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New Filing Challenges Compass Pathways' Infamous Patent on Synthetic Psilocybin

The non-profit Freedom to Operate used research from chemists and crystallographers to argue in a legal filing that Compass' form of synthetic psilocybin is not a new invention.



By [Shayla Love](#)

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In April, Carey Turnbull released [a statement](#) on behalf of his non-profit, [Freedom to Operate](#) (FTO), in which he described research underway to “establish what I know to be true: there can be no patent on psilocybin as a substance, nor on the known methods for making it or using it medically.”

be intellectual property, has been the subject of debate, especially since the mental health company Compass Pathways was granted a patent on its synthetic form of psilocybin in 2020.

What FTO has been working on all these months was finally made public, in the most rigorous challenge to Compass Pathways' patents yet: a petition for post-grant review (PGR) filed on December 15. Such petitions are filed by third parties to the Patent and Trademark Office within nine months of a granted patent. They specify which claims in a patent the filers think are invalid and why, and are supported by statements from experts, alongside examples of what has been published about or known before—"prior art."

When psilocybin is made in a lab, it can be turned into a solid through crystallization. This process creates crystals that contain atoms or molecules that repeat through space, and settle into perfectly ordered patterns. But while psilocybin crystals are all made of the same psilocybin molecules, the molecules can arrange themselves in different ways to create a variety of three-dimensional crystalline forms, called polymorphs.

Compass' patents predominantly involve a specific crystalline form of psilocybin it claims it invented, called Polymorph A. The petition filed today will call this—and the patent office's assent to Compass' claims—into question. It presents research that claims that Compass' form of psilocybin isn't actually new, but just a mixture of other psilocybin crystalline forms that have been made before; that their polymorph is a patchwork quilt of pre-existing psilocybin crystals, rather than a quilt made up of an entirely new fabric.

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**Is it Possible
to Create an
Ethical
Psychedelics
Company?**

SHAYLA LOVE

04.06.21

In response to a request for comment on the petition, Compass' Chief Communication Officer said that Compass does not comment on specifics in active patent matters. "We remain highly confident in the strength of our patents and our polymorph A is the subject of numerous granted patents from several different Patent Offices, confirming that it is novel and inventive," she wrote in an email.

Compass currently has five U.S. patents; the petition filed today will challenge the patent granted on March 16, 2021, and it's expected that additional petitions are forthcoming from FTO challenging Compass' other patents. (A petition challenging a patent Compass was granted on March 23, 2021 would have to be filed by December 23, for instance, to meet a nine-month deadline.) Each PGR petition is directed at a single patent, but future petitions will draw on a lot of the same research included in this first filing.

To challenge a patent requires meticulous proof. FTO paired up with chemists and crystallographers, performed advanced testing and analysis with x-rays, and gathered evidence from prior publications, all to claim in the petition that the form of psilocybin that Compass' patents rest on is not actually novel, but has in fact existed—and been known to exist—for at least decades.

test that existed pre-Compass. “We secured the world for samples of psilocybin that predated their patent,” said Turnbull, who is also a board member of the nonprofit Usona Institute and the nonprofit [Heffter Research Institute](#), but is not representing them in this work.

There weren’t many places that had high-quality synthetic psilocybin stored in safe conditions. One sample came from Roland Griffiths at Johns Hopkins University, stored in the Johns Hopkins University System for Controlled Substances, and was made as early as 2008. Others were much older, like this Sandoz 1963 bottle received from the National Institute on Drug Abuse Drug Supply Program (NDSP).



PHOTO COURTESY OF CAREY TURNBULL.

Compass Pathways is one of the biggest names in psychedelic medicine. Its recent [phase 2B trial](#) was the largest study of psilocybin for treatment-resistant depression, and it, along with Usona Institute and the Multidisciplinary Association for Psychedelic Studies (MAPS), will present data to the FDA for medical approval of psychedelic treatments in the next few years.

