Patents Act 1977 **Opinion Number** **07/21**

OPINION UNDER SECTION 74A

Patent	GB 2572023 B
Proprietor(s)	Compass Pathways Limited
Exclusive Licensee	none
Requester	Kohn & Associates PLLC, on behalf of Freedom to Operate Inc.
Observer(s)	Equipped 4 (IP) Limited
Date Opinion issued	28 July 2021

The request

1. The comptroller has been requested to issue an opinion as to whether the granted patent GB 2572023 B (hereafter "the patent") having a priority date of 9.10.17 is valid having regard to novelty or inventive step in respect of the following documents:

   "Folen" J. Forensic Science, April 1975, Vol 20, No.2, Folen, "X-Ray Powder diffraction Data for Some Drugs, Excipients and Adulterants in Illicit Samples", pages 348 to 372

   "Caira" Topics in Current Chemistry, January 1998, Vol 198, Caira et al, "Crystalline Polymorphism of Organic Compounds", pages 163 – 208

   "Hofmann" US Patent 3075992 Hofmann et al (referred to on page 1 of GB2527023B in paragraph 16)

   "Nichols" Synthesis 1999 No.6, Nichols et al "Improvements to the Synthesis of Psilocybin and a Facile Method for Preparing the O-Acetyl Prodrug of Psilocin" pages 935-938 (referred to on page 1 of GB2527023B in paragraphs 13 and 17)

   "Kuhnert" Archiv der Pharmazie, 1976, Vol 309, Issue 8, Kuhnert-Brandstätter et al, "Polymorphe Modifikationen und Solvate von Psilocin und Psilocybin", pages 625-631

   "Weber" J. Chem. Soc. Perkin Transactions 2, 1974, Issue 8, Weber et al, "Crystal structures of the Teonanácatl hallucinogens. Part I. Psilocybin $C_{12}H_{17}N_2O_4P$" page 942

"Shirota" J Natural Products 2003, vol 66. Shirota et al "concise large-scale synthesis of psilocin and psilocybin, principal hallucinogenic constituents of "magic mushroom" pages 885-887. Whereas this document was not cited among the opinion papers, the patent refers to it (wherein it is referred to as "JNP"), so I gave it some consideration to assist in understanding the invention. All the documents are prior art as defined under section 2(2) of the Act.

2. The first 4 documents were supplied in full with the request on 27 August 2020, the latter two as abstracts only. In addition, with the request was filed with a witness statement by Dr Poncho Meisenheimer, Senior Director of Chemistry Research and Technology Development for Promega Corporation, and Dr Alex Sherwood a Medicinal Chemist for Usona Institute, USA. As the requester put it these experts were retained by Freedom to Operate, Inc. to explain the cited prior art and to provide their expert opinion on the patentability of the above patent. Although the request for an opinion to be prepared was filed on 8 September 2020, it was not until 11 May 2021 that it was received at tribunal section so that observations could be invited. It is regretted that the process of issuing this opinion has therefore been delayed.

3. Observations filed on behalf of the proprietor were received from Equipped 4 (IP) Limited on 10 June 2021, and observations in reply were received from Kohn Associates, including a further witness statement by Drs Meisenheimer and Sherwood on 24 June 2021.

Determining if the request should be refused

4. In their letter of 10 June 21 the observer proposed that I should refuse the request to prepare an opinion, therefore I need to consider this proposal first. The basis for this request is found in Rule 94(1)(b) of the Patents Rules 2007 which provides that:

   The comptroller shall not issue an opinion if the question upon which the opinion is sought appears to him to have been sufficiently considered in any relevant proceedings.

5. The observer proposed that the matters raised had been properly considered before grant and referred to Frank's opinion request BL O/289/07 in support where it stated "It was, I believe, always the intention that the opinion service would not be used to repeat or in some way reappraise the examination of the patent performed either in this office or at the EPO." I have read this decision and do not find it dictates I should refuse this request. Where the decision on Frank's opinion request considered the provision of new evidence it found there was no new documentary evidence at all, Indeed where it considered new evidence, not considered at the time the patent was examined, the decision on Frank's opinion request cited such evidence as a fair basis for issuing an opinion. The observer proposes the arguments based on the documents I refer to in paragraph 1, is not new suggesting they were dealt with in a detailed pre-grant response filed on 23 July 2019. I have considered this response and consider it is confined to a different argument – novelty of

the present invention based on differences in the endothermic events and solvent extraction and that in any case this pre-grant argument is based on different documents. I consider there is new evidence provided with the opinion in the form of Folen, Caira, Kuhnert and Weber, and whereas Hoffman and Nichols were considered pre-grant I determine that I should consider all of the evidence, new and old, as together these documents are used in new arguments challenging the novelty and inventive step of the present claims. Therefore, I will proceed to consider the request. Before I can consider the evidence in detail, I will first consider the patent and construe the claims.

