IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FREEDOM TO OPERATE, INC.
Petitioner,

v.

COMPASS PATHWAYS LIMITED,
Patent Owner

U.S. Patent No. 10,954,259
Title: Preparation of Psilocybin, Different Polymorphic Forms, Intermediaries, Formulations and their use

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,954,259

TABLE OF CONTENTS

I. INTRODUCTION

Pursuant to 35 U.S.C. § 321 and 37 C.F.R. § 42.200, Freedom to Operate, Inc. ("Petitioner") requests post-grant review of claims 1-23 of U.S. Patent No. 10,954,259 ("the '259 Patent") (Ex. 1101[1]) assigned to Compass Pathways Limited ("Patent Owner"). This Petition demonstrates that it is more likely than not that at least one of the challenged claims is unpatentable, and a trial for post-grant review must therefore be instituted. Evidence in this petition establishes that claims 1-23 are unpatentable under 35 U.S.C. §§ 101, 103 & 112.

Petitioner respectfully requests that claims 1-23 be judged unpatentable and canceled.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(a)(1)

As set forth below and pursuant to 37 C.F.R. § 42.8(a)(1), the following mandatory notices are provided as part of this Petition.

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner Freedom to Operate, Inc. is filing this Petition further to its mission to challenge mistakenly issued patents as an independent 501(c)(3) non-profit organization. Solely for purposes of this Petition, however, the following

[1] Petitioner notes that many of the Exhibits it has filed in support of its Petition are the same as those filed in support of Petitioner's petition in PGR2022-00012. Generally, exhibits filed in this proceeding correspond to those filed in PGR2022-00012, with numbering in this proceeding beginning with "11xx". For example, Exhibit No. 1102 in the same document as Exhibit No. 1002 in PGR2022-00012. Petitioner notes, however, that the Declarations filed in each proceeding are not identical even where the declarants are the same.

additional entities may be considered real parties-in-interest: Ceruvia Lifesciences LLC, a Delaware limited liability company, and B.More Inc., a 501(c)(3) non-profit organization.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner submits that a decision this proceeding may affect, or be affected by, a decision in the proceeding captioned *Freedom to Operate, Inc. v. Compass Pathways Limited*, PGR2022-00012.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Pursuant to 37 C.F.R. § 42.8(b)(3), Petitioner provides the following designation of counsel:

Lead Counsel	**Backup Lead Counsel**
John M. Griem, Jr. (Reg. No. 40005) griem@clm.com Carter Ledyard & Milburn LLP 2 Wall Street New York, New York 10005 Tel: 212-732-3200 Fax: 212-732-3232	Theodore Y. McDonough (Reg. No. 71981) mcdonough@clm.com Carter Ledyard & Milburn LLP 2 Wall Street New York, New York 10005 Tel: 212-732-3200 Fax: 212-732-3232

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Service on Petitioner may be made by mail or hand delivery to: John M. Griem, Jr., Carter Ledyard & Milburn LLP, 2 Wall Street, New York, New York 10005. The fax numbers for lead and backup counsel are shown above. Petitioner also consents to electronic service by email at griem@clm.com.

III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.203

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.203(a) and 42.15(b).

IV. REQUIREMENTS FOR POST-GRANT REVIEW UNDER 37 C.F.R. § 42.204

A. Grounds for Standing Under 37 C.F.R. § 42.204(a)

Petitioner hereby certifies that the '259 Patent is available for post-grant review because (i) the '259 Patent is a first-to-file patent having an effective filing date of October 9, 2017; and (ii) this petition is being filed within nine months of the patent's issue date, March 23, 2021.

Petitioner further certifies that it is not barred or estopped from requesting post-grant review challenging the claims of the '259 Patent on the grounds identified herein. Neither Petitioner, nor any party in privity with Petitioner: (i) has filed a civil action challenging the validity of claims 1-23 of the '259 Patent; or (ii) is estopped from challenging the claims on the grounds identified in the petition. Claims 1-23 of the '259 Patent also have not been the subject of a prior post-grant review or a finally concluded district court litigation.

B. Identification of Challenge Under 37 C.F.R. § 42.204(b) and Relief Requested

(1) Claims for which post-grant review is requested under 37 C.F.R. § 42.204(b)(1)

Petitioner requests post-grant review of claims 1-23 of the '259 Patent.

(2) The statutory grounds on which the challenge is based under 37 C.F.R. § 42.204(b)(2)

Claims 1-23 of the '259 Patent are unpatentable for the following reasons:

- Claims 1-23 are unpatentable under 35 U.S.C. § 101 as claiming an inoperative invention, and under 35 U.S.C. § 112 as not enabled, as the claimed single phase crystalline form "Polymorph A" does not exist, and the claimed peaks are the result of a mixture of polymorphs.

- Claims 1-10 and 16-23 claim, *inter alia*, a single crystalline polymorph defined by the inventors as "Polymorph A." If, however, claims 1-10 and 16-23 are construed to allow "Polymorph A" to comprise a mixture of polymorphs of psilocybin, then they are unpatentable as obvious under U.S.C. § 103 based on V.A. Folen, *X-Ray Powder Diffraction Data for Some Drugs, Excipients, and Adulterants in Illicit Samples,* 20 J. FORENSIC SCI. 348-72 (1975) (Ex. 1102) in view of D.E. Nichols, *Psychedelics*, 68 PHARMACOL. REV. 264-355 (2016) (Ex. 1103) or, alternatively, R. Carhart-Harris et al., *Psilocybin with Psychological Support for Treatment-Resistant Depression: an Open-Label Feasibility Study*, LANCET PSYCHIATRY, *available at* https://doi.org/10.1016/S2215-0366(16)30065-7 (Published online May 17, 2015) (Ex. 1104), together with R.R. Griffiths, *Psilocybin Produces Substantial and Sustained*

Decreases in Depression, 30 J. PSYCHOPHARMACOL. Journal of Psychopharmacology 1181 –1197 (Ex. 1127), in view of Roy, J., *An Introduction to Pharmaceutical Sciences* (2011) (Ex. 1113), and the other prior art cited in the claim chart in Section IV.C.3 below, and the general knowledge of one of ordinary skill in the art described in the Declarations submitted herewith.

- Claims 11-12 and 16 are unpatentable as obvious under U.S.C. § 103 for the same reasons as Claims 1-10 and 16-23 above, in further view of the publicly available JHU Batch (as defined *infra*, Section IV.B.5.vi).

- Claims 1-7 and 21-22 are invalid under 35 U.S.C. § 112 as not enabled because the '259 Patent does not teach how to measure—in the claimed pharmaceutical composition—the claimed characteristics of Polymorph A.

Petitioner's proposed construction of the claims, the evidence relied upon, and the precise reasons why the claims are unpatentable are set forth in Sections IV.B.3 through IV.B.5, and Section VI, *infra*.

(3) How the challenged claim(s) are to be construed under 37 C.F.R. § 42.204(b)(3)

In construing claims, the Office will apply the standard used in federal courts, *i.e.,* the claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b), which is articulated in *Phillips v. AWH Corporation*, 415 F.3d 1303 (Fed. Cir. 2005). In construing claims, the Office should bear in mind that the doctrine of construing claims to preserve their validity has been limited to cases in which "after applying all the available tools of claim construction, that the claim is still ambiguous." *Phillips,* at 1318-19. (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 911 (Fed. Cir. 2004)). The Federal Circuit "repeatedly and consistently has recognized that courts may not redraft claims, whether to make them operable or to sustain their validity." *Rembrandt Data Techs., LP v. AOL, LLC*, 641 F.3d 1331, 1339 (Fed. Cir. 2011); *see also MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1332 (Fed. Cir. 2007) (noting that "validity construction should be used as a last resort, not first principle").

Petitioner submits that two limitations in the claims require construction. Those limitations and Petitioner's proposed construction are set forth in the chart below:

Term	Construction
"crystalline Polymorph A of psilocybin"	"a crystalline form of a single polymorphic phase of psilocybin defined by the patentee as Polymorph A"
"characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ"	"Identifiable by reference to an X-ray diffractogram that discloses within normal experimental error peaks at 11.5, 12.0, 14.5, 17.5 and 19.7±0.1°2θ"

(i) Claim Term 1: "crystalline Polymorph A of psilocybin"

The independent claim of the '259 Patent requires "crystalline Polymorph A of psilocybin." This claim term should be construed to require that the claimed "crystalline Polymorph A of psilocybin" be "a crystalline form of a single polymorphic phase of psilocybin defined by the patentee as Polymorph A." Under this construction, the claimed X-ray powder diffraction ("XRPD") peaks must be the result of reflections from the claimed single polymorph of psilocybin, and not the result of reflections from a mixture of different polymorphs of psilocybin.

The claims themselves confirm that the claimed crystalline Polymorph A must be a single polymorph when independent claim 1 uses the definite article "the" before "Polymorph A" in the claim term "wherein **the Polymorph A**." Ex. 1101 (Col. 69:25) (emphasis added).

The specification several times distinguishes "Polymorph A" from "Polymorph A′ ", (pronounced and referred to herein as "Polymorph A-prime"), confirming that the claimed "crystalline Polymorph A of psilocybin" refers to a single polymorph and not a mixture of polymorphs. *See* Ex. 1101 (4:42-47, 7:52-55, 26:13-17). For example, the specification says that the "polymorph determining" step in the manufacture of Polymorph A is "a water crystallization step, followed by controlled cooling and drying step, to produce high purity crystalline psilocybin, Polymorph A ***or*** Polymorph A′." Ex. 1101 (29:28-31) (emphasis added). The detailed description later says that "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′ being formed at a small scale being atypical." Ex. 1101 (32:57-60) (emphasis added). Later, the description says, "Typically, batch sizes of greater than 5 g deliver Polymorph A, while batch sizes less than 5 g deliver Polymorph A′." Ex. 1101 (35:6-8). By repeatedly distinguishing Polymorph A from Polymorph A′, the inventors defined the claimed "crystalline Polymorph A" as a single crystalline form that is different from other polymorphs of psilocybin, including for example the crystalline psilocybin described in the specification as "Polymorph A′."

Moreover, the description's repeated distinction between Polymorph A from Polymorph A-prime precludes a construction of "crystalline Polymorph A" that

permits a mixture of polymorphs that includes Polymorph A-prime. Construing the term otherwise would eliminate the inventors' express distinction between Polymorph A and Polymorph A-prime.

The proposed construction of the term "crystalline Polymorph A of psilocybin" accords with the ordinary and customary meaning that a person of skill in the art would give to the term "polymorph" used throughout in the specification in defining "Polymorph A." Among such individuals, the definition of "polymorph" is generally agreed to be "a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state." Ex. 1106 at ¶19 (citing Ex. 1115); *see also* Ex. 1131 at 428. A necessary result of that definition is that a "polymorph" consists of a single phase of a compound. Accordingly, Petitioner submits that the term "crystalline Polymorph A of psilocybin" should be construed as "a crystalline form of a single polymorphic phase of psilocybin defined by the patentee as Polymorph A."

