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. 10,947,257
Title: Preparation of Psilocybin, Different Polymorphic Forms, Intermediaries, Formulations and their use

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,947,257

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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. 10,947,257 ("the '257 Patent) (Ex. 1001) 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 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 is not aware of any related matter under 37 C.F.R. § 42.8(b)(2).

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 '257 Patent is available for post-grant review because (i) the '257 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 16, 2021.

Petitioner further certifies that it is not barred or estopped from requesting post-grant review challenging the claims of the '257 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 '257 Patent; or (ii) is estopped from challenging the claims on the grounds identified in the petition. Claims 1-23 of the '257 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 '257 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 '257 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 1-5, 9, 15-16, and 21 claim, *inter alia*, a single crystalline polymorph defined by the inventors as "Polymorph A." If, however, claims 1-5, 9, 15-16, and 21 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. 1002) in view of D.E. Nichols, *Psychedelics*, 68 PHARMACOL. REV. 264-355 (2016) (Ex. 1003) 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. 1004), together with R.R. Griffiths, *Psilocybin Produces Substantial and Sustained Decreases in Depression*, 30 J. PSYCHOPHARMACOL. Journal of Psychopharmacology 1181 –1197 (Ex. 1027), in view of M. Guo, *Potential Application of Silicified Microcrystalline Cellulose in Direct-Fill Formulations for Automatic*

Capsule-Filling Machines, PHARM. DEV. & TECH. 47-59 (2003) (Ex. 1005), or alternatively in view of Martin's Physical Pharmacy and Pharmaceutical Sciences (Ex. 1066), 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 6 and 8 are unpatentable as obvious under U.S.C. § 103 for the same reasons as Claims 1-5 and 9, 15-16, and 21 above, in further view of the publicly available JHU Batch (as defined *infra*, Section IV.B.5.vi).

- Claims 1-23 are invalid under 35 U.S.C. § 112 as not enabled because the '257 Patent does not teach how to measure—in the claimed oral dosage form—the claimed characteristics of Polymorph A (Claims 1-9, 15-16, 21), and because the Patent does not teach how to accurately measure particle size ranges of silicified microcrystalline cellulose in a final oral dosage form (Claims 10-14, 17-20, 22-23).

Petitioner's proposed construction of the claims, the evidence relied upon, and the precise reasons why the claims are unpatentable are set forth in Section IV.B.3 through IV.B.5, *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 psilocybin in the form Polymorph A"	"a crystalline form of a single polymorphic phase of psilocybin defined by the patentee as Polymorph A"
"characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and 19.7°2θ±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 psilocybin in the form Polymorph A"

The independent claim of the '257 Patent requires "crystalline psilocybin in the form Polymorph A." This claim term should be construed to require that the claimed "crystalline psilocybin in the form Polymorph A" 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 singular noun "form" and the definite article "the" before "form" in the claim term "crystalline psilocybin in **the form** Polymorph A." Ex. 1001 (Col. 69:27) (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 psilocybin in the form Polymorph A" refers to a single polymorph and not a mixture of polymorphs. *See* Ex. 1001 (4:43-48, 7:59-62, 26:17-18). 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. 1001 (29:34-37) (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. 1001 (32:64-67) (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. 1001 (35:14-16). 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 psilocybin in the form Polymorph A" 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. 1006 at ¶18 (citing Ex. 1015 at 2); *see also* Ex. 1031 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 psilocybin in the form Polymorph A" 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 peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and 19.7°2θ±0.1°2θ"

Independent claim 1 recites "Polymorph A characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and 19.7°2θ±0.1°2θ." Ex. 1001 (69:25-27). The term "characterized by peaks in an XRPD diffractogram peaks at

11.5, 12.0, 14.5, 17.5, and 19.7°2θ±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 peaks in an XRPD diffractogram" 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 peaks in an XRPD diffractogram" 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. 1006), 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. 1006, ¶42, 50, 62-66, and 73. 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. 1032 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 peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5 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 '257 Patent are unpatentable under the statutory grounds identified above is provided in the form of 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. 1002). The purpose of Folen's research was to "present X-ray powder diffraction data not available in the [contemporary] literature." Ex. 1002 at 348. In particular, Folen provided XRPD data "for compounds already compiled in the Powder Diffraction File," including psilocybin. Ex. 1002 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. 1006, ¶39.

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 '257 Patent. Ex. 1006, ¶59-61. Relevant to claim 1 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 PGR 2020-0030, 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 PGR 2020-0030 (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. 1006 at ¶75.