The Patent

6. The patent relates to crystalline psilocybin polymorph A, a formulation, uses and a method of preparation thereof, the applicants distinguish existing methods of preparing psilocybin in the prior art with those of the patent in respect of certain preparative steps, the final hydrogenation step and the resulting solvates and mixtures thereof. These differences prompted the applicants to characterise the different forms with the aim of producing the desired crystalline chemically pure psilocybin, that can be prepared at scale.

7. Polymorph A is defined in respect of analytical data, namely its X-ray powder diffraction (XRPD) diffractogram peaks and differential scanning calorimetry (DSC) thermogram. I will briefly consider these techniques in turn.

8. XRPD is a technique that allows crystalline phases of substances to be compared from the characteristic series of peaks of diffracted X-rays. The diffraction pattern is characteristic as the angle of the diffracted X-rays to the incident X-rays is related to the spacings between the layers of the crystal lattice by the Bragg equation:

$$n\lambda=2d\sin\Theta$$

wherein,

n is the order of diffraction corresponding to the whole number of wavelengths of incident X-ray radiation - where the wavelengths are in phase.

λ is the wavelength of the incident X-rays

d is the spacing between layers of molecules in the crystal lattice; and

Θ is the angle through which the X-rays are diffracted relative to the sample surface;

The angles are quoted as 2Θ as this is the measured angle of the detected radiation relative to the incident radiation.

9. DSC is a thermoanalytical technique measuring the heat required to raise the temperature of a substance, when for example a sample undergoes an endothermic change of state such as melting, it will require more heat (as

compared to a reference substance) to change its temperature by a given amount, so during melting a peak will appear in the thermogram. The claims specifically relate to the onset temperature (the beginning of the peak) for the endothermic events in the DSC thermogram for polymorph A.

10. Claim 1 defines polymorph A as showing diffractogram peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5° 2Θ±0.1°2Θ, and wherein the peak at 17.5°2Θ ±0.1°2Θ has a relative intensity compared to the peak at 14.5°2Θ ±0.1°2Θ of at least 5%. The description relates to several polymorphs and solvates but I will concentrate on those covered by the claims which protects only polymorph A. I note that the claims characterise polymorph A by the 2Θ angles with an intensity greater than 10% as found in table 1, the first 4 peaks (starting from low 2Θ) with relative intensity greater than 10% define polymorph A in claim 1, additional peaks contribute to the definition in claims 3 and 4 respectively, claim 5 relates to the entire set of 17 peaks of table 1, claim 6 relates to the absence of a diffractogram peak at 10.1°2Θ (which is stated to be characteristic of polymorph A') see paragraph 54, and claim 7 which relates to the polymorph having the diffractogram as illustrated, in Figure 7A which relates to polymorph A.

11. As well as parameters related to the XRPD diffractograms, the claims characterise polymorph A in relation to the DSC thermogram where claim 1 relates to crystalline psilocybin in the form polymorph A characterised by one or more of: b an endothermic even in a DSC thermogram having a first onset temperature of between 145°C and 155°C and a second onset temperature of between 210 and 220°C.

12. The patent refers to both thermogravimetric analysis (TGA) and DSC analyses, but I will consider in detail only the latter as that will help me determine what is meant by the parameters of the claims, the DSC thermogram of polymorph A is indicated in Figure 8a this has a large peak with an onset at 213.92°C and a peak at 223.71°C and another much shallower peak with an onset of circa 150°C (corresponding to transition of polymorph A to B, see paragraph 71) but a peak at 161.35°C, Figure 8a polymorph A and Figure 8B (polymorph A') both show the circa 150°C transition

Claim construction

13. Before considering the documents put forward in the request, I will need to construe the claims of the patent following the well-known authority on claim construction which is *Kirin-Amgen and others v Hoechst Marion Roussel Limited and others* [2005] RPC 9. This requires that I put a purposive construction on the claims, interpret it in the light of the description and drawings as instructed by Section 125(1) and take account of the Protocol to Article 69 of the EPC. Simply put, I must decide what a person skilled in the art would have understood the patentee to have used the language of the claim to mean.

