Neutral Citation [2020] EWHC 3270 (Pat)

Claim No: HP-2020-000005

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (Chd)
PATENTS COURT

Royal Courts of Justice
Rolls Building
7 Rolls Buildings
Fetter Lane
London EC4A 1NL

Date: 4 December 2020

Before:

THE HONOURABLE MR JUSTICE MARCUS SMITH

BETWEEN:

(1) NEURIM PHARMACEUTICALS (1991) LIMITED
(a company incorporated under the laws of Israel)
(2) FLYNN PHARMA LIMITED
(a company incorporated under the laws of the Republic of Ireland)

Claimants

(1) GENERICS UK LIMITED (trading as MYLAN)
(2) MYLAN UK HEALTHCARE LIMITED

Defendants

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Mr Andrew Waugh, QC and **Ms Katherine Moggridge** (instructed by **Gowling WLG (UK) LLP**) for the First Claimant

Mr Andrew Waugh, QC and **Ms Katherine Moggridge** (instructed by **Pinsent Masons LLP**) for the Second Claimant

Mr Mark Vanhegan, QC, **Mr Adam Gamsa** and **Mr Mitchell Beebe** (instructed by **Taylor Wessing LLP**) for the Defendants

Hearing dates: 29 and 30 October, 2 and 5 November 2020

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Judgment

I direct that no official note or transcription shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

Mr Justice Marcus Smith:

A. INTRODUCTION

(1) Background

1. The First Claimant – Neurim Pharmaceuticals (1991) Limited (**Neurim**[1]) – is the registered proprietor of a patent, EP (UK) 1,441,702 B1 (the **Patent**). The Second Claimant – Flynn Pharma Limited (**Flynn**) – is the registered exclusive licensee under the Patent in the United Kingdom. Although it will be necessary, from time-to-time, to differentiate between Neurim and Flynn, where such differentiation is unnecessary, I shall refer to Neurim and Flynn collectively as the **Claimants**.

2. The Patent claims prolonged release pharmaceutical formulations concerning the active ingredient melatonin to improve the restorative quality of sleep in a patient suffering from primary insomnia characterised by non-restorative sleep. The Claimants have applied to amend the Patent unconditionally, which is not opposed by the Defendants and to which no other objection has been made.[2] Where appropriate, I shall identify the amendments proposed to the Patent.

3. The pharmaceutical formulation claimed by the Patent is sold under the brand name **Circadin**. Circadin is a medicine authorised for use in the European Union, including (for present purposes) the United Kingdom. A company within the Neurim group holds a marketing-authorisation for melatonin 2mg prolonged release tablets (the description of Circadin). That company is RAD Neurim Pharmaceuticals EEC SARL (**RAD Neurim**).

4. The Patent was filed on 12 August 2002 and claims priority from 14 August 2001 (the **Priority Date**). The Patent is a "second medical use" patent. If not revoked sooner, the Patent will expire on 12 August 2022, i.e. in abot a year and eight months' time.

5. Assuming the Patent to be valid, the Defendants – Generics UK Limited and Mylan UK Healthcare Limited (collectively, **Mylan**) – threaten to infringe the Patent in the following way:[3]

> "The Defendants threaten and intend to infringe the Patent by threatening and intending to do the following act in the United Kingdom without the consent of the Claimants, namely: keep, use, dispose of and/or offer to dispose of a prolonged release melatonin product obtained directly by means of a process as claimed in at least claim 1 and being a product within the scope of claim 4 of the Patent."

[1] Annex 1 hereto lists the terms and abbreviations used in this judgment. This judgment unsurprisingly quotes extensively from the statements, reports and transcripts that were before me. In such quotations, I have corrected without marking the correction minor and immaterial typographical errors. Where I have made a substantive change (for instance, to harmonise terms) or where I have omitted words, that is identified.

[2] See paragraph 97 of the Claimants' written opening submissions.

[3] Paragraph 1 of the Amended Particulars of Infringement.

In fact, it may well be the case that Mylan has gone beyond threatening to infringe the Patent and has, by now, actually infringed. Neurim sought, but failed to obtain, an interim injunction restraining Mylan from infringing the Patent.[4] For the purposes of this judgment, nothing turns on this question.

6. The First Defendant is, itself, the holder of a marketing authorisation in the United Kingdom (as well as the European Union) for melatonin 2mg prolonged release products. Those products will be, or are already, commercialised in the United Kingdom by the Second Defendant.

(2) Issues arising

7. This dispute came on for trial in late October / early November 2020. The issues before me all concerned the validity of the Patent. Infringement was not a separate issue before me: in other words, if the Patent is valid, Mylan accepts and admits infringement.[5]

8. Mylan contends that the Patent is invalid on the following grounds:

(1) First, because the Patent lacks novelty. In order to be patentable, an invention must (amongst other things) be "new".[6] Section 2(1) of the Patents Act 1977 provides that "[a]n invention shall be taken to be new if it does not form part of the state of the art". Section 2(2) of the Act then provides:

> "The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."

Mylan contends that the Patent lacks novelty in reliance upon an article published in (1995) 18(7) Sleep 598-603 by Haimov *et al* entitled *Melatonin Replacement Therapy of Elderly Insomniacs* (**Haimov 1995**).[7]

(2) Secondly, because the Patent is obvious. In order to be patentable, an invention must (amongst other things) involve an "inventive step".[8] Section 3 of the Patents Act 1977 provides:

> "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…"

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[4] I refused the interim injunction by my order of 3 June 2020 ([2020] EWHC 1362 (Pat)). That order was affirmed by the Court of Appeal ([2020] EWCA Civ 793).

[5] Paragraph 5(c) of the Re-Amended Defence and Counterclaim provides: "It is denied that in carrying out the acts set out in paragraph 5(a) above Mylan would infringe the Patent because the Patent is invalid."

[6] Section 1(1)(a) of the Patents Act 1977.

[7] Paragraph 1 of the Grounds of Invalidity. Various papers and other materials will be referred to in this judgment. A chronological list of these materials – together with other important dates – is at Annex 2 to this judgment.

[8] Section 1(1)(b) of the Patents Act 1977.

Mylan contends that the subject matter of the Patent is obvious and did not involve an inventive step by reason of the following prior art:[9]

(a) Haimov 1995.

(b) The product **Melatonex**, which was available as a supplement in the United States of America before the Priority Date of the Patent. Melatonex is a formulation of melatonin that contains 3mg of melatonin in a prolonged release tablet. Details of Melatonex were contained in a webpage dated 1 August 2001 (i.e., before the Patent's priority date) (the **Melatonex Webpage**).[10]

(c) An article published in Biological Signals & Receptors 1999 (8:84-89) by Zisapel entitled *The Use of Melatonin for the Treatment of Insomnia* (**Zisapel 1999**).

(3) Thirdly, because the Patent is insufficient. A patent may be revoked on the ground that "the specification of the patent does not disclose the invention clearly enough and completely enough for it to be performed by a person skilled in the art".[11] Insufficiency is something of a broad church. A Patent may be insufficient because:

(a) The skilled person is unable to carry out the claimed invention given the description of it in the specification and the skilled person's common general knowledge. This form of insufficiency is often referred to as **classical insufficiency**, a term that I will adopt. In *Zipher Ltd v. Markem Systems Ltd*, Floyd J described classical insufficiency in the following terms:[12]

> "The first, or so-called classical insufficiency, is where following the express teaching of the patent does not enable the skilled addressee to perform the invention. This type of insufficiency requires an assessment by the court of the steps which it would be necessary for the skilled reader or team to take in following the teaching of the specification and in order to arrive within the claim. Plainly the steps should not include inventive ones. But a patent can also be insufficient if the steps can be characterised as prolonged research, enquiry or experiment."

(b) The patent is insufficient because its claims are too broad – **excessive claim breath insufficiency**. Again, I adopt the description of Floyd J in *Zipher Ltd*:

> "368. The second, or so-called Biogen insufficiency (after the decision in the House of Lords in *Biogen Inc v. Medeva plc*, [1997] RPC 1), is concerned with breadth of claim. An insufficiency attack on *Biogen* lines accepts that the teaching of the patent is adequate to bring the skilled

[9] Paragraph 2 of the Grounds of Invalidity.

[10] The Melatonex Webpage was extracted from the WebArchive or "Wayback machine".

[11] Section 72(1)(c) of the Patents Act 1977.

[12] [2008] EWHC 1379 (Pat) at [363].

reader within the claims, but asserts that the claims encompass products or processes which owe nothing to the teaching of the patent and which are not enabled. It is important to see how far the *Biogen* principle goes. Enablement does not necessarily involve teaching how to make each member of a class. If it were not so, ingenious infringements could never be caught. If an element of the claim can be predicted to be of general application, the patentee is entitled to claim it in general terms:

> "…[I]f the patentee…has disclosed a beneficial property which is common to [a class of products] he will be entitled to a patent for all products of that class (assuming them to be new) even though he has not himself made more than one or two of them."

369. In *Kirin-Amgen Inc v. Hoechst Marion Roussel*, [2005] RPC 9, Lord Hoffmann explained the notion of a principle of general application in this way:

> "This [i.e. the passage cited above] gave rise to a good deal of argument about what amounted to a 'principle of general application'. In my opinion there is nothing difficult or mysterious about it. It simply means an element of the claim which is stated in general terms. Such a claim is sufficiently enabled if one can reasonably expect the invention to work with anything which falls within the general term. For example, in *Genentech I/Polypeptide expression*, (T 292/85), [1989] OJ EPO 275, the patentee claimed in general terms a plasmid suitable for transforming a bacterial host which included an expression control sequence to enable the expression of exogenous DNA as a recoverable polypeptide. The patentee had obviously not tried the invention on every plasmid, every bacterial host or every sequence of exogenous DNA. But the Technical Board of Appeal found that the invention was fully enabled because it could reasonably be expected to work with any of them.
>
> This is an example of an invention of striking breadth and originality. But the notion of a 'principle of general application' applies to any element of the claim, however humble, which is stated in general terms. A reference to a requirement of 'connecting means' is enabled if the invention can reasonably be expected to work with any means of connection. The patentee does not have to have experimented with all of them.""

A good example of this form of insufficiency was provided by Jacob LJ in *H Lundbeck A/S v. Generics (UK) Ltd*:[13]

"So, for example, if a man finds a particular way of making a new substance which is 10 times harder than diamond, he cannot just claim 'a substance which is 10 times harder than diamond'. He can claim his particular method and he can claim the actual new substance produced by his method, either by specifying its composition and structure or, if that cannot be done, by reference to the method (see *Kirin-Amgen* at [90–91]) but no more. The reason he cannot claim more is

[13] [2008] EWCA Civ 311 at [61].

that he has not enabled more – he has claimed the entire class of products which have the known desirable properties yet he has only enabled one member of that class. Such a case is to be contrasted with the present where the desirable end is indeed fully enabled—that which makes it desirable forms no part of the claim limitation."

(c) The patent is conceptually uncertain. Sometimes known as insufficiency on the grounds of ambiguity, this form of insufficiency is better understood as **uncertainty insufficiency**, for the reasons given by Floyd LJ in *Anan Kasei v. Neo Chemicals and Oxides Ltd*:[14]

> "24. The form of insufficiency exemplified by *Kirin Amgen* is sometimes, inaccurately, called "ambiguity". Ambiguity usually refers to a situation where words are capable of more than one meaning. Under the Patents Act 1959 it was a ground of revocation (no longer available) that "the complete specification does not sufficiently and fairly define the invention…": see section 32(1)(i). Patent lawyers tended to abbreviate this ground, which is specifically directed to the definition of the invention, as "ambiguity": see for example *Terrell on the Law of Patents*, 12th Ed (1971) at [240]-[245]. It was recognised, however, that the mere fact that the claim was capable of two different constructions did not render the claim invalid under this ground if the normal process of construction through the eyes of the skilled person could resolve the issue. The vagueness or uncertainty of the claim had to go beyond this. The use of the word "substantially", for example in the expression "substantially as described", did not render a claim invalid for ambiguity.
>
> 25. As Lewison LJ points out in his judgment, the objection to the claim in *Kirin Amgen* is not correctly described as "ambiguity". The claim was conceptually uncertain. This type of insufficiency is far better described as "uncertainty"…Jacob J gave an example in *Milliken Denmark AS v. Walk-Off Mats Limited*, [1996] FSR 292 at 301 of a property which was required to be measured in the non-existent "Pinocchio units". That would give rise to uncertainty in the *Kirin Amgen* sense."

(d) The patent is implausible – **lack of plausibility insufficiency**. Both parties referred me to the law as stated by Lord Sumption in *Warner-Lambert Co LLC v. Generics (UK) Ltd*.[15] That statement of the law was elucidated by Arnold J in *Eli Lilly and Company v. Genentech Inc*.[16] For present purposes, it is only necessary to set out Lord Sumption's explanation of plausibility at [37] of *Warner-Lambert*:[17]

> "Plausibility is not a term of art, and its content is inevitably influenced by the legal context. In the present context, the following points should be made.

[14] [2019] EWCA Civ 1646.

[15] [2018] UKSC 56.

[16] [2019] EWHC 387 (Pat) at [523] to [531].

[17] I am quoting from the passage quoted by Arnold J at [528] of *Eli Lilly*. Arnold J helpfully inserted emphases and line breaks into the passage.

> **First**, the proposition that a product is efficacious for the treatment of a given condition must be plausible.
>
> **Second**, it is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion…
>
> But, **third**, the claimed therapeutic effect may well be rendered plausible by a specification showing that something was worth trying for a reason, ie not just because there was an abstract possibility that it would work but because reasonable scientific grounds were disclosed for expecting that it might well work. The disclosure of those grounds marks the difference between a speculation and a contribution to the art. This is in substance what the Technical Board of Appeal has held in the context of article 56, when addressing the sufficiency of disclosure made in support of claims extending beyond the teaching of the patent. In my opinion, there is no reason to apply a lower standard of plausibility when the sufficiency of disclosure arises in the context of EPC articles 83 and 84 and their analogues in section 14 of the Patents Act. In both contexts, the test has the same purpose.
>
> **Fourth**, although the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.
>
> **Fifth**, that reasonable prospect must be based on what the TBA in SALK (para 9) called "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."
>
> **Sixth**, in SALK, this point was made in the context of experimental data. But the effect on the disease process need not necessarily be demonstrated by experimental data. It can be demonstrated by *a priori* reasoning. For example, and it is no more than an example, the specification may point to some property of the product which would lead the skilled person to expect that it might well produce the claimed therapeutic effect; or to some unifying principle that relates the product or the proposed use to something else which would suggest as much to the skilled person.
>
> **Seventh**, sufficiency is a characteristic of the disclosure, and these matters must appear from the patent. The disclosure may be supplemented or explained by the common general knowledge of the skilled person. But it is not enough that the patentee can prove that the product can reasonably be expected to work in the designated use, if the skilled person would not derive this from the teaching of the patent."