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. D.E. Nichols, *Psychedelics*, 68 PHARMACOL. REV. 264-355 (2016) (Ex. 1003 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. 1012, ¶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. 1004 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. 1012, ¶8.

(iv) Martin's

Martin's Physical Pharmacy and Pharmaceutical Sciences, a popular textbook referenced by practitioners and used by students studying pharmaceutical sciences, states that "a large fraction of pharmaceutical products are offered as oral solid dosage forms (in other words, capsules and tablets)." Ex. 1010 at ¶33 (citing Ex. 1066). Martin further states that 48% of the World Health Organization Model

List of Essential Medicines are offered as tablets or capsules, and of the 100 best-selling drugs (as of 2014), 59 were offered as tablets or capsules. *Id*.

(v) Solid Dose Experts Techceuticals.

Solid Dose Experts Techceuticals, Vol. 15 (2015) (ex. 1068) (hereafter, "Techceuticals"), discloses that preparing oral dosage forms as tablets was routine as of the priority date of the '257 Patent. Ex. 1010 at ¶31 (citing Ex. 1068).

(vi) 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. 1030 at ¶6 (citing Ex. 1017). 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. 1020 at ¶8; Ex. 1030 at ¶11; Ex. 1069; Ex. 1081. 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. 1020 & 1021. 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[1]

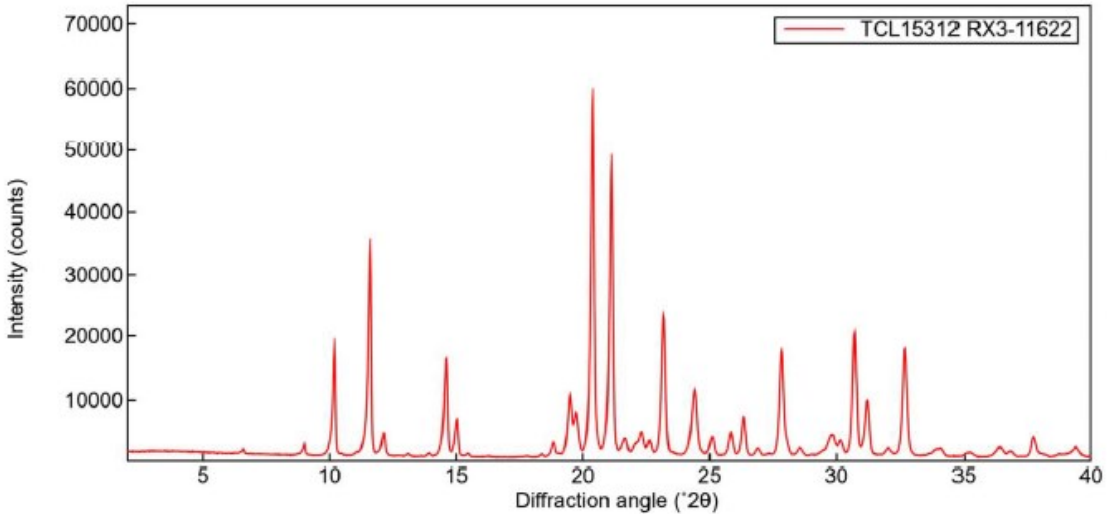
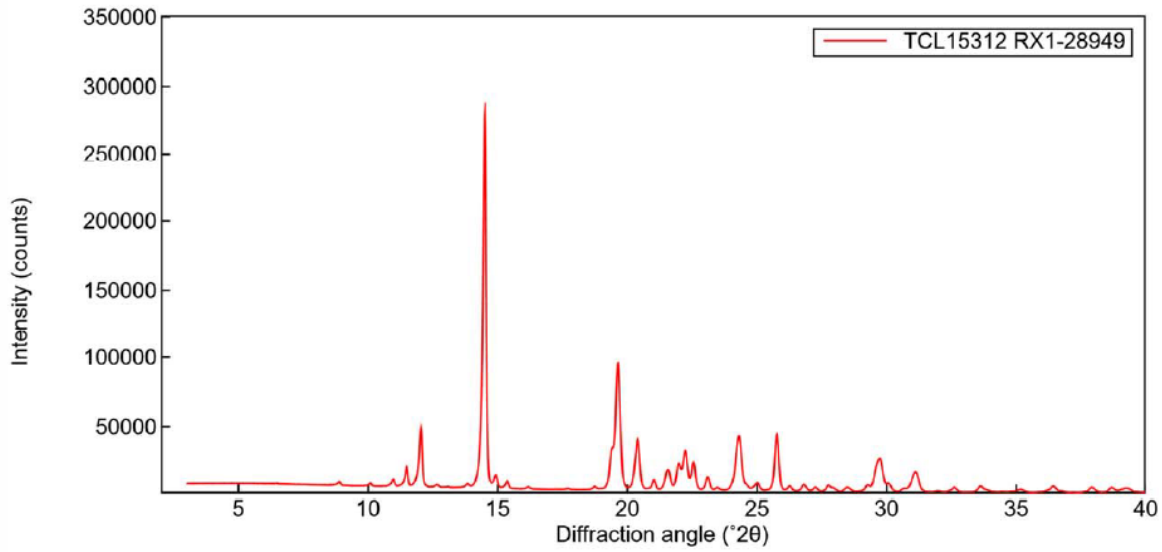