14. Section 125(1) of the Act states that:

For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.

15. And the Protocol on the Interpretation of Article 69 of the EPC (which corresponds to section 125(1)) states that:

Article 69 should not be interpreted in the sense that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Neither should it be interpreted in the sense that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patentee has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patentee with a reasonable degree of certainty for third parties.

16. The requester and observer ultimately agree, as I do with them both, as to how to construe claim 1, the claims protect claim 1 part a (wherein polymorph A is characterised by XPRD peaks) and/or b (where polymorph A is characterised by DSC events) with the additional requirement of a “purity” feature. So that claim 1 protects, either:

a) polymorph A characterised by XPRD data having the required purity, as defined in claim 1(a), i.e. peaks in an XRPD diffractogram at 11.5, 12.0, 14.5 and 17.5°2Θ±0.1°2Θ, and wherein the peak at 17.5°2Θ±0.1°2Θ has a relative intensity compared to the peak at 14.5°2Θ±0.1°2Θ of at least 5%, and a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1% including phosphoric acid as measured by 31P NMR, and psilocin as measured by HPLC;

b) polymorph A characterised by DSC data having the required purity characterised by DSC data, as defined in claim 1(b), i.e. 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 210 and 220°C %, and a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1% including phosphoric acid as measured by 31P NMR, and psilocin as measured by HPLC; or

c) polymorph A characterised by XPRD and DSC data having the required purity, as defined in claim 1 parts (a) and (b).

17. In addition I consider that claim 1 purposively construed will be understood by the person skilled in the art to represent the parameters that the patentee has found are the minimum necessary to distinguish polymorph A (of the required

purity) from other phases / compositions. For the avoidance of doubt, I am satisfied that the skilled addressee would consider that this claim is intended to encompass crystalline psilocybin and not other crystalline phases such as solvates. I consider that solvates are excluded as the description characterises the potential solvates and does not find that they have the same properties as polymorph A, see for example paragraphs 417-453. That said the addressee would be guided as to the purity of crystalline psilocybin by the parameters of each claim. Each successive claim including more parameters, therefore increasing the precision with which the psilocybin polymorph is defined, and the corresponding certainty that it encompasses no other phase or composition, that may also be encompassed by the parameters defined. Therefore, I will consider if the prior art shows that the parameters of claim 1(a) or (b) are known or obvious for predominately (greater than 97% pure crystalline psilocybin) free of solvates to determine the validity of the claims. I need not consider c in detail as it is narrower in scope than a or b alone.

Novelty

18. I will begin by considering the novelty of claim 1(a) as regards the prior art, the observer has relied on Folen in particular, in considering the novelty of claim 1(a). I will begin by comparing the XRPD data in Folen with that in the patent. The Psilocybin XRPD data in Folen (quoted in Angstrom measured lattice spacing “d”) is converted to the diffraction angles 2θ for the incident CuKα radiation also measured in Angstroms using the Bragg equation. I have checked the calculated angles and find that the Folen psilocybin XPRD data has peaks at 11.5°, 12.0°, 14.5°±0.1°2Θ , so that 3 of the 4 peaks as defined in claim 1a are found in the Folen XRPD data. The closest peak in Folen to that required by the claim at 17.5°±0.1°2Θ has a calculated 2θ of 17.9°, not 17.5° as indicated in the witness statement filed on 27 August 2020. I would note that in reaching this value I have taken the product of λ / d to 4 decimal places (the same accuracy as quoted for the CuKα radiation in Folen) so as not to introduce a rounding error and found the inverse sine and then rounded the result to 1 decimal place to correspond to the precision used in the values of the claims. I note that the 2θ of 17.5° (as quoted by the requester’s witnesses) is achieved by rounding product of lambda over d to one decimal place, I do not consider this is the way in which the skilled person would have performed this calculation, indeed this would appear to be rounding with the aim of changing the disclosure of the prior art which Kitchin LJ disapproved of in *Smith & Nephew Plc v Convatec Technologies Inc* [2015] EWCA Civ 607. I will proceed with the value derived from Folen of 17.9° 2θ some 0.2° 2θ greater than the observer calculates and some 0.4° 2θ greater than the peak as calculated by the requester’s witnesses. A 0.4° 2θ difference would correspond to approximately 1 cm of chart recording paper in the analysis of the Folen data (wherein 1inch = 1 deg 2θ). The observer points out that such analog data, such as found in Folen, can include major sources of potential error. Whereas such distortion may be possible it is unlikely that such errors would affect disproportionately this peak but not the peaks at 11.5, 12 and 14.5° 2θ where the observer does not question the precision because the correspondence between the data in Folen and the patent is far closer.