(ii) Claim Term 2: "characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ"

Independent claim 1 recites "Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ." Ex. 1101 (69:25-27). The term "characterized by X-ray powder diffraction

(XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ" should be construed to mean "Identifiable by reference to an X-ray diffractogram that discloses within normal experimental error peaks at 11.5, 12.0, 14.5, 17.5 and 19.7±0.1°2θ."

The phrase "characterized by X-ray powder diffraction (XRPD) peaks" could be construed to require either a precise match between XRPD diffractogram peaks, or to require that the XRPD diffractogram peaks be identifiable by reference to an X-ray diffractogram that discloses the referenced peaks within normal experimental error. The latter construction, that allows for experimental error and variation that would be expected by a person of ordinary skill, is the one that fits best with the specification and the way a person of ordinary skill would read an XRPD diffractogram. The claim phrase "[c]haracterized by X-ray powder diffraction (XRPD) peaks" is not defined in the specification, nor does the specification provide guidance on its definition. The claims include a range of peak locations ("±0.1°2θ"), but the specification does not explain the basis for the claimed range.

The latter construction fits with the way a person of skill would read a diffractogram to see if it is characterized by the claimed peaks. As set forth in the Declaration of Sven Lidin, Ph.D. (Ex. 1106), slight experimental errors and variation in XRPD patterns and exact peak locations and intensities can be

expected, depending on, for example, measurement techniques or the presence of other crystalline materials. Ex. 1106 at ¶50, 52, 62-66, and 77-78. Such factors can insignificantly shift single peaks in XRPD patterns for a single polymorph, but a person of ordinary skill would look at the XRPD pattern as a whole to determine if any one shift is likely a result of experimental variation. *Id.*

In considering the construction of other claims that include XRPD peaks, the court in *Astrazeneca AB v. Reddy's Laboratories, Inc.*, No. 11-2317, 2013 U.S. Dist. LEXIS 62149 (May 1, 2013) ("*Astrazeneca*") included a reference to normal experimental error. That court construed a very similar term ("characterized by the following major peaks in its X-ray diffractogram"). Ex. 1132 at 14-15. In *Astrazeneca*, the court concluded that a construction that would require an exact match was "too rigid":

> The claim language requires only that the [compound at issue] be "characterized" by the peaks in the table, not necessarily that it have a perfect one-to-one relationship. Even Defendants' expert concedes that although the X-ray diffraction of a compound will have the same "general appearance," the positions of the peaks may differ somewhat because of slight experimental errors. Plaintiffs' construction accounts for such differences, while Defendants' would not. *Id.*

In light of this recognition of the possibility of "slight experimental errors," the Court in *AstraZeneca* construed the claim term at issue in that case as "identifiable by reference to an X-ray diffractogram that includes the major peaks below." *Id*. at 15. The same reasoning was applied in *Astrazeneca AB v. Andrx Labs, LLC*, No.

14-8030, 2017 U.S. Dist. LEXIS 3990 (D.N.J. Jan. 11, 2017), in which the court construed the claim term "characterized by the following major peaks in its X-ray diffractogram," to mean "having each of the referenced major peaks in its X-ray powder diffractogram within normal experimental error." 2017 U.S. Dist. LEXIS 3990 at *131-32.

Based on the reasoning underlying the court's construction in *Astrazeneca*, and Drs. Lidin's and Kaduk's testimony, Petitioner submits that the proper construction of "characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ" is "Identifiable by reference to an X-ray diffractogram that discloses within normal experimental error peaks at 11.5, 12.0, 14.5, 17.5 and 19.7±0.1°2θ."

(4) How the construed claims are unpatentable under 37 C.F.R. § 42.204(b)(4)

An explanation of how the construed claims of the '259 Patent are unpatentable under the statutory grounds identified above is provided in the form of argument and claim charts in Section VI.B through VI.D, *infra.*

(5) Supporting evidence under 37 C.F.R. § 42.204(b)(5)

The evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identification of specific portions of the evidence that support the challenge, are provided below.

(i) Folen

In 1975, V.A. Folen reported XRPD data for drug samples, including psilocybin, and excipients and adulterants in illicit samples, not available in contemporary literature. V.A. Folen, *X-Ray Powder Diffraction Data for Some Drugs, Excipients, and Adulterants in Illicit Samples,* 20 J. FORENSIC SCI. 348-72 (1975) (Ex. 1102). The purpose of Folen's research was to "present X-ray powder diffraction data not available in the [contemporary] literature." Ex. 1102 at 348. In particular, Folen provided XRPD data "for compounds already compiled in the Powder Diffraction File," including psilocybin. Ex. 1102 at 348-49. Inasmuch as the contemporary Powder Diffraction File contained data for psilocybin, the psilocybin analyzed by Folen most likely was prepared according to the standard procedure used at that time. Ex. 1106 at ¶42.

Table 2 of Folen, the pertinent portion of which is reproduced below, presented XRPD data for psilocybin:

TABLE 2—*Continued.*

d, Å	*I/I*$_1$	*d*, Å	*I/I*$_1$	*d*, Å	*I/I*$_1$
(59) Probenecid		2.743	4	2.770	4
18.5	86	2.470	2	2.730	6
18.0	100	2.415	3	2.665	3
9.15	39	2.365	2	2.620	4
7.40	28	2.270	2	2.575	4
6.69	4	2.235	3	2.500	2
6.06	10	2.213	2	2.465	3
5.53	51	2.134	3	2.410	2
5.11	10			2.330B	2
4.98	9	(62) Psilocybin		2.230B	2
4.53	50	14.2	7	2.140B	2
4.17	29	10.0	33		
3.97	17	8.85	12	(64) Quinine Sulfate	
3.89	6	7.74	41	14.1	14
3.79	8	7.40	43	9.82	47
3.55	24	7.08	11	9.32	9
3.49	8	6.42	23	7.11	4
3.28	9	6.13	100	6.66	5
3.14	7	5.96	11	6.31	1
3.09	29	5.52	11	6.09	5
2.94	4	5.00	9	5.49	3
2.834	2	4.73	5	5.13	100
2.745	3	4.56	43	4.79	20
2.59	4	4.38	27	4.55	9
2.482	2	4.30	9	4.00	17
2.29	6	4.24	11	3.87	5
2.177	4	4.14	16	3.66	3
		4.02	22	3.54	11
(60) Prochlorperazine Dimaleate		3.86	25	3.45	17
8.84	4	3.81	20	3.40	4
6.15	25	3.67	32	3.31	4
5.50	29	3.46	20	3.26	5
5.27	20	3.34B	7	3.11	3
4.97	26	3.21B	11	2.961	8
4.68	41	3.02B	14	2.893	1

As explained in Dr. Lidin's declaration, d-spacing values provided by Folen are readily converted to their corresponding degrees 2θ values using Bragg's Equation, which allows direct comparison to the claims of the '259 Patent. Ex. 1106 at ¶61-69. Relevant to claims 1, 8, and 16 are Folen's d-spacing values at 7.74, 7.40, 6.13, 5.00, and 4.56. The chart below displays 2θ values converted, through the application of Bragg's Equation, from the d-spacing values reported by Folen:

Folen d-spacing value	**2θ**
7.74	11.4
7.40	12.0
6.13	14.4
5.00	17.7
4.56	19.5

Below are supporting calculations for the 2-theta values set forth above. These calculations were performed using Microsoft Excel and the formula 2θ=DEGREES(2*(ASIN(1*1.5406/(2*(d))))). Petitioner notes that the d-values in Folen were converted to 2θ values using Bragg's equation in PGR2020-0030, and that slightly different results for one of the d-values was reached. Petitioner now realizes that the λ value used to perform 2θ calculations during PGR2020-0030 (*i.e.*, 1.5405, taken from Folen) was not exactly correct. The correct Copper K-α wavelength value, when rounded to four decimal places, is 1.5406 Å. *See infra* at Section VII and Ex. 1106 at ¶80.

Using Bragg's Equation: $n\lambda = 2d \sin\theta$, where $n=1$ and $\lambda=1.5406$, the relevant d-values in Folen convert as follows:

11.4 2θ $\theta = \sin^{-1}(n\lambda/2d)$ $2\theta = 2(\sin^{-1}(n\lambda/2d))$ $2\theta = 2(\sin^{-1}(1*1.5406/(2*7.74))$ $2\theta=11.4233$ $2\theta=11.4$	**12.0 2θ** $\theta = \sin^{-1}(n\lambda/2d)$ $2\theta = 2(\sin^{-1}(n\lambda/2d))$ $2\theta = 2(\sin^{-1}(1*1.5406/(2*7.4))$ $2\theta=11.95$ $2\theta=12.0$
14.4 2θ $\theta = \sin^{-1}(n\lambda/2d)$ $2\theta = 2(\sin^{-1}(n\lambda/2d))$ $2\theta = 2(\sin^{-1}(1*1.5406/(2*6.13))$ $2\theta=14.4378$ $2\theta=14.4$	**17.7 2θ** $\theta = \sin^{-1}(n\lambda/2d)$ $2\theta = 2(\sin^{-1}(n\lambda/2d))$ $2\theta = 2(\sin^{-1}(1*1.5406/(2*5.00))$ $2\theta=17.7246$ $2\theta=17.7$
19.5 2θ $\theta = \sin^{-1}(n\lambda/2d)$ $2\theta = 2(\sin^{-1}(n\lambda/2d))$ $2\theta = 2(\sin^{-1}(1*1.5406/(2*4.56))$ $2\theta=19.4507$ $2\theta=19.5$	

(ii) Nichols

Nichols presents a comprehensive review of psychedelics, including psilocybin, and addresses areas such as their mechanism of action, effects, and potential therapeutic value, including in treating anxiety and major depressive disorder ("MDD"). D.E. Nichols, *Psychedelics*, 68 PHARMACOL. REV. 264-355 (2016) (Ex. 1103 at 323-25). In presenting support for psilocybin's potential therapeutic value, Nichols summarized the results of studies which demonstrated

substantial decreases in depression in patients treated with psilocybin. *Id; see also* Ex. 1112 at ¶9.

(iii) Carhart-Harris

Carhart-Harris reported the results of an "open-label feasibility trial [of] 12 patients . . . with moderate-to-severe, unipolar, treatment-resistant major depression [who] received two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." R. Carhart-Harris et al., *Psilocybin with Psychological Support for Treatment-Resistant Depression: an Open-Label Feasibility Study*, LANCET PSYCHIATRY, *available at* https://doi.org/10.1016/S2215-0366(16)30065-7 (Published online May 17, 2015) (Ex. 1104 at 1 (Methods)). The reported results demonstrated that "[r]elative to baseline, depressive symptoms were markedly reduced 1 week . . . and 3 months . . . after high-dose treatment," *id*. at 1 (Findings), and provide "support for the safety and efficacy of psilocybin for treatment-resistant depression." *Id*. at 1 (Interpretation); *see also* Ex. 1112 at ¶8.

