NEWS RELEASE

Navigating mental health: COMPASS Pathways' psilocybin research programme

2018-11-11

Article written for the MAPS Bulletin Winter 2018

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I first came to psychedelic research from a very personal experience with the limitations of psychiatry. I am a physician. George Goldsmith, my partner in life and business, has worked on complex regulatory and ethical issues of public-private collaboration. But despite our backgrounds, nothing prepared us for the devastation caused by the failure of the mental health care system when my son became ill. Even when the best doctors in the best institutions gave up on us, I kept looking for solutions. As we shared our story with friends and strangers, we realized that all of us are affected by the mental health crisis. And in the depth of our despair, we were still aware of how fortunate we were: we had resources and connections, and we could understand and assess the risks and benefits of emergent evidence for novel approaches. We resolved to make a difference for families who are in dire need of better treatments.

The early days

George and I were impressed by the vision and scientific rigor of the researchers at the Multidisciplinary Association for Psychedelic Studies (MAPS) and the Heffter Research Institute. Immediately after our first Heffter Board meeting in 2014, we offered not only financial support to the field, but help with regulatory strategy so that patients could benefit sooner. Despite significant challenges, we remain true to these commitments four years later.

In 2015, we created a US/UK non-profit, COMPASS, to support a pragmatic research project into psilocybin for psychological distress in hospice on the Isle of Man. Margaret Simpson, the visionary CEO of the hospice center, secured the support of the government, and together we received permission to train the first group of psychedelic therapists with psilocybin. There was only one obstacle: the psilocybin was not yet available from the Usona Institute or from the University of Wisconsin, both of which were also doing psilocybin research. Rather than wait, some of COMPASS' Board of Trustees members recommended that we manufacture psilocybin ourselves. Given our mission, and uncertainty about the availability of psilocybin made under current Good Manufacturing Practices (cGMP), we followed their recommendation.

From its establishment in 2015 through its dissolution in 2017 (more on this later), COMPASS was 100% funded by George and me. No other donor funding was ever raised. We anticipated that if we followed the published process of synthesis, the cost of manufacturing would be in the range of £350,000 to £750,000 ($460,000 to nearly $1 million). We set out to create our supply for research in Europe. However, while we shifted our focus to the manufacturing of GMP psilocybin, the hospice CEO retired, the political leadership of the Isle of Man changed, and the opportunity passed.

The process of synthesis and formulation turned out to be much more complex and expensive than anticipated. We funded this work out of our personal funds, and the ever-rising cost was simply outside of our reach. That led George and me to seek legal advice to establish a drug manufacturing company eligible for tax credits under a UK government program that helps underwrite the cost of medicine research and development. That option, as well as other government incentives, is not available for non-profits. We formed that company, COMPASS Pathways Technologies Ltd, in June 2016.

In August 2016, Heffter researchers asked us to write a regulatory commentary on the upcoming publication of two landmark studies of psilocybin for cancer-related distress. Our advisor, the former head of the UK regulator, the Medicines and Healthcare products Regulatory Agency, Professor Sir Alasdair Breckenridge, agreed to do this. Heffter researchers also agreed for us to share the studies with the European Medicine Agency's Scientific Advice Working Party in October 2016, a few weeks prior to the studies' publication. The meeting with the EMA team was pragmatic, collaborative, and sobering. The regulators acknowledged the early evidence of efficacy, but encouraged us to focus on the indication of major depression instead. We shared the details of these discussions with both Heffter and Usona to help inform their regulatory strategy and further study designs.

We took a sabbatical to consider our options. It was clear there were no political barriers to developing psilocybin as a medicine should the science meet regulatory standards. If we wanted to explore the therapeutic potential of psilocybin for depression, we were expected to take the traditional clinical development path, just like any other Investigational Medicinal Product (IMP). This meant we needed to go back to basics, starting with preclinical and

simple dose-finding studies. It also meant the overall cost of development of psilocybin for the indication of depression would be over £100 million ($130 million).

