

**PATENT COOPERATION TREATY**  
**PCT**  
**THIRD PARTY OBSERVATION**  
**(PCT Administrative Instructions Part 8)**

Applicant's or agent's file reference P36244WO1	
International application number PCT/GB2022/053123	International filing date (day/month/year) 07 Dec 2022 (07/12/2022)
Applicant BECKLEY PSYTECH LIMITED	
Third party observation submitted by Sisi LI	Observation submitted on behalf of Porta Sophia
Date of submission(day/month/year) 16 Aug 2023 (16/08/2023)	Language of observation English

**Basis and contents of observation**

1. The observation is made on the basis of the claims in the international application as filed.
2. The observation comprises:  
References to documents: 8  
Uploaded copies of documents: 8
3. Further explanations:  
Uploaded copies of documents: 0

## Citation # 1(Periodical article) (# uploaded documents:1):

Author: Robert B Kargbo, Alexander Sherwood, Andrew Walker, Nicholas V Cozzi, Raymond E Dagger, Jessica Sable, Kelsey O'Hern, Kristi Kaylo, Tura Patterson, Gary Tarpley, Poncho Meisenheimer	Title of article: Direct Phosphorylation of Psilocin Enables Optimized cGMP Kilogram-Scale Manufacture of Psilocybin	Title of Periodical: ACS Omega	Publication Date: 14 Jul 2020 (14/07/ 2020)
Issue Number of Periodical: Volume 5 Issue 27	Publisher of Periodical:	Place of publication:	
Page range of article within periodical:	ISBN:	ISSN:	
DOI: 10.1021/acsomega.0c02387			
Most relevant passages or drawings: Pages 16964-16965		Relevant to Claims: 1, 6, 7, 8, 12, 23	
Brief explanation of relevance: From pages 16964-16965 "3-(2-(Dimethylamino)ethyl)-1H-indol-4-yl Dihydrogen Phosphate (6)... The mixture was filtered under the nitrogen atmosphere and washed in turn with 20-25 °C purified water (1 × 1 vol, 1 × 2 vol) (based on crude psilocybin discharge weight) and pulled dry under the nitrogen atmosphere for at least 2 h. The solid was dried at 35-45 °C under vacuum for at least 24 h and subsequently at 50-60 °C (target 55 °C) under vacuum for at least 24 h. This is to convert the trihydrate form initially isolated to the desired anhydrate form A by XRPD. A white solid was afforded (31% yield, 1.21 kg, 99.7% area ultraperformance liquid chromatography (UPLC))."; relevant to WO2023105222 claims 1, 6, 7, 8, 12, 23.  *From the application of interest WO2023105222 page 4 paragraph 2 "In an embodiment, the inert gas is substantially free of water and/or oxygen. In an embodiment, the inert gas is nitrogen."			

## Citation # 2 (Patent/utility model) (# uploaded documents: 1):

Country code: US	Publication number: 10519175	Document kind code: B2	
Patent Applicant/Patent Owner: COMPASS Pathways Limited	Title of invention: Preparation Of Psilocybin, Different Polymorphic Forms, Intermediates, Formulations And Their Use		
Link to document:			
Publication Date: 31 Dec 2019 (31/12/2019)	Filing Date: 09 Oct 2018 (09/10/2018)	Priority Date:	
Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: claims 1, claim 17-18, table 38, [0345], [0048], [0149]-[ 0154], [0081], [0039], [0021], [0032]-[0034]		Relevant to Claims: 2, 3, 4, 5, 10, 11..	
Brief explanation of relevance: From [0048]: "In one embodiment, crystalline psilocybin Polymorph A is a highly pure crystalline form of Polymorph A, for example, psilocybin comprises at least 90% by weight, such as 95%, such as 99%, such as 99.5% of Polymorph A." relevant to WO2023105222 claims 2, 3, 4, 5  From claim 1: "A method of treating drug resistant depression comprising orally administering to a subject in need thereof a therapeutically effective amount of an oral dosage form, wherein, the oral			

dosage form comprises: crystalline psilocybin in the form Polymorph A characterized by peaks in an XRPD diffractogram at 11.5, 12.0, 14.5, 17.5, and  $19.7^{\circ}2\theta \pm 0.1^{\circ}2\theta$ , 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.” relevant to WO2023105222 claims 2, 3, 4, 5