(iv) Griffiths

R.R. Griffiths, *Psilocybin Produces Substantial and Sustained Decreases in Depression*, 30 J. PSYCHOPHARMACOL. 1181–1197 (2016) (Ex. 1127), studied the effects of psilocybin in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. In Griffiths, "Psilocybin doses were administered in identically appearing opaque, size 0 gelatin capsules, with lactose

as the inactive capsule filler." Ex. 1127 at 1183. Griffiths reported that "High-dose psilocybin produced large decreases in . . . measures of depressed mood and anxiety," with "clinically significant decreases in depressed mood and anxiety" at 6-month follow-up. *Id.* at 1181.

(v) Martin's

Martin's Physical Pharmacy and Pharmaceutical Sciences, a popular textbook referenced by practitioners and used by students studying pharmaceutical sciences, states that "the most essential and most popular pharmaceutical products are offered as oral solid dosage forms such as capsules and tablets." Ex. 1110 at ¶28 (citing Ex. 1166). Martin further states that 72% of the World Health Organization Model List of Essential Medicines are offered as oral formulations, with 59% offered as tablets or capsules, and of the 100 best-selling drugs (as of 2007), 68 were offered as oral formulations, with 66 of those offered as tablets or capsules. *Id*.

(vi) Solid Dose Experts Techceuticals.

Solid Dose Experts Techceuticals, Vol. 15 (2015) (Ex. 1168) (hereafter, "Techceuticals"), discloses that preparing pharmaceutical compositions as tablets was routine as of the priority date of the '259 Patent. Ex. 1110 at ¶31 (citing Ex. 1168).

(vii) JHU Batch

In or about August, 2008, Dr. David Nichols of the University of North Carolina created a batch of approximately 24 grams psilocybin in his laboratory at the School of Pharmacy and Pharmaceutical Sciences, Robert H. Heine Pharmacy Building, Purdue University, West Lafayette, IN 47907-1333, which he identified as "Lot 10415-25" (referred to herein as the "JHU Batch"). Ex. 1130 at ¶6 (citing Ex. 1117). On or about October 30, 2009, Dr. Nichols sent to Dr. Roland R. Griffiths, a Professor in the Departments of Psychiatry and Neurosciences at the Johns Hopkins University ("JHU") School of Medicine approximately 20 grams of the JHU Batch. *Id.* at ¶7. On or about June 6, 2012, Dr. Nichols sent Dr. Griffiths an additional sample from the JHU Batch. *Id.* at ¶8.

On or about July 21, 2021, the JHU Research Pharmacy sent 100 milligrams of the JHU Batch to Triclinic Labs for analysis. Ex. 1120 at ¶8; Ex. 1130 at ¶11; Ex. 1169; Ex. 1181. Triclinic subsequently collected an XRPD pattern, as well as TGA data, for the JHU Batch and reported its results in a report dated December 2, 2021. Exs. 1120 & 1121. Triclinic's XRPD diffractograms for the JHU Batch—collected using both reflection and transmission geometry—are reproduced below:

Figure 6: XRPD Pattern of JHU Batch—Reflection[2]

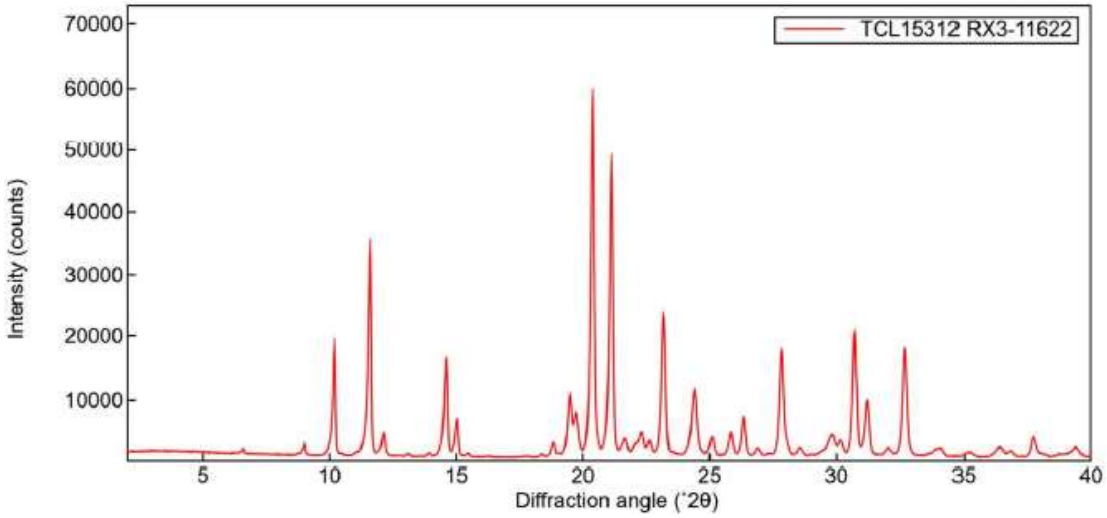
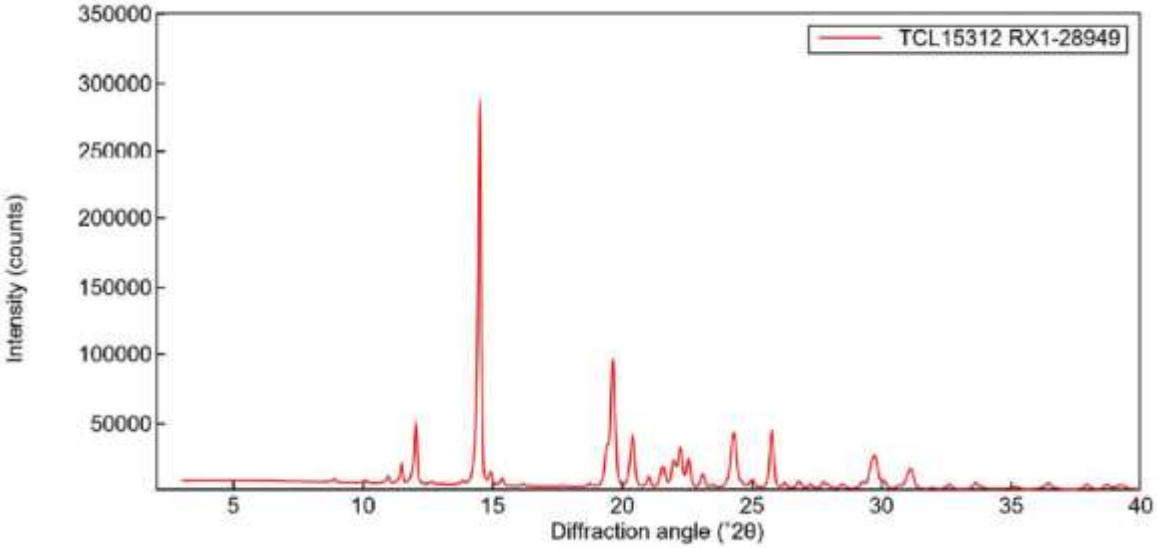


Figure 7: XRPD Pattern of JHU Batch—Transmission[3]



Additionally, of the 27 peaks identified in the '259 Patent as characteristic of Polymorph A-prime, 26 appear in the XRPD peak listings of the JHU Batch. Ex. 1106 ¶60 (*Comparing* Ex. 1101 (7:24-50) *with* Ex. 1121). The peaks generated

[2] Ex. 1121 at 4.

[3] Ex. 1121 at 7.

from analysis of the JHU Batch which correspond to peaks purportedly characteristic of Polymorph A-prime are as follows:

Polymorph A-prime		**JHU Batch[4]**		**JHU Batch[5]**	
XRPD Peak Positions (°2θ)[6]	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**
5.5	4.89	-	-	-	-
10.1	4.09	10.2	27	10.1	1
11.5	22.05	11.6	55	11.5	5
12.0	22.77	12.1	6	12.0	20
14.5	100	14.6	26	14.5	100
14.9	11.29	15.0	10	14.9	4
17.5	1.08	-		17.7	0
18.7	2.44	18.8	3	18.7	1
19.4	23.02	19.5	15	19.4	15
19.6	33.7	19.7	10	19.6	48
20.3	17.01	20.4	100	20.4	20
21.1	12.08	21.1	79	21.0	2
21.6	8.51	21.7	4	21.5	8
22.2	15.54	22.1	2	22.2	15
22.6	8.78	22.6	3	22.5	9
23.1	10.11	23.2	37	23.1	4
24.3	21.83	24.4	17	24.3	29

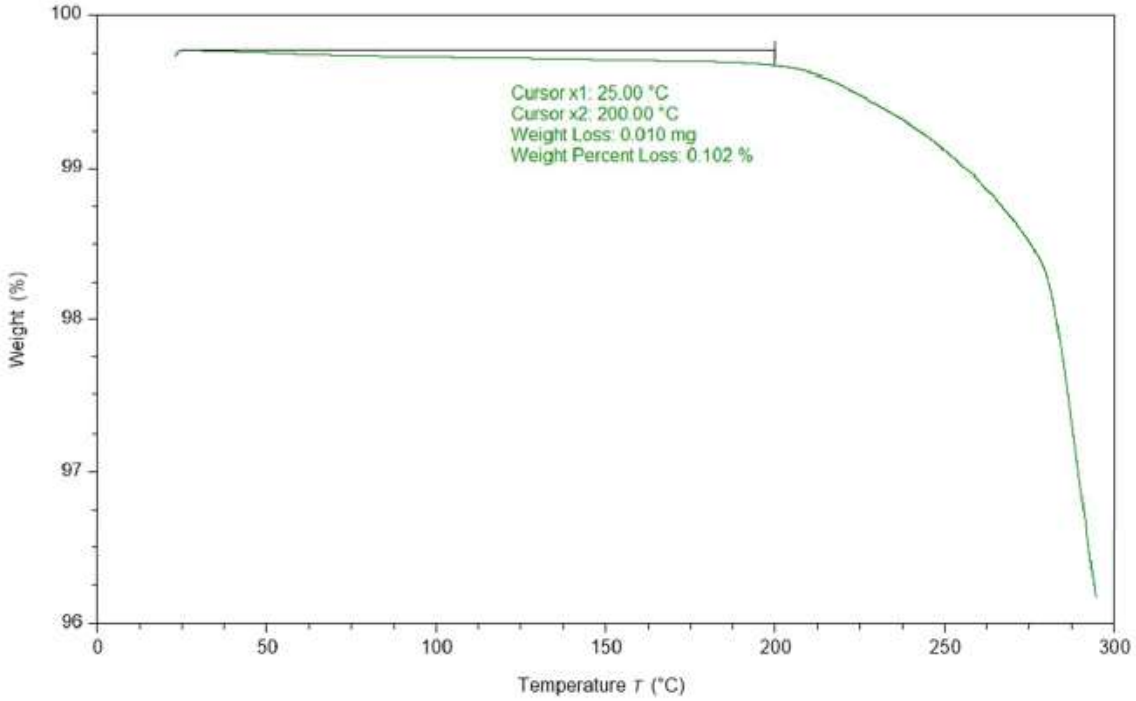
[4] Collected using reflection geometry. Ex. 1120 at ¶11; Ex. 1121.

[5] Collected using transmission geometry. Ex. 1120 at ¶11; Ex. 1121.