19. Nonetheless because the conversion of analog data from a paper trace to a tabulated set of peaks is amenable to many sources of error and because a small error in the angle may produce a relatively large change in the measurement of d derived from the Bragg equation (as shown by my own calculations that a rounding error can give rise to a large difference in the calculated value of the spacing d) I consider that all 4 peaks of claim 1a have counterparts in Folen.

20. As regards the remaining parameters the ratio of the peak intensity of the 17.5° 2θ peak (as I find it the 17.9° 2θ peak) to the most intense peak at 14.5 2θ is greater than 5% as required by the claim.

21. As regards the purity parameter, there is scant reference to the purity of the samples used to derive the data in Folen, the samples are stated to be "Reagent grade chemicals… whenever possible", I do not consider there is enough information to conclude that the sample of Folen has the required purity. Therefore, Folen does not anticipate the invention as defined in claim 1(a).

22. None of the other documents cited in the request include any XPRD data and so these documents do not anticipate the present claims as regards claim 1(a).

23. Turning to the novelty of claim 1(b). As regards the DSC data the patent proposes that the second endothermic event with an onset between 210°C and 220°C corresponds to a melting point (see paragraph 67), given that this event is consistently found in the dehydrated phase (see paragraph 23) and in the DSC thermograms of either polymorph A or A' (paragraph 67) I consider it is clear that this transition corresponds to the melt. A melting temperature for psilocybin is also quoted in the prior art documents of Hofmann, Nichols and Kuhnert;

> *"The resulting 3-(2'-difnethylaminoethyl)-4-pbosphoryloxy-indole crystallizes out as small, massive, colorless prisms of M.P. 210-212 (decomposition)"* Hofmann
>
> *"This product was dried under high vacuum to produce solvent-free psilocybin, which had mp 212–213 °C)"* Nichols
>
> *"Psilocybine….melts between 210 and 230° with decomposition"* Kuhnert

Whereas the onset temperature is not quoted in the prior art I consider that the person skilled in the art would understand these melting points of the prior art to correspond to the onset temperature of the melt of psilocybin in a DSC thermogram. Therefore, the second endothermic event is known in the art. The only document to mention any other transition that may correspond to the first endothermic event is Kuhnert, when it says:

> *"After desolvation, which occurs on the hydrate at about 100° and on*

the methanol solvate at about 145°, the same solvent free form results from both solvates".

The requester also refers to Weber which describes the crystal structure of the monomethanolate salt. I do not see that this latter document assists me other than to show that a monomethanolate solvate is known. Therefore, it is only Kuhnert that I will consider further as regards claim 1(b).

24. Kuhnert indicates a methanol solvate with loss of methanol at 145°C and melting at between 210 and 230°C. I consider this would provide a corresponding DSC thermogram, with a TGA plot showing significant loss of weight at 145°C and melt at 210-230°C.

25. Whereas the 145°C endothermic event in the patent would be understood to relate to a phase that does not comprise appreciable solvent, the 145°C event in Kuhnert clearly relates to the methanol solvate, clearly a pure methanol solvate of psilocybin would comprise more than 3% methanol (10.3% according to the patent, see paragraph 442). Therefore, even if Kuhnert relates to a phase that meets the parameters of both endothermic events I do not consider that the addressee would consider Kuhnert to teach a phase that meets the purity parameter, and is in nay case excluded as it relates to a solvate (see my paragraph 17). Therefore the present claims are novel as regards Kuhnert.

26. Having found no evidence that is considered to anticipate either claims part 1(a) or 1(b), all other claims being dependent thereon, I consider the invention is novel, as regards the prior art identified in the request.

Inventive step

27. To determine whether or not an invention defined in a particular claim is inventive over the prior art, I will rely on the principles established in Pozzoli SPA v BDMO SA [2007] EWCA Civ 588, in which the well-known Windsurfing steps were reformulated:

(1)(a) Identify the notional "person skilled in the art";
(1)(b) Identify the relevant common general knowledge of that person;
(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
(4) Viewed without any knowledge of the alleged invention as claimed, determine whether those differences constitute steps which would have been obvious to the person skilled in the art.

