Intellectual Property Office

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**PATENTS ACT 1977**

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| APPLICANT | Reverspah LLC |
| ISSUE | Whether patent application GB 2219338.7 complies with section 1(1)(b) |
| HEARING OFFICER | Dr Rowena Dinham |

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**DECISION**

**Introduction**

1 This decision relates to whether patent application GB 2219338.7 ("the application") entitled "*Method of treating severe forms of pulmonary hypertension*" complies with the Patents Act 1977 ("the Act").

2 The application was originally filed under the Patent Cooperation Treaty ("PCT") on 24 August 2021, in the name of Reverspah LLC ("the applicant"), claiming priority from an earlier-filed US patent application US 16/910,447 filed on 24 June 2020. The application was published as WO 2021/263250 A3[1] on 30 December 2021.

3 The application entered the UK national phase on 21 December 2022 and was republished as GB 2612210 A on 26 April 2023. The period for putting this application in order under section 20 of the Act was extended as-of-right under rule 108(2) of the Patents Rules 2007 ("the Rules") to 24 February 2025. A further request for a two-month discretionary extension under section 20 of the Act has also been allowed, taking the extended section 20 date to 24 April 2025. Should I find that the application is to be remitted to the examiner, then the applicant has the option to request at least one further two-month extension to this compliance date under rule 108(3), providing that they do so before the expiry of a two-month period beginning 24 April 2025.

4 There have been multiple rounds of correspondence between the applicant and the examiner. The latest claims are those filed on 23 April 2024, with the latest description being that originally filed at the UK Office on 21 December 2022. The most recent examination report, dated 3 October 2024, maintains an inventive step objection whereby claim 1, at least, is purported to define a collocation of two known

[1] WO2021263250 METHOD OF TREATING SEVERE FORMS OF PULMONARY HYPERTENSION

integers[2]. It is on this matter that I am required to issue a decision, based on the papers on file.

5 The examiner issued a pre-hearing report on 14 February 2025, reiterating the issues that were set out in the most recent examination report and suggesting that the main point of consideration is whether the patent application supports, or makes plausible, the assertion that there is a synergistic effect between the two active ingredients of the claimed composition which is used for the treatment of pulmonary arterial hypertension (PAH).

6 The applicant has since provided the UK Office with a copy of a recent Notice of Allowance issued by the USPTO in connection with the corresponding US application 16/910447. This was filed on 21 February along with the allowed claims which are essentially identical to the claims of the current application.

**The invention**

7 The application concerns a composition comprising a copper chelator comprising a tetrathiomolybdate [$(MoS_4)^{-2}$] salt (TTM) and at least one other active agent comprising diethylcarbamazine (DEC), which is an anti-inflammatory and an inhibitor of the 5-lipoxygenase enzyme (5-LO). High levels of copper were shown to be elevated in patients and rat models of PAH, and in rats TTM was found to reopen vessel lumina and cut the pulmonary arterial pressure in half. DEC was also seen to reopen occluded vessels in rats, thereby reducing the degree of PAH, the number of obliterated arterioles and the degree of perivascular inflammation. The applicant asserts that the combination of TTM and DEC invokes a synergistic response, and hence provides improved therapeutic composition for the treatment of PAH.

**The claims**

8 The most recent set of claims, filed on 23 April 2024 consists of 11 claims, with two independent claims, 1 & 8, which are set out below:

> *1. A composition comprising:*
> *a copper chelator comprising a tetrathiomolybdate salt;*
> *at least one other active agent selected from the group comprising diethylcarbamazine,*
> *and*
> *a pharmaceutical acceptable carrier.*
>
> *8. A composition for use in treating pulmonary arterial hypertension (PAH) in a patient in need thereof, comprising administering to the patent a therapeutically effective amount of a copper chelator comprising a tetrathiomolybdate salt and a therapeutically effective amount of at least one other active agent comprising diethylcarbamazine.*

[2] The combination of a series of known or obvious features, each playing its usual part in the final entity, will be a matter of design or mere collocation, not of invention. See the Manual of Patent Practice ("MoPP") para. 3.17.