Compass, unlike Usona and MAPS, is a for-profit company that went public in September 2020. By being one of the first public psychedelic for-profit companies, it has raised questions about what standard business practices the psychedelics community will find acceptable or ethical—like aggressive patent strategies or taking money from investors like [Paypal founder Peter Thiel](#).

[Lawyers](#), [activists](#), and [journalists](#) have previously called out Compass for broad claims in current

granted, including some claims that describe rudimentary aspects of the setting where the therapy takes place, like furniture and music, and others that include applications for psilocybin that far exceed the treatment of depression, which is the condition its patents largely focus on. How patents will impact ownership, roll out, price, and decision-making around psychedelic therapy is unresolved, though anyone who owns them will potentially wield a lot of influence.

Patent the Basic Components of Psychedelic Therapy?

SHAYLA LOVE

02.09.21

“Whoever does end up with these patents would be able to really dictate the use of them, either by using them to get revenue through licensing, or by using them to shape what the competition looks like by choosing to license to some and not others,” Graham Pechenik, a patent attorney at Calyx Law, previously told Motherboard. Even before psychedelics are approved for medical use, which companies have the resources to acquire the most IP could sway investor decisions.

The challenges on this polymorph patent filed today are the first significant opposition to IP in the psychedelic field. It highlights one procedural way in which psychedelic intellectual property might be pushed back against again in the future—but only if those with enough resources decide to do so.

Patents are described in the U.S. Constitution, and their intended purpose is to reward innovation by giving an inventor a right to exclude others from benefiting from their invention for 20 years. The biomedical and pharmaceutical worlds regularly exercise this right when developing new medicines. Christian Angermayer, the cofounder of ATAI Life Sciences and funder of Compass, has written that this is just how drugs are developed.

“Indeed, many drugs based upon natural products have been developed over the last few decades without outrage over commercialization,” he wrote in an open letter to author and psychedelic investor and philanthropist Tim Ferriss.

Patents are supposed to be granted on inventions that are new, not obvious to someone else with expertise in that field, and that are useful. This is where patents on psychedelics have offered some unique challenges. Because psychedelics have been illegal for so long, there's concern that its prior art isn't as readily available or accessible as is other kinds of research. For example, a patent application from this year made claims on a way to synthesize psilocybin with E. coli. But scientists claim they had published on that very topic in 2017.

“Patents are good for true innovations,” David Casimir, an IP lawyer who helped create a psychedelic prior art database called Porta Sophia, previously told Motherboard. “They let companies raise money to do their development, to sponsor their clinical trials. That's all very important. Bad patents are bad for everyone, except maybe the patent owner who owns

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Psychedelics Are a Billion-Dollar Business, and No One Can Agree Who

increase in cost, it slows down access to the market. It makes things more expensive.”

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09.23.21

Four out of five of Compass’ U.S. patents have claims on Polymorph A, its crystalline form of psilocybin, and the other claims a different crystalline form that includes a water molecule. In a press release for its fifth U.S. patent, George Goldsmith, the CEO and co-founder of COMPASS Pathways, said, “Patents enable us to continue to do the highest quality clinical research so we can work to bring therapies to patients who are suffering with serious mental health challenges and have few options.”

Turnbull is not anti-patent, he said. FTO is pushing back against whether Compass’ “inventions” are actually novel or non-obvious—and emphatically believes they are not.

“There are an almost infinite number of novel contributions to be made to the future of psychedelic science,” Turnbull wrote in FTO’s statement. “That there is a molecule named psilocybin and that it can be useful in treating depression is not one of them.”

The research that FTO facilitated tasked scientists both with characterizing the existing crystalline forms of psilocybin and comparing them with old samples, and assessing whether or not Compass had really discovered a new crystalline form. The petition filed today claims that Compass’ Polymorph A is not novel, but a combination of other crystalline forms that were already made before, and contains statements from James Kaduk, a crystallographer and research professor of Chemistry at Illinois Tech University, and Sven Lidin, dean of the faculty of science at Lund University and former Chairman of the Nobel Committee for Chemistry.