Figure 7: XRPD Pattern of JHU Batch—Transmission[2]



[1] Ex. 1021 at 4.

[2] Ex. 1021 at 7.

Additionally, of the 27 peaks identified in the '257 Patent as characteristic of Polymorph A-prime, 26 appear in the XRPD peak listings of the JHU Batch. Ex. 1006 ¶57 (*Comparing* Ex. 1001 (7:22-48) *with* Ex. 1021). The peaks generated from analysis of the JHU Batch which correspond to peaks purportedly characteristic of Polymorph A-prime are as follows:

Polymorph A-prime		**JHU Batch[3]**		**JHU Batch[4]**	
XRPD Peak Positions (°2θ)[5]	**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

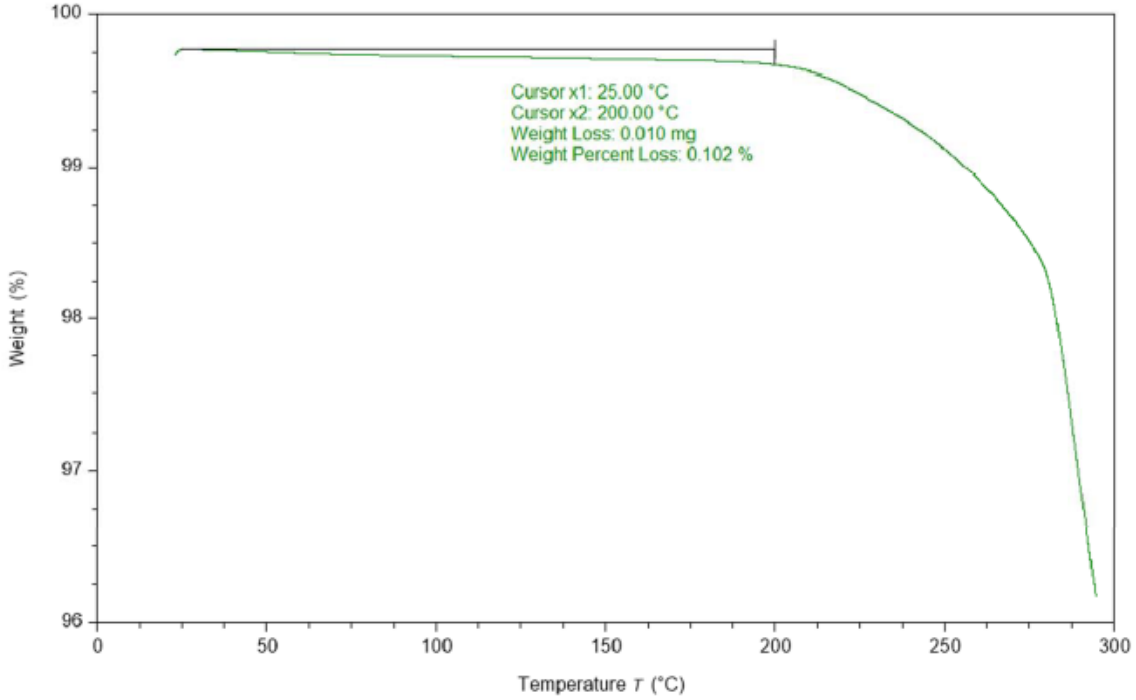
[3] Collected using reflection geometry. Ex. 1020 at ¶11; Ex. 1021.

[4] Collected using transmission geometry. Ex. 1020 at ¶11; Ex. 1021.

[5] Ex. 1001 (7:22-48).