Mylan's case on sufficiency is pleaded as follows in the Grounds of Invalidity:

"3. Further or in the alternative the scope of each of the Claims exceeds the technical contribution of the Patent:

a. Each of the Claims specifies that the claimed formulation or medicament is for "improving the restorative quality of sleep in a patient suffering from primary insomnia characterized by non-restorative sleep" (the "Claimed Effect"). The Patent fails to make plausible that the Claimed

Effect is achieved; there is no reason disclosed for supposing that the implied assertion of efficacy of the claim is true.

b. Further or in the alternative the Patent fails to make plausible that the Claimed Effect is achieved for patients younger than 55 years old; there is no reason disclosed for supposing that the implied assertion of efficacy of the claim is true for patients younger than 55 years old.

4. Further or in the further alternative the specification does not contain any directions or explanation as to the meaning of the term "restorative quality of sleep". The term is so ambiguous, uncertain or lacking in sufficient meaning as to mean that the skilled person would be unable to determine whether they were working the invention of any of the Claims.

5. Further or in the further alternative, should the Claimants contend that the Claims require "non-restorative sleep" to be measured in any particular way, the skilled person would not be enabled, (either at all or without undue burden), by reading the specification with their common general knowledge to work the invention of the Claims."

9. I noted in paragraph 1 above that Flynn is registered as the exclusive licensee of the Patent in the United Kingdom. If that is right, then Flynn is – by virtue of section 67(1) of the Patents Act 1977 – entitled to bring these proceedings in its own right. In this case, Flynn's status as exclusive licensee – and so its standing to bring these proceedings – is in dispute.

(3) Structure of the judgment

10. The issues of validity are, obviously, central to this judgment. Novelty (or the lack of novelty) is considered in Section E below; inventiveness (or the lack of any inventive step) is considered in Section F below; and (in)sufficiency is considered in Section G below.

11. Before considering these matters, however, it is necessary to consider a number of anterior matters:

(1) Section B below describes the witnesses and the evidence that were before me. Section B also addresses the manner in which this trial was conducted in the circumstances of the COVID-19 pandemic.

(2) Section C below considers the "person skilled in the art" (in the case of the Patent) and that person's (or persons', in the case of a team) "common general knowledge". These concepts are relevant to all of the validity questions that this judgment addresses, and it is appropriate to establish the nature of the person(s) skilled in the art and the concomitant common general knowledge of such person(s) at the outset, before considering questions of validity.

(3) Section D below considers the true construction of the Patent. This, too, is a matter involving the skilled person and common general knowledge. Neurim suggested that as Mylan had admitted infringement, "there is no real issue of construction to the properly informed skilled person "with the mind willing to

understand"."[18] Given the points taken by Mylan in relation to – for instance – sufficiency,[19] it is clear that the Patent will have to be construed, and I reject the notion that merely because infringement is not in issue, construction can fall by the wayside.

12. Sections E, F and G, as I have described in paragraph 10 above, deal with the validity issues arising. Finally:

(1) Section H deals with the question of Flynn's status as exclusive licensee.

(2) Section I sets out my conclusions, and the manner in which this dispute is to be disposed of.

B. THE HEARING

(1) The evidence

13. I heard evidence from three witnesses: two experts and one witness of fact. In the order in which they were called, I heard from:

(1) *Professor Thomas Roth.* Professor Roth was called as an expert witness on behalf of the Claimants:

(a) Professor Roth is the founder and Director of the Henry Ford Sleep Disorders Center, a Professor of Internal Medicine and Psychiatry at the University of Michigan School of Medicine and a Consulting Professor and Advisor for the Division of Public Mental Health and Public Sciences for Stanford Medicine. Professor Roth has worked extensively and written prolifically in the field of sleep medicine. In his third expert report (**Roth 3**), he describes his area of expertise as follows:

> "2.2 I have approximately fifty years of clinical and research experience in sleep medicine, a speciality or subspeciality devoted to the diagnosis and therapy of sleep disturbances and disorders.
>
> 2.3 …my professional experience in the field of sleep medicine spans sleep homeostatic processes, circadian processes, sleep loss, sleep fragmentation, sleep pathologies, and the effects of pharmacologic agents on normal sleep/wake function and on sleep disorders.
>
> 2.4 My role has always involved a combination of clinical research and clinical practice. The research component has included teaching residents and physicians completing sleep medicine fellowships, research for the United States National Institute of Health ("NIH"), industry and foundation-sponsored research regarding the matters described in the previous paragraph. The clinical component has involved patient care and the supervision of residents and fellows delivering patient care, primarily supervising the diagnosis and management of patients with sleep disorders.

[18] Neurim's written opening submissions at paragraph 24(a).

[19] Set out in paragraph 8(3) above.

> 2.5 I estimate that 65-80% of my work in sleep medicine has involved the diagnosis and management of insomnia. The main focus of my research has always been related to the different phenotypes of insomnia, the pathophysiology of insomnia, and the different approaches to the pharmacological management of insomnia, with brief forays into sleep apnea, narcolepsy and restless leg syndrome."

(b) Professor Roth submitted two expert reports:

(i) Roth 3 (which, for ease of reading, gathered together and then supplemented material from two previous reports – **Roth 1** and **Roth 2** – in a single document), dated 27 August 2020.

(ii) A second report, dated 28 September 2020 (**Roth 4**), which was written in response to the first report of Mylan's expert, Professor Morgan.

(c) Professor Roth gave evidence remotely (from the United States), by way of video-link. Although, as I shall describe, the trial was largely conducted in person, it was not sensible (particularly in present circumstances) for Professor Roth to travel to London.

(d) Professor Roth gave evidence on the afternoons of Day 1 (29 October 2020) and Day 2 (30 October 2020). That was because of the time difference between Michigan (where Professor Roth resides) and London. They were long afternoons. Despite a small but perceptible lack of synchronicity between the audio and video feeds when Professor Roth gave evidence (which made cross-examining Professor Roth more difficult for Mr Vanhegan, QC, Mylan's leading counsel, as it was difficult to assess whether the Professor had finished his answer) I consider that I was well able to assess Professor Roth's demeanour as a witness.

(e) Professor Roth is undoubtedly a colossus in his field,[20] and his evidence reflected this. Professor Roth was able to answer any question within his expertise that was put to him with precision, clarity and confidence. His energy and enthusiasm for his subject was formidable, and shone through.

(f) I have no doubt that the evidence of Professor Roth represented that of one of the foremost sleep medicine experts in the world today, and I consider that Professor Roth was, when giving evidence, doing his absolute best to assist the court. Moreover, Professor Roth was obviously familiar with patents and the concepts and issues underlying patent litigation such as this. That, no doubt, is at least in part because Professor Roth has given evidence in other patent proceedings, most involving Circadin. I note this not because Professor Roth was a "gun for hire", which was hinted at by

[20] That was apparent from his *curriculum vitae* and, indeed, from Professor Morgan's comment at Transcript Day 3/p.470 ("The guy is immense…"). Although Professor Morgan sought to qualify this endorsement by reference to Professor Roth's age ("his contribution has to be seen in a sort of historical context"), Professor Roth was an extremely impressive witness.

Mylan in cross-examination and suggested in terms in closing,[21] and which suggestion I reject, but because his understanding of these concepts and issues enabled the Professor to translate his expertise into answers that would assist the court. The notions of the "person skilled in the art" and "common general knowledge" were no strangers to Professor Roth, and enabled him to give his evidence clearly and helpfully.

(g) There are two reservations that I must bear in mind when considering Professor Roth's evidence, and I stress that neither have anything to do with his quality as an expert or his integrity in giving evidence:

(i) First, Professor Roth had a level of expertise well-beyond that of the person skilled in the art, and I have sought to ensure, when considering Professor Roth's evidence, that the person skilled in the art in this case is not over-qualified for this reason. In other words, I have asked myself whether Professor Roth, in his evidence, had appropriately "dialled back" his own expertise when giving evidence in relation to the skilled person and common general knowledge that person would have. My findings, in this judgment, as to the skilled person and common general knowledge take this factor very much into account.

(ii) Secondly, as I describe more fully below, the skilled person is a skilled person as understood in this jurisdiction. Whilst I accept that sleep medicine is international in outlook, and that Professor Roth has an international and a United Kingdom expertise, I must also recognise that the bulk of his experience and work has been focussed in the United States. Again, that is a matter that I bear in mind.

(2) *Dr David Fakes.* Dr Fakes was called as a witness of fact by Flynn:

(a) Dr Fakes is the Chief Executive Officer and a director of Flynn. He is one of the founders of the company and has been a director and shareholder since 2004.

(b) Dr Fakes gave evidence in person on the morning of Day 2 (30 October 2020), essentially in relation to Flynn's (alleged) status as the exclusive licensee of Circadin. For the purposes of trial, he gave a single witness statement (albeit his fourth in the proceedings) dated 28 August 2020 (**Fakes 4**).

(c) Dr Fakes presented as a careful and straightforward witness. A great deal of what he was asked about – namely the construction and true meaning of the licensing agreements between Neurim and Flynn – were actually matters of law, on which he could (as he readily acknowledged) give no meaningful evidence. He did his best to assist the court, and I accept his evidence, but I have found it to be (for these reasons) of limited assistance.

[21] See, in particular, paragraph 35 of Mylan's written closing submissions.

(3) *Professor Kevin Morgan.* Professor Morgan was called as an expert witness on behalf of Mylan:

(a) Professor Morgan is Emeritus Professor of Psychology and Director of the Clinical Sleep Research Unit at the School of Sport, Exercise and Health Sciences at Loughborough University and an independent consultant in sleep science. He graduated with a degree in Psychology in 1978 from the University of Ulster, completed a thesis in drug treatments for insomnia at the University of Edinburgh and (after four years at the University of Sheffield) moved to the University of Loughborough in 1999.

(b) Professor Morgan's first statement (**Morgan 1**) provides:

> "1.6 In 1999, I moved to the School of Sport, Exercise and Health Sciences at Loughborough University, where I remained for 20 years, becoming Director of the Clinical Sleep Research Unit and Director of Loughborough Psychology. While at Loughborough University, I was an Associate Editor for Behavioural Sleep Medicine (Lawrence Erlbaum) (2004-2019), Age and Aging (Oxford University Press) (1999-2003) and Ageing and Society (Cambridge University Press) (1998-2004); served as Special Advisor to the Committee on Safety of Medicines (CSM) (2005); served on the executive committee of the British Sleep Society (2002-2006); and was a review Panel Member for the NICE review of hypnotic drugs. I also consulted a number of companies in the sleep industry, including: Sharp Laboratories of Europe Ltd; Age UK/Met Office; British Paralympic Association, Department of the Environment, Food and Rural Affairs; Sealy Inc; and Key Travel Inc.
>
> 1.7 In 2001, I was a Professor of Psychology within the Sleep Research Centre, Loughborough University. I had an established international reputation in sleep research and human aging (I had published the seminal textbook "Sleep and Ageing" in 1987. As at 2001, I was conducting research into the epidemiology and treatment of adult insomnia (and particularly late-life insomnia). For example, I was principal investigator on one of the largest clinical trials of cognitive-behavioural therapy for insomnia ever conducted, had recently published a textbook on the management of sleep and insomnia in nursing practice (Churchill Livingstone 1999), had contributed a chapter on the Sleep and Ageing to the international text "Treatment of Late Life Insomnia" (Lichstein & Morin, 2000), and had organised and chaired an international symposium on Sleep and Aging at the World Congress of Gerontology, Vancouver, July 2001.
>
> 1.8 I was elected Fellow of the Academy of Social Sciences in 2003 and I am Associate Fellow of the British Psychological Society. I am a Member of the European Sleep Research Society and a Member of the Sleep Research Society (US)."

(c) Professor Morgan submitted three expert reports:

(i) Morgan 1, dated 28 August 2020. Roth 3 and Morgan 1 were exchanged at (roughly) the same time. Morgan 1 did, however, take some account of the content of Roth 1 and Roth 2 which (to an extent at least) were incorporated into Roth 3.

(ii) A second report, dated 28 September 2020 (**Morgan 2**), which was written in response to Roth 3.

(iii) A third report, 21 21 October 2020 (**Morgan 3**), which I admitted over Mr Waugh, QC's (leading counsel for Neurim and Flynn) objections.

(d) Professor Morgan gave evidence in person on Day 3 (2 November 2020). This was a long day – we began sitting at 10:00am and concluded Professor Morgan's evidence at about 5:00pm. Despite breaks, it was evident that Professor Morgan was tiring by the end of the day, and I am very grateful to him for enabling the evidence to be concluded in accordance with the trial timetable. However, I do take into account, when considering Professor Morgan's evidence, that he was subjected to a long and tiring day in the witness box.

(e) There was some suggestion on the part of Neurim and Flynn that Professor Morgan was not appropriately expert for this case. I reject that submission. It is certainly true that Professors Roth and Morgan presented distinct but overlapping expertise. Thus:

(i) Professor Roth, as I have described, was an expert in sleep medicine pure and simple, which of course included (as a sub-speciality within the Professor's speciality) sleep medicine in aged persons, including those over age 55 – the group of persons at which the Patent, at least in its amended form, was specifically targeted.

(ii) Professor Morgan's speciality was and is both more general and more specific, in that his work covers human ageing much more generally. That is evident from his publications, where ageing is the common theme, not sleep medicine. Of course, the effect of ageing on sleep and sleep patterns is an important aspect of Professor Morgan's speciality, and it is no surprise that within his (Professor Morgan's) specialism, sleep in aged persons formed a significant sub-speciality.

I am, thus, very conscious that I was presented with experts in two distinct but overlapping fields, and I bear that in mind when consider the evidence of both Professors. But I find Professor Morgan to be as much an expert in his field as Professor Roth was in his own.

(f) Professor Morgan gave his evidence calmly and with, on the face of it, a subdued authority. Unlike Professor Roth, whose specialism was sleep medicine, Professor Morgan considered the phenomenon of sleep in the aged rather more holistically, to include aspects not related to sleep medicine (such as cognitive behavioural therapy). Inevitably, this meant that his knowledge in relation to the pharmacological aspects of sleep was shallower than that of Professor Roth (who, conversely, had less knowledge than Professor Morgan in relation to these non-pharmacological aspects of sleep). I see this, quite simply, as a function of the different nature of the expertise of the two Professors. However, since

the matters in issue between the parties concern sleep medicine, it is unsurprising (as I find) that Professor Roth spoke with greater weight that Professor Morgan on the key issues.

