

19 June 2012

## **PATENTS ACT 1977**

APPLICANT                                  GW Pharma Limited

ISSUE    Whether patent application number  
GB0707610.2 complies with sections  
14(5)(c), 14(5)(b) and 1(2)(a)

HEARING OFFICER                          Mrs S Chalmers

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## **DECISION**

### **Introduction**

- 1 Patent application GB 0707610.2 entitled “New use for cannabinoid-containing plant extracts” was filed on 19 April 2007 and published as GB 2448535A on 22 October 2008. The unextended compliance date for the application was 29 November 2011 but has been extended under rules 108(2) and 108(3) such that the compliance date is now 30 July 2012.
- 2 Despite amendment of the claims, the examiner has maintained that the invention claimed lacks clarity and support under section 14(5) and is excluded as a discovery under section 1(2)(a) on the grounds that it is defined by a mechanism of action. The applicant disagreed and these matters came before me at a hearing on 1 May 2012 to resolve the issue. The applicant was represented by Mr Dominic Schiller on behalf of the patent attorneys Harrison Goddard Foote. Ms Fiona Warner (examiner), Dr S. David Evans (hearing assistant) and Dr Graham Feeney (observer and technical assistant) were also in attendance. I confirm that my decision takes into account the documents and inventor’s declaration filed with the agent’s email and letter of 17 and 21 February 2012 respectively.

### **The application**

- 3 The application relates to the use of cannabinoid-containing plant extracts in the prevention or treatment of diseases or conditions that are alleviated by blockade of the TRP (transient receptor potential) channels. Specifically, it is known that up-regulation of activity of the TRPM8 channel occurs in the presence of certain tumour cells including prostate cancer cell carcinomas and other primary human tumours such as breast, colon, lung and skin cancer.

- 4 In particular, the application relates to the use of one or more phytocannabinoids selected from cannabidiol (CBD), cannabigerol (CBG) and cannabidiolic acid (CBDA) to prevent or treat cancer of the prostate where TRPM8 activity is essential for the cancers survival.

### Claims

- 5 I have made my decision on the basis of the amended claims filed on 24 January 2012 which consist of 10 claims. Claim 1, which is in second medical use format, reads:

*“One or more phytocannabinoids, which are TRPM8 antagonists, selected from the group consisting of: cannabidiol (CBD); cannabigerol (CBG); and cannabidiolic acid (CBDA) for use in the prevention or treatment of cancer of the prostate, where TRPM8 activity is essential for the cancers survival.”*

- 6 Claims 2-10 are dependent on claim 1 and detail the plant source of the phytocannabinoids, the extraction technique, the relative amounts of the specific phytocannabinoids in an extract, the optional presence of other cannabinoids such as tetrahydrocannabinol (THC) and dosage forms.

### The law

- 7 Section 1(2)(a) reads:

*1(2) It is hereby declared that the following (among other things) are not inventions for the purposes of this Act, that is to say, anything which consists of –*

*(a) a discovery, scientific theory or mathematical method;*

- 8 The relevant parts of section 14(5) read as follows:

*14 (5) The claim or claims shall –*

*(a) ...;*

*(b) be clear and concise;*

*(c) be supported by the description; ..*

*(d) ....*

### Arguments

- 9 At the hearing, Mr Schiller’s arguments focused on the issues of support and clarity. He acknowledged that the leading UK case law in relation to support was *Prendergast*<sup>1</sup>, but observed that the two subsequent decisions by the EPO Board of Appeal, namely *Salk*<sup>2</sup> and *US Government*<sup>3</sup> were also relevant. He also noted

<sup>1</sup> Prendergast’s Applications [2000] RPC 446

<sup>2</sup> Salk Institute v Karo Bio AB T0609/02

<sup>3</sup> The Government of the United States of America T 0491/08

that *El-Tawil*<sup>4</sup> referred to *Salk* in paragraph 25 in relation to support and what the requirements were. Mr Schiller was of the opinion that, in assessing support, one could look at the state of the art at the filing date and tie this in with the data present in an application as filed in order to provide adequate support. In his view, the application as filed, which disclosed that certain cannabinoids are antagonists of the TRPM8 receptor, could be combined with the state of the art which disclosed that TRPM8 was essential for the survival of androgen-dependent prostate cancer cells, in order to provide the required support.