28. Taking these in turn, I should first identify the person skilled in the art, and their common general knowledge. Neither the observer or the requester has given me the benefit of their opinions as to the nature of the person skilled in the art or their common general knowledge. However, I consider the person

skilled in the art is a preparative organic chemist with an interest in methods for use in scaling up laboratory scale methods so as to achieve quantities of sufficient size for pharmaceutical uses. Such a chemist would consult or have the necessary knowledge of the standard analytical methods used to ensure each batch can be produced with sufficient quality assurance of its consistent composition, stability and purity. They would be aware of standard techniques used in scale up and of the need to investigations forms such as polymorphs. Such a person or team would be aware of the desirability of a single polymorph and how its presence could be determined, and would have a practical knowledge of techniques so that they could identify possible quality assurance problems or benefits from the output of the analytical techniques used. They would have some knowledge of the current pharmaceutical uses and formulations of psilocybin. I consider the person skilled in the art to be common for both claims 1(a) and 1(b).

29. Now turning to the inventive concept or construing the claim. I consider the inventive concept of claim 1(a) to be, a phase of psilocybin (polymorph A), being the characteristic product of a preparative method used to prepare psilocybin at high purity. The polymorph A phase being characterised by particular peaks in its XRPD diffractogram distinguishing it from other psilocybin phases or compositions. It is implicit in this assessment that as more parameters are used to define polymorph A in successive claims the more likely it becomes that the substance encompassed by the claim is precisely the polymorph described.

30. Turning to claim 1(b), I consider the inventive concept of claim 1(b) is, a phase of psilocybin (polymorph A), being the characteristic product of a preparative method used to prepare psilocybin at high purity. Polymorph A being characterised by endothermic events in its DSC thermogram distinguishing it from other psilocybin phases. It is implicit in this assessment that as more parameters are used to define polymorph A in successive claims the more likely it becomes that the substance encompassed by the claim is precisely the polymorph described.

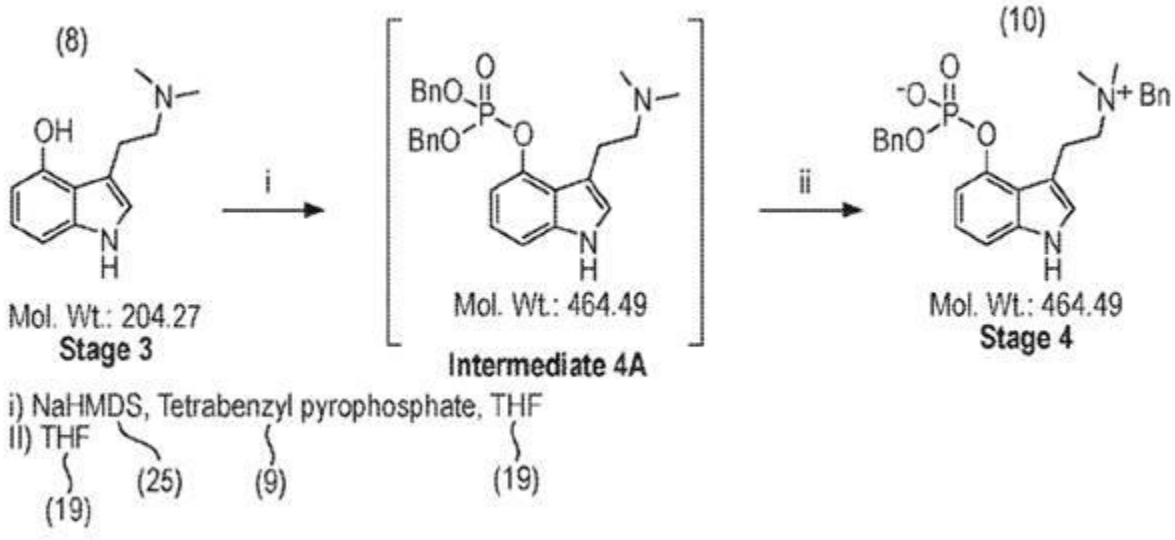
31. As regards step 3 and 4 of Windsurfing/Pozzoli I will consider the Caira document first. I begin here as the argument in respect of this document stands alone, and as I see it applies to both claim 1(a) and 1(b) equally. Therefore, I will consider the differences between Caira and the inventive concept and decide if these differences would have been obvious to the person skilled in the art.

32. The requester argues that polymorph A is not inventive as it is the result of conventional work in the pharmaceutical industry because it is well known that “when investigated for a sufficiently long period will show that there is more than one polymorph - see for example Caira, especially the paragraph bridging pages 165 and 166”. I consider that the person skilled in the art would find it within their common general knowledge to investigate polymorphs. In respect of Caira the requester goes on to propose that routine screening to identify polymorphs would therefore lead to polymorph A, and that an inventive step would only result for the polymorph if it was considered to show unexpected properties.