[6] Ex. 1101 (7:22-48).

Polymorph A-prime		JHU Batch[4]		JHU Batch[5]	
XRPD Peak Positions (°2θ)[6]	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**
25.1	4.36	25.1	5	25.0	2
25.8	15.4	25.8	6	25.8	19
26.3	4.28	26.3	10	23.3	1
26.8	2.86	26.9	2	26.8	2
27.8	5.96	27.8	30	27.7 and 27.9	1 and 2
28.6	1.91	28.5	2	28.5	2
29.7	10.56	29.9	5	29.6 and 29.7	4 and 16
31.1	7.35	31.2	16	31.1	11
32.6	3.72	32.7	30	32.6	2
33.8	1.54	33.9	1	33.8	1

TriClinic's TGA thermogram is reproduced below (Exs. 1120 and 1121 at 11):



(viii) Prior art teaching purity of active pharmaceutical ingredients

As explained in the Declaration of Raj Suryanarayanan, Ph.D., the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH") brings together the pharmaceutical industry and regulatory authorities to develop scientific and technical guidelines. Ex. 1110 at ¶24. The ICH Topic Q 3 A (R2) includes guidance on impurities and impurity testing in drug substances (hereinafter, "ICH Guidance"). *Id*.; Ex. 1164. As Dr. Suryanarayanan testified, practitioners regularly reference and follow ICH's guidance.

ICH Guidance provides the reporting threshold, identification threshold and qualification threshold for impurities based on the daily maximum dose, and it is evident from the Guidance that impurities even at very low levels need to be reported, identified and qualified. For example, administration of 2g/day or less of a drug substance requires reporting impurities at and above 0.05%, and administration of more than 2g/day of a drug substance requires reporting impurities at and above 0.03%. Ex. 1110 at ¶24; Ex. 1164 at 11.

United States Pharmacopeial ("USP") purity specifications ("USP Standards") also demonstrate that a high level of purity is typical in drugs, including drugs used to treat depression such as Fluoxetine Hydrochloride (Prozac®) and Imipramine Hydrochloride. The USP Standards for those two drugs require that they contain not less than 98% API by dry weight. Ex. 1170. Additionally, the USP Standards require that total impurities in Fluoxetine Hydrochloride be not more than 0.50%, and in Imipramine Hydrochloride not more than 1%, and that no single impurity exceed 0.10%. Ex. 1110 at ¶25; Ex. 1170.

(ix) Roy

Roy, J., "An Introduction to Pharmaceutical Sciences" (2011)) teaches that the use of excipients is an essential and elementary aspect of drug formulation. *See generally* Ex. 1113 at 111-40.

V. SUMMARY OF THE '259 PATENT

The '259 Patent issued on March 23, 2021 and is titled *Preparation of Psilocybin, Different Polymorphic Forms, Intermediates, Formulations and Their Use.* It names Derek John Londesbrough, Christopher Brown, Julian Scott Northen, Gillian Moore, Hemant Kashinath Patil, and David E. Nichols as the inventors. The '259 Patent relates to the "large-scale production of psilocybin for use in medicine." Ex. 1101 (Abstract). The specification states that psilocybin is a plant-based molecule which acts as a psychedelic and has been used to treat various disorders, such as mood disorders and alcoholic disorders. Ex. 1101 (1:37-40). The '259 Patent states that an object of the purported invention is to provide chemically pure psilocybin of consistent polymorphic form for administration to humans. Ex. 1101 (3:30-32).

A. Effective Filing Date of the '259 Patent

The '259 Patent issued from U.S. Patent Application No. 17/116,739 filed December 9, 2020. The '739 Application is a continuation of application No. 16/920,223, filed July 2, 2020, which is a continuation of application No. 16/679,009, filed on November 8, 2019, which is a continuation of application No. 16/155,386, filed on October 9, 2018, which now is Patent No. 10,519,175. The '259 Patent claims priority to three foreign applications, 1716505.1(GB) (Oct. 9,

2017), 1810588.2(GB) (Jun. 28, 2018), and 1816438.4(GB) (Oct. 9, 2018). Only for the purposes of this proceeding, Petitioner has assumed that the earliest effective filing date of the '259 Patent is not earlier than October 9, 2017.

B. The '259 Patent's Prosecution History

The applicant filed the '739 Application on December 9, 2020 with 30 original claims, together with a preliminary amendment cancelling claims 1-30 and introducing new claims 31-53 together with a request for prioritized examination which was granted on January 8, 2021. *See* Ex. 1160. As a result of the preliminary amendment, the '739 Application contained three independent claims (claims 31, 38, and 46 as filed). Claim 31 was directed to a "pharmaceutical composition" comprising, *inter alia*, "crystalline Polymorph A of psilocybin," claim 38 was directed to "Crystalline Polymorph A of psilocybin," and claim 46 was directed to a "method of treating major depressive disorder" by administration of "crystalline Polymorph A of psilocybin." *Id*. at 2-4. On January 20, 2021, the applicant filed a terminal disclaimers to application 16/920,223 (which issued as U.S. Patent No. 10,947,257 on March 16, 2021) and to U.S. Patent No. 10,519,175. Ex. 1161. A Notice of Allowance was issued on January 27, 2021.

C. Person of Ordinary Skill in the Art

A person of ordinary skill in the art in the field of the '259 Patent on October 9, 2017, would have had an advanced degree (i.e., a Master's degree with two or more years of experience, or a Ph.D.) in inorganic or organic chemistry, chemical engineering, pharmacology, or a related discipline. Such a person of skill in the art would be familiar with medicinal chemistry or pharmaceutical chemistry, and with analytical methods to characterize and differentiate solid forms of compounds, particularly XRPD, but also including differential scanning calorimetry ("DSC") and thermogravimetric analysis ("TGA"). Alternatively, one of ordinary skill could have less education and approximately five or more years of relevant experience. *See* Ex. 1106 at ¶38.

D. The '259 Patent's Specification

The '259 Patent purports to describe several polymorphic forms of psilocybin, including forms the applicant called "Polymorph A," "Polymorph A′ " (i.e., Polymorph A-prime), "Hydrate A", and "Polymorph B." Other relevant portions of the specification are described above in the discussion of claim construction in Section IV.B.3.

The specification teaches that XRPD is used to characterize the crystalline form of psilocybin and identifies the conditions under which XRPD data should be collected:

> The solid state form of Psilocybin is determined by XRPD. XRPD diffractograms were collected on a diffractometer (such as a PANalytical X′Pert PRO or equivalent) using Cu Kα radiation (45 kV, 40 mA), θ-θ goniometer, focusing mirror, divergence slit (½″), soller slits at both incident and divergent beam (4 mm) under ambient conditions. The data collection range was 3-35°2θ with a continuous scan speed of 0.2° s^{-1}. The resulting diffractogram is compared to that of a reference diffractogram of Polymorph A or A′ to ensure that it is concordant (FIG. 7a or 7 b respectively).

Ex. 1101 (53:38-48). While claims 1-7 of the '259 Patent claims are directed to a "pharmaceutical composition" (see *infra* Section V.D), the specification does not teach how to characterize or measure the claimed characteristics of psilocybin in the pharmaceutical composition.

E. The '259 Patent's Claims

Independent claims 1, 8, and 16 of the '259 Patent claims:

> 1. A pharmaceutical composition, comprising crystalline Polymorph A of psilocybin and a pharmaceutically acceptable excipient, wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7±0.1 °2θ,
>
> wherein the crystalline psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis., and no single impurity of greater than 1%.
>
> 8. Crystalline Polymorph A of psilocybin, wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1,

14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, wherein the psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis.

16. A method of treating major depressive disorder, the method comprising: administering a therapeutically effective amount of crystalline Polymorph A of psilocybin to a patient in need thereof,

wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, and

wherein the psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis.

Claims 2-7 depend directly from claim 1, claims 9-15 depend directly from claim 8, and claims 17-23 depend directly or indirectly from claim 16. The dependent claims are reproduced below.

2. The pharmaceutical composition of claim 1, wherein the composition is a capsule.

3. The pharmaceutical composition of claim 1, wherein the composition is a tablet.

4. The pharmaceutical composition of claim 1, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.

5. The pharmaceutical composition of claim 1, wherein the composition comprises about 5 mg of the crystalline Polymorph A of psilocybin.

6. The pharmaceutical composition of claim 1, wherein the composition comprises about 10 mg of the crystalline Polymorph A of psilocybin.

7. The pharmaceutical composition of claim 1, wherein the composition comprises about 25 mg of the crystalline Polymorph A of psilocybin.

* * *

9. The crystalline psilocybin of claim 8, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.

10. The crystalline psilocybin of claim 8, wherein the Polymorph A is characterized by a XRPD diffraction pattern that is substantially the same as shown in FIG 7*a*.

11. The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by a water content of <0.5% w.w.

12. The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by a <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C.

13. The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having an onset temperature of between 205° C. and 220° C.

14. The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by an endothermic even in a DSC thermogram having an onset temperature of between 145° C. and 155° C.

15. The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by one or more of the following:

a) a loss on drying of no more than 2% w/w;

b) residue on ignition of no more than 0.5% w/w;

c) assay (on a dry basis) of 95-103% by weight as measured by HPLC;

d) residual solvent content of no more than 3000 ppm methanol; 5000 ppm ethanol, 720 ppm THF, and 890 ppm toluene, as measured by high resolution gas chromatography (HRGC);

e) phosphoric acid content of no more than 1% w/w as measured by ^{31}P NMR; and

f) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of:

i. no more than 1.5 ppm Cd;

ii. no more than 1.5 ppm Pb;

iii. no more than 4.5 ppm As;

iv. no more than 9.0 ppm Hg;

v. no more than 15 ppm Co;

vi. no more than 30 ppm V;

vii. no more than 60 ppm Ni;

viii. no more than 165 ppm Li; and

ix. no more than 30 ppm Pd.

* * *

17. The method of claim 16, wherein about 5 mg of the crystalline Polymorph A of psilocybin is administered.

18. The method of claim 16, wherein about 10 mg of the crystalline Polymorph A of psilocybin is administered.

19. The method of claim 16, wherein about 25 mg of the crystalline Polymorph A of psilocybin is administered.

20. The method of claim 16, wherein the crystalline Polymorph A of psilocybin is orally administered.

21. The method of claim 20, wherein the crystalline Polymorph A of psilocybin is administered in a capsule.

22. The method of claim 20, wherein the crystalline Polymorph A of psilocybin is administered in a tablet.

23. The method of claim 16, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.

VI. DETAILED EXPLANATION UNDER 37 C.F.R. § 42.204(b)

The '259 Patent purports to disclose several forms of crystalline psilocybin. As relevant here, those forms are Polymorph A, Polymorph A-prime, and Polymorph B. *See generally* Ex. 1101 (4:4-13:21). According to the '259 Patent, Polymorph A is distinguished from Polymorph A-prime by the presence of a peak in an XRPD diffractogram for Polymorph A at about 17.5°±0.1°2θ. Ex. 1101 (4:42-47; 7:52-54).