(g) Unlike Professor Roth, Professor Morgan was far less conversant with patents and the concepts and issues underlying patent litigation. Again, I stress that this is in no way a criticism, but it did represent a real problem in terms of the weight to be attached to Professor Morgan's evidence. As I describe, the skilled person not merely has a common general knowledge in the matter at hand, he or she also has something of a grasp of patents and their operation. Professor Morgan lacked this, and it became evident at times during the course of his evidence that he was reading the Patent in a way that the skilled person would not.

(h) The last point that I make in relation to Professor Morgan's evidence concerns less his oral evidence and more the written reports he submitted before the hearing and which he affirmed represented his expert opinion when he gave his evidence in-chief. I am afraid that Morgan 1 and Morgan 2 (Morgan 3 is a short and not particularly material report) were, in critical respects, disingenuous documents, written in a manner that seemed to me calculated, not to assist, but to mislead, the court. I am very conscious that this is the most serious criticism that one can make of an expert, and I do not make it lightly. The main points that have compelled me to this conclusion are dealt with fully in paragraphs 62 and 67 of this judgment, and I have sought to be clear throughout this judgment why I am not accepting evidence on certain points. Because the points go very much to the substance of the issue that I must determine, it is not possible to anticipate them here, save in the most general of terms. Suffice it to say, for the reasons given in these paragraphs, I am not confident that I can rely on Professor Morgan's reports, save with a degree of caution and reserve that a judge would not normally attach to the report of an expert.

(i) As is normal practice, a draft of this judgment was circulated, on terms of strict confidentiality, to the parties and their legal advisors. Professor Morgan did not see the draft. Counsel for Mylan – in addition to identifying typographical errors and making other points – questioned the appropriateness of my criticisms of Professor Morgan, and referred me to the decision of the Court of Appeal in *Re W* ([2016] EWCA Civ 1140), a case which considered (in rather different circumstances) the extent to which it was appropriate to make factual findings in relation to persons not directly before the court (i.e., witnesses not parties), but named as part of a fact-finding exercise conducted by a judge in the Family Court. Whilst I do not consider *Re W* to be precisely on point, I have re-visited the draft with Mylan's points regarding Professor Morgan specifically in mind. I am grateful to Mylan for raising the matter so clearly – it was right to do so. However, having considered the matter most carefully, I have not materially changed the terms of the draft, and I should explain why:

(i) An expert is responsible for his or her evidence, including the precise wording of any report submitted to the court under the name of that expert. In many cases, the expert will be in need of, and will

receive, assistance from the solicitors (or other lawyers) who have retained that expert. That is entirely understandable, but only serves to enhance the importance of the expert being entirely satisfied that his or her opinion is properly reflected in the report(s) submitted in that expert's name. This is the duty of the expert, and it is not one that can be delegated.

(ii) An expert will be giving opinion evidence in relation to a subject-matter with which a lay person – specifically, in this case, the judge – will be unfamiliar. That is why the evidence is needed. It is incumbent on the expert not merely to present evidence that is technically correct, but that makes a fair presentation of the expert's opinion. If the expert does not do that, then criticism is liable to follow.

(iii) It must be emphasised that such criticism is not intended in any way to be personal or punitive. It is an intrinsic part of assessing the weight to be attached by the court to the expert evidence that is adduced before it. The criticisms that I have made of Professor Morgan must be seen in this light. They are made purely and simply because I need to explain to the reader of this judgment precisely why I have preferred – on critical points – the evidence of Professor Roth over that of Professor Morgan. That has involved a very close parsing of material parts of Professor Morgan's written evidence, together with the oral evidence he gave in relation to that written evidence.

(iv) To put the same point differently: it would be unacceptable for me to say simply that I preferred the evidence of Professor Roth over that of Professor Morgan, without saying why. Oftentimes, the "why" will turn on technical matters of legitimate dispute between the experts, and the judge will explain why the approach of one expert has been preferred over that of another, it being accepted that each expert was doing his or her best to assist the court. That is the ordinary case. This – for reasons that I have set out in this judgment – is not such a case.

(v) The suggestion was made that the substance of the criticisms I have made of Professor Morgan's evidence were not put to Professor Morgan. I do not accept this contention. All of the aspects of Professor Morgan's reports that I have seen fit to criticise were put to Professor Morgan by Mr Waugh, QC. I have – as is my duty – drawn my own conclusions from the totality of the evidence. The manner and form in which I have evaluated Professor Morgan's evidence in light of the totality of the evidence is – as it should be – a matter for me.

(2) The form of the hearing

14. The trial of these proceedings was conducted in public. Although there were elements of the documents before me that were confidential, it was possible to hold the proceedings in public without referring, in open court, to these confidential materials.

15. The trial was a "hybrid" hearing. This was not because Professor Roth gave his evidence remotely, by way of video-link, although that is indeed how Professor Roth gave his evidence. The courts have, for many years, taken evidence remotely by way of video-link, and Professor Roth's manner of giving evidence was no more than an example of this established practice.

16. Apart from Professor Roth, all of the central participants in the trial – counsel, key persons in the litigation teams of the solicitors, representatives of the clients and witnesses – were present in court. However, although I had the use of the one of the Rolls Building's "super-courts", due to social distancing compelled by the COVID-19 pandemic, there was not enough room for all of the parties' legal teams (broadly understood), and no room for the public.

17. The approach that should be taken in these circumstances was considered at the pre-trial review. The approach which I ordered was that any person interested should obtain, via email from me,[22] a link to the video-stream of the proceedings. My order of 5 October 2020 provided as follows in paragraph 4:

> "Subject to any alternative direction by the Court, the Trial will be heard as an in-person trial. Irrespective of this, the Trial shall also proceed on a hybrid basis in the following manner:
>
> (a) The Trial shall also be conducted via Skype for Business and the Trial participants, irrespective of whether the Trial is going ahead as an in person trial, shall have laptops available to be able to follow the proceedings via a link provided in advance (the "Link") by Sparq, who will provide technical assistance. Sparq are permitted to set up audiovisual equipment in the Courtroom as needed to facilitate the display of the proceedings via the Link. Sparq and Marten Walsh Cherer shall have permission to record the proceedings solely for the purposes of the recording and transcription of the proceedings.
>
> (b) The parties shall provide to the Court a list of named individuals at least 3 days in advance to whom the Link is to be provided. Such individuals will be in various specific locations outside the physical courtroom. It shall be explained to the named individuals that following the Trial by way of the Link is an extension of the court proceedings and that their location outside the physical courtroom will be deemed by the Judge to be a part of and extension to the physical courtroom. Accordingly, the rules that apply in the ordinary course to court proceedings will apply to such remote locations. In particular, no recording or photographing of images on the screen is permitted; and to do so will amount to contempt of court.
>
> (c) The document management system CaseLines shall be used alongside (to the extent necessary) hard copy bundles."

[22] More particularly, I acted though Sparq, the party engaged by the parties to set up the video-facility. They acted in co-operation with my clerk, who of course liaised with me.

18. The manner in which proceedings are conducted in court is, subject to overriding mandatory rules, a matter for the trial judge. There are, of course, norms that judges will follow in the ordinary case, but – in exceptional cases – exceptional measures can and should be adopted. Obviously, it is important that proceedings be conducted as close as possible to the norm, but departures from the norm can be and are justified where the broader interests of public justice and the efficient conduct of proceedings require. In this case, the link to the video-stream was justified in order *(i)* to ensure public access to what were public proceedings; and *(ii)* to enable all of the relevant persons in the relevant legal teams to attend, if only (in some cases) remotely.

C. SKILLED PERSON AND COMMON GENERAL KNOWLEDGE

(1) Summary of the law

(a) The "person skilled in the art"

19. The "person skilled in the art" is expressly referred to in the statutory provisions relating to obviousness and insufficiency. The correct identification of such a person (or team of persons) can have important consequences for the identification of the common general knowledge in the art, the construction of the specification, and therefore for the issues of infringement and/or validity.[23] As Jacob LJ explained in *Technip France SA's Patent*:[24]

> "The "man skilled in the art" is invoked at many critical points of patent law. The claims of a patent must be understood as if read by that notional man – in the hackneyed but convenient phrase the "court must don the mantle of the skilled man". Likewise many questions of validity (obviousness, and sufficiency for instance) depend upon trying to view matters as he would see them…"

20. As *Terrell* notes,[25] disputes as to the identity of the person skilled in the art often involve the following questions:

(1) What is the relevant art?

(2) Should the "person skilled in the art" be taken as comprising a team, each member bringing a particular skill, and if so then what is the composition of that notional team?

(3) What are the attributes and qualification, and in particular the level of skill, of the notional skilled person or team?

On all such matters, evidence is admissible.

21. The general characteristics or attributes of a person skilled in the art were described by Lord Reid in *Technograph v. Mills & Rockley*[26] and expanded upon by Jacob LJ in *Technip France SA's Patent*:[27]

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[23] Drawing on Birss *et al*, *Terrell on Patents*, 18th ed (2016) (***Terrell***) at [8-02].

[24] [2004] RPC 32 at [37].

[25] *Terrell* at [8-23].

"It is settled that this man, if real, would be very boring – a nerd. Lord Reid put it this way in [*Technograph*]:

> "…the hypothetical addressee is a skilled technician who is well acquainted with workshop technique and who has carefully read the relevant literature. He is supposed to have an unlimited capacity to assimilate the contents of, it may be, scores of specifications but to be incapable of a scintilla of invention. When dealing with obviousness, unlike novelty, it is permissible to make a "mosaic" out of the relevant documents, but it must be a mosaic which can be put together by an unimaginative man with no inventive capacity."

The no-mosaic rule makes him also very forgetful. He reads all the prior art, but unless it forms part of his background technical knowledge, having read (or learnt about) one piece of prior art, he forgets it before reading the next unless it can form an uninventive mosaic or there is a sufficient cross-reference that it is justified to read the documents as one.

He does, on the other hand, have a very good background technical knowledge – the so-called common general knowledge. Our courts have long set a standard for this which is set out in the oft-quoted passage from *General Tire v. Firestone Tire & Rubber*,[28] which in turn approves what was said by Luxmoore J in *British Acoustic Films*.[29] For brevity I do not quote this in full – Luxmoore J's happy phrase "common stock of knowledge" conveys the flavour of what this notional man knows. Other countries within the European Patent Convention apply, so far as I understand matters, essentially the same standard.

The man can, in appropriate cases, be a team – an assembly of nerds of different basic skills, all unimaginative. But the skilled man is not a complete android, for it is also settled that he will share the common prejudices or conservatism which prevail in the art concerned."

(b) Common general knowledge

22. Drawing again from *Terrell*:[30]

"Common general knowledge means "the information which, at the date of the patent in question, is common knowledge in the art or science to which the alleged invention relates, so as to be known to duly qualified persons engaged in that art or science"; in other words, it is part of the mental equipment necessary for competency in that art or science concerned, such as every worker in the art may be expected to have as part of his technical equipment. In the context of construction, Aldous LJ explained in *Lubrizol v. Esso Petroleum*:[31]

> "Patent specifications are intended to be read by persons skilled in the relevant art, but their construction is for the Court. Thus the court must adopt the mantle of the notional skilled addressee and determine, from the language used, what the notional skilled addressee would understand to be the ambit of the claim. To do that it is often necessary for the Court to be informed as to the meaning of technical words and phrases and what was, at the relevant time, the common general knowledge; the knowledge that the notional skilled man would have.""

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[26] [1972] RPC 346 at 355.

[27] [2004] RPC 32 at [7] to [10]. Quoted in *Terrell* at [8-42].

[28] [1972] RPC 457 at 482.

[29] 53 RPC 221 at 250.

[30] At [8-56].

[31] [1998] RPC 727 at 738.

(c) Territoriality and its significance

23. I bear in mind that the Patent is a United Kingdom designation of a European patent, and that when considering the identity of the skilled person and the common general knowledge that such a person would have, I must view matters from the perspective of a skilled person in the United Kingdom's.

24. That, as it seems to me, follows from the nature of the property before me, that is, a United Kingdom patent. In *Actavis v. Lilly*,[32] Lord Neuberger stated:

> "A patent is interpreted on the basis that it is addressed to a person or group of persons who is or are likely to have a practical interest in the claimed invention, i.e., through the eyes of a person skilled in the art."

The skilled person will be looking at an invention that is claimed within the United Kingdom and whose territorial ambit is defined by the United Kingdom, and that must be the starting point for determining the nature of the skilled person. A United Kingdom designation of a European patent confers no rights outside the territorial scope of the United Kingdom.

25. It follows that the common general knowledge of the skilled person must be known in the United Kingdom. In *Generics v. Warner-Lambert*, Arnold J stated:[33]

> "…Counsel for Warner-Lambert submitted that matter relied on as being common general knowledge must be shown to be common general knowledge in the UK, but counsel for Mylan and Actavis disputed that this was necessary. Although I only received limited argument on the point, it seems to me that, at minimum, it must be shown that the matter in question was common general knowledge in the UK. The reason for this is that, whether one is concerned with the validity of a European Patent (UK), or a UK Patent, one is concerned with a right in respect of the UK. It is true that the prior art may have been published anywhere in the world, but I do not think that alters the need for the skilled team to consider that art as if they were located in the UK. I do not think it matters that a fact was common general knowledge in (say) China, if it was not common general knowledge here. The position may be different if all the persons skilled in a particular art in the UK are acquainted with the position in China, but no point of that kind arises here…"

26. Of course, that does not mean that the skilled person will not have an international outlook, and will not consider prior art published anywhere in the world.

(d) Knowledge of the law

27. Patents are technical documents, and the skilled person must have sufficient understanding of patent law to appreciate the general nature and function of a patent specification and claims. Thus, in *Kirin-Amgen v. Hoechst Marion Roussel (No 2)*,[34] Lord Hoffmann noted:

> "But the person skilled in the art (who must, in my opinion, be assumed to know that basic principles of patentability) might well have thought that the claims were restricted to existing

[32] [2017] UKSC 48 at [22].

[33] [2015] EWHC 2548 (Pat) at [124].

[34] [2004] UKHL 46 at [78].

technology because of doubts about sufficiency rather than lack of foresight about possible developments."

28. *Terrell* says this:

> "8-49 In *Virgin v. Premium Aircraft Interiors*, the Court of Appeal applied this principle [viz, Lord Hoffmann's dictum cited above] and held that the skilled reader, probably with the benefit of skilled advice, would have in mind the explicit drafting conventions by which a patent and its claims are framed. When considering the claim, the reader would in particular have in mind the fact that reference numerals are not to be used to limit a claim, and the nature of the two-part claim structure in which features found in the prior art are incorporated into the pre-characterising portion. Furthermore, it was said that:
>
> > "because the skilled reader knows that the patentee is trying to claim something which he, the patentee, considers to be new, he will be strongly averse to ascribe to the claim a meaning which covers that which the patentee acknowledges is old."
>
> 8-50 Nevertheless, the question is one of construction and whether what is claimed is or is not new will depend on, rather than be determinative of, the construction of the claim. The court also held that the skilled reader would know about the practice of divisional applications and that this might affect their understanding of a claim because they will know that there are or may be aspects of what is described in the patent which are actually claimed in some other patent or patents divided out from the original application."