Polymorph A-prime		JHU Batch[3]		JHU Batch[4]	
XRPD Peak Positions (°2θ)[5]	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**	**Peak Positions (°2θ)**	**Rel. Intensity (%)**
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
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 (Ex. 1020 and 1021 at 11):



(vii) 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. 1010 at ¶25. The ICH Topic Q 3 A (R2) includes guidance on impurities and impurity testing in drug substances (hereinafter, "ICH Guidance"). *Id*.; Ex. 1064. 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. 1010 at ¶25; Ex. 1064 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. 1070. 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. 1010 at ¶26; Ex. 1070.

(viii) Prior art teaching the use of SMCC

The Handbook of Pharmaceutical Excipients (Ex. 1065), a reliable, authoritative and comprehensive source of information on pharmaceutical excipients, contains a monograph of silicified microcrystalline cellulose. The monograph states:

> Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation. Silicified microcrystalline cellulose also appears to have beneficial properties for use in the formulation of powder filled capsules.

Ex. 1065 at 139.

M. Guo*, Potential Application of Silicified Microcrystalline Cellulose in Direct-Fill Formulations for Automatic Capsule-Filling Machines,* 8 PHARM. DEV. & TECH. 47-59 (2003) (Ex. 1005), teaches that the use of SMCC as an excipient was routine and well-understood before the priority date of the '257 Patent. Guo states that "[s]ilicified microcrystalline cellulose [] has physico-mechanical properties that may be of advantage in hard gelatin capsule formulations" and "SMCC could be a suitable direct-fill excipient for hard shell capsule formulations." Ex. 1005, Abstract. Finally, M. Siven et al., *Challenge of*

paediatric compounding to solid dosage forms sachets and hard capsules – Finnish perspective, 69 J. PHARMA. & PHARMACOL. 593-602, reported the use of SMCC to improve content uniformity. Ex. 1079 at 600.

V. SUMMARY OF THE '257 PATENT

The '257 Patent issued on March 16, 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 '257 Patent relates to the "large-scale production of psilocybin for use in medicine." Ex. 1001 (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. 1001 (1:37-40). The '257 Patent states that an object of the purported invention is to provide chemically pure psilocybin of consistent polymorphic form for administration to humans. Ex. 1001 (3:27-29).

A. Effective Filing Date of the '257 Patent

The '257 Patent issued from U.S. Patent Application No. 16/920,223, filed July 2, 2020. The '223 Application 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

‘257 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 ‘257 Patent is not earlier than October 9, 2017.

B. The ‘257 Patent’s Prosecution History

The applicant filed the ‘223 Application on July 2, 2020 with 53 claims, together with a preliminary amendment cancelling claims 1-30 and a request for prioritized examination which was granted on July 21, 2020. As a result of the preliminary amendment, the ‘223 Application contained a single independent claim (claim 31 as filed) which claimed “crystalline psilocybin in the form Polymorph A” but did not characterize the claimed “Polymorph A” by reference to peaks in an XRPD diffractogram.

On August 13, 2020, the examiner issued an office action rejecting all of the pending claims based on nonstatutory double patenting over claims 1-18 of the ‘175 Patent, and as indefinite under § 112. Ex. 1060. The later rejection was based on claim 31’s failure to specify the characteristics by which “Polymorph A” can be identified, which required reference to the specification in violation of “modern claim practice” which requires claims to “stand alone to define an invention.” *Id.* at 7. The examiner suggested that “x-ray diffraction data be added to the claims.” *Id.* The office action also objected to the applicant’s information

disclosure statement, which was "28 pages long and cite[d] over 580 references," and stated "[b]urying one reference in one hundred IDS references is like citing nothing." *Id.* at 4-5 (quoting *Penn Yan Boats, Inc. v. Sea Lark Boats, Inc. et. al.*, 175 USPQ 260 (S.D. Fla. 1972); *Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co.*, 24 USPQ2d 1801 (N.D. Ind. 1992); *Moling PLC v. Textron, Inc.*, 48 F.3d 1172, 1184 (Fed. Cir. 1995)).

An Examiner Interview was conducted on October 8, 2020, during which the applicant contended that reference to XRPD peaks in the claims was unnecessary to identify the characteristics of the claimed "Polymorph A." Ex. 1061. By Amendment filed November 13, 2020, the applicant amended claim 31 to include XRPD peaks by which the claimed "Polymorph A" could be characterized, amended claim 38.d) to require analysis by high resolution gas chromatography, corrected typographical errors in claims 36, 38, 40, and 45-50. Ex. 1062. The applicant filed a supplemental amendment on November 19, 2020 to correct certain errors and omissions in its November 13 amendment which made that amendment non-compliant. Ex. 1067. The supplemental amendment did not substantively amend any claims.