However, the '259 Patent does not disclose any novel polymorphic forms of psilocybin. Rather, the inventors failed to appreciate that their "Polymorph A" was a mixture of Polymorph A-prime and Polymorph B, which is created by inadequately controlled drying at large scale. Ex. 1106 at ¶53; Ex. 1108 at ¶19-20. Because the claims of the '259 Patent claim crystalline psilocybin in a *single* polymorphic form, all of the claims are invalid under 35 U.S.C. §§ 101 and 112, as explained below in Section VI.B.

If the claims requiring so-called "Polymorph A" characterized by certain peaks are construed to permit a mixture of polymorphs that includes the five

required peaks, then claims 1-10 and 16-23 are made obvious by prior art identified below in Section VI.C under 35 U.S.C. § 103.

Claims 1-7 and 21-22 are invalid for another reason—lack of enablement under 35 U.S.C. §§ 112. The '259 Patent does not teach how to measure—in the claimed pharmaceutical composition or in a capsule or tablet—the claimed characteristics of Polymorph A.

A. Standard for Institution of Review

Title 35, Section 324(a) of the United States Code provides that a post-grant review may be instituted when a petition filed under 35 U.S.C. § 321, if such information is not rebutted, demonstrates that it is more likely than not that at least one of the claims challenged in the petition is unpatentable. *See also* Patent Trial and Appeal Board Consolidated Trial Practice Guide, Nov. 2019, at 53. In addition, 35 U.S.C. § 324(b) provides that the determination required under 35 U.S.C. § 324(a) may also be satisfied by a showing that the petition raises a novel or unsettled legal question that is important to other patents or patent applications.

B. Claims 1-23 are Unpatentable Under 35 U.S.C. § 101 and 112 as Claiming an Inoperative Invention And As Not Enabled

Section 101 requires as a condition of patentability that an invention be "useful" and, "accordingly, the subject matter of the claim must be operable." *Process Control Corp. v. HydReclaim Corp*., 190 F.3d 1350, 1358 (Fed. Cir.

1999); *see also In re Hu*, 848 Fed. Appx. 416, 426 (Fed. Cir. 2021) (affirming rejection of claims where "there [was] not scientific support for the claimed [invention]," and "the experimental data and explanations [were] inadequate to support the novel results and scientific principals asserted" by the applicant.").

Interpreted as Petitioner advocates, claim 1 requires a "crystalline form of a single polymorphic phase of psilocybin defined by the patentee as Polymorph A," which is "identifiable by reference to an X-ray diffractogram that discloses within normal experimental error peaks at 11.5, 12.0, 14.5, 17.5 and 19.7±0.1°2θ." However, no such "Polymorph A" of psilocybin exists. "Polymorph A" is in fact a mixture of two polymorphs also disclosed in the '259 Patent—Polymorph A-prime and Polymorph B. The Declarations of Sven Lidin Ph.D. (Ex. 1106) and James Kaduk, Ph.D. (Ex. 1108) explain this conclusion in detail. *See* Ex. 1106 at ¶¶4, 30-32, 50-57, and Ex. 1108 at ¶¶4, 16-21, and 46-48.

As Dr. Lidin explains, polymorphs of the same substance never have major XRPD peak positions that are identical, except for one extra peak. If the peaks are almost all the same, and there is one additional peak, that indicates that there is another crystal form present as an impurity. The nature of XRPD measurement and the physical properties of crystals makes the existence of two distinct crystal polymorphs having near-identical XRPD patterns virtually impossible. Ex. 1106 at ¶54.

As Dr. Kaduk explains, a known challenge in process-scale active pharmaceutical ingredient isolation is heterogeneous heating during the final isolation step with vacuum drying. Ex. 1108 at ¶19 (citing Exs. 1124-26). However, the '259 Patent neglects to address the possibility that the material described as "Polymorph A" (i.e., Compass Polymorph A), with the weak 17.5° 2θ XRPD reflection, consisted of a mixture of Polymorph A-prime and Polymorph B. Ex. 1108 at ¶19. Notably, the inventors created and recognized the existence of a mixed phase sample (Ex. 1101 at Fig. 7F and Col. 3:10-12) ("The XRPD diffractogram [] suggested a mixed phase of Polymorph A′ . . . and Polymorph B"), but either ignored or overlooked the significance of their findings.

Together with the dynamics of large-scale API drying, the observation of a prominent reflection at 17.5 °2θ in the diffractogram for "Polymorph B" and the thermal interconversion behavior reported by the inventors between "Compass Polymorph A" and "Polymorph B" indicated to Dr. Kaduk that the '259 Patent's claimed "Compass Polymorph A" is not a novel polymorph at all but instead is a mixture of "Polymorph A-prime" and "Polymorph B", which was produced through inadequately controlled drying at large scale. Ex. 1108 at ¶20.

Quantitative phase analysis ("QPA") by Rietveld Method ("RM") was identified as a viable approach to determine whether Compass Polymorph A is actually a mixture of crystal forms. Ex. 1106 at ¶55; Ex. 1108 at ¶22. QPA by

RM relies on fitting an experimental diffraction pattern from a suspected multiphase sample with a calculated profile based on the crystal structures for each of the phases. The calculated model considers the sum of the individual crystal structure parameters, unit-cell dimensions, peak shapes, widths, backgrounds, and preferred orientation effects. Ex. 1108 at ¶23 (citing Ex. 1143).

QPA results for Compass Polymorph A indicated that it consisted of a mixture of both Polymorph A-prime and Polymorph B phases. The approximate ratio of Polymorph A-prime to Polymorph B was 81:19. Dr. Kaduk determined that the Rietveld plot for Compass Polymorph A clearly indicates that the perturbation at 17.5 °2θ, which the '259 Patent states is the distinguishing feature of the material, was a reflection contributed by Polymorph B. Ex. 1108 at ¶46-47. The work supporting Dr. Kaduk's determination was recently published by *Acta Crystallographica* Section C. *Id.* at ¶51. The article is entitled *Psilocybin: crystal structure solutions enable phase analysis of prior art and recently patented examples*, a copy of which is submitted as Ex. 1185.

Dr. Lidin, based on his knowledge and expertise, and after reviewing Dr. Kaduk's Declaration, succinctly explains that "the '259 Patent's claim to a single phase of 'crystalline Polymorph A of psilocybin . . . characterized by [XRPD] peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1, and 19.7°2θ±0.1°2θ' is erroneous

and scientifically meaningless, because "Polymorph A" is a mixture of Polymorph A-prime and Polymorph B." Ex. 1106 at ¶57.

Claims 1, 8, and 16 are therefore not "useful" because they are incapable of being practiced. Claims 1, 8, and 16, therefore, are invalid as inoperative, as are all of their dependent claims (which are all the claims in the '259 Patent).

In any event, the five XRPD peaks required for "Polymorph A" in the '259 Patent claims do not correspond to any novel *single* polymorphic form of psilocybin which the '259 Patent requires and which the inventors regarded as their invention, rendering all of the claims inoperative and invalid under § 101.

For the same reason, the '259 Patent is invalid as not enabled under § 112. A specification cannot be enabling where a claim is impossible to practice. *See, e.g., Trustees of Boston Univ. v. Everlight Electronics*, 896 F.3d 1357 (Fed. Cir. 2018) (holding claim invalid where the "full scope" of the claimed invention could not be practiced because it was "impossible" to do so). The '259 Patent claims a *single* polymorphic form of psilocybin characterized by an XRPD diffractogram with five particular peaks, but no such polymorph of psilocybin exists. Consequently, it is impossible to practice the "full scope" of the claims of the '259 Patent.

C. Claims 1-12, 15, and 16-23 Are Obvious Under 35 U.S.C. § 103

A patent claim is invalid "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. "Obviousness is a question of law based on underlying findings of fact." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1372 (Fed. Cir. 2019) (internal quotation and citation omitted). "Those underlying findings of fact include: (1) the scope and content of the prior art, (2) differences between the prior art and the claims at issue, (3) the level of ordinary skill in the pertinent art, and (4) the presence of evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, and unexpected results." *Id.* (citing *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966)) (internal quotations omitted). In conducting an obviousness analysis, the Board also "considers whether a skilled artisan would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so." *Id.* (citation and quotation omitted).

As set forth in the claim chart below, if claims 1-12, 15, and 16-23 of the '259 Patent are not considered invalid under Section 101 and 112, they are

rendered obvious by Folen (Ex. 1102) and/or the JHU Sample, in view of Nichols (Ex. 1103), or alternatively Carhart-Harris (Ex. 1104), together with Roy (Ex. 1113), Martin's (Ex. 1166) and/or Techceuticals (Ex. 1178), and ICH Guidance (Ex. 1164) and/or USP Standards (Ex. 1170).

In reading Folen, a person of ordinary skill would recognize that the claimed XRPD peaks which characterize "Polymorph A" are taught by Folen. As further explained in the Lidin Declaration, Folen's peaks convert to 11.5, 12.0, 14.5, 17.7 and 19.5°2θ. The first three of these peaks are directly within the claimed range of ±0.1°2θ. The second two peaks are within ±0.2°2θ. A person of ordinary skill would also recognize in reading Folen that it used older equipment and manual methods of assigning d-values, which might create some variability in measuring exact peak locations. For this and the other reasons explained in the Liden Declaration, these latter two peaks would be seen by a person of ordinary skill in this field as disclosing the claimed peaks at 17.5 and 19.7°2θ ±0.1°2θ. Ex. 1106 at ¶ 31-45, 61-67 and 70-75. Dr. Kaduk's work confirms that the psilocybin analyzed by Folen was characterized by XRPD reflections that were consistent primarily with Polymorph A-prime, although both Polymorph B and Hydrate A also were detectible. Ex. 1108 at ¶46, 49. Dr. Kaduk concluded that Polymorph B and Hydrate A undoubtedly were present in the Folen sample and his analysis of Folen demonstrates that these three predominant crystalline forms of psilocybin existed

as early as 1975, and that variable amounts of these three phases could be expected in historical samples of psilocybin made and used in clinical trials before 2017. *Id.*

The recently revived interest in using psilocybin to treat MDD and other disorders would lead a POSA to combining the teachings of the prior art to create the invention claimed in the '259 Patent. A motivation to combine may be found in many sources, such as "market forces, design incentives, the interrelated teachings of multiple patents[,] any need or problem known in the field of endeavor at the time of invention and addressed by the patent[,] and the background knowledge, creativity, and common sense of the person of ordinary skill." *Perfect Web Techs., Inc. v. Info USA, Inc.*, 587 F.3d 1324, 1328-29 (Fed. Cir. 2009) (citation and internal quotations omitted). Additionally, "[w]here the level of ordinary skill in the art is high, and the claim applies a known solution to a known problem, it is likely the product not of innovation but of ordinary skill and common sense." *Praxair Distrib. Mallinckrodt Hosp. Prods. IP*, 890 F.3d 1024, 1037 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)) (quotation omitted).