**Matters to be addressed**

9 In their pre-hearing report, the examiner sets out their position that the application fails to meet the requirements for inventive step[3] because the application as filed does not make it plausible that there is a synergistic interaction between TTM and DEC in the treatment of PAH. In their previous examination reports, the examiner cites two documents that demonstrate that both TTM and DEC, separately, have been suggested for the treatment of PAH:

> D1: *Am J Resp Cell Mol Biol*; Vol 46 (5), 2012 Boggard *et al* "*Copper dependence of angioproliferation in pulmonary arterial hypertension in rats and humans"*, pages 582-591.
>
> D2: *Toxicol Appl Pharmacol*; Vol 333, 26 August 2017, Ribiero *et al* "*Diethylcarbamazine: a potential treatment drug for pulmonary hypertension?"*, pages 92-99

Because these two compounds are individually suggested for the treatment of PAH, the examiner considers that, in the absence of any synergistic interaction, the claims relate to a collocation of two known integers. They have deferred other matters, such as updating of the search.

10 Therefore, the only issue to be decided is whether the invention defined in the claims meets the requirements of section 1(1)(b). In reaching my decision I can confirm that I have carefully considered the documents on file.

**The Law**

11 The relevant provisions of the Act are reproduced below:

> ***Section 1(1)***
>
> *A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –*
>
> *(a) the invention is new;*
>
> ***(b) it involves an inventive step;***
>
> *(c) it is capable of industrial application;*
>
> *(d) the grant of a patent for it is not excluded by subsections (2) and (3) or section 4A below;*
>
> *and references in this Act to a patentable invention shall be construed accordingly.*

and

[3] Section 1(1)(b)

**Section 3**

*An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).*

12 When assessing inventive step, the structured approach set out in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*[4]*,* and reformulated as the "Windsurfing/Pozzoli" test in *Pozzoli SPA v BDMA SA*[5] is usually followed. However, in the present situation, the disagreement between the applicant and the examiner is whether, for the purposes of inventive step, the claims relate to one or two inventions. Specifically, as held by Lord Hoffman in *SABAF*[6]:

> "..*before you can apply s.3 and ask whether the invention involves an inventive step, you first have to decide what the invention is. In particular, you have to decide whether you are dealing with one invention or two or more inventions. Two inventions do not become one invention because they are included in the same hardware. A compact motor car may contain many inventions, each operating independently of each other but all designed to contribute to the overall goal of having a compact car. That does not make the car a single invention."*.

13 Lord Hoffmann went on to reference passages from the EPO Guidelines for Substantive Examination[7] as being useful in the assessment of collocations (my emphasis):

> *"The EPO guidelines say that 'the invention claimed must normally be considered as a whole'. But equally, one must not try to consider as a whole what are in fact two separate inventions. What the Guidelines do is to state the principle upon which you decide whether you are dealing with a single invention or not. If the two integers interact upon each other, if there is synergy between them, they constitute a single invention having a combined effect and one applies section 3 to the idea of combining them. If each integer '**performs its own proper function independently of any of the others'**, then each is for the purposes of section 3 a separate invention and it has to be applied to each one separately"*

14 In the present case, the inventive step dispute arises as to whether it is a collocation or a synergistic combination of TTM and DEC. As such, if there is a synergistic interaction between TTM and DEC then the composition will be inventive in light of what is known in the prior art and the common general knowledge of the skilled person[8]. However, if there is no synergistic interaction between the two, then for the purposes of inventive step, I must consider whether the use of TTM in the treatment of PAH is novel and inventive, and, separately, whether the use of DEC in the

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[4] *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd, [1985] RPC 59*
[5] *Pozzoli SPA v BDMA SA [2007] EWCA Civ 588*
[6] *SABAF SpA v MFI Furniture Centres Ltd [2005] RPC 10, House of Lords*
[7] G-VII, 7. Combination vs. juxtaposition or aggregation - Guidelines for Examination (epo.org)
[8] This is acknowledged by the examiner in paragraph [4] of their examination report of 3 October 2024

treatment of PAH is novel and inventive, and if they are not, then the invention relates to a mere collocation of known integers[9].

