph refers to a well-defined crystalline structure, where the molecules are attached to each other in a repeatable pattern. A good example of this is C6 (carbon). Carbon will bond to itself six times to form the commonly known "benzene ring" molecule. However, the way these C6 molecules bond to each other can take different crystalline or polymorphic forms, such as diamond vs graphite. Both polymorphs are the same molecule—but one, diamond, is the hardest substance known and the other, graphite, one of the softest. This is an extreme example, but clearly shows why it is so important to understand the chemistry of any molecule that is being developed for human use.

Thankfully, in the case of MDMA, the polymorphism is not as extreme as carbon. But previously in the literature, based on the limited investigations, there was thought to be only one polymorph form of MDMA ("The ecstasy and the agony; compression studies of 3,4-methylenedioxymethamphetamine [MDMA]", Acta Crystallographica Section B Structural Science, Crystal Engineering and Materials, 2015).

This MDMA polymorph form is the same that has been used in all MAPS sponsored studies to date, now known as "Form 1," previously characterized through X-ray powder diffraction (XRPD). It is by far the most stable of the forms, and to force the MDMA molecules into the new polymorphs (Form 2 and Form 3) it requires manipulation using different solvents and crystallization techniques. Both Form 2 and Form 3 are metastable to Form 1, meaning that they easily revert to Form 1. However, now that their presence is known, identification of these forms has been added to the release and stability specifications via a method sensitive enough to identify them (even in small quantities relative to Form 1).

Although the commercial development of the MDMA drug product is yet to start, the first drug product batches manufactured via an automated process have provided us clear areas for improved understanding of the physical properties of MDMA and its the current excipients, the substances used to provide flowability and lubrication during the encapsulation process.

From our API development work specifically around crystallization we have found no way to ensure the MDMA crystals are uniform in size. Therefore, no particle size distribution specification has been set to date. As we move into commercial drug product development, where not only the chemical but physical properties need to be controlled and uniform from batch to batch, this will be the next focus. What is our desired particle size? How does this affect the excipient compatibility, flowability, and ultimate content uniformity of our drug product?

As with our ongoing clinical trials to understand the MDMA safety and efficacy profile to its fullest, the chemistry of MDMA is an ongoing development process. We are continuously gathering data on both the API and the drug product, and communicating our findings to the relevant regulatory authorities to align our current understanding of shelf life and release controls. We look forward to continuing to share and publish this data, in line with MAPS' values of transparency and open science

The chemistry of MDMA is a work in progress, and it's an exciting time to be a part of it, especially as the output of these fully validated commercial batches of API and drug product will be those that are available for the first patients to receive MDMA-assisted psychotherapy outside of clinical trials. Commercial MDMA will therefore support broad patient access post-licensure, something that MAPS has been working toward for over 35 years.

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