Administration of psilocybin to a subject requires a delivery method for the drug, that the method chosen consistently deliver the desired dosage, and that the drug be safe for administration to humans. A POSA desirous of administering psilocybin to a patient to treat MDD would know that administration could be

accomplished through use of a pharmaceutical composition, including capsules and tablets, which are among the most widely used oral dosage forms. *See* Ex. 1110 at ¶28. The POSA also would know that impurities in a drug product should be minimized, and would look to USP Standards and other authoritative guidance, particularly standards for drugs with the same indications as psilocybin. *See id.* at ¶35. The POSA also would know that use of excipients is an essential and elementary aspect of drug formulation. *See id.* at ¶37. A POSA also would be aware of prior art reporting psilocybin dosage amounts administered to subjects suffering from MDD and the results of those administrations, and would find it obvious to create dosage forms that delivered the dosage amount of 5, 10, and 25 mg. *See id.* at ¶38-41.

Set forth below is a claim chart identifying each item of prior art corresponding to each of the challenged claims. Where no prior art is identified, the claims are not being challenged under § 103; Petitioner's grounds of invalidity for those claims is limited to § 101 and 112 as explained herein.

Claim		Prior Art
1.	A pharmaceutical composition, comprising crystalline Polymorph A of psilocybin and a pharmaceutically acceptable excipient, wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, wherein the psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis.	Griffiths expressly teaches a pharmaceutical composition of psilocybin and an excipient. Ex. 1127 at 1183 ("Psilocybin doses were administered in identically appearing opaque, size 0 gelatin capsules, with lactose as the inactive capsule filler.). Folen discloses crystalline psilocybin having XRPD peaks at: • d=7.74, which converts to 11.4°2θ and would be understood as the same as the claimed peak at 11.5±0.1°2θ; • d=7.40, which converts to 12.0°2θ and would be understood as the same as the claimed peak at 12.0±0.1°2θ; • d=6.13, which converts to 14.4°2θ and would be understood as the same as the claimed peak at 14.5±0.1°2θ, • d=5.00, which converts to 17.7°2θ and would be understood as the same as the claimed peak at 17.9±0.1°2θ; and • d=4.56, which converts to 19.5°2θ and would be understood as the same as the claimed peak at 19.7±0.1°2θ. Ex. 1106 at ¶64. The USP Standards for Fluoxetine Hydrochloride and Imipramine Hydrochloride —drugs used to treat depression—require that they contain not less than 98% API by dry weight. Ex. 1170. Additionally, the USP Standards require that total impurities in Fluoxetine Hydrochloride be not more than 0.50%, and in Imipramine

		Hydrochloride not more than 1%, and that no single impurity exceed 0.10%. Ex. 1170 *See also* Ex. 1110 at ¶25. Roy teaches that "Excipients are an essential and integral part of medicine." Ex. 1113 at 115.
2.	The pharmaceutical composition of claim 1, wherein the composition is a capsule.	See prior art cited for Claim 1, *supra*. Carhart-Harris treated patients with two 5 mg capsules, or five 5 mg capsules. Ex. 1104 at 3. Nichols reported administration of psilocybin using capsules. Ex. 1103 at 271.
3.	The pharmaceutical composition of claim 1, wherein the composition is a tablet.	See prior art cited for Claim 1, *supra*. Martin's reports that tablets are among the most popular dosage forms. Ex. 1166 at 564. *See also* Ex. 1110 at ¶28.
4.	The pharmaceutical composition of claim 1, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.	See prior art cited for Claim 1 *supra*. Folen discloses crystalline psilocybin having XRPD peaks at: • d=4.38, which converts to 20.3°2θ and would be understood as the same as the claimed peak at 20.4±0.1°2θ; • d=4.02, which converts to 22.1°2θ and would be understood as the same as the claimed peak at 22.2±0.1°2θ; • d=3.67, which converts to 24.2°2θ and would be understood as the same as the claimed peak at 24.3±0.1°2θ; • d=3.46, which converts to 25.7°2θ and would be understood as the same as the

		claimed peak at 25.7±0.1°2θ; Ex. 1106 at ¶67-68.
5.	The pharmaceutical composition of claim 1, wherein the composition comprises about 5 mg of the crystalline Polymorph A of psilocybin.	See prior art cited for Claim 1, *supra*. Carhart-Harris treated patients with two 5 mg capsules, or five 5 mg capsules. Ex. 1104 at 3.
6.	The pharmaceutical composition of claim 1, wherein the composition comprises about 10 mg of the crystalline Polymorph A of psilocybin.	See prior art cited for Claim 1, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1104 at 3. *See also* Ex. 1110 at ¶29.
7.	The pharmaceutical composition of claim 1, wherein the composition comprises about 25 mg of the crystalline Polymorph A of psilocybin.	See prior art cited for Claim 1, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1104 at 3. *See also* Ex. 1110 at ¶29.
8.	Crystalline Polymorph A of psilocybin, wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θ, wherein the psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis.	Folen discloses crystalline psilocybin having XRPD peaks at: • d=7.74, which converts to 11.4°2θ and would be understood as the same as the claimed peak at 11.5±0.1°2θ; • d=7.40, which converts to 12.0°2θ and would be understood as the same as the claimed peak at 12.0±0.1°2θ; • d=6.13, which converts to 14.4°2θ and would be understood as the same as the claimed peak at 14.5±0.1°2θ, • d=5.00, which converts to 17.7°2θ and would be understood as the same as the

		claimed peak at 17.9±0.1°2θ; and • d=4.56, which converts to 19.5°2θ and would be understood as the same as the claimed peak at 19.7±0.1°2θ. Ex. 1106 at ¶64. The USP Standards for Fluoxetine Hydrochloride and Imipramine Hydrochloride —drugs used to treat depression—require that they contain not less than 98% API by dry weight. Ex. 1170. Additionally, the USP Standards require that total impurities in Fluoxetine Hydrochloride be not more than 0.50%, and in Imipramine Hydrochloride not more than 1%, and that no single impurity exceed 0.10%. Ex. 1170 See also Ex. 1110 at ¶28.
9.	The crystalline psilocybin of claim 8, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.	See prior art cited for Claim 8, *supra*. Folen discloses crystalline psilocybin having XRPD peaks at: • d=4.38, which converts to 20.3°2θ and would be understood as the same as the claimed peak at 20.4±0.1°2θ; • d=4.02, which converts to 22.1°2θ and would be understood as the same as the claimed peak at 22.2±0.1°2θ; • d=3.67, which converts to 24.2°2θ and would be understood as the same as the claimed peak at 24.3±0.1°2θ; • d=3.46, which converts to 25.7°2θ and would be understood as the same as the claimed peak at 25.7±0.1°2θ; Ex. 1106 at ¶67-68.

10.	The crystalline psilocybin of claim 8, wherein the Polymorph A is characterized by a XRPD diffraction pattern that is substantially the same as shown in FIG. 7*a*.	See prior art cited for Claim 8, *supra*. Folen would generate "an XRPD diffraction pattern that is substantially the same as shown in FIG. 7*a*." Ex. 1106 at ¶69.
11.	The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by a water content of <0.5% w/w.	See prior art cited for Claim 8, *supra*. Triclinic's report demonstrates that the JHU Sample, which is the anhydrous polymorphic from of psilocybin the patentee refers to as Polymorph A-prime and the primary component of the mixture of Polymorph A (Ex. 1108 at ¶46-47) is characterized by a water content of <0.5% w/w. Ex. 1120 at ¶18; Ex. 1121 at 11.
12.	The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by a <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C.	Triclinic's report demonstrates that the JHU Sample, which is the anhydrous polymorphic from of psilocybin the patentee refers to as Polymorph A-prime and the primary component of the mixture of Polymorph A (Ex. 1108 at ¶46-47) undergoes <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C. Ex. 1120 at ¶18; Ex. 1121 at 11.
13.	The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having an onset temperature between 205° C. and 220° C.	
14.	The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is	

	further characterized by an endothermic event in a DSC thermogram having an onset temperature of between 145° C. and 155° C.	
15.	The crystalline psilocybin of claim 8, wherein the crystalline psilocybin is further characterized by one or more of the following: a) a loss on drying of no more than 2% w/w; b) residue on ignition of no more than 0.5% w/w; c) assay (on a dry basis) of 95-103% by weight as measured by HPLC; d) residual solvent content of no more than 3000 ppm methanol; 5000 ppm ethanol; 720 ppm THF, and 890 ppm toluene, as measured by high resolution gas chromatography (HRGC); e) phosphoric acid content of no more than 1% w/w as measured by ^{31}P NMR; and f) Inductively Coupled Plasma Mass Spectrometry (ICP-MS) elemental analysis of: i. no more than 1.5 ppm Cd; ii. no more than 1.5 ppm Pb; iii. no more than 4.5 ppm As;	See prior art cited for Claim 8, *supra*. Triclinic's report demonstrates that the JHU Sample, which is the anhydrous polymorphic from of psilocybin the patentee refers to as Polymorph A-prime and the primary component of the mixture of Polymorph A (Ex. 1108 at ¶46-47) is consistent with a loss on drying of no more than 2% w/w. Ex. 1120 at ¶18; Ex. 1121 at 11.

	iv. no more than 9.0 ppm Hg; v. no more than 15 ppm Co; vi. no more than 30 ppm V; vii. no more than 60 ppm Ni; viii. no more than 165 ppm Li; and ix. no more than 30 ppm Pd.	
16.	A method of treating major depressive disorder, the method comprising: administering a therapeutically effective amount of crystalline Polymorph A of psilocybin to a patient in need thereof, wherein the Polymorph A is characterized by X-ray powder diffraction (XRPD) peaks at 11.5±0.1, 12.0±0.1, 14.5±0.1, 17.5±0.1 and 19.7±0.1 °2θm and, wherein the psilocybin has a chemical purity of greater than 97% and no single impurity of greater than 1% as determined by HPLC analysis.	Nichols reports: • "Grob et al. (2011) reported nonsignificant trends for benefits of psilocybin compared with placebo on measures of depression and anxiety. Compared with pretreatment baseline, however, the patients' Spielberger State-Trait Anxiety Inventory (STAI) trait anxiety subscale scores revealed a significant reduction in anxiety at 1 and 3 months after treatment. Similarly, the patients' Beck Depression Inventory (BDI) scores showed an improvement of mood that reached significance at 6 months compared with baseline." Ex. 1103 at 323. • "These encouraging results in such a small study led to extension of this approach by two groups, one at Johns Hopkins University (JHU) and the other at New York University (NYU), in studies that were recently completed. These are two reasonably large, well powered phase 2 trials of psilocybin-assisted psychotherapy in patients suffering from cancer related psychosocial distress (CRPD)." Ex. 1103 at 323.