We knew we would not be able to raise the necessary funds through donations since the clinical research was still in an early stage, and the indication of depression is among the most challenging ones. If we were to spend over £100 million on drug development, we wanted the solutions to be affordable, scalable and sustainable. In February 2017, we made the decision to establish a for-profit life sciences company. We renamed the for-profit drug development company to COMPASS Pathways. We started the process to wind-down the non-profit shortly thereafter. The only asset that we developed that had value following the EMA advice to focus on the indication of treatment resistant depression was the name and the branding work we commissioned. While this was of no value to anyone else, we purchased this asset for the same amount it cost to develop. This was independently reviewed and approved by the non-profit board of trustees.The non-profit was only funded by us personally and had no outstanding obligations to others, so the transition to for-profit was legally and logistically straightforward.

Manufacturing and patenting

While psilocybin is a naturally occurring molecule, psilocybin as an Investigational Medicinal Product or IMP is a regulatory entity that includes a detailed description of a GMP-compliant, scalable and reproducible manufacturing process; associated preclinical data; and ongoing safety data collected in clinical trials. The IMP can be thought of as a product's fingerprint, so that regulators can recognize the safety and efficacy evidence gathered in the clinical trials as it relates to this unique product. The creation of an IMP is an extremely complex and expensive process that requires sustainable funding and a serious multi-disciplinary team effort. Based on our experience and the regulatory input from EMA, we now estimate that the development process will continue through marketing authorization and cost over £3 million (nearly $4 million).

In the process of synthesis, formulation and creation of preclinical data, we reached out to the researchers at Heffter and Usona with offers to share experience and ever rising cost, the last conversation being at PS17 in Oakland. Shortly after, the initial phases of the synthesis and formulation were completed, and psilocybin became the Investigational Medicinal Product. From that point on, for the reasons of data consistency, there was no regulatory acceptable mechanism of "sharing" it other than through standard licensing agreements for the use of IMP. This is the way clinical research regulation works around the world.

As the previously published synthesis processes did not scale to meet regulatory standards, we had to invent our own process. As he would have done for anyone who would have asked for his help, David Nichols advised our manufacturing team. With his support our team has solved over 60 distinct technical problems in the synthesis and formulation process. Some of these inventions became the basis for our manufacturing patents. In general, patents provide an opportunity for an organization willing not only to take a significant financial risk to recoup the

expenses, but more importantly, to ensure integrity of the data collected before and after the approval.

Our patents do not preclude others from creating a range of different solutions for the synthesis and formulation of psilocybin; nor do they preclude the use of naturally occurring mushrooms, extracts, or any other products created by alternative synthesis and formulation routes. Equally, our patents do not prevent other clinicians from using our product or any psilocybin-containing products in conjunction with the types of therapy or psychological support they judge to be helpful, as long as it does not jeopardize patient safety. Lastly, neither our patents, regulatory strategy, nor pricing strategy have an impact on the practices of the underground community of practitioners in nonclinical settings.

Our exclusive contract with the drug manufacturer does not prevent others from choosing among many different competing manufacturers through the standard Request for Proposal (RFP) process. The advances of science may now offer new creative solutions for the synthesis and formulation of psilocybin with new partners for those who are willing and able to spend the time, effort, and funds to create an alternative psilocybin-based IMP.

While we have created the supply of psilocybin for our own research, we have made the unusual decision to share it with qualified independent researchers free of charge in exchange for being able to use their safety data. This is not a commercial decision, but yet another way to accelerate the generation of clinically relevant evidence that may ultimately improve patient outcomes.

This process has proven to be challenging at times. As we have learned, university legal departments and technology transfer offices are vigilant about the potential Intellectual Property (IP) that might be created in the process of investigator-initiated studies. This IP, despite the best intentions of the researchers, does not belong to the scientists, who have limited say in how it is used by their institutions. In the event of IP creation, Technology Transfer Offices have a legal obligation to license it out to the 'highest bidder' with the most aggressive and scalable business model that will generate the most return for the academic institution. Even though such IP would be created by independent researchers with our IMP, in order to use the invention, we still have to compete with other commercial entities who might have different ethics or commercial goals.

This is an important consideration for the signatories of the **Statement on Open Science and Open Praxis** who work for academic institutions, as they need to align with their institutions on terms of IP licensing. The core principle of the statement is that knowledge created by signatories is open to all – that is, the knowledge is to be given away unconditionally by relinquishing researchers' rights to protect it and to control who gets to use it after it becomes public.

We believe our patent strategy offers some protection against uses that may not be fully aligned with our mission to create access to innovative treatments for as many people as possible at an affordable cost to patients and

healthcare systems.