29. I labour this aspect of the skilled person because – for reasons that I have already mentioned and that I describe more fully in this judgment – it seemed to me that Professor Morgan lacked the necessary understanding of the "nuts and bolts" of patents and patent law, including as to the question of common general knowledge, and that this had the unfortunate effect of skewing in unpredictable ways his evidence and rendering it unreliable.

(2) Approach

30. In reality, the patent in issue, the skilled person and the skilled person's common general knowledge are three mutually supporting pillars in terms of determining what is required to understand the Patent.

31. My approach, in this case, is to begin with the content and terms of the Patent, and then to work from this to consider what other material and information would form part of the skilled person's common general knowledge.

(3) The present case

(a) Indications from the Patent

32. The Patent describes the field of the invention claimed as follows:[35]

[35] Patent/[0001].

"The present invention relates to a method for treating primary insomnia (as defined by DSM-IV or nonorganic insomnia as defined by ICD-10) when characterised by non-restorative sleep, and to the use of melatonin in the manufacture of a medicament for this purpose."

33. The terms "DSM-IV" and "ICD-10" are terms of art. **DSM-IV** refers to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*. This was the edition current as at the Patent's Priority Date. It was common ground between the experts – and indeed, obvious from the Patent itself – that this document (or the material parts which I consider below) formed a part of the skilled person's common general knowledge.

34. DSM-IV materially provides:

(1) Under "Sleep Disorders" at 551:

> "The sleep disorders are organised into four major sectors according to presumed etiology. **Primary Sleep Disorders** are those in which none of the etiologies listed below (i.e., another mental disorder, a general medical condition, or a substance) is responsible. Primary Sleep Disorders are presumed to arise from endogenous abnormalities in sleep-wake generating or timing mechanisms, often complicated by conditioning factors. Primary Sleep Disorders in turn are subdivided into **Dyssomnias** (characterised by abnormalities in the amount, quality or timing of sleep) and **Parasomnias** (characterised by abnormal behavioral or psychological events occurring in association with sleep, specific sleep stages, or sleep-wake transitions)."

(2) The skilled person would have understood the term Primary Sleep Disorder, and that it was a sleep disorder that could be distinguished from what can be termed a **Secondary Sleep Disorder**, where there is:[36]

(a) Sleep Disorder Related to Another Mental Disorder.

(b) Sleep Disorder due to Another Medical Condition.

(c) Substance-Induced Sleep Disorder.

In short, Primary Sleep Disorders are characterised by the absence of certain factors that (may) render sleep disordered.

(3) Under "Dyssomnias" at 553:

> "Dyssomnias are primary disorders of initiating or maintaining sleep or of excessive sleepiness and are characterised by a disturbance in the amount, quality, or timing of sleep…"

(4) **Primary Insomnia** is considered in Section 307.42. That section concludes with a "box" summarising the "Diagnostic criteria for 307.42 Primary Insomnia", which provides as follows:

> "A. The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.

[36] To adopt the terminology used in DSM-IV.

B. The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, or a Parasomnia.

D. The disturbance does not occur exclusively during the course of another mental disorder (e.g., Major Depressive Disorder, Generalised Anxiety Disorder, a delirium).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition."

(5) Section 307.42 says this under "Diagnostic Features" at 553:

"The essential feature of Primary Insomnia is a complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep that lasts for at least 1 month (Criterion A) and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning (Criterion B). The disturbance in sleep does not occur exclusively during the course of another sleep disorder (Criterion C) or mental disorder (Criterion D) and is not due to direct physiological effects of a substance or a general medical condition (Criterion E).

Individuals with Primary Insomnia most often report a combination of difficulty falling asleep and intermittent wakefulness during sleep. Less commonly, these individuals may complain only of nonrestorative sleep, that is feeling that their sleep was restless, light, or of poor quality. Primary Insomnia is often associated with increased physiological or psychological arousal at nighttime in combination with negative conditioning for sleep. A marked preoccupation with and distress due to the inability to sleep may contribute to the development of a vicious cycle: the more the individual strives to sleep, the more frustrated and distressed the individual becomes and the less he or she is able to sleep. Lying in a bed in which the individual has frequently spent sleepless nights may cause frustration and conditioned arousal. Conversely, the individual may fall asleep more easily when not trying to do so (e.g., while watching television, reading, or riding in a car). Some individuals with increased arousal and negative conditioning report that they sleep better away from their own bedrooms and their usual routines. Chronic insomnia may lead to decreased feelings of well-being during the day (e.g., deterioration of mood and motivation; decreased attention, energy, and concentration; and an increase in fatigue and malaise). Although individuals often have the subjective complaint of daytime fatigue, polysomnographic studies usually do not demonstrate an increase in physiological signs of sleepiness."

(6) The skilled person would have been aware that Primary Insomnia is indicated by one or more of three characteristics:

(a) Difficulty in initiating sleep – which is also called sleep (onset) latency.

(b) Difficulty in maintaining sleep.

(c) Non-restorative sleep.

These characteristics, I stress and as the skilled person would have known, can co-exist or exist separately without affecting the characterisation of Primary Insomnia.

(7) Criterion C in the "box" referred to – amongst other aspects of an individual's sleep condition – **Circadian Rhythm Sleep Disorder**. Because circadian rhythms feature in the common general knowledge at issue in this case, it is necessary to set out what a skilled person would understand by this from DSM-IV. Under the heading "Differential Diagnosis", at 555-556, is the following passage:

> ""Normal" sleep duration varies considerably in the general population. Some individuals who require little sleep ("short sleepers") may be concerned about their sleep duration. **Short sleepers** are distinguished from those with Primary Insomnia by their lack of difficulty falling asleep and by the absence of characteristic symptoms of Primary Insomnia (e.g., intermittent wakefulness, fatigue, concentration problems, or irritability).
>
> Daytime sleepiness, which is a characteristic feature of Primary Hypersomnia,[37] can also occur in Primary Insomnia, but is not as severe in Primary Insomnia. When daytime sleepiness is judged to be due to insomnia, an additional diagnosis of Primary Hypersomnia is not given.
>
> Jet Lag and Shift Work Types of Circadian Rhythm Sleep Disorder are distinguished from Primary Insomnia by the history of recent transmeridian travel or shift work. Individuals with the Delayed Sleep Phase Type of Circadian Rhythm Sleep Disorder report sleep-onset insomnia only when they try to sleep at socially normal times, but they do not report difficulty falling asleep or staying asleep when they sleep at their preferred times.
>
> …"

35. **ICD-10** refers to the 10th revision of the International Classification of Mental and Behavioural Diseases (**ICD**). This was the revision current as at the Patent's Priority Date. Again, it was common ground, and obvious from the Patent itself, that this formed a part of the skilled person's common general knowledge.

36. ICD-10 materially provides:

(1) Under the heading "Nonorganic sleep disorders" (at [F51], pp181-182):

> "This group of disorders includes:
>
> (a) dyssomnias: primarily psychogenic conditions in which the predominant disturbance is in the amount, quality, or timing of sleep due to emotional causes, i.e., insomnia, hypersomnia, and disorder of sleep-wake schedule; and

[37] It is unnecessary to consider Primary Hypersomnia further for the purposes of the matters here in issue. Suffice it to say that the essential feature of Primary Hypersomnia, according to DSM-IV, is "excessive sleepiness for at least 1 month as evidenced either by prolonged sleep episodes or by daytime sleep episodes occurring almost daily…" (at 557).

(b) parasomnias: abnormal episodic events occurring during sleep; in childhood these are related mainly to the child's development, while in adulthood they are predominantly psychogenic, i.e., sleepwalking, sleep terrors, and nightmares.

This section includes only those sleep disorders in which emotional causes are considered to be a primary factor. Sleep disorders of organic origin such as Kleine-Levin syndrome (G47.8) are coded in Chapter VI (G47.-) of ICD-10. Nonpsychgenic disorders including narcolepsy and cataplexy (G47.4) and disorders of the sleep-wake schedule (G47.2) are also listed in Chapter VI, as are sleep apnoea (G47.3) and episodic movement disorders which include nocturnal myoclonus (G25.3). Finally, enuresis (F98.0) is listed with other emotional and behavioural disorders with onset specific to childhood and adolescence, while primary nocturnal enuresis (R33.8), which is considered to be due to a maturational delay of bladder control during sleep, is listed in Chapter XVIII of ICD-10 among the symptoms involving the urinary system.

In many cases, a disturbance of sleep is one of the symptoms of another disorder, either mental or physical. Even when a specific sleep disorder appears to be clinically independent, a number of associated psychiatric and/or physical factors may contribute to its occurrence. Whether a sleep disorder in a given individual is an independent condition or simply one of the features of another disorder (classified elsewhere in Chapter V or in other chapters of ICD-10) should be determined on the basis of its clinical presentation and course, as well as of therapeutic considerations and priorities at the time of the consultation. In any event, whenever the disturbance of sleep is among the predominant complaints, a sleep disorder should be diagnosed…"

Thus, although the terminology is different, the skilled person would have understood ICD-10 to be drawing the same distinction between Primary Sleep Disorders and Secondary Sleep Disorders as was drawn in DSM-IV.

(2) Under the heading "Nonorganic insomnia" (at [F51.0], pp182-183):

"Insomnia is a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time. The actual degree of deviation from what is generally considered as a normal amount of sleep should not be the primary consideration in the diagnosis of insomnia, because some individuals (the so-called short sleepers) obtain a minimal amount of sleep and yet do not consider themselves as insomniacs. Conversely, there are people who suffer immensely from the poor quality of their sleep, whilst quantity is judged subjectively and/or objectively as within normal limits.

Among insomniacs, difficulty falling asleep is the most prevalent complaint, followed by difficulty staying asleep and early final wakening. Usually, however, patients report a combination of these complaints. Typically, insomnia develops at a time of increased life-stress and tends to be more prevalent among women, older individuals and psychologically disturbed and socioeconomically disadvantaged people. When insomnia is repeatedly experienced, it can lead to an increased fear of sleeplessness and a preoccupation with its consequences. This creates a vicious circle which tends to perpetuate the individual's problem.

…"

(3) Under the heading "Diagnostic guidelines" (p183):

"The following are essential clinical features for a definite diagnosis:

(a) the complaint is either of difficulty falling asleep or maintaining sleep, or of poor quality of sleep;

(b) the sleep disturbance has occurred at least three times per week for at least 1 month;

(c) there is preoccupation with sleeplessness and excessive concern over its consequences at night and during the day;

(d) the unsatisfactory quantity and/or quality of sleep either causes marked distress or interferes with ordinary activities in daily living.

Whenever unsatisfactory quantity and/or quality of sleep is the patient's only complaint, the disorder should be coded here. The presence of other psychiatric symptoms such as depression, anxiety or obsessions does not invalidate the diagnosis of insomnia, provided that insomnia is the primary complaint or the chronicity and severity of insomnia cause the patient to perceive it as the primary disorder. Other coexisting disorders should be coded if they are sufficiently marked and persistent to justify treatment in their own right. It should be noted that most chronic insomniacs are usually preoccupied with their sleep disturbance and deny the existence of any emotional problems. Thus, careful clinical assessment is necessary before ruling out a psychological basis for the complaint."

37. The Patent then describes the background to the invention.[38] This description emphasises the quality of sleep aspect of inorganic insomnia (to use ICD-10 terminology) or non-restorative sleep aspect of Primary Insomnia (to use DSM-IV terminology). Thus:

(1) Referring to the definition of Primary Insomnia in DSM-IV, it is noted that "according to the definition, non-restorative sleep alone is sufficient to establish the diagnosis of Primary Insomnia, provided it results in impaired daytime functioning".[39]

(2) Referring to ICD-10, the Patent states that it:[40]

"…described nonorganic insomnia as "a condition of unsatisfactory quantity and/or quality of sleep". It goes on to state that "there are people who suffer immensely from the poor quality of their sleep, while sleep in quantity is judged subjectively and/or objectively as within the normal limits."

Summarising the ICD-10 diagnostic guidelines,[41] the Patent states "there is repeated emphasis in ICD-10 on the equal importance of quality of sleep and quantity of sleep in the diagnosis of insomnia."[42]

The Patent states that "[t]he invention thus relates to primary insomnia (DSM-IV) or nonorganic insomnia (ICD-10)",[43] and within those conditions to the characteristics of quality of sleep or non-restorative sleep.

[38] Patent/[0002]-[0012].

[39] Patent/[0003].

[40] Patent/[0004].

[41] Which are set out above.

[42] Patent/[0005].

38. After summarising (some of) the art in this area,[44] to which I will return, the Patent states:

> "[0011] Thus, there appears to be little or no evidence from published articles, that administration of exogenous melatonin (or other melatonergic agents, melatonin agonists or melatonin antagonists), in the dosages contemplated by the present invention, would be likely to improve the restorative quality of sleep in subjects affected by primary insomnia characterised by non-restorative sleep.
>
> [0012] However, in contrast with the results of the above published papers, the present inventors have surprisingly found that melatonin (and other melatonergic agents, melatonin agonists or melatonin antagonists) in fact improves the restorative quality of sleep in subjects suffering from primary insomnia…"

39. The invention is then summarised. Referring to the terms of the Patent as amended, the relevant paragraphs provide as follows:[45]

> "[0013] The present invention provides in one aspect, use of a prolonged release formulation comprising melatonin in unit dosage form, ~~each unit dosage~~ comprising ~~0.025 to 10~~ 2 mg of melatonin, in the manufacture of a medicament for improving the restorative quality of sleep in a patient aged 55 years or older suffering from primary insomnia characterised by non-restorative sleep, wherein the medicament comprises also at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers, adjuvant or carrier.
>
> [0014] In another aspect, the invention provides a medicament for use in improving the restorative quality of sleep in a patient aged 55 years or older suffering from primary insomnia characterised by non-restorative sleep, which comprises a prolonged release formulation comprising melatonin in unit dosage form, ~~each unit dosage~~ comprising ~~0.025 to 10~~ 2 mg of melatonin, and at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers, adjuvant or carrier. **Also disclosed is a medicament, for use in improving both the quality and quantity of sleep, in primary insomnia, which comprises at least one compound selected from melatonin, other melatonergic agents, melatonin agonists and melatonin angtagonists, and at least one additional therapeutic agent selected from anxiolytics, antidepressants, hypnotics, sedatives, antihypertensives, analgesics, dopaminergic agonists, antipsychotics, minor tranquilizers, anorectics and anti-inflammatory drugs, in addition to at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers adjuvant or carrier**."