		• "The first of these trials of psilocybin-assisted psychotherapy for CRPD was completed by Roland Griffiths and his colleagues at JHU (Griffiths, 2015). In that study, 56 individuals were enrolled and randomized to receive two treatments with psilocybin (high dose versus low dose) in a randomized, crossover design, and 51 participants completed at least one psilocybin session. All 51 participants had a potentially life-threatening cancer diagnosis, with 65% having recurrent or metastatic disease. All participants had a DSM-IV diagnosis [including adjustment disorder with anxiety; adjustment disorder with anxiety and depressed mood, chronic; dysthymic disorder; generalized anxiety disorder; major depressive disorder (MDD); or a duel diagnosis of generalized anxiety disorder and MDD, or generalized anxiety disorder and dysthymic disorder]." Ex. 1103 at 323-24. • "Griffiths (2015) concluded that a single moderate to high dose of psilocybin, if given under supportive conditions to carefully screened and prepared participants, produced substantial and enduring decreases in anxiety and depression in patients with a life-threatening cancer diagnosis." Ex 1103 at 324. Carhart-Harris reported: • the results of an "open-label feasibility trial [of] 12 patients . . . with moderate-to-severe, unipolar, treatment-resistant major depression [who] received two oral doses

		of psilocybin (10 mg and 25 mg, 7 days apart) . . . ." Ex. 1104, Abstract. • "Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference –11·8, 95% CI –9·15 to –14·35, p=0·002, Hedges' g=3·1) and 3 months (–9·2, 95% CI –5·69 to –12·71, p=0·003, Hedges' g=2) after high-dose treatment." Ex. 1104, Abstract. *See also* Ex. 1112 at ¶7-13. Folen discloses crystalline psilocybin having XRPD peaks at: • d=7.74, which converts to 11.4°2θ and would be understood as the same as the claimed peak at 11.5±0.1°2θ; • d=7.40, which converts to 12.0°2θ and would be understood as the same as the claimed peak at 12.0±0.1°2θ; • d=6.13, which converts to 14.4°2θ and would be understood as the same as the claimed peak at 14.5±0.1°2θ, • d=5.00, which converts to 17.7°2θ and would be understood as the same as the claimed peak at 17.9±0.1°2θ; and • d=4.56, which converts to 19.5°2θ and would be understood as the same as the claimed peak at 19.7±0.1°2θ. Ex. 1106 at ¶60. The USP Standards for Fluoxetine Hydrochloride and Imipramine Hydrochloride —drugs used to treat depression—require that they contain not less than 98% API by dry weight. Ex. 1170. Additionally, the USP Standards require that

		total impurities in Fluoxetine Hydrochloride be not more than 0.50%, and in Imipramine Hydrochloride not more than 1%, and that no single impurity exceed 0.10%. Ex. 1170 *See also* Ex. 1110 at ¶25.
17.	The method of claim 16, wherein about 5 mg of the crystalline Polymorph A of psilocybin is administered.	See prior art cited for Claim 16, *supra*. Carhart-Harris treated patients with two 5 mg capsules, or five 5 mg capsules. Ex. 1104 at 3. *See also* Ex. 1110 at ¶29.
18.	The method of claim 16, wherein about 10 mg of the crystalline Polymorph A of psilocybin is administered.	See prior art cited for Claim 16, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1104 at 3. *See also* Ex. 1110 at ¶29.
19.	The method of claim 16, wherein about 25 mg of the crystalline Polymorph A of psilocybin is administered.	See prior art cited for Claim 16, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1104 at 3. *See also* Ex. 1110 at ¶29.
20.	The method of claim 16, wherein the crystalline Polymorph A of psilocybin is orally administered.	See prior art cited for Claim 16, *supra*. Martin's teaches that 72% of the World Health Organization Model List of Essential Medicines are offered as oral formulations, with 59% offered as tablets or capsules, and of the 100 best-selling drugs (as of 2007), 68 were offered as oral formulations, with 66 of those offered as tablets or capsules. Ex. 1166 at 564.
21.	The method of claim 20, wherein the crystalline Polymorph A of psilocybin is	See prior art cited for Claims 16-20, *supra*.

	administered in a capsule.	
22.	The method of claim 20, wherein the crystalline Polymorph A of psilocybin is administered in a tablet.	See prior art cited for Claim 20, *supra*. Martin's reports that tablets are among the most popular dosage forms. Ex. 1166 at 564. *See also* Ex. 1110 at ¶28.
23.	The method of claim 16, wherein the Polymorph A is further characterized by at least one peak selected from the group consisting of 20.4±0.1, 22.2±0.1, 24.3±0.1, and 25.7±0.1 °2θ.	See prior art cited for claim 16, *supra*. Folen discloses crystalline psilocybin having XRPD peaks at: • d=4.38, which converts to 20.3°2θ and would be understood as the same as the claimed peak at 20.4±0.1°2θ; • d=4.02, which converts to 22.1°2θ and would be understood as the same as the claimed peak at 22.2±0.1°2θ; • d=3.67, which converts to 24.2°2θ and would be understood as the same as the claimed peak at 24.3±0.1°2θ; • d=3.46, which converts to 25.7°2θ and would be understood as the same as the claimed peak at 25.7±0.1°2θ; Ex. 1106 at ¶67-68.

D. Claims 1-7 and 21-22 Are Invalid As Not Enabled

"A patent must enable the full scope of the claimed invention, and the failure to do so renders the claim invalid." *See Trustees of Boston University v. Everlight Electronics Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018). Here, claims 1-7 claim "a pharmaceutical composition," and claims 21-22 claim a method of treating MDD by administering "crystalline Polymorph A" in a capsule or tablet. Petitioner

submits that a POSA would understand that term to refer to the drug product—i.e., the tablet, capsule, or other oral dosage form administered to a patient—and not the raw materials used to manufacture the final drug product. *See, e.g., Ferring B.V. v. Watson Labs, Inc.*, 764 F.3d 1382, 1388 (Fed. Cir. 2014) (In ANDA proceeding involving "oral dosage form," stating that "the relevant inquiry is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product. What is *likely to be sold*, or, preferably, *what will be sold*, will ultimately determine whether infringement exists" and observing that plaintiff's expert "testified that none of the *tablets* produced by [defendant]" were infringing) (emphasis added).

The '259 Patent, however, does not teach how to analyze the claimed pharmaceutical composition to determine whether the claimed characteristics of Polymorph A or its purity limitations are present. As explained by Dr. Suryanarayanan, polymorphic characterization of the claimed crystalline psilocybin in a pharmaceutical composition is impossible when the peaks in the XRPD diffractogram of excipients may overlap or interfere with the peaks generated by the '259 Patent's claimed form of crystalline psilocybin. Ex. 1110 at ¶49-52. Peaks generated by excipients such as microcrystalline cellulose ("MCC") or silicified microcrystalline cellulose ("SMCC") present in the claimed pharmaceutical composition will interfere or overlap with several characteristic

peaks of Polymorph A, likely making it impossible to detect many if not all of the peaks claimed for Polymorph A. *Id.* at ¶50-51. Consequently, a POSA would be unable to attribute the presence of the claimed peaks to the crystalline psilocybin rather than to the MCC or SMCC. *Id.* at ¶54-57.

The pharmaceutical composition of claims 2 and 3 is comprised of, *inter alia,* crystalline "Polymorph A" characterized by particular XRPD peaks in the form of a capsule (claim 2) or tablet (claim 3). Claims 21 and 22 similarly claim a method of treating MDD by administering "crystalline Polymorph A" in a capsule or tablet. As explained by Dr. Suryanarayanan, manufacturing a drug product was known as of the priority date to potentially result in processing induced phase transformations in APIs. Ex. 1110 at ¶53. Additionally, it is not possible for a POSA to attribute *to the crystalline "Polymorph A"* impurities that exist in a pharmaceutical composition. Ex. 1110 at ¶55-57.

VII. The Board's Decision Denying Institution of Post-Grant Review of Patentee's Related US Patent 10,519,175 Should Be Given No Weight

Petitioner acknowledges the Board's August 20, 2020 decision denying institution of post-grant review of U.S. Patent No. 10,519,175 (the " '175 Patent") in PGR 2020-0030. The '175 patent shares the same specification with the '259 Patent and also claims "Polymorph A" by reference to the same five XRPD peaks as the '259 patent. Ex. 1106 at ¶72-73. Petitioner respectfully submits that the

Board's decision denying institution of post-grant review of the '175 should not be given any weight in connection with the Board's decision on the instant petition.

The Board's decision in PGR 2020-0030 is not instructive here for several reasons. Petitioner offers new grounds for invalidity directed to the claims at issue here which were not presented in connection with the '175 Patent, including grounds under Section 101 and 112. In addition, new evidence demonstrates that the '259 Patent's "Polymorph A" is not a single polymorph, but rather is a mixture of two separate polymorphs.

Additionally, even if the Board construes the '259 Patent's claims to cover a mixture of two polymorphs that disclose at least the five claimed peaks, Petitioner has offered new evidence and analysis explaining why Folen discloses the claimed Polymorph A, and why the other claim limitations are taught by the prior art. Importantly, it appears that an incorrect wavelength value was used when calculating 2θ values using Bragg's Equation during the course of PGR 2020-0030. The correct Copper K-α wavelength value, when rounded to four decimal places, is 1.5406 Å. Ex. 1106 at ¶80. Folen, however, appears to have used the value 1.5405 Å, and that value appears to have been used for 2θ calculations in PGR 2020-0030. *See* Ex. 1122 at 13, n.11. Using the correct wavelength value results in a 2θ value of 19.5° for Folen's d-spacing value at 4.56, which is within ±0.2°2θ of the claimed peak at 19.7°2θ. *Id.* at ¶62-65.

As Dr. Lidin explains, a person of ordinary skill in the art would have considered even a peak at 19.45°2θ (or 19.4°2θ) to be equivalent to 19.7°2θ ±0.1°2θ. The shift of the position of the peak at 19.7°2θ can be explained by the overlap between peaks from the two polymorphs Polymorph A-prime and Polymorph B, a conclusion based on new evidence, as well as the Folen measurement issues discussed *supra*. Ex. 1106 at ¶73. Dr. Lidin's opinion is supported by the peer-reviewed QPA analysis of Dr. Kaduk, which takes both peak position and intensity into account and fully quantifies the diffraction pattern of "Polymorph A" as a mixture of Polymorph A-prime and Polymorph B. *Id*.; Ex. 1108 at ¶48, 49.

VIII. CONCLUSION

Claims 1-23 of the '259 Patent are unpatentable for the reasons set forth above. The Petition demonstrates that it is more likely than not that at least one of the challenged claims is unpatentable. Post-grant review of claims 1-23 is accordingly requested.

Dated: December 22, 2021

Respectfully submitted,
Carter Ledyard & Milburn LLP

/ *John M. Griem, Jr.* /
John M. Griem, Jr.
Reg. No. 40005

griem@clm.com
Theodore Y. McDonough
Reg. No. 71981
mcdonough@clm.com
2 Wall Street
New York, New York
212-732-3200

Attorneys for Petitioner,
Freedom to Operate, Inc.