33. In so doing the requester rather glosses over the steps necessary to identify polymorphs including the polymorph A of psilocybin and prepare them at the desired high purity.

34. The patent proposes that at least paragraphs 109, 242 265, 274, 303, 341, 364, are differences between the process of the invention (depicted in its entirety in Figures 2-6) and the admitted art documents Shirota or Nichols. Some of these differences are minor or within the common general knowledge of the person skilled in the art, such as monitoring levels of impurities. This would encourage me to find that polymorph A is not inventive in that it is an arbitrary polymorph providing no associated technical contribution. However, some of the differences between the process of the invention and Shirota or Nichols relate to changes to reaction conditions or reagents that are stated to have desirable effects on safety, ease of isolation / purity which are not the result of routine optimisation. Such differences are not obvious as they give rise to a technical contribution.

35. I will illustrate with steps that I consider are obvious and non-obvious. The synthetic steps in Shirota and the patent are undoubtedly similar, so for just the first step of the synthesis both Shirota and the patent start from 4-hydroxyindole and use acetic anhydride in pyridine and dichloromethane to form 4-acetylindole. In Shirota the 4-acetylindole product is dissolved in ethyl acetate and washed with water and saturated salt solution which is then evaporated to dryness, whereas in the patent when the reaction has gone to completion the dichloromethane is swapped for heptane followed by washing in solutions of sodium bicarbonate and citric acid. Comparing these choices of solvent or washing techniques in isolation it is not difficult to conclude that the steps of the present invention are amenable to routine experimentation as compared to Shirota, but when the steps have apparent beneficial effects on safety and product recovery and have knock on effects on latter steps, these are less obvious to the person skilled in the art. So for example the step of Figure 5 of the patent (see below) differs from that of the prior art in the use of sodium hexamethyldisilazide (NaHMDS) as opposed to butyllithium,



using butyllithium provides the product intermediate 4A at high yield in the prior art (so is not a good candidate for routine optimisation) but using NaHDMS appears to facilitate a more facile step (ii) above, not requiring the solvent exchange as used in Shirota or the impurities that result from the water based work up as is used in the equivalent step in Nichols (first full paragraph on page 936). Ultimately, the accumulation of the steps that differ between the prior art and the patent and the benefits that flow from some of them are considered to provide an inventive step for claim 1(a) or 1(b) as compared to Caira.

36. Therefore, I do not find that the skilled person would find it obvious to perform the preparative and purification methods of the invention to arrive at the product of polymorph A given their common general knowledge or Caira, both of which are considered to direct the person skilled in the art to investigate polymorphs.

37. I will now consider the other documents starting with Folen, the differences between it and the inventive concept and if these differences would have been obvious to the person skilled in the art.

38. Before I consider the diffractogram data from Folen I should address its purity as this may determine how reliable the person skilled in the art would consider the diffractogram data to be.

39. The observer states that Folen provides “tabulated XRPD peak data…for an illicit sample of “psilocybin”, however I do not consider this to be the case. I have read Folen in full and consider its aim is to provide reference XRPD data that may be used in the identification of illicit substances including wherein the illicit sample is “cut” with adulterants, the samples are prepared with reagent grade materials where possible and the spectra of common adulterants are also provided, therefore the person skilled in the art would consider that the data relates to a reagent grade sample or at least a sample without the common adulterants, if Folen showed XRPD data for an illicit sample of psilocybin per se it would not satisfy the purpose of the study. Therefore, I do not consider that the person skilled in the art would be dissuaded from considering the Folen XRPD data at face value.

40. I consider the person skilled in the art would consider Folen to show a diffractogram for psilocybin of reagent grade purity, Folen shows peaks within the experimental error quoted by the patent for 3 of 4 of the characteristic peaks of claim 1(a) and is considered sufficiently close to the value of the 4th peak that the person skilled in the art would consider it to be within the experimental error by which the methods in Folen were used to derive the data.

41. The difference between claim 1(a) and Folen therefore lies in the purity parameter:

> “a chemical purity of greater than 97% by HPLC, and no single impurity of greater than 1% including phosphoric acid as measured by 31P

NMR, and psilocin as measured by HPLC”

42. As I have said above regarding novelty (paragraph 21), Folen differs from the inventive concept in that it does not provide enough information as to the purity of the psilocybin used and the requirements of claim 1(a). Therefore, I must consider if purifying reagent grade psilocybin (such as appears to have been the source of psilocybin in Folen) is within the skilled person’s common general knowledge or may be found elsewhere in the prior art.