40. The words in **bold** are, I should stress, my emphasis. I shall return to their significance in due course. However, I should make clear now that I regard these words as essentially inconsistent with the teaching of the Patent and the inventions claimed therein.

41. A detailed description of the invention follows, at [0015] to [0021], which last paragraph refers to the fact that "[t]he invention will be illustrated by the following **Examples**". There then follow five Examples, variously described as:

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[43] Patent/[0005].

[44] Patent/[0006]-[0010].

[45] Amendments are marked up by underlining or ~~strikethrough~~.

(1) **Reference Example 1**: Patent/[0022]-[0025].

(2) **Example 2**: Patent/[0026]-[0028].

(3) **Example 3**: Patent/[0029]-[0031].

(4) **Reference Example 4**:[46] Patent/[0032]-[0034].

(5) **Example 5**: Patent/[0035].

42. It will be necessary to consider various of these Examples in due course. For present purposes, however, it is important to note that the skilled person would appreciate their significance as follows:

(1) It will be necessary to consider the plausibility – in the sense of lack of plausibility insufficiency – in due course.[47] One thing, however, is clear: it is not for the patent to prove conclusively the invention that it claims. The standard is the far lower one of "plausibility".

(2) The Examples must be seen in that light, and it is for this reason that the Patent refers to the Examples as "illustrating" the invention. Professor Morgan, however, seemed to consider that the Patent needed to say far more about the plausibility of the invention than is, in fact, the case. This became clear when Professor Morgan was being cross-examined by Mr Waugh, QC on behalf of the Claimants, regarding the prior art:[48]

Q (Mr Waugh, QC)	You say, "…this would include patients complaining of non-restorative sleep". You draw this sort of approach with respect to the prior art, but you do not give this concession to the patent, do you?
A (Professor Morgan)	The patent is missing data. It is missing information. There is information there that does not allow you to make inferential steps as you move through. The biggest and most egregious missing piece is that which connects a conclusion that the participants were suffering from insomnia characterised by non-restorative sleep. That arrives from participants who had insomnia.
Q (Mr Waugh, QC)	But therein lies the double-standard, Professor, because for this very reason you are prepared to assume with the prior art that these patients would include patients complaining of non-restorative sleep?
A (Professor Morgan)	Yes.
Q (Mr Waugh, QC)	And Professor Roth say, "Well, we see that the restorative value of their sleep is improved and, therefore, we can reasonably conclude that there has

[46] The word "Example" does not appear, but that is clearly a typographical error.

[47] As to lack of plausibility insufficiency, see paragraph 8(3)(d) above.

[48] Transcript/Day 3/pp.620*ff*.

	been an improvement in their non-restorative sleep". You are prepared to make that inference, and it is [Haimov 1995] and [Zisapel 1999], but you are not prepared to fill in that missing information…
A (Professor Morgan)	Then I should clarify. There is a difference between saying that within Haimov's sample and within the narrative you have just been speaking about, where primary insomnia is being use as a collective, then within that there will be patients, …there are likely to be patients, with non-restorative sleep. That is a reasonable inference. The patent actually states universally that it applies at the end of Example 4,[49] that it applies to patients with insomnia characterised by non-restorative sleep. In other words, all of them have non-restorative sleep and we are basing that on question 4 from the [Leeds Sleep Questionnaire[50]].
Q (Mr Waugh, QC)	That is your take, Professor.
A (Professor Morgan)	That is what it says in the Patent.
Q (Mr Waugh, QC)	Professor Roth has a different take, and in that sense, Professor, you agreed with me earlier that the patients in the Patent, there would be a cohort of patients in there that had non-restorative sleep?
A (Professor Morgan)	Yes, there would have been some, likely.
Q (Mr Waugh, QC)	Therefore, if you gave melatonin, and you saw that the non-restorative sleep was improved, as Professor Roth says, you can conclude that there were patients in that cohort who were characterised by having non-restorative sleep?
A (Professor Morgan)	I would agree with that, but that is different from saying that the cohort, the entire group, were characterised by non-restorative sleep. They were not.
Q (Mr Waugh, QC)	Where does it say that? I do not think anybody has ever said…
A (Professor Morgan)	The Patent says that.
Q (Mr Waugh, QC)	The Patent says that you can treat patients characterised by non-restorative sleep with melatonin, and the Examples are an example of treating a cohort of patients, some, many, who…
A (Mr Waugh, QC)	Whose insomnia is characterised by non-restorative sleep. That is what it says.

This passage shows the very reverse of a meeting of minds, in terms of a basic understanding of patent law concepts. I do not consider that Professor Morgan could, if he were a layman (which, of course, he was not holding himself out to

[49] Professor Morgan misspoke. He was referring to Example 2, which concludes: "Conclusions. These results show that melatonin enhanced the restorative value of sleep in these primary insomnia patients."

[50] A document that I shall come to consider.

be), particularly be blamed for reading Patent/[0028] literally. The conclusion expressed in Example 2 is that:

"These results show that melatonin enhanced the restorative value of sleep in these primary insomnia patients."

That is – read literally – a very definite conclusion. But the fact that it is not, or may not be, justified in absolute terms by the data set out in Example 2 is by no means fatal to the Patent. The Patent – as I will come to – must satisfy the minimum standard of plausibility. However, implicit in Professor Morgan's evidence was a far higher standard that the Patent must <u>prove</u> (to some unarticulated standard other than plausibility) that which it asserted. Of course, bare assertion is not enough – but Professor Morgan's evidence in relation to both the prior art and the teaching of the patent was substantially undermined by Professor Morgan's failure to appreciate the essential "nuts and bolts" of patent law. It may be that Mr Waugh, QC, was right in suggesting that Professor Morgan was applying "double-standards". If so, and I make no finding in that regard, this was simply because Professor Morgan never articulated in his evidence what standards he was seeking to apply when giving his opinion.

(3) The Patent differentiates between "Reference Examples" (Examples 1 and 4) and "Examples" (Examples 2, 3 and 5). The skilled person would understand that the word "Reference" indicated that the example in question was not purporting to describe something within the claims of the Patent.[51]

43. Finally, the **Claims** are set out. Although only Claims 1 and 4 were of direct relevant to the issues before me, it is appropriate to set out the Claims (in their English form) in their entirety:[52]

"1. Use of a prolonged release formulation comprising melatonin in unit dosage form, ~~each unit dosage~~ comprising ~~0.025 to 10~~ <u>2</u> mg of melatonin, in the manufacture of a medicament for improving the restorative quality of sleep in a patient <u>aged 55 years or older</u> suffering from primary insomnia **characterised by** non-restorative sleep, wherein the medicament comprises also at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers, adjuvant or carrier.

2. Use according to claim 1, wherein the medicament is further **characterised by** at least one of the following features:

(i) it is adapted for oral, rectal, parenteral, transbuccal, intrapulmonary (e.g., by inhalation) or transdermal administration;

(ii) it is in depot form which will release the melatonin slowly in the body, over a preselected time period.

[51] See, for example, *Liqwd Inc v. L'Oreal LLC*, [2018] EWHC 1394 (Pat) at [78].

[52] **Bold** emphasis in original. I highlight the amendments to the claims in the amended Patent by use of <u>underlining</u> and ~~strikeout~~. No-one referred me to the German and French versions of the Claims. These versions did not carry through the same amendments as applied to the English language claims, and ought to be amended consistently.

3. Use according to claim 1 or claim 2, wherein said prolonged release formulation includes an acrylic resin.

4. A medicament for use in improving the restorative quality of sleep in a patient aged 55 year or older suffering from primary insomnia **characterised by** non-restorative sleep, which comprises a prolonged release formulation comprising melatonin in unit dosage form, ~~each unit dosage~~ comprising ~~0.025 to 10~~ 2 mg of melatonin, and at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers, adjuvant or carrier.

5. Medicament for use according to claim 4, which is further characterised by at least one of the following features:

   (i) it is adapted for oral, rectal, parenteral, transbuccal, intrapulmonary (e.g., by inhalation) or transdermal administration;

   (ii) it is in depot form which will release the melatonin slowly in the body, over a preselected time period.

6. Medicament for use according to claim 4 or claim 5, wherein said prolonged release formulation includes an acrylic resin."

44. It is appropriate to say something about the nature and meaning of the Claims at this point:

(1) Claim 1 is a "Swiss-style" or "use" claim of the form "use of substance X in the manufacture of a medicament for treating disease Y". As *Terrell* notes, "[s]uch a form is permissible in order to provide protection for inventions relating to second medical use",[53] as the Patent is. *Terrell* explains the background to such claims as follows:

> "2-49 The permissibility of second medical use claims has been considered both in the EPO and in the national courts. In summary, such claims were held allowable under the original (1973) version of the EPC and remain allowable, albeit on a different basis, under the EPC 2000.
>
> 2-50 In the EPO, in the *EISAI* case, it was held that, whilst a claim to the method of use could not be permitted under the 1973 version of the convention, a claim to the use of a product for the manufacture of a medicament for a specified new and inventive medical use could be permitted (the so-called Swiss type of claim), the Swiss national patent office having instituted a practice of allowing such claims [1984] OJ EPO 581 (contrary to the established practice in the German national patent office). The EPO in *EISAI* concluded that there was no discernible intention in the EPC or in the *travaux préparatoires* to exclude such claims. This reasoning was approved in *Wyeth's Application*, where the Patents Court sat *en banc*.
>
> 2-51 In *Actavis v. Merck*, the Court of Appeal held that second medical use claims were allowable even where the novelty resided solely in a new dosage regime or other form of administration of a substance. It noted that such claims were allowed in the EPO, Germany, and New Zealand and concluded that there was

[53] *Terrell* at [9-268].

> no clear ratio to the contrary in *Bristol Myers Squibb Co v. Baker Norton Pharmaceuticals Inc*. Furthermore, even if there had been a clear ratio to the contrary in one of its own previous decisions, the Court of Appeal should follow clear European Patent Office authority, as an exception to the rule in *Young v. Bristol Aeroplane Co Ltd*, given the importance of a common European approach to patentability."

(2) Claim 4 is the equivalent under the European Patent Convention as amended in 2000 (**EPC 2000**).

(b) The Skilled Person

45. It is trite that these matters all must be resolved as at the Priority Date, and that is the date that I use in this judgment.

46. The Patent relates – as I have described – to the prolonged release of melatonin to treat primary insomnia characterised by nonrestorative sleep. As is clear from ICD-10 (a publication of the World Health Organisation) and DSM-IV (a publication of the American Psychiatric Association), this was an area of medicine that was international in outlook.

47. Both experts addressed their understanding of the skilled person in their reports and in their evidence before me:

(1) Professor Roth, relying heavily on the wording of the Patent at [0001], and its reference to DSM-IV and ICD-10, said this about the skilled person in Roth 3:

> "5.4 Primary insomnia is a term of art whose meaning is understood by the skilled person, and which I consider in more detail below. The diagnostic criteria for primary insomnia provide that primary insomnia may be characterised by, among other things, a complaint of non-restorative sleep.
>
> 5.5 The Patent is for a pharmacological treatment, or medication, specifically using sustained release melatonin to treat a patient with primary insomnia characterised by non-restorative sleep. Therefore, the person to whom the Patent is directed will have experience in the pharmacological management of primary insomnia.
>
> 5.6 The Patent is directed to a sleep medicine clinician like myself, who has studied and/or practised extensively in the area of primary insomnia and who has significant expertise in primary insomnia and the diagnostic guidelines used in the diagnosis of insomnia, including the DSM and ICD."

(2) Professor Morgan's understanding of the skilled person was altogether broader and vaguer than that of Professor Roth, who did not accept Professor Morgan's description of the skilled person.[54] Professor Morgan noted that, in 2001, "[s]leep medicine was an emerging field in the UK…with few specialist sleep research clinicians with a practice that was limited to the treatment of sleep disorders".[55] Most insomnia would be treated by general practitioners,[56] who "while acting as

[54] See Roth 4 at paragraph 3.11.

[55] Morgan 1 at paragraph 3.5.

[56] Morgan 1 at paragraph 3.5.

recipients and translators of knowledge from the skilled person or team, would not themselves be considered "skilled persons"."[57] Turning to who the skilled person or team would be (as opposed to who that person/team would not be), Professor Morgan said this in Morgan 1:

> "3.5 …Chronobiology is a field of biology focused on biological rhythms and therefore chronobiologists were also interested in melatonin and the circadian rhythm (both now and in 2001). Not all chronobiologists would have been part of the skilled team but researchers and research clinicians in sleep medicine would draw upon the expertise of chronobiologists in their work, for example when papers of chronobiologists were published in mainstream journals about the clinical uses of melatonin (e.g. The Lancet, Sleep etc.). Chronobiologists would also publish in more specialised literature (e.g. the Journal of Pineal Research) which would not be routinely read by researchers or research clinicians.
>
> 3.6 In the domain of clinical sleep research in 2001, the typical experience and skillset of research clinicians and researchers would have been very similar. Most research clinicians and researchers would be MD/PhD or post-doctoral quantitative scientists with backgrounds in clinical trials, whilst their academic and clinical training may have varied each would be familiar with the phenomenology of, and diagnostic criteria for insomnia disorders, aware of the available and emerging therapeutic options, and acquainted with the regulatory structures which dictated the need for and phase of clinical research, and the clinical context in which putative treatments would ultimately be deployed. The research clinicians and researchers would both sit side by side in panels which ultimately agreed such matters as diagnostic criteria, optimal treatment approaches, research methodologies and, where appropriate, the regulation of drug treatments. For example I sat on the Committee on Safety of Medicines in 2005 which discussed clinical guidance in relation to insomnia-related products.
>
> 3.7 In addition researchers and research clinicians would often have had several years of experience working with the pharmaceutical industry with the experience/knowledge in the design of trials necessary for drug development and knowledge of medical statistics. Researchers and research clinicians would therefore need to know the detail of good clinical study design, the need for identification of primary end points, the role of a placebo, the avoidance of bias and how to interpret data.
>
> 3.8 The Patent also discusses various pharmaceutical carriers etc. necessary to make a medicament comprising slow release melatonin. Accordingly the skilled person or team would also encompass a pharmacologist so as to be able to make the slow release medicament containing melatonin.
>
> 3.9 In summary my view is that the skilled addressee of Patent would include research clinicians with a special interest in the treatment of insomnia, and researchers (both clinical and nonclinical) involved in sleep research. It also includes pharmacologists with product formulation, knowledge and experience."