From table 38: “Material Name: psilocybin

APL-117-6085-06: 1.0

APL-117-6085-07: 5.0” relevant to WO2023105222 claims 10

From [0345] “APL-117-6085-06 and APL-117-6085-07 both exhibited improved powder flow, but the blend uniformity for both formulations was poorer than APL-117-6085-03.” relevant to WO2023105222 claims 10

From claim 17: “The method of claim 1 wherein the oral dosage form comprises silicified microcrystalline cellulose with a particle size range from about 45 to 150 microns.” relevant to WO2023105222 claims 11

From claim 18: “Claim 18. The method of claim 17, wherein the oral dosage form comprises 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.” relevant to WO2023105222 claims 11

\*From the application of interest WO2023105222 page 4 paragraph 8 “In an embodiment, the polymorph A' product has a narrow particle size distribution. In an embodiment, the particle size distribution can be between 5 microns and 200 microns. In an embodiment, the particle size distribution can be between 50 microns and 150 microns. In an embodiment, the particle size distribution can be between 100 microns and 125 microns.”

From [0149]: “Preferably Polymorph A is an isostructural variant with an XRPD diffractogram as illustrated in FIG. 7a and a DSC thermograph as illustrated in FIG. 8a.” relevant to WO2023105222 claims 14, 15, 16, 17

From [0150]: “More preferably the psilocybin is recrystallized in typically about 10-20 volumes of water, heated with agitation to a temperature of at least 70° C., polish filtered with a suitable cut off (typically, below 5 µm), seeded at a temperature of about 70° C., and cooled in a controlled manner to about 5° C. over a period of more than 2 hours.” relevant to WO2023105222 claims 14, 15, 16, 17

From [0151]: “More preferably the method comprises controlled cooling which drops the temperature by about 5° C.-15° C. an hour, more preferably about 10° C. an hour.” relevant to WO2023105222 claims 14, 15, 16, 17

From [0152]: “Preferably the polish filter step is done through an appropriately sized filter such as a 1.2 µm in line filter.” relevant to WO2023105222 claims 15, 16, 17

From [0153]: “Preferably the agitation is by stirring at about 400-500 rpm, typically about 450 rpm.” relevant to WO2023105222 claims 15, 16, 17

From [0154]: “Preferably the seed is psilocybin Hydrate A. In one embodiment, 0.1% weight or less of seed is added to the process.” relevant to WO2023105222 claims 15, 16, 17

From [0081]: “... The solution was cooled to ambient temperature, at approx. 10° C./hour, seeding with Psilocybin Hydrate A (0.001×stage 5 charge) at 68-70° C ...” relevant to WO2023105222 claims 17

From [0039]: “The term “about” when used in reference to numerical ranges, cut-offs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed

value ..." relevant to WO2023105222 claims 17

From [0021]: "... The product was collected by filtration and washed with ethanol to provide a white needle crystalline form with a melting point 190° C.-198° C." relevant to WO2023105222 claims 18

From [0033]: "In accordance with a first aspect of the present inventions there is provided crystalline psilocybin in the form Polymorph A or Polymorph A', characterised by one or more of:" relevant to WO2023105222 claims 22, 23, 24

From [0034]: " a. peaks in an XRPD diffractogram at 11.5, 12.0 and 14.5°2θ±0.1°2θ;" relevant to WO2023105222 claims 22, 23, 24