10 Mr Schiller stated that a journal article *Zhang*<sup>5</sup> was the “key state of the art” at the filing date of the present application. The declaration by the inventor, Dr Vincenzo Di Marzo (hereafter “*Di Marzo*”), which accompanied the agent’s letter of 21 February 2012 was key to understanding what the terminology in *Zhang* meant and to the clarity of the claim.

11 Mr Schiller then turned to the *Di Marzo* declaration and drew my attention to section 2.1 which reads as follows:

*In this documentation that I provided in order for the subject patent application to be drafted I wrote the following, ....“....On the other hand TRPM8 activity seems to be essential for prostate cancer cell survival [cross-reference to Zhang] ... Thus TRPM8 antagonists might provide new therapeutic tools for this widespread type of carcinoma.”*

12 Mr Schiller pointed out that in referencing *Zhang*, this part of the *Di Marzo* declaration reflected the inventor’s rationale, reasoning and thinking at the time. Mr Schiller acknowledged that the inventor had written that TRPM8 activity *seems* to be essential for prostate cancer cell survival, rather than make a definite link between them. However, he suggested that this lack of certainty was merely due to the way in which scientists write a hypothesis, rather than an expression of any doubt about the link between TRPM8 and the cancer cells.

13 Mr Schiller then proceeded to discuss *Zhang* in some detail to determine the specifics of what that document taught. He observed that the language used in claim 1 of the present application closely matched the title of *Zhang*. Mr Schiller also pointed out that “the fact that the prostate cancer cells are androgen-dependent indicates that they are hormone-dependent”. He further argued that “the title itself could almost be read as evidence that TRPM8 is required for the survival of androgen-sensitive cells, which is effectively what it is being claimed in the language used.”

14 Mr Schiller then turned to the abstract of *Zhang* to distinguish between androgen-insensitive and androgen-sensitive prostate cancer cells which reads:

*Although TRPM8 was detected in the androgen-insensitive PC-3 cell line, no evidence was obtained for regulation of its expression by androgen.*

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<sup>4</sup> *El Tawil v The Comptroller General of Patents* [2012] EWHC 185 (Ch)

<sup>5</sup> *Cancer Research*, Vol. 64, 2004, (Lei Zhang and Gregory John Barritt), “*Evidence That TRPM8 is an Androgen-Dependent Ca<sup>2+</sup> Channel Required for the Survival of Prostate Cancer Cells*”, pages 8365-8373

- 15 Mr Schiller pointed out that this particular receptor was not responsive in androgen-insensitive prostate cancer cells. He acknowledged that the TRPM8 was detected in these cells but that it was not being expressed or over expressed. The next sentence of the abstract reads:

*The results of experiments using LNCaP cells, the TRPM8 antagonist capsazepine, and small interference RNA targeted to TRPM8 indicate that TRPM8 is required for cell survival.*

- 16 Mr Schiller argued that in contrast, however, TRPM8 was required for the survival of the androgen-sensitive prostate cancer cells. In the final sentence, the abstract reads:

*These results indicate that TRPM8...may be a potential target for the action of drugs in the management of prostate cancer.*

- 17 Mr Schiller pointed out that the key to what the applicant was doing was to recognise that the claimed cannabinoids were good TRPM8 antagonists – which is he argued was what the present application shows – and tying that to *Zhang*. Mr Schiller thought that with this information, it was very credible to treat the hormone-sensitive prostate cancers with these cannabinoids.

- 18 Mr Schiller then referred to other parts of *Zhang* to reaffirm the difference in TRPM8 expression between androgen-insensitive and androgen-sensitive prostate cancer cells. Specifically, he highlighted that the known TRPM8 antagonist capsazepine reduced the survival of androgen-sensitive cells by the induction of apoptosis. *Zhang* also disclosed that the known TRPM8 antagonist capsazepine significantly decreased the viability of androgen-sensitive prostate cancer cells. Mr Schiller therefore concluded that the effect of the capsazepine on cell apoptosis and cell viability clearly demonstrated that the antagonist was providing a potentially therapeutic effect. By analogy, he argued that the claimed cannabinoid TRPM8 antagonists would have the same effect. I note, however, that these tests are *in vitro*, rather than *in vivo*.