(3) I am afraid that I found Professor Morgan's definition of the skilled person/team to be so vague as to be useless. Whilst I fully appreciate that, in 2001, and even

[57] Morgan 1 at paragraph 3.5.

today, according to Professor Morgan, sleep medicine is not a recognised NHS consultant post,[58] I decline to accept that the United Kingdom cannot offer up as a skilled person someone having the combination of the research and clinical experience described by Professor Roth in paragraph 5.6 of Roth 3. It seems to me that the sort of research expertise described by Professor Morgan would have to go hand-in-hand with the sort of clinical experience described by Professor Roth. I simply do not see how, given that research into Primary Insomnia involves considering people suffering from Primary Insomnia, a researcher could so isolate him- or herself so as to avoid all clinical work. I consider that whilst Professor Morgan does mention clincal work as being part of the skilled person's portfolio of skills, he understates the importance of this.

(4) I fully appreciate that Professor Roth's centre of gravity as an expert lay in the United States. Nevertheless, Professor Roth is of international standing, with significant experience of work in the United Kingdom. I consider his description of the skilled person to be eminently translatable to this jurisdiction, and I adopt it. To the extent that Professor Morgan's definition was different to that of Professor Roth, I reject it for the reasons I have given.

48. Accordingly, the skilled person for the purposes of this case is a sleep medicine clinician, who has studied and/or practised extensively in the area of Primary Insomnia and who has significant expertise in Primary Insomnia and the diagnostic guidelines used in the diagnosis of insomnia, including the DSM and ICD (the **Skilled Person**).

49. However, I should say that I am in no sense using Professor Roth as a proxy for the Skilled Person, albeit that the Skilled Person would have a background, training and experience similar to that of Professor Roth. Even in 2001, Professor Roth had a level of experience and expertise above that of the Skilled Person and – it would follow – a personal common general knowledge in excess of the Skilled Person. I take that very much into account when considering the common general knowledge that the Skilled Person would have as at the Priority Date.

(c) Common general knowledge

(i) Introduction

50. In this case, at least, common general knowledge is not to be identified by reference simply to a list of publications, which the Skilled Person would have read and digested. Still less is the Skilled Person going to be informed by lists of publications obtained through a keyword search of the scientific literature.[59] Whilst I have no doubt that the Skilled Person would or could use searches to augment his or her learning and knowledge, the Skilled Person would not be primarily reliant on such searches for his or her common general knowledge.

[58] Morgan 1 at footnote 7.

[59] So-called "bibliometrics". Professor Morgan appeared to rely on bibliometrics as a measure of common general knowledge: see, for instance, paragraph 4.60 of Morgan 1. I am very sceptical as to whether this is a helpful approach when considering the essentials of what the Skilled Person would have as his or her common general knowledge.

51. The Skilled Person's common general knowledge is best understood and explained by reference to a series of topics or issues arising out of the subject-matter of the Patent, with which the Skilled Person would have been familiar and would have been concerned to understand. These topics or issues would have been as follows:

(1) The nature of Primary Insomnia and the position of non-restorative sleep within Primary Insomnia.

(2) The co-existence (or otherwise) of non-restorative sleep with other indications of Primary Insomnia.

(3) Primary Insomnia and Circadian Rhythm Sleep Disorder.

(4) How Primary Insomnia, in general, and non-restorative sleep in particular, are diagnosed.

(5) Methods of treatment for Primary Insomnia, in general, and non-restorative sleep in particular.

(ii) The nature of Primary Insomnia and the position of non-restorative sleep within Primary Insomnia

52. It was common ground that the starting point for ascertaining the Skilled Person's common general knowledge would be DSM-IV and ICD-10. Not only are these taken as read in the Patent, it was the clear evidence of Professors Roth and Morgan that these materials would have formed part of the Skilled Person's common general knowledge.[60]

53. Although their terminology differs, the diagnostic approach described in each document is – in fundamental terms – the same:

(1) DSM-IV identifies Primary Sleep Disorders, sometimes using the term Primary Insomnia, and differentiates these from Secondary Sleep Disorders. ICD-10 refers to Primary Sleep Disorders/Primary Insomnia as nonorganic sleep disorders/nonorganic insomnia.

(2) These equivalences are explicitly recognised in Appendix H to DSM-IV, which equates Primary Insomnia to nonorganic insomnia by citing the relevant ICD-10 paragraph number – F51.0.[61]

(3) In terms of diagnostic indicators, DSM-IV refers to "non-restorative sleep", whilst ICD-10 references "poor quality of sleep", both as a complaint that may subsist on its own or in conjunction with other complaints.[62] The three diagnostic indicators/criteria are as follows:

DSM-IV	**ICD-10**

[60] Paragraph 6.8 of Roth 3; paragraphs 4.3(c)(i) and (ii) of Morgan 1.

[61] See paragraph 36(1) above.

[62] That equivalence was asserted by Professor Roth and accepted by Professor Morgan: Transcript Day 3/p.518.

"difficulty in initiating sleep"	"difficulty falling asleep"
"difficulty in maintaining sleep"	"difficulty maintaining sleep"
"non-restorative sleep"	"poor quality of sleep"

Table 1: Primary Insomnia/nonorganic insomnia diagnostic indicators

I shall, in this judgment, use the DSM-IV and ICD-10 terminology interchangeably, but with (perhaps) a greater use of the DSM-IV terminology. One point that must be observed is that whereas "non-restorative sleep" would appear to be a technical term, without a lay alternative meaning, the term "poor quality of sleep" contains within it a critical ambiguity: it can refer to the technical, ICD-10, term; but it can, equally, be used in the ordinary sense of "I had a bad night's sleep last night". Which meaning is intended is a question of context and construction to which I shall have to pay attention in this judgment.

(iii) The co-existence (or otherwise) of non-restorative sleep with other indications of Primary Insomnia

54. It would, of course, be entirely wrong to consider that these diagnostic indicators or criteria only present alone and not in conjunction with other indicators or criteria. Whilst it is perfectly possible for an individual to present only with non-restorative sleep/poor quality of sleep, equally an individual may suffer from two or more such issues. The Skilled Person would know this.

55. Professor Morgan referred to a paper (**Ohayon 1997**)[63] which (amongst other things) provided data in relation to the extent to which poor quality of sleep co-existed with other diagnostic indicators:

(1) The paper defined its terms as follows:[64]

> "Subjects were classified as dissatisfied with quality of sleep (DQS) if they reported dissatisfaction with their sleep or use of sleep-enhancing medication at the time of the study. If they reported satisfaction with their sleep and did not take sleep-enhancing drugs, they were classified instead as satisfied with quality of sleep (SQS). The indicators of insomnia were defined as follows:
>
> 1) Difficulty initiating sleep (DIS): Complaint of a long sleep latency at sleep onset, that is, a sleep latency longer than 30 minutes identified by the subject as a major problem.
>
> 2) Difficulty maintaining sleep (DMS): Nocturnal awakenings with great difficulty or inability to resume sleep or identification of difficulty maintaining sleep as a major problem.

[63] Ohayon, Caulet and Guilleminault. *How a General Population Perceives its Sleep and How This Relates to the Complaint of Insomnia*, (1997) 20(9) American Sleep Disorders Association 715-723. Cited at Morgan 1/§4.24.

[64] I have inserted some spacing to make the paragraph easier to read.

3) Nonrestorative sleep (NRS): Sleep of normal duration but accompanied by a complaint of tiredness at awakening, lack of normal, rested feeling after nocturnal sleep, or inability to get going in the morning.

4) Early morning awakening (EMA): Complaint of short nocturnal sleep duration due to abnormal awakening before 5:00am or at least 1.5 hours prior to the desired wake-up time, along with inability to resume sleep, or identification of early morning awakening as a major problem.

These definitions are similar to those of the International Classification of Sleep Disorders [ICSD-90(23)]. The definition of insomnia was also based on the criteria of [DSM-IV]…and 3rd edition, revised…, and included the requirement that the complaint be of at least 1 month's duration at the time of the interview.

Subjects were further classified according to whether one or more indicators of insomnia were reported or identified. Thus, the sample was divided into four major subgroups: DQS+I, DQS-I, SQS+I, and SQS-I. These subgroups were further analysed according to number and type of insomnia indicators."

The significance of the "+I" or the "-I" is as follows:

"Subjects were classified as either satisfied or dissatisfied with quality of sleep (SQS or DQS), with or without insomnia indicators (+I or -I)."

(2) Pausing there, two points fall to be made:

(a) The reference to DSM-IV is explicit. There is also reference to the International Classification of Sleep Disorders (**ICSD**), to which Professor Roth and Professor Morgan also made reference. It appeared to be the case that the ICSD was used almost exclusively by sleep researchers and rarely used in practice as a diagnostic tool. I am satisfied that it, too, would have formed a part of the Skilled Person's common general knowledge, but since no-one identified any material dissonance between DSM-IV, ICD-10 and ICSD, I shall keep my references to ICSD to the minimum, as they add nothing.

(b) As I have already noted, it is necessary to beware terminological traps. Whilst the paper refers to nonrestorative sleep or NRS – obviously a reference to that term in DSM-IV – the general classification of DQS – dissatisfied with quality of sleep – obviously uses the term "quality of sleep" in a manner entirely different to the use of that term in ICD-10 (which is not referenced in the paper). This is not, in any sense, a criticism, merely a warning (and probably not needed in the case of the Skilled Person, but one I bear very much in mind for myself).

(3) Table 4 in the paper provides the following data:

Symptom	**DQS+I**	**SQS+I**	**Total**
Non-restorative sleep (sole indicator)	2.2%	1.9%	4.1%
Women (n=895)	3.1%	2.1%	5.2%

Men (n=827)	1.3%	1.6%	3.0%
Two or more symptoms	6.9%	0.8%	7.7%
Women (n=895)	8.9%	0.7%	9.6%
Men (n=827)	4.7%	1.0%	5.7%

Table 2: Data extracted from Table 4 of Ohayon 1997

I do not read very much into these figures, save to note that the Skilled Person would expect non-restorative sleep to present either as a solitary indicator of Primary Insomnia or else as an indicator in conjunction with others.

(iv) Primary Insomnia and Circadian Rhythm Sleep Disorder

56. I have referred above to Circadian Rhythm Sleep Disorder, which typically occurs where – for instance, due to transmeridian travel or shift work – an individual's "body clock" gets out of synchronisation with the times at which that individual would like to sleep.

57. Although there is a similarity between Primary Insomnia and Circadian Rhythm Sleep Disorder, it is superficial only. The individual suffering from Circadian Rhythm Sleep Disorder has no difficulty going to sleep *per se*, merely as to when that individual goes to sleep. In other words, instead of feeling sleepy at bedtime, the individual feels sleepy when he or she wants to be awake. By contrast, an individual suffering from Primary Insomnia has difficulty getting to sleep.

58. The distinction was made very clearly by Professor Roth in cross-examination:[65]

Q (Mr Vanhegan, QC) So the key aspect of [Circadian Rhythm Sleep Disorder] is that a patient wishes to sleep at socially abnormal or unconventional times, is that not correct?

A (Professor Roth) No, CRSD says a patient wants to sleep at a socially normal time, but his rhythm is at a socially unacceptable time.

Q (Mr Vanhegan, QC) In practice, Professor, what it means is that the patient wishes to sleep at socially abnormal times, i.e., wants to go to sleep either very early or very late, but not during conventional time periods?

A (Professor Roth) I do not understand where you get the statement that he "wants" to sleep, there.

Q (Marcus Smith J) I think we have a linguistic issue there. I think by "wants", Mr Vanhegan is meaning "needs" or "feels the need to"…I think if you read it in that light, you may be able to answer the question…

A (Professor Roth) With that definition, the answer is absolutely correct, my Lord.

Q (Mr Vanhegan, QC) …Is it not a key aspect of CRSD that a patient has difficulty

[65] Transcript Day 1/pp.150*ff*.

going to sleep or staying asleep, is that not correct?

A (Professor Roth) That is not correct.

Q (Mr Vanhegan, QC) Just to be absolutely clear, Professor, it is not a key aspect of CRSD that a patient has difficulty going to sleep or staying asleep? That is not a key aspect, is it?

A (Professor Roth) Again, we are talking at cross-purposes. You know, if a person has a circadian rhythm sleep disorder it means that he or she is complaining of difficulty falling asleep or staying asleep, and that difficulty is due to a mismatch between where their biological clock is or where their body wants to go to sleep, versus where they socially want to go to sleep...

59. It is clear to see why DSM-IV sought to differentiate Circadian Sleep Rhythm Disorder from Primary Insomnia, and the Skilled Person would have been well aware of the need to be able to differentiate the two.

(v) Diagnosing non-restorative sleep

60. It was Professor Roth's position that the diagnosis of Primary Insomnia generally, and non-restorative sleep in particular, was subjective. Because this was a point on which he and Professor Morgan did not necessarily see eye-to-eye, I begin by a quotation from Roth 3, which sets out Professor Roth's position on this:[66]

"6.35 As at the Priority Date, I would expect the skilled person to have a working understanding of the definition of primary insomnia in the DSM-IV and the definition of nonorganic insomnia in the ICD-10, and to understand that those diagnoses are intended to be equivalent. I would expect the skilled person to understand the following as part of their background/common general knowledge.

6.36 First, primary insomnia is a persistent complaint of difficulty falling asleep, maintaining sleep, or of non-restorative sleep (called "poor quality of sleep" in the ICD-10). Both the DSM-IV and the ICD-10 diagnostic criteria direct attention to the patient's "complaint". This underscores that the diagnosis of primary insomnia is made based on the patient's subjective report of difficulty falling asleep or maintaining sleep, or their subjective feeling that their sleep has not been restorative.

…

6.39 Because primary insomnia is diagnosed based on the patient's complaint of difficulty falling asleep, maintaining sleep, or of non-restorative sleep, the primary method of diagnosis is by taking a thorough medical (including sleep) history. In addition to exploring the nature and duration of the patient's dissatisfaction with their sleep, the sleep history should cover other aspects of the diagnostic criteria, such as daytime impairment and distress (criterion B in the DSM-IV; criteria C and D in the ICD-10). The history taking will also elicit information relevant to determining whether the insomnia is "primary" or "nonorganic", for example by discussing other symptoms or medical conditions and substance use (criteria C to E in the DSM-IV; general discussion under the "Diagnostic guidelines" heading in the ICD-10).

[66] Emphasis added.