43. The requester states that the purity parameter is a desiderata as there is “no process limitation specified in claim 1 that controls the achievement of the desirable result of high purity” and in the second witness statement “It cannot be invention to define a desired chemical purity value of a chemical material that is already known”. Whereas it is considered common general knowledge in the art to perform standard purification methods, I do not consider that there can be no invention in purification techniques per se, as I have already concluded in paragraph 35 in respect of Caira. Therefore, contrary to the requesters view I need to consider if the person skilled in the art can achieve the purity parameter for psilocybin from sources such as used for the analytical work in Folen.

44. Of the documents that indicate any measure of purity none give precise figures for the percentage impurities, the main indication I have as to psilocybin purity in the prior art is as implied by the narrow melting point range as found in Hofmann and Nichols. From this narrow range I would expect the person skilled in the art to conclude from their common general knowledge that either Hofmann or Nichols had been prepared at an overall purity of 97% or higher. The psilocybin prepared in Nichols shows some additional steps intended to enhance purity of the final product by recrystallisation. The psilocybin in Nichols is recrystallised from methanol not water as in the present invention, the observer distinguishes Nichols from the present invention on this basis alone, presumably on the assumption that water recrystallisation is the only way to provide the polymorph that meets the parameters of the claims. However, insofar as Nichols states that the product was dried under vacuum and found to be solvent free, I do not consider the difference in solvent to be of consequence. The only other evidence I can glean from the documents as to the purity of the product in Nichols is the elemental analysis quoted for each element which gives a percentage difference of less than 2% from the expected value, when it states:

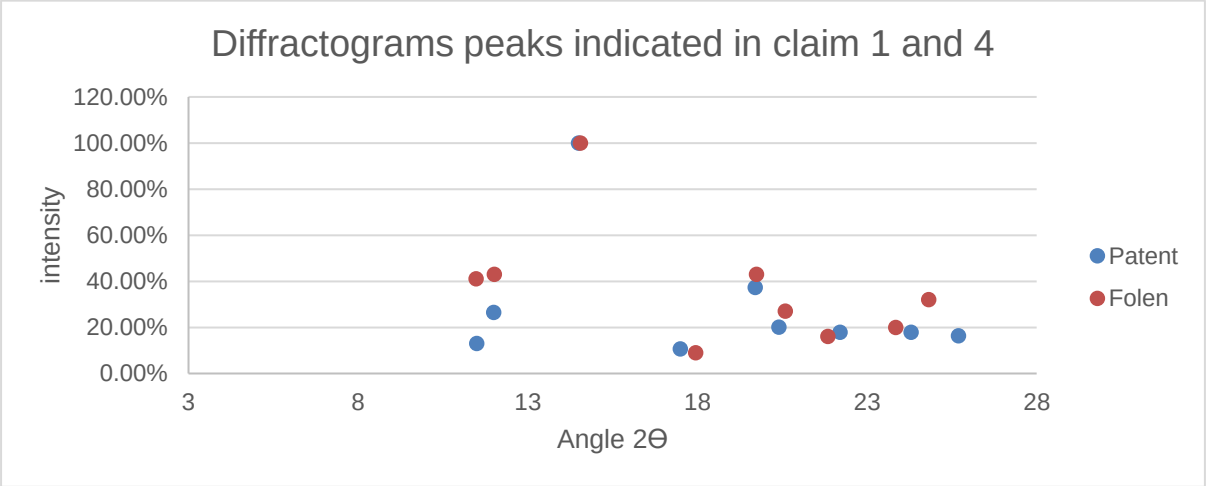
> “Anal. **Calcd.** for C12H17N2O4P (284.25): C 50.71, H 6.03, N 9.86, P 10.90; **found**: C 50.37, H 5.91, N 9.68, P 10.75.” (emphasis added)

Therefore, I consider the person skilled in the art has a purification technique at their disposal in Nichols that they would be confident would give a purity greater than 97% overall, furthermore the person skilled in the art would assume given the high overall purity that any one impurity would contribute a relatively small fraction of the overall impurity, and so would be likely to contribute less than 1% including phosphoric acid or psilocybin.