**Analysis**

15 It is the examiner's position that there is nothing in the application as filed that makes it plausible that there is synergy between TTM and DEC in the treatment of PAH. Whilst the examiner acknowledges that the application discloses statements that suggest that the combination might be synergistic, they also consider that other passages within the description suggest that TTM and DEC, as a 5-LO inhibitor, act via their usual mechanisms which are separate from each other. It is due to this lack of interaction that the examiner considers that there is no synergy, and that the combination is a mere collocation.

16 The applicant on the other hand considers that there is synergy, and in their letter of 12 September 2024 they claim that *"the rationale for combining tetrathiomolybdate (TTM) with diethylcarbamazine (DEC) is based on the knowledge that the TTM and the DEC have different mechanisms of action which together work synergistically to accomplish the therapeutic goal which is to bring the lung vessels back to normal. Indeed, DEC is known to reduce inflammation and is added to reduce inflammation and to enhance the effectiveness of TTM"*.

17 The applicant has also provided evidence from various sources to support this. Specifically, a witness statement from Joanna Pinto declaring that TTM and DEC are highly likely to produce a co-amorphous combination having enhanced solubility and hence greater bioavailability, was provided with the letter dated 23 April 2024. There is also a declaration by Dr Norbert F Voelkel (one of the inventors), filed on 12 September 2025.

18 It is well established that any synergistic effect must be *described* in the application as filed[10,11]. The examiner does not appear to dispute that there is, at least, an assertion of a synergistic effect between TTM and DEC in the application and refers to paragraph [87] of the description. This passage states that it is "*likely that the copper chelator comprising a TTM salt, and a 5-LO inhibitor work synergistically in PAH*" and goes on to set out in detail how a TTM salt induces anoikis[12], reduces inflammation and promotes stem cell differentiation, whereas 5-LO inhibition is likely to decrease inflammation and inhibit 5-LO-dependent cell growth. I also note that paragraph [85] points out that 5-LO is expressed more in pulmonary vessels of patients with severe PAH. I am in agreement with the examiner that there is at least an assertion of a synergistic effect in the application.

19 However, the examiner considers that this assertion of synergy is not *plausible*. In particular they point out that paragraph [87] is merely speculative and goes on to state that TTM and 5-LO inhibitors operate by entirely different mechanisms of action, with Table 2 pointing out that TTM and 5-LO inhibition *may* be synergistic.

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[9] As the use of TTM and DEC in the treatment of PAH are separately known from D1 and D2, respectively

[10] *Glaxo Group Ltd's Patent* [2004] RPC 43

[11] *Richardson-Vicks Inc.'s Patent* [1995] RPC 568 at 581

[12] Anoikis is a form of apoptosis which occurs when cells lose attachment to the extracellular matrix and neighbouring cells, and is important in prevention of abnormal cell growth

They also refer to paragraphs [26]-[29] and [85]-[88] which disclose the separate mechanisms of action and conclude from this that because the compounds act via different pathways then there can be no synergy.

20 There is a range of case law relating to plausibility. In the context of plausibility and inventive step, the most common issue arises where the claimed technical effect that distinguishes the invention from the prior art is not plausible, most commonly observed in the case of "selection inventions"[13]. However, regardless of the area of patent law that "plausibility" is being applied to, the test is a "threshold test", which can be satisfied by a disclosure that is "credible" as opposed to speculative[14]. Therefore, is it credible from the specification as filed, when read through the eyes of the skilled person, that there would be a synergistic interaction between TTM and DEC?

21 Neither the examiner nor the applicant has considered who the skilled person might be. In my opinion, they would be a team consisting of clinical pharmacologist specialising in cardiopulmonary disorders, a physician with experience in PAH. Between them they would be aware of the pathogenesis of PAH and the cellular mechanisms targeted by therapies, and particularly how these mechanisms and pathways can interact.