> 6.40 A comprehensive medical (including sleep) history should be supplemented by a physical examination. In some cases, it may also be helpful to ask the patient to complete a sleep diary in which the patient records matters such as their bedtime, arising time, medications, alcohol use, estimated time to fall asleep, estimated duration of sleep, estimated number of awakenings, and the quality of their sleep/restorative quality of their sleep. A physical examination and a sleep diary can assist in identifying whether the insomnia is "primary/nonorganic" or secondary to some other cause. A sleep diary may also assist in assessing the nature and severity of the patient's sleep disturbances.
>
> 6.41 As at the priority date, objective methods for monitoring a patients sleep – polysomnography and actigraphy – were used frequently in research but were not indicated for the routine assessment, diagnosis and treatment of insomnia. If abnormal physiological events during sleep (such as sleep apnea or periodic limb movements) are the suspected cause of insomnia, polysomnography is necessary to confirm or exclude those possibilities. Actigraphy, which provides data on activity patterns over multiple days, can be useful in assessing sleep-wake schedule disorders, i.e. circadian rhythm sleep disorders.
>
> 6.42 I have been asked by the Instructing Solicitors whether actigraphy and/or polysomnography can be useful in assessing whether an insomnia patient's sleep is non-restorative or whether that patient has experienced an improvement in the restorative quality of their sleep. Both actigraphy and polysomnography have a multitude of outputs such as total sleep time, sleep latency and sleep efficiency. Importantly, no output of actigraphy or polysomnography has been validated for the purpose of determining whether a patient's sleep is non restorative, or whether that patient has experienced an improvement in the restorative quality of their sleep. The restorative quality of sleep can only be determined based on the patient's subjective report. There are no data to suggest that an improvement in the qualitative aspects of sleep can be measured objectively. In addition, there are no data to support the use of techniques such as actigraphy or polysomnography with an improvement in an insomnia patient's subjective experience of the restorative quality of their sleep."

61. It is clear that Professor Roth considered that all aspects of Primary Insomnia – difficulty in initiating sleep, difficulty in maintaining sleep and nonrestorative sleep – were subjective in their nature and in their diagnosis. Indeed, whilst it may be possible to measure some of these aspects – for instance, the time a person spends asleep – a purely objective diagnosis (i.e., a diagnosis based upon purely external measures) is difficult because "difficulty in initiating sleep", "difficulty in maintaining sleep" and "non-restorative sleep" all contain subjective elements based upon the individual experience of the (non-) sleeper. Thus, whilst it may be possible, through polysomnography and actigraphy, to say that an individual fell asleep at 11:00pm, such external measures cannot say how long that individual was actually trying to fall asleep (i.e., latency is, inevitably, subjective).

62. Whatever the position as regards Primary Insomnia characterised by difficulty in initiating sleep and difficulty in maintaining sleep, it is clear that Primary Insomnia characterised by non-restorative sleep is a purely subjective phenomenon because only the individual in question can say whether his or her sleep has been restorative. More specifically:

(1) Professor Roth's unequivocal evidence was to this effect.[67]

(2) Professor Morgan appeared to accept that non-restorative sleep was a subjective phenomenon.[68] In a book co-authored by him,[69] Professor Morgan stated:

> "Sleep is a very private experience and subjective reports provide descriptions of sleep as it is experienced by the sleeper. Broadly, these reports may be of two kinds: experiences of sleep quality; and estimates of sleep quantity. As regards sleep quality, it should be emphasised that the experience of sleep is accessible only to the individual sleepers. Only they know whether their sleep has been restful and refreshing. In addition, criteria for a 'good night's sleep' are also, to some extent, personal. Whether individuals sleep for 2 hours per night, or for 10 hours per night, if they awake, satisfied with their sleep quality, and can function efficiently during the day, then their sleep may be considered satisfactory (or normal for them)."

(3) However, despite this acceptance, Professor Morgan appeared to suggest that it was common general knowledge that this essentially subjective phenomenon could be objectively measured:[70]

> "4.47 Actigraphy is another objective method of monitoring a person's rest/activity cycles. A small device is worn to measure gross motor activity. The unit is usually in a wristwatch-like package worn on the wrist…
>
> 4.48 At its most simple, actigraphic measurements are movement 'counts' recorded over time. Signal processing algorithms can then be applied to determine whether the movement patterns are associated with the sleeping or waking state. From this, sleep latency and total sleep duration can be determined, and the sleep duration used to calculate sleep efficiency. The activity level can also indicate motility of the subject during sleep (activity level). By 2001, more sophisticated actigraphs measured not only movement but also heart rate, etc and different algorithms were applied to assess different aspects of a patient's sleep. It was found that actigraphy "may also provide an index of sleep quality": Lichstein and Morin (2000). Therefore, actigraphy, with the appropriate interpretive algorithm, could be used to assess/estimate not only the physical characteristics of sleep which the actigraph measured/monitored but also as a proxy for the subjective aspects such as "quality" of sleep. The skilled person would understand that lower activity levels (representing more restful sleep) would mean the subject is more likely to report an increase in the quality of sleep. Higher activity levels would indicate the subject is experiencing restless sleep, and would be a proxy for poorer quality of sleep (in the context of ICD-10, i.e. non-restorative sleep).
>
> 4.49 A 'state-of-the-science' review of actigraphy findings, commissioned by the American Sleep Disorders Association (ASDA), was published in May 1995

[67] See paragraph 60 above, which stance Professor Roth maintained when giving his evidence.

[68] E.g., paragraph 4.22 of Morgan 1: ""Non-restorative sleep" is defined as the subjective feeling that sleep has been insufficiently refreshing…"; also paragraph 4.20 of Morgan 1.

[69] Morgan and Closs, *Sleep Management in Nursing Practice: An Evidence-Based Guide*, 1999 (**Morgan and Closs 1999**) at p74.

[70] Morgan 1 (emphasis added).

(**Sadeh *et al* 1995**).[71] This review informed the official ASDA guidance, which was simultaneously published in the same journal.[72] In the section on the use of actigraphy in drug studies, [Sadeh et al 1995] notes:

> "In most studies, the anticipated decrease in activity (associated with higher sleep quality) has been reported."

At the time, this was a reasonable reporting standard to adopt. There was still a flexibility in the ways in which actigraphy was interpreted but in general, if high levels of motility were recorded during sleep, the skilled person was entitled to infer that the patients were having a more restless sleep and would be more likely to awaken complaining of being less refreshed.

4.50 This same review notes:

> "Many researchers have used some measures of activity counts that are to some extent arbitrary and relate to the physical features of the analog movement detector as well as to the sampling rates and summary interval used. Because different researchers have used different devices with distinct physical and electronic features, such measures preclude interstudy comparison, and the results are hard to interpret."

4.51 The quote reflects the position at the Priority Date in that it was difficult to compare subjective results and data from different studies as there was not a reporting standard on the threshold value and epoch duration. This allowed for differing results based on differing parameters."

I am afraid that I reject this evidence, not merely as not representing the understanding of the Skilled Person, but as not representing the true position, in 2001 (or earlier), as to how non-restorative sleep might be diagnosed. Because this is an unequivocal rejection of Professor Morgan's expert evidence, I need to explain my reasons with some care:

(a) Morgan 1/§4.48 contains a single reference to the academic literature, that is to Lichstein and Morin, *Treatment of Late Life Insomnia*, 2000 (**Lichstein and Morin 2000**) at p.94.[73] Certainly, there is a sentence (which Professor Morgan accurately quotes) which reads as follows:

> "Actigraphy may also provide an index of sleep quality; it has been shown that movement during sleep is strongly related to sleep diary ratings of sleep quality (Horne, Pankhurst, Hume and Diamond, 1994)."

This is the only sentence in this part of the book dealing with actigraphy and sleep quality. Whether "sleep quality" is being used in the ICD-10 sense or in a looser sense is not made clear.[74] There is only one reference

[71] Saheh, Hauri, Kripke and Lavie, *An American Sleep Disorders Association Review: The role of actigraphy in the evaluation of sleep disorders*, published in (1995) 18(4) Sleep 288-302.

[72] ASDA, *An American Sleep Disorders Association Report: Parameters for the Use of Actigraphy in the Clinical Assessment of Sleep Disorders* (**ASDA 1995**), published in (1995) 18(4) Sleep 285-287.

[73] Footnote 31 in Morgan 1.

[74] This is not intended as a criticism: sleep quality can, quite properly, be used in a non-technical (i.e., non-ICD-10) way.

provided, to **Horne 1994**. When that paper is turned up, it is quite clear that Lichstein and Morin are not making any statement about actigraphy being capable of measuring or diagnosing non-restorative sleep or poor quality of sleep in the ICD-10 sense:

(i) The paper is (unpromisingly for Professor Morgan's purposes) entitled *A Field Study of Sleep Disturbance: Effects of Aircraft Noise and Other Factors on 5,742 Nights of Actimetrically Monitored Sleep in a Large Subject Sample*.

(ii) The summary provides as follows:

> "This field study assessed the effects of nighttime aircraft noise on actimetrically measured sleep in 400 people (211 women and 189 men; 20-70 years of age; one per household) habitually living at eight sites adjacent to four UK airports, with different levels of night flying. Subjects wore wrist-actimeters for 15 nights and completed morning sleep logs. A sample of 178 nights of sleep electroencephalograms (EEGs) were recorded synchronously with actigrams. The EEG was used to develop filters for the the raw actigrams, in order to (1) estimate sleep onset and (2) compare actigrams with aircraft noise events (ANEs). Actigrams, filtered to detect the onset of discrete movements, were able to detect 88% of all EEG-determined periods of interim wakefulness of > 15 seconds and periods of movement time of > 10 seconds. The main findings were: (1) actimetry and self-reports showed that only a minority of ANEs affected sleep, and, for most of our subjects, the domestic and idiosyncratic factors have much greater effects; (2) despite large between site variations in ANEs, the difference between sites in overall sleep disturbance was not significant; (3) there was a diminished actimetric response to ANEs in the first hour of sleep and, apparently, also in the last hour of sleep; (4) men had significantly more discrete movements than women and were more likely to respond to ANEs…"

(iii) It is quite clear that this article, whilst it has a great deal to contribute to the correlation between sleep and aircraft noise, says literally nothing about actigraphy and the measurement of non-restorative sleep in insomniacs. Indeed, it is not even known whether the individuals in the study were insomniacs. That does not appear to have been screened for (either way) in the compilation of the sample population.

I do not consider that the passage that I have underlined in the quote of paragraph 4.48 of Morgan 1 to be supported by the literature cited by Professor Morgan in that paragraph. I do not consider that this passage reflects what Lichstein and Morin 2000 was saying. Professor Morgan's failure to reference Horne 1994 is disappointing; and does not reflect what I would expect an expert to say in these circumstances when providing expert opinion evidence.

(b) Turning to Sadeh *et al* 1995 – which was quoted in paragraphs 4.49 and 4.50 of Morgan 1 – there is (again) no support for the proposition advanced by Professor Morgan that actigraphy can be used to diagnose non-restorative sleep. The paper concludes:

> "The role of actigraphy in the assessment of sleep disorders have been strongly supported in some areas and only partially supported or rejected in others…
>
> The following statements summarize our impressions and best judgment on the role of actigraphy in the evaluation of sleep disorders. Actigraphy provides a cost effective method for longditudinal, natural, assessment of sleep-wake patterns. The method can be used to distinguish between wakeful and sleep states, with wide margins of error for subjects lying awake motionless (e.g., insomnia patients). Despite differences in its accuracy level, actigraphy can assess the rest-activity patterns of insomniacs and individuals with schedule disorders who require repeated, longitudinal monitoring (or when a more elaborated sleep analysis is not required). Although actigraphy is sensitive to sleep-related respiratory disturbances, it is not suitable for assessing such disturbances. A clinical diagnosis and consideration of treatment should always be based on full-laboratory testing. Finally, actigraphy is not suitable for clinical assessment in cases in which the subject may have some underlying motivation to feign a sleep problem (e.g., insurance claims, avoiding undesired jobs or military tasks)."
>
> Again, it seems to me that Professor Morgan should not have cited the paper without some proper explanation as to what it actually taught or explained.

(c) It follows that the quotation from Sadeh *et al* 1995 in paragraph 4.49 of Morgan 1 and (in particular) Professor Morgan's statement in the text that follows the quotation from Sadeh *et al* 1995 is also misleading.

(d) Paragraph 4.49 of Morgan 1 states that Saheh *et al* 1995 "informed the official ASDA guidance", the implication being that what Professor Morgan says about Sadeh *et al* 1995 is reflected in ASDA 1995. Not only does ASDA 1995 not support the proposition advanced by Professor Morgan, it appears to contradict it. Thus, ASDA 1995 states:

> "…Even though actigraphy is less intrusive and less expensive than PSG [polysomnography], the findings from these two objective tests do not usually add to the diagnosis of insomnia in most patients. The diagnosis of insomnia is best determined by obtaining an accurate and thorough history.
>
> …
>
> Actigraphy is not indicated for the *routine* diagnosis, assessment of severity, or management of any of the sleep disorders, including the insomnias, obstructive sleep apnea syndrome and periodic limb movement disorder."

63. I find that the Skilled Person would understand that Primary Insomnia characterised by non-restorative sleep would be diagnosed in the manner described by Professor Roth in the passages set out in paragraph 60 above, that is by ascertaining (typically by taking a history) how, subjectively, the patient considered his or her quality of sleep (using that term in the ICD-10 sense).

64. Questionnaires might be used to obtain this data. Because it featured in the trial, I should describe one such questionnaire, namely the **Leeds Sleep Evaluation Questionnaire**:

(1) This questionnaire was considered in a paper Parrott and Hindmarch, *Factor Analysis of a Sleep Evaluation Questionnaire* published in (1978) 8 Psychological Medicine 325-329 (**Parrott and Hindmarch 1978**).

(2) The questionnaire is set out in an appendix to the paper, and is as follows:

"**The Sleep Evaluation Questionnaire**

How would you compare getting to sleep using the medication with getting to sleep normally, i.e., without medication?

1. Harder than usual / easier than usual

2. Slower than usual / quicker than usual

3. Felt less drowsy than usual / felt more drowsy than usual

How would you compare the quality of sleep using the medication with non-medicated (your usual) sleep?

4. More restless than usual / more restful than usual

5. More periods of wakefulness than usual / fewer periods of wakefulness than usual

How did your awakening after medication compare with your usual pattern of awakening?

6. More difficult than usual / easier than usual

7. Took longer than usual / took shorter than usual

How did you feel on waking?

8. Tired / alert

How do you feel now?

9. Tired / alert

How was your sense of balance and coordination upon getting up?

10. More clumsy than usual / less clumsy than usual

Note. A 10cm line separates the 2 halves of each question. The questionnaire instructions are:

'Each question is answered by placing a vertical mark on the answer line. If no change was experienced, then place your mark in the middle of the line. If change was experienced, then the position of your mark will indicate the nature and extent of the change, i.e. large changes near the ends of the line, small changes near the middle.'"

(3) There was a good deal of debate before me about what these questions – in particular, questions 4 and 5 – were getting at. Mr Vanhegan, QC, contended that questions 4 and 5 were directed at quality of sleep in the non-technical sense. In other words, the answers to such questions would take account of factors like

slow sleep latency or wakefulness in the middle of the night, which (whilst obviously relevant to insomnia in general terms) are not relevant to insomnia characterised by non-restorative sleep. Professor Roth did not accept this characterisation of the questions, and considered that they were in fact directed to quality of sleep in the ICD-10 sense and were, therefore, directed to the question of non-restorative sleep.