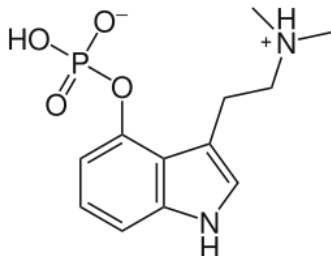
To understand the petition requires some deeper explanation of what crystal polymorphism is. As mentioned, crystals are special because of how organized they are internally: They are solids made up of atoms that repeat in an ordered way throughout three-dimensional space. But the same molecule can form a number of different crystal structures. That means the molecules arrange themselves into different shapes—those different shapes are called polymorphs.

It’s something of a mystery why these different crystal shapes occur, and how many of them there are for each molecule. “Crystal polymorphism” was first noticed two centuries ago in inorganic compounds, and shortly after that in organic compounds. In the 1960s, it was discovered that different crystal shapes can sometimes have varying properties, like melting points or solubility. This has relevance in pharmaceuticals—one crystal form, for example, can be easier to make into a consumer product than another.

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many databases show that around 67 to 88 percent of compounds exhibit polymorphism, but with most only having two to three; less than 2 percent of compounds have four or more polymorphs. Some scientists are currently working on predicting polymorphs from a molecule's structure, though they can't predict reliably which polymorphs will appear in the lab when crystals are being made.

Here's the psilocybin molecule:



When psilocybin is made into a solid, the repeating position of its atoms in three-dimensional space makes up its crystalline shapes. Some crystalline forms of psilocybin can include other molecules, like water or methanol that crystallizes with it, but some are just psilocybin.

X-ray powder diffraction is a tool to refract x-rays off different crystalline samples. The differences in shape translate to differences in the reflections, or peaks, in an X-ray powder diffractogram. Each polymorph has its own unique set of peaks that define its crystalline form—a fingerprint of sorts.

Most of the crystalline forms of psilocybin are already known. In a preprint [from 2020](#), chemists from Usona Institute screened for possible psilocybin polymorphs, finding 10 unique crystalline solid forms of psilocybin. Only two or three of those are “pharmaceutically relevant,” meaning easily synthesized for best use in humans.

Alex Sherwood, an organic chemist at Usona and senior author of the preprint, described to Motherboard three of the “pharmaceutically relevant” polymorphs. When you crystallize psilocybin from water, it makes a crystalline form called a “trihydrate,” which means it's a crystalline form containing both psilocybin molecules and water.

There is a common technique in chemistry in which a wet crystal is either dried in a vacuum or heated up to remove other molecules. When the trihydrate is dried, a process occurs called interconversion: The crystalline form converts to another crystalline form, creating a new polymorph without water molecules. Once the water is removed, the psilocybin molecule atoms rearrange, and you have a new polymorph. Usona has called this polymorph “Form A,” and Compass referred to it in its patents as A' or A Prime.

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11.30.21

Compass called Polymorph B. That polymorph occurs when A Prime is heated again and the molecules rearrange into yet another new shape, Polymorph B. (For consistency, I'll be using Compass' nomenclature for the polymorphs.)

Compass' first patents claim it invented another polymorph called Polymorph A. It distinguished A from A Prime by the appearance of its x-ray powder diffractogram.

In its patent, Compass wrote that initially, in the crystallization process, it found that drying Hydrate A led to A Prime, and when it heated A Prime again, it got Polymorph B, as expected. But when it scaled up their production, meaning making greater quantities, it had an "unexpected" observation, which is that there was an unusual appearing fingerprint for its large scale batches. Its diffractogram looked a lot like A Prime, but had additional peaks at certain positions, specifically at one position called "17.5°2θ."

The XRPD diffractogram obtained for Polymorph A' does not demonstrate a perturbation at ca. ~17°2θ to the same extent as Polymorph A. The perturbation in the XRPD diffractogram at ca. ~17°2θ is more pronounced for psilocybin produced at large scale (compared to that obtained at small scale) and was unexpected. Applicant has demonstrated that the Hydrate A is the only polymorphic form that exists across a range of temperatures with no diffraction peak in the 17°2θ theta region (see FIG. 7d). This strongly suggests a collapse of Hydrate A upon dehydration to yield Polymorph A or A' that varies with scale and that Polymorph A is the true form with Polymorph A' formed at a small scale being atypical.