INDEX OF EXHIBITS

No.	Description
Exhibit 1101	U.S. Patent No. 10,954,259
Exhibit 1102	Folen, V.A. X-Ray Powder Diffraction...J. Forensic Science, Apr. 1975, Vol. 20, No. 2.
Exhibit 1103	Nichols, D.E. Psychedelics, Pharmacol Rev 68, April 2016, 264-355.
Exhibit 1104	Carhart-Harris R. et al. Psilocybin with Psychological Support.. Lancet Psychiatry, www.thelancet.compsychiatry, 2016
Exhibit 1105	Guo M. et ano. Potential Application of Silicified Microcrystalline... Pharmaceutical Development And Technology Vol. 8, No. 1, 2003, 47-59.
Exhibit 1106	Declaration of Sven Lidin, Ph.D.
Exhibit 1107	Curriculum Vitae-Sven Lidin, Ph.D.
Exhibit 1108	Declaration of James A. Kaduk, Ph.D.
Exhibit 1109	Curriculum Vitae-James A. Kaduk, Ph.D.
Exhibit 1110	Declaration of Raj Suryanarayanan, Ph.D.
Exhibit 1111	Curriculum Vitae-Raj Suryanarayanan, Ph.D.
Exhibit 1112	Declaration of Charles L. Raison, M.D.
Exhibit 1113	Roy, J. An Introduction to Pharmaceutical Sciences, Biohealthcare, UK (2011)
Exhibit 1114	Arlin, J.B. et al. Experimental Crystal Structure Determination, 1-3, 2021.
Exhibit 1115	Bernstein J. Polymorphism in Molecular Crystals, International Union Of Crystallography, Oxford, 2002
Exhibit 1116	Boratto, M. H. Semiconducting and Insulating Oxides.... 2018, Thesis Ph.D. UNESP, School of Science.
Exhibit 1117	D.E. Nichols, Synthesis of High Purity Psilocybin: Lot 10415-25, Nov. 1, 2009.

Exhibit 1118	June 6, 2012 letter from D. Nichols to R. Griffiths.
Exhibit 1119	April 15, 2014 letter from C. Kim to E. Elder.
Exhibit 1120	Declaration of Brett D. Bobzien
Exhibit 1121	Triclinic Labs Report, Characterization of Psilocybin, Dec. 2, 2021
Exhibit 1122	Decision denying Post-Grant Review, PGR 2020-0030.
Exhibit 1123	USP35-(941) Physical Tests X-Ray Powder Diffraction.
Exhibit 1124	Ottoboni S. et al. Understanding API Static Drying .... Org. Process Res. Dev. 2020, 24, Oct. 16, 2020, 2505-2520.
Exhibit 1125	Airaksinen S. et al. Comparison of the Effects of Two Drying Methods, International Journal of Pharmaceutics 276 (2004) 129-141.
Exhibit 1126	Lim H.L. et al, Understanding and Preventing Agglomeration in a Filter Drying Process, Powder Technology, 300 (2016) 146-156.
Exhibit 1127	Griffiths R.R. et al. Psilocybin Produces Substantial and Sustained Decreases in Depression ...Journal of Psychopharmacology, Vol. 30 (12) 1181-1197.
Exhibit 1128	Curriculum Vitae-Charles L. Raison, M.D.
Exhibit 1129	Excerpt from Diagnostic and Statistical Manual of Mental Disorders, Am. Psychiatric Assn. 5th Ed. 2013.
Exhibit 1130	Declaration of Roland R. Griffiths, Ph.D.
Exhibit 1131	Excerpt from Dictionary of Chemistry 6th Edition.
Exhibit 1132	*Astrazeneca AB v. Reddy's Laboratories, Inc.*, No. 11-2317, 2013 U.S. Dist. LEXIS 62149 (May 1, 2013)
Exhibit 1133	Baker R. W. et al. Molecular Structures of Hallucinogenic Substances...Molecular Pharmacology, 9, 1973, 23-32.
Exhibit 1134	Petcher, T. J. et ano. Crystal Structures of the Teonanhcatl Hallucinogens, J. Chem Soc. Perkins Trans. 2, 8,1974.
Exhibit 1135	Kuhnert-Brandstatter M. et ano. Polymorphe Modifikationen und Solvate von Psilocin und Psilocybin, Arch. Pharm, 1976
Exhibit 1136	Hofmann A. et al. Psylocybin and Psilocin, Fasciculus, Vol. XLII,1959, 167-168.
Exhibit 1137	U.S. Patent No. 3,192,111

Exhibit 1138	U.S. Patent No. 3,183,172
Exhibit 1139	Nichols D. E et ano. Improvements to the Synthesis of Psilocybin.. Synthesis 1999, No. 6, 935-938.
Exhibit 1140	Kargbo R. B. et al. Direct Phosphorylation of Psilocin..., ACS Omega 2020, 5, 16959-16966.
Exhibit 1141	Sherwood A. M. et al. An Improved, Practical, and Scalable...Synthesis 2020, 52, 688-694.
Exhibit 1142	dos Santos et al. Antidepressive, Anxiolytic....Ther Adv Psychopharmacol, 2016, Vol. 6 (3) 193-213.
Exhibit 1143	Hill R. J. Expanded Use of the Rietveld Method... Powder Diffraction, Vol. 6, No. 2, June 1991.
Exhibit 1144	Groom C.R. et al. The Cambridge Structural Database, Acta Cryst. (2016). B72, 171-179.
Exhibit 1145	Lee P. L. et al. A Twelve-Analyzer Detector System, J. Synchrotron Rad. (2008). 15, 427-432.
Exhibit 1146	Wang J. et al. A Dedicated Powder Diffraction Beamline.., Review of Scientific Instruments 79, 085105 (2008).
Exhibit 1147	Antao S. M. et al. State-Of-The-Art High-Resolution Powder.., The Canadian Mineralogist, Vol. 46, (2008) 1501-1509.
Exhibit 1148	Toby B. H. et ano. GSAS-II The Genesis of a Modern Open-Source.., J. Appl. Cryst. (2013) 46, 544-549.
Exhibit 1149	Sykes R. A. et al. New software for Statistical Analysis..,.J. Appl. Cryst. (2011). 44, 882-886.
Exhibit 1150	Bruno I. J. et al. Retrieval of Crystallographically-Derived Molecular Geometry Information, J. Chem. Inf. Comput. Sci. 2004, 44, 2133-2144.
Exhibit 1151	Kresse G. et ano. Efficiency of Ab-Initio Total Energy Calculations..., Computational Materials Science 6 (1996) 15-50.
Exhibit 1152	Dovesi R. et al. Quantum-mechanical Condensed Matter Simulations.., WIREs Comput. Mol Sci. 2018, 1-36.
Exhibit 1153	Gatti C. et al. Crystal Field Effects On The Topological Properties.., J. Chem. Phys. 101, 10686 (1994).
Exhibit 1154	Peintinger M.F. et al. Consistent Gaussian Basis Sets of Triple-Zeta., Journal of Computational Chemistry 2012, 1-9.
Exhibit 1155	Louër D. et ano. Some Further Considerations In Powder Diffraction.., Powder Diffraction 29 (S2), December, 2014.

Exhibit 1156	Kourkoumelis K. Powdll a Reusable .net Component for.., Powder Diffr., Vol. 28, No. 2, June 2013, 142.
Exhibit 1157	Curriculum Vitae-Roland R. Griffiths.
Exhibit 1158	Zeeh Pharmaceutical Experiment Station Certificate of Analysis for Lot No. 10415-25
Exhibit 1159	Barrett F. S. et al. Double-blind Comparison of the Two Hallucinogens Psilocybin..., Psychopharmacology (Berl). 2018 October, 235 (10) 2915-2927.
Exhibit 1160	Claims of '739 Application as Filed and Preliminary Amendment
Exhibit 1161	Terminal Disclaimer.
Exhibit 1162	Placeholder.
Exhibit 1163	Prabhu S. L. et ano. Impurities And Its Importance In Pharmacy, Int. Journal of Pharma. Sciences Review and Research, Vol. 3, Issue 2, July – August 2010, Article 012.
Exhibit 1164	ICH Topic Q 3 A (R2) Impurities In New Drug Substances, 2006.
Exhibit 1165	Excerpts of Handbook of Pharma Excipients.
Exhibit 1166	Martin's Physical Pharmacy and Pharmaceutical Sciences, 2011
Exhibit 1167	Placeholder.
Exhibit 1168	The Manufacturing Process, Solid Dose Experts Techceuticals, Vol. 15 (2015).
Exhibit 1169	Documentation of shipment of sample from JHU Batch to Triclinic Labs
Exhibit 1170	USP Standards, 2000
Exhibit 1171	Sixsmith, D. Effect of Compression on MCC, J. Pharm. Pharmac., 1977, 29, 33-36.
Exhibit 1172	Curriculum Vitae-Brett D. Bobzien
Exhibit 1173	Placeholder.
Exhibit 1174	Altomare A. et al. Expo2013: A Kit Of Tools For Phasing Crystal Structures From Powder Data, Journal of Applied Crystallography, 2013

Exhibit 1175	Patra S. Return of the Psychedelics..... Asian Journal of Psychiatry 24, 2016, 51-52.
Exhibit 1176	Grob C. et al. Pilot Study of Psilocybin Treatment for Anxiety, Arch Gen Psychiatry. 2011;68, 1, 71-78.
Exhibit 1177	Ross S. et al. Rapid and Sustained Symptom Reduction.. Journal of Psychopharmacology, 2016, Vol. 30, 12, 1165-1180
Exhibit 1178	Petzoldt C. et al. An Example of How to Handle Amorphous Fractions...European Journal of Pharmaceutics and Biopharmaceutics 86, 2014.
Exhibit 1179	Placeholder.
Exhibit 1180	Tobyn M. et al. Physicochemical Comparison Between Microcrystalline... International Journal of Pharmaceutics 169, 1998, 183–194.
Exhibit 1181	Packing Slip, JHU Pharmacy to Triclinic, 7-21-2021
Exhibit 1182	Triclinic Labs Inc. SOP Controlled Substances.
Exhibit 1183	Declaration filed in PGR2020-0030.
Exhibit 1184	Shirota et al. Concise Large-Scale Synthesis of Psilocin and Psilocybin, Principal Hallucinogenic Constituents of "Magic Mushroom", Principal... J. Nat. Prod. 2003, 66, 885-887
Exhibit 1185	Sherwood, A.M., et al. Psilocybin: Crystal Structure Solutions Enable Phase Analysis Of Prior Art And Recently Patented Examples, 2022, Acta Cryst. C78

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

This Petition for Post-Grant Review complies with the type-volume limitation of 18,700 words, comprising 11,648 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

This Petition for Post-Grant Review complies with the general format requirements of 37 C.F.R. §42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman.

Respectfully submitted,
Carter Ledyard & Milburn LLP

_/ *John M. Griem, Jr.* /
John M. Griem, Jr.
Reg. No. 40005
griem@clm.com

ADDENDUM B: PROOF OF SERVICE OF THE PETITION

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(b) on the Patent Owner by overnight Federal Express of a hard-copy of this Petition for Post-Grant Review and electronic copies (on DVD) of supporting materials at the correspondence addresses of record for the '259 Patent:

COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington DC 20004

Dated: December 22, 2021

/ *John M. Griem, Jr.* /
John M. Griem, Jr.
Reg. No. 40005
griem@clm.com
Carter Ledyard & Milburn LLP