22 The specification discusses how, in PAH, TTM will induce anoikis in the abnormal lumen-obliterating cells, it reduces vascular cell inflammation and promotes differentiation of stem cells in and around the pulmonary vascular lesions. Paragraph [30] states that the administration of TTM leads to anoikis, and the reduction in the abnormal cells leads to a reduction in the inflammatory response. Figures 2-5 support this, demonstrating (through expression of anoikis markers) that administration of TTM induces anoikis in lung tissue from the PAH rat model, SuHx. They also show a decrease in inflammation and a decrease in the number of c-kit+ precursor cells in this SuHx lung tissue. From this, and their knowledge of copper-dependent mechanisms in abnormal cell growth and signalling, the applicants conclude that TTM would target the abnormal cells that obliterate the lumen in severe PAH[15].

23 The specification goes on to describe how expression of 5-LO is increased in damaged PAH lung vessel endothelial cells when compared to normal cells, and the role it plays in promoting inflammation, and the various inflammatory factors that are activated. Figures 7 & 8 show that administration of DEC reopens occluded vessels and reduces inflammation. The applicants conclude that 5-LO inhibitors such as DEC work by inhibiting the inflammatory factors that are induced by 5-LO in PAH cells and reduce 5-LO dependent cell growth, which can lead to vascular remodelling and damage. They also consider that DEC affects developing PAH and is partially effective once angio-obliterative PAH has been established[16].

24 Whilst the experiments shown demonstrate the effects of TTM and DEC independently on lung tissue in the SuHx model, at paragraph [87] the applicant

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[13] See, for example, *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2010] RPC 9

[14] *Actavis Group PC EHF & Anr v Eli Lilly and Company* [2015] EWHC 3294 (Pat) at paragraphs [177] and [178]

[15] See paragraphs [26]-[31] of the specification

[16] See paragraph [86] of the specification

asserts that "*it is likely that [a TTM salt] and a 5-LO inhibitor work synergistically in PAH*". They go on to point out that TTM induces anoikis, leading to the death of phenotypically abnormal pulmonary vascular cells, and that 5-LO inhibition would decrease inflammation and inhibit 5-LO-dependent cell growth. However, they have not provided any examples demonstrating a combination of the effects of TTX and DEC. The question therefore is whether this assertion, based upon experiments where TTM and DEC are administered separately, is plausible?

25 I acknowledge that there is no clear evidence that the administration of TTM and DEC together would result in a synergistic effect. However, as noted above, the threshold for whether a technical effect is plausible is whether such an effect is *credible*. The skilled person would appreciate that inflammation and cellular proliferation plays a key role in the pathogenesis of PAH, through build-up of inflammatory cells as well as vascular remodelling. They would also be aware that both the inflammatory cascade and cellular differentiation is complex and finely balanced, with different factors and different pathways having interconnecting regulatory roles.

26 Taking lumen occlusion in PAH as an example, it is known in the art that this is driven by inflammation, which leads to lumen occluding abnormal cell growth that resists apoptosis. The skilled person reading the specification would know that TTM acts by inducing anoikis (a form of apoptosis) in these abnormal cells, leading to obliteration of the occlusion. They would also recognise that DEC would complement this by inhibiting growth of the abnormal 5-LO expressing cells, and by reducing inflammation, which in turn leads to a reduction in the lumen occluding cell growth, as indicated by the applicant at paragraph [87] of the specification.

27 The applicant has also provided later submissions in order to support their assertion of a synergistic interaction, in the form of two witness declarations and further explanations of the mechanisms of TTM and DEC. I note that in *Generics v Yeda*[17] there was much discussion around whether evidence demonstrating any technical effect had to be available at the priority date, with Floyd LJ concluding that later evidence may be adduced to **support** a technical effect **made plausible by the specification**.

28 The first witness declaration is from Joanna Pinto, stating that TTM and DEC are highly likely to produce a co-amorphous combination having enhanced solubility and hence greater bioavailability[18]. This is the first mention of any specific chemical properties of the combination, and whilst the skilled person may recognise from the crystal structure that TTM and DEC may provide a co-amorphous combination, I do not believe that this is something that was in the minds of the applicant when considering a synergistic interaction between TTM and DEC as suggested in the application. I therefore do not regard this declaration as supporting a technical effect made plausible by the specification and so will not consider it further.