Based on this, Compass wrote in the patent, it had invented a new polymorph, distinct from Polymorph A Prime and Polymorph B. In the patent it describes Polymorph A as the "true form" of psilocybin, and claims that Polymorph A prime, which is formed at small scales, is atypical.

The petition filed today argues that this is not the case. "Our point is that by calling this a new crystal form or structural variation on a crystal form, they have misdescribed it," said Jack Griem, a lawyer for Freedom to Operate.

What the research in the filing suggests is that Polymorph A isn't novel: The extra peak in the "fingerprint" of the diffractogram indicates that some of the crystal forms had started to interconvert from Polymorph A Prime to Polymorph B, the petition asserts. The hypothesis in the filing is that when the production of synthetic psilocybin was scaled up, it led to inconsistencies in heating and drying, and to a splotchy crystalline terrain: Some crystals are still in form A Prime, and some are in B, which is what led to the different diffractogram.

In the petition, crystallographer Kaduk described how he determined the crystal structures for the three well-known polymorphs and then mathematically modeled mixtures of those different polymorphs to predict what the corresponding diffractograms would look like.

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analyzing each sample, it allowed him to test the hypothesis that it has been these three forms of crystalline psilocybin (trihydrate, A Prime, and B) that have been produced again and again, in varying combinations.

Additionally, the petition re-examines a publication from 1975 by chemist V.A. Folen, who published the first X-ray powder diffraction on a sample of psilocybin. Kaduk's statement described the 1975 diffractogram in detail, and how Folen, too, reported a mixture of those same three polymorphs. Turnbull said that the petition argues the case that these same three crystalline forms have been made over and over since psilocybin was first synthesized—and that Compass' Polymorph A is no different.

Compass will now have three months to respond to each filing. Then, the Patent Trial and Appeal Board, a collection of administrative judges with expertise in science and patent law, will make a decision as to whether the petitioner demonstrates that at least one of the challenged claims is “more likely than not” unpatentable—and whether the case should proceed to a trial.

If the Board moves forward with the trial, there will be a discovery period followed by a hearing at the patent office, where judges will ask questions of the applicant. After that, they will issue a decision on the patents within 18 months of filing, per petition. (There is also an appeals process that could take place after, which goes directly to the Federal Circuit, which is the Court of Appeals for all past decisions.)

Compass could respond in a variety of ways. It could try to challenge the filing procedurally, or address the content directly. For example, it could argue that this specific mix of polymorphs—if they agree that's what it is—is novel in itself, or try to still contend it found a novel crystalline form. This is where patent law will step in over science—will it be considered non-obvious and useful to have different proportions of what already exists, if that's the case? Another unanswered aspect is whether there's something about Compass's crystalline form that makes it easier to encapsulate or formulate, or offers some other novel benefit.

In addition to the petition filing today, several researchers hired by FTO have submitted a manuscript of additional and orthogonal findings to an academic crystallography journal, where it will be peer-reviewed and scrutinized for accuracy—by people who arguably have little stake in Compass Pathways. The manuscript is still under review and a preprint is forthcoming soon. It's possible that if the petition does lead to a trial, such a manuscript could be referred to as evidence in the future.

The psychedelic community, as well as other companies in the space looking to file patents and gain intellectual property, will be watching the outcome of this case closely. Whether or not it's successful, the filing also reveals the immense cost and time needed to challenge patents after they are granted.

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**The False
Promise of
Psychedelic
Utopia**

SHAYLA LOVE

11.01.21

around half of that money, came from Patrick Hinson, and once he felt certain the petition would be making a strong case, he began to accept donations from others to make up the other half.

In Turnbull’s statement from April, he wrote that, “The money I have invested in FTO to fight Compass’s bad patents is an example of a “negative marginal product”: the time and cost defending psilocybin are not trivial and could better be employed developing psychedelic medicines.”

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