- 19 Mr Schiller acknowledged that the present wording of the claims presented an ‘all or nothing’ scenario for the applicant because there was no amendment that could be made. He acknowledged that the language in claim 1 relating to TRPM8 being “essential for the cancers survival” was the only language present in the application as filed. He added that this language was critical to distinguish the present invention from a prior art paper *Ligresti*<sup>6</sup> which disclosed the anticancer effect of various cannabinoids on hormone-insensitive prostate cancer.

- 20 Mr Schiller argued that the language used in claim 1 was clear to the person skilled in the art as per the *Di Marzo* declaration and that the wording in *Zhang* clearly supported the distinction between androgen-insensitive and androgen-sensitive prostate cancer. He also drew my attention to the second Written

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<sup>6</sup> The Journal of Pharmacology and Experimental Therapeutics, Vol. 318, No. 3, 2006, (Alessia Ligresti *et al*), “Antitumor Activity of Plant Cannabinoids With Emphasis on Human Breast Carcinoma”, pages 1375-1387

Opinion mailed on 21 February 2012 in relation to PCT/GB2011/050487 (published as WO 2011/110866 A1). He pointed out that, in relation to clarity, the international examiner had commented in the Written Opinion for PCT/GB2011/050487 that document D3 (the patent in suit) disclosed the treatment of TRPM8 dependent hormone-sensitive prostate cancer. Mr Schiller argued that although this document was written after the filing date of the present application, it shows in his opinion what the person skilled in the art would understand by the terms used in the application in suit.

- 21 Mr Schiller then turned to another prior art document *Tsaveler*<sup>7</sup> which was referred to in the agent's letter of 6 December 2011. He observed that although this document preceded *Zhang*, one section was particularly significant, i.e. part of the right-hand column under *Fig. 10*, the first full sentence of which reads:

*Of the three studied cell lines, only LNCaP, the sole trp-p8 expresser, was found to be androgen-dependent.*

- 22 Mr Schiller argued that this clearly distinguished the trp-p8 (a synonym of TRPM8) expression between the androgen-dependent prostate cancer cells (LNCaP) and the androgen-independent prostate cancer cells (DU 145 and PC-3).
- 23 In respect of the present application, Mr Schiller reiterated that the key to establishing support for the claims was what the person skilled in the art would recognise. In his view, the state of the art at the time of filing, together with the fact that the applicant had shown that the claimed cannabinoids acted in the same way as capsazepine, logically led the person skilled in the art to conclude that the claimed cannabinoids would be a good agent for treating androgen-dependent prostate cancer.
- 24 Mr Schiller then turned to the relevant case law. He again acknowledged that the key UK precedent was *Prendergast*, but was of the opinion that "the issue is not so much what *Prendergast* says or doesn't say, the reality is that it comes down to the facts of the respective cases". Mr Schiller said that it was his understanding that there was no support present in the application under consideration in *Prendergast*. He argued that the situation with the present case was that the legal tests were the same but the difference was there was significant support. Mr Schiller said that "the example shows the three cannabinoids that the applicant is trying to protect are TRPM8 antagonists and therefore, by cross-referencing to the state of the art at the time, the applicant has that link which provides the credible evidence."
- 25 Mr Schiller argued that while *Prendergast* sets out what was required to establish support, *Salk* and *US Government* helped to clarify what was meant by 'credible'. In his view, the issue to be avoided was totally speculative patent applications.
- 26 Mr Schiller turned first to *US Government* (which relates to sufficiency) although

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<sup>7</sup> Cancer Research, Vol. 61, 2001, (Larissa Tsaveler *et al*), "*Trp-p8, a Novel Prostate-Specific Gene, is Up-Regulated in Prostate Cancer and Other Malignancies and Shares High Homology With Transient Receptor Potential Calcium Channel Proteins*", pages 8365-8373

he was of the opinion that it was the same scenario as support. The last sentence of the first paragraph of paragraph 6 of the Reasons for the Decision reads:

*As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.*

- 27 Mr Schiller argued that the applicant was relying on this passage because the prior art provided the second half of the story. He added that the “key bit from the applicant’s perspective is that the invention lies in the recognition that these cannabinoids are TRPM8 antagonists”. The next part of paragraph 6 reads:

*...it is required that the patent application provides some information in the form of, for example, experimental tests, to the effect that the claimed compound, administered as stated in the claims, has a direct effect on a metabolic mechanism...*

- 28 Mr Schiller said that this passage was important because it was referred to in paragraph 25 in *El-Tawil* and thus was relevant to UK law. In his opinion, the relevant information that the applicant had provided was the fact that the claimed cannabinoids were antagonists of the TRPM8 receptor. In conjunction with what was known in the state of the art (*Zhang*), he argued that that the person skilled in the art would recognise clearly that they have a direct effect on the metabolic mechanism specifically involved in the disease.

- 29 Mr Schiller stressed the importance of the final part of paragraph 6 because it went beyond the requirements of *Prendergast*:

*...this mechanism being either known from the prior art or demonstrated in the application per se. Once this evidence is available from the patent application, then post-published evidence may be taken into account, but only to back up the findings of the use of the ingredient as a pharmaceutical, and not in itself to establish sufficiency of disclosure.*

- 30 Mr Schiller acknowledged that this mechanism had not been demonstrated in the application *per se*, but stated that the key was whether it was known in the prior art. He pointed out that Example 8 of WO 2011/110866 A1 was an example of such post-published evidence and demonstrates that the rationale and the reasoning for what the applicant was doing was sound and not ‘pulled out of thin air’ or totally speculative. Mr Schiller added that there was very strong rationale for what the applicant was claiming based on what was disclosed in *Zhang*. He said that “the inventor sat down, recognised the activity, realised the application for it and decided to pursue it.” Mr Schiller added that “the application was filed based on what the applicant thought was sufficient, credible information at the time based on the activity and what was known. He tied the two together and drew the conclusions.”

- 31 Mr Schiller reiterated that the fact that the mechanism was known from the prior art was absolutely critical. He acknowledged that was not enough in itself to

establish sufficiency, but argued that “the (TRPM8) antagonism of the cannabinoids is what shows the activity together with what was known from the prior art enabled the applicant to do that”. He said that was the essence of his argument and why the applicant believed they have done enough. Mr Schiller admitted that it might have been nice to do more, but that was not the issue. The issue was whether the applicant had done enough to support what is being claimed.

32 Mr Schiller again turned to paragraph 6 of *US Government*, the last paragraph of which reads:

*Following the rationale of decision T 609/02 (supra)[Salk] it has to be examined if such a mechanism, which could form an acceptable basis for generic claim 1, is known from the prior art.*

33 Mr Schiller said that this passage tied in with *Salk* and emphasized that the term “could”, rather than “would”, was used in relation to whether a mechanism could form an acceptable basis. Mr Schiller noted that based on the particular circumstances of *US Government*, the applicant had not done enough. In contrast, however, he argued that based on the facts in the present case, which were different, the applicant had done enough.

34 Mr Schiller then turned to *Salk*, paragraph 9 at line 11 which reads:

*...As a consequence, under Article 83 EPC, unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application...*

35 Mr Schiller contended that the application together with *Zhang* provided the required suitability. The following part of *Salk*, paragraph 9 reads:

*The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical.*

36 Mr Schiller argued that the first sentence in the above passage was very much what *Prendergast* was about. With regard to the last sentence in the above passage, he pointed out that “there is not merely a verbal statement in the present application, but evidence that the cannabinoids are TRPM8 antagonists and genuine proof that that is the case.” However, he did not elaborate on where that evidence was to be found in the application.