29 The second declaration is from the inventor himself, provided with the applicant's letter of 12 September 2024. Dr Voelkel is clearly an eminent figure, well respected in the field of cardiovascular pulmonary studies, and in his witness statement he

[17] *Generics [UK] Ltd (t/a Mylan) v Yeda Research and Development Co Ltd & Anor* [2013] EWCA Civ
[18] Provided with the applicant's letter dated 23 April 2024

provides further information in support of a synergistic effect between TTM and DEC. Whilst the declaration focusses mainly on the disclosures of documents cited by the examiner (but which are not relevant for the assessment of synergy), at paragraphs [17] and [20] Dr Voelkel explains how the targeting of multiple angiogenic and inflammatory factors using TTM and DEC results in further, effective, reductions in inflammation. Similar explanations are provided in the applicant's responses to the examination reports. The crux of these submissions is an acknowledgement that TTM and DEC work through different mechanisms, with TTM inducing anoikis, which is key in the obliteration of occluded vessels, as well as reducing inflammation, and with DEC further reducing inflammation which contributes to vascular damage (which itself leads to vessel occlusion). These are consistent with the brief assertion made at paragraph [87] of the specification. Again, with no experimental evidence provided, would these arguments be a credible indication of synergy to the skilled person with an understanding the complexities of targeting inflammatory and cellular responses in patients?

30 I believe that the arguments for and against a plausible synergistic interaction are finely balanced here. However, given that the threshold for plausibility is that the asserted effect is *credible*, and in light of the discussions in both the application as filed and in the later submissions of Dr Voelkel of the mechanisms of actions via the inflammatory system, which is known to involve complex interactions, as well as in their complementary effects on vessel occlusion, I am inclined to agree with the applicant that it is plausible that there is a synergistic interaction between TTM and DEC.

31 I further note that in his assessment of collocations in *SABAF,* Lord Hoffman stated "*..if each integer '**performs its own proper function independently of any of the others'** then each is for the purposes of section 3 a separate invention".* The specification clearly describes how TTM and DEC lead to a reduction in inflammation and abnormal cell growth in PAH, and that they do so by regulation of apoptotic and inflammatory pathways. These pathways are a complex network of interconnected cell signalling mechanisms which are well known to impact upon each other in other disease models[19]. It is also well established in the art that pro-inflammatory agents act synergistically within these pathways[20], and therefore targeting different pro-inflammatory mechanisms leads to improved treatments for diseases. Therefore, on the balance of probabilities, and in light of what the skilled person would read from the specification as filed in combination with their common general knowledge in relation to the specifics of the pathogenesis of PAH, I consider that the invention is not merely a collocation.

32 I therefore conclude that the synergistic response described in the application is plausible. I also find that it is unlikely that TTM and DEC act independently of each other and therefore this combination amounts to more than a mere collocation.

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[19] For example, the targeting of different inflammatory and cell signalling pathways in order to provide more effective treatments for cancer is well known in the art. In this regard, whilst not deemed to be part of the skilled person's common general knowledge, I am aware of documents linking the pathways that impact anoikis and 5-LO in cancer, which further supports a synergistic interaction (see, for example *Biochim Biophys Acta*, Vol 1833 (12), December 2013, Paoli *et al*. "*Anoikis molecular pathways and its role in cancer progression*", pages 3481-3498)

[20] See, for example *Cytokine Growth Factor Rev*, Vol 16 (6), December 2005, Gouwy ***et al.*** *"Synergy in cytokine and chemokine networks amplifies the inflammatory response"*, pages 561-580

Therefore claims 1 and 8 define a single invention, relating to the synergistic combination of TTM and DEC, and as such are inventive.

**Conclusion**

33 I have found that claims 1 and 8 satisfy the requirements of section 1(1)(b) of the Act. It follows that dependent claims 2-7 and 9-11 are also inventive. The application is therefore remitted back to the examiner to complete the examination process.

**DR ROWENA DINHAM**

Patent Examination Group Head