C. Person of Ordinary Skill in the Art

A person of ordinary skill in the art in the field of the '257 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. 1006 at ¶35.

D. The '257 Patent's Specification

The '257 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. 1001 (53:62-54:8). While the '257 Patent claims are all directed to an "oral dosage form" (see *infra* Section V.D), the specification does not teach how to determine how to characterize or measure the claimed characteristics of the claimed components in the oral dosage form.

E. The '257 Patent's Claims

Independent claim 1 of the '257 Patent—the only independent claim—claims:

> 1. An oral dosage form comprising:
>
> a therapeutically effective amount of crystalline psilocybin in the form Polymorph A characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and 19.7°2θ±0.1°2θ, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%; and
>
> silicified microcrystalline cellulose.

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 oral dosage form of claim 1 comprising about 1 mg to 40 mg of crystalline psilocybin in the form Polymorph A.
>
> 3. The oral dosage form of claim 2 comprising about 5 mg of crystalline psilocybin in the form Polymorph A.
>
> 4. The oral dosage form of claim 2 comprising about 10 mg of crystalline psilocybin in the form Polymorph A.
>
> 5. The oral dosage form of claim 2 comprising about 25 mg of crystalline psilocybin in the form Polymorph A.
>
> 6. The oral dosage form of claim 1, wherein the crystalline psilocybin is further characterized by having either:
>
> i. a water content of <0.5% w/w; or
>
> ii. <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C.
>
> 7. The oral dosage form of claim 1, wherein the crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145° C. and 155° C. and a second onset temperature of between 205 and 220° C.
>
> 8. The oral dosage form of claim 1, 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.

9. The oral dosage form of claim 1, wherein the crystalline psilocybin has no single impurity of greater than 0.5%.

10. The oral dosage form of claim 1, further comprising silicified microcrystalline cellulose with a particle size range from about 45 to 150 microns.

11. The oral dosage form of claim 10, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to 150 microns.

12. The oral dosage form of claim 11, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline

cellulose is the second variant having a particle size of about 90 to 150 microns.

13. The oral dosage form of claim 11, wherein about 20% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 80% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

14. The oral dosage form of claim 11, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.

15. The oral dosage form of claim 1, wherein the dosage form is a capsule.

16. The oral dosage form of claim 1, wherein the dosage form is a tablet.

17. The oral dosage form of claim 11, wherein the dosage form is a capsule.

18. The oral dosage form of claim 11, wherein the dosage form is a tablet.

19. The oral dosage form of claim 12, wherein the dosage form is a capsule.

20. The oral dosage form of claim 12, wherein the dosage form is a tablet.

21. A method of treating major depressive disorder comprising orally administering to a subject in need thereof the oral dosage form of claim 1.

22. A method of treating major depressive disorder comprising orally administering to a subject in need thereof the oral dosage form of claim 11.

23. A method of treating major depressive disorder comprising orally administering to a subject in need thereof the oral dosage form of claim 12.

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

The '257 Patent purports to disclose several forms of crystalline psilocybin. As relevant here, those forms are Polymorph A, Polymorph A-prime, Polymorph B. *See generally* Ex. 1001 (4:4-13-21). According to the '257 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. 1001 (4:43-46; 7:50-53).

However, the '257 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. 1006 at ¶50; Ex. 1008 at ¶19. Because the claims of the '257 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 1-9, 15-16, and 21 requiring so-called "Polymorph A" characterized by certain peaks are construed to permit a mixture of polymorphs that includes the five required peaks, then they are made obvious by prior art identified below in Section VI.C under 35 U.S.C. §§ 103.

All of the claims are invalid for another reason – lack of enablement under 35 U.S.C. §§ 112. The '257 Patent does not teach how to analyze the claimed oral dosage form to determine whether the claimed purity and other characteristics of "Polymorph A" are present (Claims 1-9, 15-16, 21), or to determine whether SMCC is present in the claimed particle size ranges (Claims 10-14, 17-20, 22-23).

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 '257 Patent—Polymorph A-prime and Polymorph B. The Declarations of Sven Lidin Ph.D. (Ex. 1006) and James Kaduk, Ph.D. (Ex. 1008) explain this conclusion in detail. *See* Ex. 1006 at ¶¶4, 29, 31, 47-54, and Ex. 1008 at ¶¶4, 20-21, and 46-47.

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. 1006 at ¶51.