37 Paragraph 9 of *Salk* continues:

*...It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application...*

38 Mr Schiller argued that the required information was that cannabinoids were TRPM8 antagonists and that the mechanism was known from the prior art as spelt out in the *Di Marzo* declaration. Mr Schiller also contended that the pharmaceutical effect *in vitro* was met by *Zhang* because it disclosed apoptosis, immunotherapy staining and even a dose-responsive effect (in Fig. 5A), particularly at 50µmol/litre capsazepine. He added that the applicant had therefore demonstrated that the effect was present in the prior art.

39 Mr Schiller then turned to paragraph 10 of *Salk* at line 12, which reads:

*...in technical terms, of a definite link between the ingredient and the mechanism allegedly involved in the disease state. The presence of a cause/effect relationship is, thus, made plausible...*

40 Mr Schiller argued that “the inference is that it (the evidence) does not have to be credible; it just has to be plausible, which is even less of a test than required in *Prendergast*.” He added that “the evidence was very credible, but I prefer to demonstrate plausibility, rather than absolute credibility.”

41 Mr Schiller said that Section 13 of *Salk* summed up what was required. It reads:

*In summary, sufficiency of disclosure must, in principle, be shown to exist at the effective date of a patent. If the description of the patent specification, like in the present case, provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such subject-matter.*

42 Mr Schiller contended that “the applicant had provided an awful lot more than a vague indication in showing good antagonism”. He also argued that “when you get into the details of the materials and methods in *Zhang* and what it teaches, perhaps you have to be more of a scientist to really recognise and understand the meat that is there.” Mr Schiller said that was why the *Di Marzo* declaration was so significant. He posed the question: how far do you have to go not to be speculative and have something that is credible and significant?

43 Mr Schiller then turned to the examiner’s pre-hearing report of 8 March 2012 and the three main issues raised there. These are whether the claims are supported by the description, whether the (primary) claim is clear in scope and whether the claim is defined by a mechanism of action and thus an excluded discovery. Mr Schiller argued that the claim was not defined by a mechanism of action and that the applicant was applying a discovery, rather than a discovery *per se*. He said that the applicant had a potential therapeutic treatment, namely, to treat early



stage hormone-sensitive prostate cancer. Mr Schiller argued that there was a discovery, i.e. that the claimed cannabinoids were TRPM8 antagonists, but this knowledge was used in a therapeutic application.

## Analysis

- 44 The level of support for the further medical use of a substance is governed by the judgment in *Prendergast's Applications* and re-affirmed in the recent decision in *El Tawil*. In *Prendergast*, Neuberger J held:

*"... whether there is an adequate description, for the purposes of section 14(5)(c) of the 1977 Act must be judged by reference to the nature of the application. There is obvious force in the contention that, where you have a claim for the use of a known active ingredient in the preparation of a medicament for the treatment of a particular condition, **the specification must provide, by way of description, enough material to enable the relevantly skilled man to say this medicament does treat the condition alleged, and that pure assertion is insufficient.**"* (my emphasis)

- 45 Thus, the **specification** (my emphasis) must provide the necessary support. The objection cannot be overcome by subsequent filing of evidence which supports the claims – the evidence must be provided in the application as filed. The judge also held that if tests were to be relied on they need not be "full rigorous detailed and conclusive tests":

*"The tests, can, where appropriate, be very rudimentary. It would be wholly inappropriate, and indeed impractical, to lay down what the tests should be in each case, but it is clear that, in general, relatively rudimentary tests will do."*

- 46 The same point is made in *Salk*, a decision of the EPO Board of Appeal (referenced in *El Tawil*) at paragraph 9:

*"The boards of appeal have accepted for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals, are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se."*

- 47 And at paragraph 15:

*"... If the description of the patent specification, like in the present case, provides no more than a vague indication of a possible medical use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such*

*subject matter.*”