From [0032]: "It is yet a further object of the invention to formulate the psilocybin of the invention in a form suitable for administration to human subjects and use it in medicine, particularly in the treatment of central nervous system disorders (CNS)..." relevant to WO2023105222 claims 24

**Citation # 3(Web page) (# uploaded documents:1):**

Author:		Title of Page Or Article: Quiet! Seed Crystals Growing. A Crystal Growing Activity	
URL: <a href="https://www.flinnsci.com/api/library/Download/fcd83e5a579b470f9c0acc678ac6564c">https://www.flinnsci.com/api/library/Download/fcd83e5a579b470f9c0acc678ac6564c</a>			
DOI:			
Name of Website:		Publication Date:	Retrieval Date: 16 Aug 2023 (16/08/2023)
Most relevant passages or drawings: Quote from webpage		Relevant to Claims: 18-21	
Brief explanation of relevance: From page 4: "A good seed crystal is about 1/4 to 1/8 inch long." relevant to WO2023105222 claims 18-21			

Citation # 4(Web page) (# uploaded documents:1):

Author:		Title of Page Or Article: THERMAL APPLICATIONS NOTE. Purge Gas Recommendations for use in Modulated DSC	
URL: <a href="https://web.archive.org/web/20170329133925/https://www.tainstruments.com/pdf/literature/TN44.pdf">https://web.archive.org/web/20170329133925/https://www.tainstruments.com/pdf/literature/TN44.pdf</a>			
DOI:			
Name of Website:	Publication Date: 29 Mar 2017 (29/03/2017)	Retrieval Date: 16 Aug 2023 (16/08/2023)	
Most relevant passages or drawings: Quote from website page 1-3		Relevant to Claims:	
<p>Brief explanation of relevance:</p> <p>From website page 1-2: "Purge Gas Flow Rates The purge gas flow rate used in a MDSC experiment should be carefully set and regulated. Inconsistencies in flow rates during an experiment can cause inaccuracies in measured heat flow, especially when using helium. Figure 2 illustrates this effect. This figure shows the calibrated cell constant (indium, <math>\Delta H = 28.4 \text{ J/g}</math>) as a function of flow rate using both nitrogen and helium. Note that with a nitrogen purge, the calibrated cell constant is virtually independent of purge gas flow rate, in between 10 ml/min. and 100 ml/min. However, when helium is used, there is a considerable dependence of the cell constant on the purge gas flow rate, especially at low rates. Thus when using helium, an accurate and precise flowmeter should be used, so that the flow rate does not fluctuate during the experiment, or in between experimental runs. Further, it is good practice to leave the purge gas flowing even when the instrument is not in use, to minimize any potential discrepancies in flow rate from run to run." relevant to WO2023105222 claims 9</p> <p>From website page 3: "Summary and Recommendations</p> <ul style="list-style-type: none"> <li>• A flowing inert purge gas should always be used when performing a DSC or MDSC experiment.</li> <li>• Nitrogen is the preferred purge gas, although helium may be use if faster cooling rates or wider modulation parameters are desired.</li> <li>• Using a reliable flowmeter, flow rates of 50 ml/min (nitrogen) or 25 ml/min (helium) should be introduced into the Purge port, and 50 ml/min (nitrogen or helium) should be introduced into the Vacuum port.</li> <li>• Make sure the flowmeter has a delivery pressure of at least 5 psi, to insure stable flow." relevant to WO2023105222 claims 9</li> </ul>			

Citation # 5(Web page) (# uploaded documents:1):