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. 1008 at ¶19 (citing Exs. 1024-26). However, the '257 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. 1008 at ¶19. Notably, the inventors created and recognized the existence of a mixed phase sample (Ex. 1001 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 '257 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. 1008 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. 1006 at ¶52; Ex. 1008 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. 1008 at ¶23 (citing Ex. 1043).

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 '257 Patent states is the distinguishing feature of the material, was a reflection contributed by Polymorph B. Ex. 1008 at ¶46-47. The work supporting Dr. Kaduk's determination was recently accepted for publication by *Acta Crystallographica* Section C, and is in press. Id. at ¶50. The article is entitled *Psilocybin: crystal structure solutions enable phase analysis of prior art and recently patented examples*, an in-press proof of which is submitted as Ex. 1085.

Dr. Lidin, based on is knowledge and expertise, and after reviewing Dr. Kaduk's Declaration, succinctly explains that "the '257 Patent's claim to a single phase of 'crystalline psilocybin in the form Polymorph A characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, 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. 1006 at ¶54.

Claim 1 is therefore not "useful" because it is incapable of being practiced. Claim 1, therefore, invalid as inoperative, as are all of its dependent claims (which are all the claims in the '257 Patent).

In any event, the five XRPD peaks required for "Polymorph A" in the '257 Patent claims do not correspond to any novel *single* polymorphic form of psilocybin which the '257 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 '257 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 '257 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 '257 Patent.

C. Claims 1-9, 15-16, and 21 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 1-9, 15-16, and 21 of the '257 Patent are not considered invalid under Section 101 and 112, they are rendered obvious by Folen (Ex. 1002) in view of Nichols (Ex. 1003), or alternatively

Carhart-Harris (Ex. 1004), and Griffiths (Ex. 1027), together with The Handbook of Pharmaceutical Excipients (Ex. 1065), Siven (Ex. 1079) and, alternatively or in conjunction with, Guo (Ex. 1005).

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. 1006 at ¶ 38-42, 61-66 and 71-75. 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. 1008 at ¶48. 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 '257 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 oral dosage forms, including capsules and tablets, which are among the most widely used oral dosage forms. *See* Ex. 1010 at ¶33, 48-49. The POSA also would know that impurities in a drug product should be minimized, and would look to USP standards for guidance, particularly standards for drugs with the same indications as psilocybin. *See id.* at ¶37-38. The POSA also would know that excipients used in a formulation must permit consistent dosing in the oral dosage form, and would be aware of prior art teaching that use of SMCC could achieve that result. *See id.* at ¶39-42. 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 between 1-40 mg, including the particular amounts of 5, 10, and 25 mg. *See id.* at ¶43-47.

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.	An oral dosage form comprising: a therapeutically effective amount of crystalline psilocybin in the form Polymorph A characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and 19.7°2θ±0.1°2θ, wherein the crystalline psilocybin has a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1%; and silicified microcrystalline cellulose.	Carhart-Harris and Nichols expressly teach oral administration of psilocybin in the form of a capsule. Exs. 1003, 1004. 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. 1006, ¶60. The USP Standards for Fluoxetine Hydrochloride and I—drugs used to treat depression—require that they contain not less than 98% API by dry weight. Ex. 1070. 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. 1070 *See also* Ex. 1010 at ¶26, 36-38.

		The Handbook of Pharmaceutical Excipients states: "Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation. Silicified microcrystalline cellulose also appears to have beneficial properties for use in the formulation of powder filled capsules." Ex. 1065 at 139. Additionally, Guo teaches that "[s]ilicified microcrystalline cellulose [] has physico-mechanical properties that may be of advantage in hard gelatin capsule formulations" and "SMCC could be a suitable direct-fill excipient for hard shell capsule formulations." Ex. 1005, Abstract. Siven reported that the use of SMCC yielded the best drug recovery and minimal variation in content uniformity in compounded powders. Ex. 1079 at 600.
2.	The oral dosage form of claim 1 comprising about 1 mg to 40 mg of crystalline psilocybin in the form Polymorph A.	See prior art cited for Claim 1, *supra*. Griffiths administered to patients, on the lower end of its range 1 mg per 70 kg (approximately 154 lbs.). On the high end of the dosage range in Griffiths, patients were administered 30 mg per 70 kg. Griffiths therefore teaches administration of 40 mg of psilocybin to a patient of approximately 93.3 kg (approximately 206