- 48 Mr Schiller has contended that the prior art existent at the time of filing can be used to complement biological and/or medical data present in the application as filed. He has relied on two EPO decisions, i.e. *US Government* and *Salk* to make his case. He has argued that, since these decisions are post *Prendergast*, *US Government* and *Salk* are relevant to UK law, particularly as *Salk* is referenced in the recent Patents Court decision *El-Tawil*.
- 49 The first point I would make about *US Government* and *Salk* is that the relevant issue in these European decisions is one of sufficiency, rather than support. Secondly, as EPO Technical Board of Appeal decisions, *US Government* and *Salk* are highly persuasive, but are not binding on me, unlike UK case law. The issue in *El-Tawil* was that there was no support in the application as filed for the claimed second medical use. Taken in context, it seems to me that the judge was quoting *Salk* to reinforce the teaching in *Prendergast* that there must be some rudimentary tests in the application as filed, rather than re-defining the legal requirement for support. I therefore do not think that the law has moved on since *Prendergast* and it remains a binding UK decision.
- 50 Is the second medical use claimed in claim 1 is supported by the description? I will briefly consider what is disclosed in the application as filed:
- (i) The applicant has asserted that the TRPM8 channel may be blockaded and that this may be of use in prevention or treatment of conditions which are alleviated by said blockade eg cancer, more specifically of the prostate, breast, colon, lung or skin (page 1; pages 9,10);
  - (ii) Up-regulation of TRPM8 activity occurs in the presence of certain tumour cells including prostate (emphasis added) but I note that the disclosure does not state that the tumour cells themselves express TRPM8;
  - (iii) The examples demonstrate that certain cannabinoids blockade the TRPM8 channel (Table 2, pages 19-20) and it is stated that “TRPM8 antagonists might provide new therapeutic tools for the treatment of cancers where TRPM8 activity is essential for the cancer cells survival.”
- 51 Mr Schiller has argued (on the basis of paragraph 9 of *Salk*) that the required level of support was that cannabinoids are TRPM8 antagonists and that the mechanism was known from the prior art as mentioned in the *Di Marzo* declaration. He also contended that the pharmaceutical effect *in vitro* was met by *Zhang* because it disclosed apoptosis, immunotherapy staining and even a dose-responsive effect (in Fig. 5A) by capsazepine.
- 52 In my view, the specification as filed shows only that the cannabinoids as claimed in claim 1 blockade the TRPM8 channel. The description does not show that this antagonism (blockade) does anything at all to prostate cancer cells, let alone the hormone-sensitive subgroup specifically. Put another way, there is not “enough material to enable the relatively skilled man to say this medicament does treat the condition alleged” as required by *Prendergast* and re-affirmed in *El-Tawil*. Furthermore, *Prendergast* states that the **specification** as filed must provide the

support for the medical use and that the objection cannot be overcome by the subsequent filing of evidence which supports the claim. There is no reference whatsoever to *Zhang* (or any other specific prior art) in the application as filed to back up the applicant's assertion. I therefore find that the disclosure in the specification does not provide the required support for the second medical use claimed.

53 In any case, even if the law did allow me to take into account evidence not included in the specification, I do not think that the teaching in *Zhang* is as clear as Mr Schiller contends. I agree with him that some parts of this paper, including the title and abstract, teach that TRPM8 is essential for the survival of androgen-dependent prostate cancer cells. I also agree that *Zhang* teaches that a known TRPM8 antagonist, capsazepine kills androgen-sensitive LNCaP cells by apoptosis. However, I agree with the examiner that *Zhang* additionally teaches that a known TRPM8 agonist, menthol also kills the same androgen-sensitive LNCaP cells by apoptosis. The fact that both a TRPM8 antagonist and a TRPM8 agonist kill androgen-sensitive prostate cancer cells, is a contradiction, thus the overall teaching of *Zhang* is that a TRPM8 antagonist and/or a TRPM8 agonist might be useful in treating hormone-sensitive prostate cancer. I think that this document teaches that TRPM8 may be a potential target in the treatment of prostate cancer. I cannot see, however, how the teaching of *Zhang* would lead the skilled person to conclude that *only* TRPM8 antagonists would be useful for the treatment of TRPM8 dependent hormone-sensitive prostate cancer and to the use of the claimed cannabinoids.