Our focus: improving outcomes for the maximum number of people

Many people have asked us about our business model. Given that we are in the early stages of the development, the model is still evolving and will largely depend on the conditions of the regulatory approvals. In general, US law focuses on private companies maximizing value for shareholders only. UK corporate law is different: it requires us to create value for both shareholders and stakeholders. As a UK-based company, every COMPASS Pathways Board meeting starts with a reminder of this commitment.

Businesses might have different strategies to create value for shareholders. Charging high prices and stifling competition is one of them, but it is not **the approach we plan to take**. Instead, our goal is to provide broad access to all in need regardless of their ability to pay, creating greater value for health systems and translating to lower health insurance premiums and decreased healthcare cost. This is the approach our shareholders invested in and continue to support.

The high cost of clinical trials and drug development aside, the cost of manufacturing GMP psilocybin itself post-regulatory approval is likely to be relatively low. The future cost of Psilocybin Therapy will be determined at the point of care delivery by the treatment models, the services provided by the treatment centers, but mainly by the fees of individual providers. The creation of reimbursable models of care then becomes essential if we are to ensure that everyone who would benefit from Psilocybin Therapy can access it regardless of their ability to pay. It might be that “a thousand flowers will bloom” – and eventually the best models will prevail simply through quality and price competition, or that treatments will be rolled out in a more regulated way. This will require constant feedback and frequent course correction, as we continue to learn from our collective experience.

One way to decrease this uncertainty and ensure the accessibility of the treatment is by engaging in frequent in-depth conversations with the regulators and payers early in the process, just as we suggested after our first Heffter Board meeting in 2014. This remains our main strategy today.

To date, we have had conversations with regulators in many different countries in Europe and North America. We have assembled hundreds of pages of detailed feedback on the clinical development of psilocybin for depression and other indications, and on regulators’ general views of the challenges and opportunities for the clinical development of psilocybin. We share these insights regularly with MAPS. We also offered to share our plans and experience with Usona and Heffter. However, we understand that the psychedelic community is facing many challenges as it grows and some might not consider these perspectives a priority at this time.

We realize now that we could have taken more time to communicate with researchers who supported us during our early non-profit stage. At that time, we simply assumed that we were all motivated by the urgent need to create

safe, effective, and sustainable options for patients. In our drive to get things done, we may have unintentionally hurt some people by not communicating clearly enough about our intentions and decision process that led us to move from non-profit to profit and from a focus on existential distress in cancer patients to treatment-resistant depression. We sincerely regret this and intend to do a better job in the future. Today, many researchers have continued working with us, while others have chosen not to, citing their discomfort with a for-profit approach. We respect their choice.

We also appreciate that not everyone agrees with our model. We believe different models of care and organizational structure can co-exist, and we embrace healthy competition through creating alternative solutions. We also understand that in the diverse psychedelic community, there is a range of views on how to move forward. We appreciate the dedication, skills, and achievements of those who have chosen to work on legalization efforts, and we do not think our models are contradictory. In fact, arguments for decriminalization can be enhanced by the evidence generated in large-scale clinical trials conducted according to the highest regulatory standards. Regardless of the results of the trials, the individual patient experiences and extensive safety data collected and published in the process can be of significant value in helping change public and legislative opinions.

The “elders” of psychedelic research have triumphed at what they set out to do. The world is paying attention, patients and clinicians are hopeful, leading research institutions are hosting conferences and developing research ideas, and institutional and private funders are willing and able to support further development. Scientists and clinicians now have a real chance to offer hope and help for millions of people suffering from psychological distress, regardless of their spiritual practices or ideological convictions.

The field of psychedelic research is entering a new chapter. This is both exciting and highly uncertain, as this work has never been done at scale and in full public view. Working in this historically sensitized and highly regulated space takes a wide range of skills, experience, sustainable funding, teamwork and collaborations across disciplines. With care and respect for differences of opinions, we know it is possible to have a constructive and thoughtful dialogue, and to collaborate in the interests of patients in need. We at COMPASS Pathways are committed to doing our part. We look forward to sharing lessons of successes and challenges with many of you in the future.

In the meantime, my son has recovered and now lives a happy and productive life. This was inconceivable just three years ago. Our story is not simply the story of a miracle cure, but the story of access to innovation, particularly for those who cannot afford it. We will have walked this challenging path so other families do not have to do so.