		lbs.). Ex. 1010 at ¶44; Ex. 1027.
3.	The oral dosage form of claim 2 comprising about 5 mg of crystalline psilocybin in the form Polymorph A.	See prior art cited for Claims 1 and 2, *supra*. Carhart-Harris treated patients with two 5 mg capsules, or five 5 mg capsules. Ex. 1004 at 3.
4.	The oral dosage form of claim 2 comprising about 10 mg of crystalline psilocybin in the form Polymorph A.	See prior art cited for Claims 1 and 2, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1004 at 3.
5.	The oral dosage form of claim 2 comprising about 25 mg of crystalline psilocybin in the form Polymorph A.	See prior art cited for Claims 1 and 2, *supra*. Carhart-Harris treated patients with "two oral doses of psilocybin (10 mg and 25 mg, 7 days apart)." Ex. 1004 at Summary (Methods)
6.	The oral dosage form of claim 1, wherein the crystalline psilocybin is further characterized by having either: i. a water content of <0.5% w/w; or ii. <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C.	See prior art cited for Claim 1, *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. 1008 at ¶46) undergoes <0.5% w/w loss in the TGA thermogram between 25° C. and 200° C. Ex. 1020 at ¶18; Ex. 1021 at 11.
7.	The oral dosage form of claim 1, wherein the crystalline psilocybin is further characterized by an endothermic event in a DSC thermogram having a first onset temperature of between 145° C. and 155° C. and a second onset temperature of	

	between 205 and 220° C.	
8.	The oral dosage form of claim 1, 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 31P 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	See prior art cited for Claim 1, *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. 1008, ¶46), is consistent with a loss on drying of no more than 2% w/w. Ex. 1020 at ¶18; Ex. 1021 at 11.

	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.	
9.	The oral dosage form of claim 1, wherein the crystalline psilocybin has no single impurity of greater than 0.5%.	See prior art cited for Claim 1, *supra*. The USP Standards require that Fluoxetine Hydrochloride contain total impurities of not more than 0.50%, and that no single impurity exceed 0.10%. Ex. 1010 at ¶37-38; Ex. 1070.
10.	The oral dosage form of claim 1, further comprising silicified microcrystalline cellulose with a particle size range from about 45 to 150 microns.	
11.	The oral dosage form of claim 10, further comprising a mixture of two silicified microcrystalline cellulose variants wherein the first variant has a particle size from about 45 to 80 microns and the second variant has a particle size of about 90 to	

	150 microns.	
12.	The oral dosage form of claim 11, wherein about 30% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 70% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.	
13.	The oral dosage form of claim 11, wherein about 20% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 80% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.	
14.	The oral dosage form of claim 11, wherein about 15% or less of the microcrystalline cellulose is the first variant having a particle size from about 45 to 80 microns and about 85% or more of the microcrystalline cellulose is the second variant having a particle size of about 90 to 150 microns.	
15.	The oral dosage form of claim	See prior art cited for Claim 1, *supra*.

	1, wherein the dosage form is a capsule.	Carhart-Harris employed "psilocybin in size 0 capsules." Ex. 1004 at 3; *see also* Ex. 1010 at ¶32, 45. Nichols teaches administration of psilocybin via a capsule. Ex. 1003 at 271. *See also* Ex. 1066 at 564, demonstrating that capsules are used to administer some of the most essential and most popular pharmaceuticals.
16.	The oral dosage form of claim 1, wherein the dosage form is a tablet.	See prior art cited for Claim 1, *supra*. Martin's reports that "a large fraction of pharmaceutical products are offered as oral solid dosage forms (in other words, capsules and tablets)[,]" and that 48% of the World Health Organization Model List of Essential Medicines are offered as tablets or capsules, and of the 100 best-selling drugs (as of 2014), 59 were offered as tablets or capsules. Ex. 1066 at 546.
17.	The oral dosage form of claim 11, wherein the dosage form is a capsule.	
18.	The oral dosage form of claim 11, wherein the dosage form is a tablet.	
19.	The oral dosage form of claim 12, wherein the dosage form is a capsule.	
20.	The oral dosage form of claim 12, wherein the dosage form is a tablet.	
21.	A method of treating major depressive disorder	See prior art cited for Claim 1, *supra*.

	comprising orally administering to a subject in need thereof the oral dosage form of claim 1.	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. 1003 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. 1003 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 1003 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 1003 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. 1004, 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. 1004, Abstract.
22.	A method of treating major depressive disorder comprising orally administering to a subject in need thereof the oral dosage form of claim 11.	
23.	A method of treating major depressive disorder comprising orally administering to a subject in need thereof the oral dosage form of claim 12.	