54 With regard to *Tsaveler*, I agree with Mr Schiller that the passage he has quoted discloses that TRPM8 is only expressed in the androgen-dependent LNCaP cells, rather than the androgen-independent PC-3 cells. However, the sentence that follows the passage in *Tsaveler* quoted by Mr Schiller warns against reading too much into *in vitro* expression data:

*However, conclusions based exclusively on patterns of expression of proteins in vitro by established cell lines have to be drawn with considerable caution.*

55 I would therefore agree with the examiner's analysis of *Tsaveler*: namely that it teaches TRPM8 expression in prostate cancer but that this expression is not specific to this type of cancer. Although not discussed at the hearing, I do not consider that the other prior art documents – alone or in combination – raised in the rounds of correspondence between the applicant and the examiner provide the teaching on which Mr Schiller relies. In summary, I do not consider that the overall teaching of the prior art is that TRPM8 is essential for the survival of androgen-dependent prostate cancer cells and that TRPM8 antagonists would be useful for the treatment of TRPM8 dependent hormone-sensitive prostate cancer.

56 The next question I must decide is whether claim 1 is clear in scope. More particularly, does the definition of prostate cancer by reference to TRPM8 activity being essential for the cancer's survival amount to defining a claim by a mechanism of action? Mr Schiller has contended that the claim is not defined by such a mechanism. In support of this argument, he referred to the wording in *Zhang*, referred to the *Di Marzo* declaration and presented at the hearing the

second Written Opinion mailed on 21 February 2012 in relation to PCT/GB2011/050487 (published as WO 2011/110866 A1).

- 57 With regard to the Written Opinion, at the time of writing this decision, this document does not appear on the part of EPO website or that of WIPO that relate to online file inspection. Thus, it has to be assumed that this document is not yet publicly available. In any case, I fail to see the relevance of this document. Even if it were publicly available, the fact that an international examiner has labeled the present case as disclosing the treatment of TRPM8 dependent hormone-sensitive prostate cancer does not necessarily mean that the claim is clear.
- 58 Regarding the *Di Marzo* declaration and the similarity of the language with that used in claim 1, the declaration may well reflect the inventor's rationale, reasoning and thinking at the time. However, it does not necessarily clarify the scope of the claim. Thus, I do not consider that the *Di Marzo* declaration removes any obscurity in the primary claim.
- 59 Turning to the wording in *Zhang*, I do not believe that this document imparts clarity to claim 1 either. This document explores the possibility that TRPM8 activity may be involved in prostate cancer and tests for its expression in androgen-insensitive and androgen-sensitive prostate cancer cells. Whilst TRPM8 is expressed in the androgen-sensitive cells, it is also present in the androgen-insensitive cells. Therefore, I do not think that *Zhang* teaches that these types of cells can be clearly distinguished solely by reference to TRPM8.
- 60 As noted by the examiner, it is not possible to determine what is meant by "cancer of the prostate, where TRPM8 activity is essential for the cancer's survival" as defined in claim 1. The applicant has not shown how the skilled person would assess whether a cancer requires TRPM8 activity in order to survive. Therefore, the claim places an undue burden on any third party wishing to determine the scope of the claim.
- 61 I agree with the examiner that the applicant has sought to distinguish the disease state defined in claim 1 by a mechanism of action alone. This issue was addressed in paragraphs 18-22 of *El-Tawil*, which reaffirmed the judgment in *Bristol-Myers Squibb co v Baker Norton Pharmaceuticals* [1999] RPC 253 that defining a second medical use claim in terms how a treatment works is irrelevant. I therefore find that the claim is unclear but, insofar as it can be understood is defined by a mechanism of action and therefore amounts to a discovery which is not patentable under section 1(2)(a).

## **Conclusion**

- 62 I find that the claims lack clarity and support as required by section 14(5). It also appears that the disease state of claim 1 is distinguished by a mechanism of action alone and hence is not patentable under section 1(2)(a). I have carefully reviewed the specification and do not think that any saving amendment is possible. I therefore refuse the application.

## **Appeal**

- 63 Under the Practice Direction to Part 52 of the Civil Procedure Rules, any appeal must be lodged within 28 days.

**MRS S E CHALMERS**

Deputy Director acting for the Comptroller