Author:		Title of Page Or Article: Supersaturated Solution	
URL: <a href="https://web.archive.org/web/20200612073412/http://home.miracosta.edu/dlr/info/super_saturation.htm">https://web.archive.org/web/20200612073412/http://home.miracosta.edu/dlr/info/super_saturation.htm</a>			
DOI:			
Name of Website:	Publication Date: 12 Jun 2020 (12/06/2020)	Retrieval Date: 16 Aug 2023 (16/08/2023)	
Most relevant passages or drawings: Quote from webpage		Relevant to Claims:	
Brief explanation of relevance: From webpage: "The most important thing to remember, however, is that you cannot form crystals unless you have a supersaturated solution. By definition, the solution would be either saturated or unsaturated. Crystal formation can only occur when you have an unstable supersaturated solution. Examples are honey or syrup, which if allowed to stand, crystals will form. But for either unsaturated or saturated solutions, no crystals can form. This is the importance of a supersaturated solution" relevant to WO2023105222 claims 12			

Citation # 6(Web page) (# uploaded documents:1):

Author:		Title of Page Or Article: VACUUM FOR LABORATORIES	
URL: <a href="https://www.vacuubrand.com/context/brochures/en/VACUU_LAN_Flyer_19_EN_Screen.pdf">https://www.vacuubrand.com/context/brochures/en/VACUU_LAN_Flyer_19_EN_Screen.pdf</a>			
DOI:			
Name of Website:	Publication Date:	Retrieval Date: 06 Aug 2023 (06/08/2023)	
Most relevant passages or drawings: Quote from website page 4		Relevant to Claims:	
Brief explanation of relevance: From website page 4: "Fine vacuum (1 mbar - 10 <sup>-3</sup> mbar) Describes the range below rough vacuum to 10 <sup>-3</sup> mbar. Typical applications are Schlenk lines, freeze-drying and molecular distillation." relevant to WO2023105222 claims 1  * From the application of interest WO2023105222 page 4 paragraph 3 "In an embodiment, the reduced pressure is a mild vacuum. In an embodiment, the reduced pressure is below atmospheric pressure, optionally the pressure is between 0.1 and 100mbar, further optionally between 0.5 and 20mbar, still further optionally between 1 and 10mbar. In an embodiment, the flow rate of the inert gas is adapted to maintain the selected pressure."			

Citation # 7(Web page) (# uploaded documents:1):

Author:		Title of Page Or Article: Seed Crystal	
URL: <a href="https://web.archive.org/web/20201209202659/https://en.wikipedia.org/wiki/Seed_crystal">https://web.archive.org/web/20201209202659/https://en.wikipedia.org/wiki/Seed_crystal</a>			
DOI:			
Name of Website: Wikipedia retrieved from Web Archive	Publication Date: 08 Dec 2020 (08/12/2020)	Retrieval Date: 16 Aug 2023 (16/08/2023)	
Most relevant passages or drawings: Quote from webpage		Relevant to Claims:	
Brief explanation of relevance: From webpage: "The large crystal can be grown by dipping the seed into a supersaturated solution, into molten material that is then cooled, or by growth on the seed face by passing vapor of the material to be grown over it." relevant to WO2023105222 claims 12			

Citation # 8(Web page) (# uploaded documents:1):

Author:		Title of Page Or Article: Cimarec+ stirrers, hotplates, and stirring hotplates. OPERATING MANUAL AND PARTS LIST	
URL: <a href="https://assets.thermofisher.com/TFS-Assets/LED/manuals/CimarecHotplates-Stirrers%20v17%2020170308.pdf">https://assets.thermofisher.com/TFS-Assets/LED/manuals/CimarecHotplates-Stirrers%20v17%2020170308.pdf</a>			
DOI:			
Name of Website:	Publication Date: 22 Feb 2017 (22/02/2017)	Retrieval Date: 16 Aug 2023 (16/08/2023)	
Most relevant passages or drawings: Quote from website page 25		Relevant to Claims:	
Brief explanation of relevance: From website page 25: "Setting the Stirring Speed Your Cimarec+ stirring hot plate has an electronic feed-back speed control which will maintain a speed set-point from 50 rpm through 1500 rpm at $\pm 5.0\%$ . (Maximum speed is dependent on viscosity of the solution.)" relevant to WO2023105222 claims 13			