D. Claims 1-23 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 1-23 of the '257 Patent claim an "oral dosage form." Petitioner submits that a POSA would understand that term to refer to the final 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 '257 Patent, however, does not teach how to analyze the claimed oral dosage form to determine whether the claimed characteristics of Polymorph A or its purity limitations are present (Claims 1-9, 15-16, 21), or to determine whether SMCC is present in the claimed particle size ranges (Claims 10-14, 17-20, 22-23). As explained by Dr. Suryanarayanan, polymorphic characterization of the claimed crystalline psilocybin in an oral dosage form is impossible when the peaks in the XRPD diffractogram of excipients may overlap or interfere with the peaks generated by the '257 Patent's claimed form of crystalline psilocybin. Ex. 1010 at ¶54-59. Peaks generated by SMCC present in the claimed oral dosage form 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 ¶56-57. Consequently, a POSA would be unable to attribute the presence of the claimed peaks to the crystalline psilocybin rather than to the SMCC. *Id.* at ¶54-57.

The oral dosage form of Claim 1 is comprised of, *inter alia,* crystalline "Polymorph A" characterized by particular XRPD peaks. 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. 1010 at ¶58. Additionally, it is not possible for a POSA to attribute *to the crystalline "Polymorph A"* impurities that exist in a final drug product. Ex. 1010 at ¶60-62.

The same reasoning applies to claims 7 and 8. When presented with a DSC thermogram for an oral dosage form containing crystalline psilocybin, which unquestionably show more than two endothermic events as a result of impurities and excipients (Ex. 1010, ¶68-70), a POSA will not be able to ascribe any particular event to the crystalline psilocybin, rather than another ingredient in the final drug product. *Id*. Nor can a POSA determine whether loss on drying, or residual solvent content, in a final drug product can be attributed to crystalline psilocybin and not another ingredient. Ex. 1010, ¶71.

Similarly, the '257 Patent fails to enable a POSA how to ascertain the SMCC particle size ranges in an oral dosage form. The size of ingredients in an oral dosage form change as a result of the manufacturing process, and accurate measurement of the size of ingredients in a final oral dosage form is a known and notoriously challenging problem in the field which the '257 Patent does not purport to solve. Ex. 1010, ¶72-73 (discussing Sixsmith, Ex. 1071, which teaches

that compression of microcrystalline cellulose during formation of an oral dosage form can affect the particle size of the microcrystalline cellulose).

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 '257 Patent and also claims "Polymorph A" by reference to the same five XRPD peaks as the '257 patent. (*see* Ex. 1006 at ¶67-69). 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 '257 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 '257 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. 1006 at ¶75. 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. 1022 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 ¶61, 75.

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. 1006 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. 1008 at ¶48, 49.

VIII. CONCLUSION

Claims 1-23 of the '257 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 15, 2021

Respectfully submitted,
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INDEX OF EXHIBITS

No.	Description
Exhibit 1001	U.S. Patent No. 10,947,257
Exhibit 1002	Folen, V.A. X-Ray Powder Diffraction...J. Forensic Science, Apr. 1975, Vol. 20, No. 2.
Exhibit 1003	Nichols, D.E. Psychedelics, Pharmacol Rev 68, April 2016, 264-355.
Exhibit 1004	Carhart-Harris R. et al. Psilocybin with Psychological Support..Lancet Psychiatry, www.thelancet.compsychiatry, 2016
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Exhibit 1006	Declaration of Sven Lidin, Ph.D.
Exhibit 1007	Curriculum Vitae-Sven Lidin, Ph.D.
Exhibit 1008	Declaration of James A. Kaduk, Ph.D.
Exhibit 1009	Curriculum Vitae-James A. Kaduk, Ph.D.
Exhibit 1010	Declaration of Raj Suryanarayanan, Ph.D.
Exhibit 1011	Curriculum Vitae-Raj Suryanarayanan, Ph.D.
Exhibit 1012	Declaration of Charles Raison, M.D.
Exhibit 1013	Hancock B. et ano. Characteristics and Significance of the Amorphous... Journal of Pharmaceutical Sciences, Volume 86, Number 1, January, 1997
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Exhibit 1030	Declaration of Roland Griffiths, Ph.D.

Exhibit 1031	Excerpt from Dictionary of Chemistry 6th Edition.
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Exhibit 1061	Applicant Initiated Interview Summary re: U.S. Patent Application No. 16/920,223

Exhibit 1062	USPTO Amendment, November 13, 2020
Exhibit 1063	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.
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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 11,547 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.

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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 '257 Patent:

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