45. Given the disclosures of Folen and Nichols the person skilled in the art would

understand that they could recrystallise the psilocybin obtained at reagent grade if possible (as found in Folen) in the minimum amount of hot methanol with the addition of isopropanol and cooling to recrystallise psilocybin at high purity (as found in Nichols), and showing the XRPD peaks of Folen. Therefore, I consider claim 1a to be obvious having regard to Folen and Nichols.

46. I will proceed to decide if the other claims relating to XRPD data are obvious. To do so I have graphically compared the peaks from Folen with the closest corresponding peaks in the patent, see below. The plots include the intensity, it is noted that this differs markedly for some of the peaks such as at 11.5°, 12° and 25.7° 2Ɵ but I cannot take this into account as the intensity of the peaks is not a claimed parameter.



47. I have had to be selective in comparing the peaks in Folen with those of the patent, as there are more peaks in Folen than in the table 1 of the patent but as I state in paragraph 17 this is permissible given how I have construed the claim. I consider that the person skilled in the art purposively construing the claim would consider the peak positions in Folen and the patent to correspond within the experimental error for each of the peaks at 19.7, 20.4°, 22.2° and 24.3° but not for 25.7° 2Ɵ which insofar as it is 0.88° 2Ɵ from the corresponding peak in Folen is not considered within the ambit of experimental error. As such I find claim 3 (which requires a peak at one of 19.7, 20.4, 22.2, 24.3 or 25.4° 2Ɵ) but not claims 4, 5 or 7 or the claims appended thereto (which require all these peaks), to be rendered obvious by a combination of the teaching of documents Folen and Nichols. As regards claim 6 which requires an absence of a peak at 10° 2θ, I have calculated that such a peak is present in the diffractogram of Folen, so the invention is inventive as compared to claim 6. As well as claim 1 and 3 I consider that claims 10-20 are additionally within the common general knowledge of the person skilled in the art, in that claims 10-11 are considered differing measures of purity that could be achieved by the person skilled in the art having reference to Nichols, and claim 12 is *prima facie* merely a matter of scaling known methods such as Nichols. Claim 13-20 are considered within

the common general knowledge of the person skilled in the art as these claims encompass conventional uses of psilocybin.

48. Having exhausted the documents that relate to the parameter of claim 1(a) I will now consider the inventive step of claim 1(b) further, as I have so far only examined it in respect of Caira.

49. I have already decided on the person skilled in the art, their common general knowledge and the inventive concept of claim 1(b) see paragraphs 28 and 30 above. So I will now consider the documents showing a data relating to the endothermic events such as in DSC data. I have already decided in paragraph 23 that Kuhnert is the only relevant document in this regard.

50. Kuhnert shows a methanol solvate having a DSC plot with a first endothermic event at 145 °C and a second endothermic event that coincides in part with that of the claim at 210-220°C, the difference between Kuhnert and the inventive concept lies in the purity of the phase, to achieve the required purity would require the person skilled in the art to seek a highly pure psilocybin phase from the methanol solvate which comprises a great deal of methanol "impurity", whereas this is an unlikely starting point, I consider the skilled person would be further dissuaded from starting from Kuhnert (I have considered the full document in addition to the abstract in machine translation, which I quote from below) in that the methanol solvate loses solvent over a broad range of temperatures:

> "The DSC thermogram of the methanol solvate corresponds in principle with the thermomicroscopic examination result. A powerful endothermic peak at 144 -indicates the desolvation. In contrast, the melting peak is very broad, the baseline rises beforehand, both a sign of decomposition"

This suggests to the person skilled in the art that the methanol solvate is a poor candidate for achieving a highly pure phase (as may be the case if methanol was lost over a small temperature range and well below the decomposition temperature). Therefore, I consider the person skilled in the art would not be led from Kuhnert to the present invention of claim 1(b), so claim 1(b) is inventive as regards Kuhnert.

51. I note that the distinct thermogram for the methanol solvate as found in Kuhnert (as compared to the sharp melting point indicated in Nichols) gives me a little more confidence in the conclusions as to the purity of the psilocybin derived from Nichols in that although the psilocybin of Nichols was also prepared in methanol it does appear to have a methanol solvate characteristic thermogram.

52. There being no other documents that I consider provide a suitable starting point for the person skilled in the art to meet the inventive concept of claim 1(b) I consider that claim 1(b) in this respect is inventive.

Opinion

53. In summary I consider that claims 1, 3 and 10-20 are not inventive, based on Folen and Nichols.

Application for review

54. Under section 74B and rule 98, the proprietor may, within three months of the date of issue of this opinion, apply to the comptroller for a review of the opinion.

Jason Bellia
Examiner

NOTE

This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Office.