(4) I do not consider that this debate was particularly helpful in terms of resolving the issues before me. The fact is that the questionnaire is only as good as the use it is put to by a clinician or researcher. In a poorly conducted trial, participants may not be appropriately selected in terms of what is being tested for, and the questionnaire may not be fit for purpose or appropriately explained. Context is everything, and I do not consider that I am particularly assisted by consideration of the questionnaire independent of a particular study or research programme.

(5) That said, since the matter was debated before me, I should express a view as to what the Skilled Person would understand by the questionnaire, viewing it on its own and independent of a particular study or research programme. Viewed in this light, I have no doubt that the Skilled Person would attach a technical meaning to the term "quality of sleep" – i.e., would understand it to be a reference to non-restorative sleep – rather than using it as a layman would, to take into account all factors that make up a "good night's sleep" – i.e., difficulty going to sleep, waking up in the night, waking up early, and not being restored by sleep (and so on).

(6) I reach this conclusion for the following reasons:

(a) The Skilled Person will be seeking answers to the questions posed in the questionnaire for a reason. The Skilled Person will be seeking to measure something – and it is obvious that the Skilled Person will regard the questions in the questionnaire as being directed to the established characteristics of insomnia. In short, the Skilled Person, using the questionnaire for purposes of understanding Primary Insomnia, will consider that the questions are directed to the diagnostic criteria for that condition.

(b) Indeed, it is very clear from the article that that is exactly how the authors perceive the questions:[75]

> "Hypnotic drugs generally aid getting to sleep and improve its quality…but awakening is often made more difficult, and behaviour in the mornings following medicated sleep is sometimes impaired…An initial questionnaire was devised to cover different aspects of sleep and early morning behaviour, with questions being generated from a literature survey…The initial questionnaire was slightly modified on the basis of comments made by normal and insomniac subjects in 2 pilot studies (unpublished). The remaining 10 questions comprised the present Sleep Evaluation Questionnaire. The questions were grouped into the following 4 chronological areas:

[75] At p.325 (omitting references and adding emphasis).

(1) The ease of getting to sleep (GTS); questions 1, 2 and 3.

(2) The perceived quality of sleep (QOS); questions 4 and 5.

(3) The ease of awakening from sleep (AFS); questions 6 and 7.

(4) The integrity of behaviour following wakefulness (BFW); questions 8, 9 and 10.

…"

(c) Accepting that the significance of these questions would be coloured *(i)* by the date at which the questions would be asked (here: the Priority Date is the relevant date when seeking to understand what the person asking these questions would be intending) and *(ii)* by the nature of the investigation itself (a factor unknown in this context), I have no doubt that the Skilled Person would regard QOS or quality of sleep as being used in its technical sense, in particular given that the questions are targeted at specific and separate chronological aspects of a night's sleep of a given individual. Thus, QOS is chronologically distinct from *(i)* GTS and *(ii)* AFS. To allow difficulty in getting to sleep to colour perceived quality of sleep would be to misunderstand the significance of the chronological segmentation of these questions.[76]

(vi) Methods of treatment for Primary Insomnia in general, and non-restorative sleep in particular

65. I should stress that I am, in this section, considering the Skilled Person's common general knowledge as at the Priority Date, but disregarding the teaching of the Patent, whatever that teaching might be. I should also say that I am – for the purposes of this section – disregarding the pleaded prior art. I will, of course, consider that prior art in detail when I turn to consider the issues of (in)validity that arise in this case.

66. It was well-understood, as at the Priority Date, that benzodiazepines and related drugs were hypnotics capable of use in ameliorating or eliminating Primary Insomnia and so could be indicated for the treatment of Primary Insomnia. However, there were distinct disadvantages to the use of such hypnotics, particularly in the aged. This was common general knowledge in the United Kingdom (as well as internationally, including the United States). Where there was a difference – but I do not consider it to be a relevant one – was the extent to which the use of benzodiazepines differed according to jurisdiction. That, in my judgment, had nothing to do with the common general knowledge as to these drugs, but merely reflected a different attitude to the known disadvantages in their use. More specifically:

(1) In paragraph 6.53 of Roth 3, Professor Roth stated:

[76] Professor Morgan considered that the Skilled Person would not understand the questionnaire in this way: paragraphs 3.10 to 3.11 of Morgan 2. He considered (paragraph 3.11 of Morgan 2) that a response to question 4 of the questionnaire "reflects the totality of a subject's experience of different insomnia symptoms. Certainly, this is how the skilled person as at 2001 would have understood responses to questionnaire items which required those with insomnia symptoms to rate their quality of sleep". For the reasons I have given, I do not accept this evidence.

"Benzodiazepine receptor agonists are, and were at the Priority Date, the mainstay for the pharmacological management of insomnia. As reflected in the balance of the Consensus Paper [a document that I shall come to describe later on in this judgment], benzodiazepine receptor agonists include classic benzodiazepines (such as triazolam, temazepam and flunitrazepam) and the newer non-benzodiazepine-receptor agonists. The latter, including zopiclone, zolpidem and zaleplon, are sometimes referred to as the "z-drugs". These z-drugs are sometimes referred to as non-benzodiazepines as they do not have a benzodiazepine structure. However, they all bind to the benzodiazepine receptor of the $GABA_A$ complex. Like the classic benzodiazepines, they are also all indicated one or more quantitative aspects of insomnia (i.e., sleep induction, maintenance and/or early awakening) but none have been shown to improve, or are approved to treat, the qualitative aspect of insomnia (i.e., the restorative quality of sleep)."

(2) In Morgan 1, Professor Morgan considered the treatments of insomnia generally. These paragraphs do not appear to be confined to treatment for Primary Insomnia:

"4.32 In 2001, treatments for insomnia included sleep hygiene advice, cognitive behavioural therapy (CBT) and pharmacological treatments. Pharmacological treatments included benzodiazepines and "Z" drugs, antidepressants, antipsychotics, sedating antihistamines and herbal remedies. Pharmacological treatments were effective in the short term but, by 2001, longer-term use (which was common) had become the subject of clinical and social concern. All benzodiazepines were associated with tolerance, dependence, withdrawal symptoms, and psychomotor performance deficits. Some of these drugs were also associated with psychiatric symptoms and personality changes. Cognitive Behavioural Therapy for Insomnia (CBT-I) was, in comparison, both effective and safe. Reviewing 48 clinical studies of Cognitive Behavioral Therapy for Insomnia (CBT-I), Morin et al (1999) concluded that an average of 5 hours CBT-I produced significant and lasting improvements in both sleep structure and subjective sleep satisfaction among 70-80% of treated patients.

4.33 In 2001, we were at a cross-over point where the disadvantages of long-term benzodiazepine use were widely recognised and clinical and research attention was increasingly focussed on drugs (and non-pharmacological treatments) that could treat insomnia without side effects. As referenced in paragraph 4.3(d) the (then) Committee on the Review of Medicines published a systemic review of benzodiazepine drugs which was relevant at this time. It was conducted to update prescribing guidance on official "data sheets" for all benzodiazepines (i.e., benzodiazepines used as both anti-anxiety and hypnotic drugs) information from which accompanies any given drug in the British National Formulary. The shorter acting benzodiazepine hypnotics were indicated for "short term treatment of insomnia (this indication is not applicable to oxazepam)". It was acknowledged that "the short half-life of this group of benzodiazepines may offer advantages in the treatment of the elderly". Longer acting benzodiazepines were indicated for "short-term treatment of insomnia where daytime sedation is acceptable."

A few points must be made in relation to these paragraphs (and other parts of Morgan 1):

(a) These paragraphs are explicitly dealing with insomnia generally. Paragraphs 4.34 and 4.35 of Morgan 1 then address the treatment of Primary Insomnia as at 2001. Professor Morgan notes that "the treatment of a patient suffering from primary insomnia would typically be the same,

no matter which diagnostic symptom of the primary insomnia had been identified".[77] Professor Morgan goes on to say that "[i]f a drug was found to be beneficial for treatment of primary insomnia, it would typically be expected to benefit all aspects of primary insomnia and not just the symptoms of primary insomnia reported by a particular patient."[78]

(b) Professor Morgan does not, in his paragraphs dealing with Primary Insomnia, suggest any other forms of treatment other than those described in his paragraphs on insomnia generally.[79] In particular, Professor Morgan does not suggest in these paragraphs that melatonin was indicated for the treatment of Primary Insomnia. He does say this about melatonin:[80]

> "As I reference above in paragraph 3.2, treatment options were strongly influenced by international research and consensus, but differences in the way research and sleep medicine were organised within different countries remained influential. An example is that, in 1995, the then UK Medicines Control Agency ruled that melatonin was "medicinal by function", and as such required a drug license and should not be available over the counter. At the same time, however, melatonin remained available over the counter in other countries, most notably the US."

Of course, I accept that regulation of medicines and pharmaceuticals varies from jurisdiction to jurisdiction. But I fail to see the relevance of the assertion (no doubt correct) that melatonin was differently regulated in the United Kingdom when compared to the United States. What would be relevant was if melatonin was in some way indicated as "medicinal by function in terms of improving non-restorative sleep". But Professor Morgan comes nowhere close to making this statement in these paragraphs, and I am afraid that I regard the quotation above more as a gratuitous reference to melatonin in the period prior to 2001 than as actually assisting me in the issues I must determine.

(c) I do not accept that the Priority Date – or the period around the Priority Date – represented some kind of "cross-over" point at which the attitudes towards the use of benzodiazepines was changing and the direction of research was energised towards alternative approaches to the treatment of insomnia. On this point, I prefer the evidence of Professor Roth, who considered that the concerns regarding benzodiazepines and other hypnotics existed well before the Priority Date and persist to this day:

(i) In paragraph 4.19 of Roth 4, Professor Roth comments as follows:

> "In relation to paragraph 4.33 [of Morgan 1], Professor Morgan suggests that in 2001 there was a "cross-over point" in relation to new treatments for insomnia. I do not consider that the skilled person would consider

[77] Paragraph 4.34 of Morgan 1.

[78] Paragraph 4.35 of Morgan 1.

[79] Although Professor Morgan does repeat, in the latter half of paragraph 4.35, the concern regarding the use of benzodiazepines in older patients.

[80] Paragraph 4.34 of Morgan 1.

2001 as a cross-over point and I am not aware of any reason why it would be regarded in that way."

(ii) Professor Roth was cross-examined on this:[81]

Q (Mr Vanhegan, QC)	As at the Priority Date, the skilled person knew that there were severe problems with benzodiazepine agonists to treat insomnia and primary insomnia, especially in elderly patients. Is that not correct?
A (Professor Roth)	It depends how you define severe problems and how you define in terms of prevalence.
Q (Mr Vanhegan, QC)	Let us again see if we can break it down, Professor. This is all in the UK, all as at 2001. It had been known that for a long time, prior to 2001, all benzodiazipine therapy should be withdrawn unless used or given on an occasional basis, in relation to the elderly?
A (Professor Roth)	I have no idea why that became an issue in 2001. I think it was an issue before 2001 and continues to be an issue beyond 2001…There is great concern. There is great concern about the use of benzodiazepines in the elderly, absolutely. …
Q (Mr Vanhegan, QC)	What I am suggesting is that all of those [i.e., downsides to prescribing benzodiazepines, which Professor Roth accepted] would have been well-known to the skilled person as at 2001 and that as a result of those known effects in the elderly people, there was a strong demand in the UK not to prescribe benzodiazepines to elderly patients, if at all possible?
A (Professor Roth)	I do not know how to answer that question other than they are still and were then and continue to be the most commonly prescribed treatments for insomnia.
Q (Mr Vanhegan, QC)	The fact that they may be the most common does not negate the point I am putting to you, is it, professor, which is, as at 2001, there was a strong drive not to prescribe them to the elderly because of all those side effects?
A (Professor Roth)	First of all, I do not think it has anything to do with 2001. There has been a continuous

[81] Transcript Day 1/pp.186ff.

> concern about the…use of benzodiazepines in all populations, including the elderly.

(d) As I noted in paragraph 66(2)(a) above, Professor Morgan considered that the use of benzodiazepines and other hypnotics in the case of Primary Insomnia would be used to treat all presentations of Primary Insomnia and would be considered to benefit all such presentations. I do not understand Professor Morgan to be saying that the treatment of non-restorative sleep had specifically been considered and that benzodiazepines were specifically beneficial to the case of non-restorative sleep. Rather, Professor Morgan was saying that benzodiazepines were prescribed with an altogether broader brush, where no distinction was drawn between the three different symptoms of Primary Insomnia. If Professor Morgan was going further, then I do not accept his evidence.

(e) In reply, Professor Roth said this:[82]

> "In paragraphs 4.34 to 4.35 [of Morgan 1], Professor Morgan suggests that treatment of primary insomnia would typically be the same "irrespective of the diagnostic symptom" (i.e., sleep initiation, sleep maintenance, [non-restorative sleep]) and that a treatment found to be effective for one of the diagnostic complaints of primary insomnia reported by a patient would also typically be expected to benefit patients suffering from other complaints of primary insomnia. I do not agree. In 2001, no treatment had been found to be effective in treating [non-restorative sleep] in primary insomnia patients…"

67. Professor Roth was clear in his evidence that, as at the Priority Date, there was no treatment for non-restorative sleep and – relatedly – there was no recognition that melatonin might play a role in the successful treatment of complaints of non-restorative sleep. Professor Morgan's evidence on this point was, I am sorry to say, not satisfactory when coming from someone presenting as an expert in this area. That evidence was, in the first place, nebulous in the extreme; and, to the extent that Professor Morgan could be understood to be advancing clear propositions, they were simply unsupported by the other evidence before me (including the material referred to by Professor Morgan in his own reports). Once again, it is important to state with specificity why this is the case, since I am disbelieving and rejecting Professor Morgan's evidence:

(1) As Neurim and Flynn made clear,[83] this case is unusual in that there were a number of papers setting out the general consensus amongst persons skilled in the art on this point just before the Priority Date. I begin with a description of these **Consensus Papers**:

(a) The first such paper that I will refer to is Roth, Hajak and Üstün, *Consensus for the Pharmacological Management of Insomnia in the New Millenium*, published in 2001 55(1) International Journal of Clinical Practice 42-52 (the **Roth Consensus Paper 2001**. This paper arose out of

[82] Paragraph 4.20 of Roth 4.

[83] See, for example, paragraph 76 of Neurim and Flynn's written opening submissions. Since the point was an important one, it is unsurprising that the point was made on several occasions.

the XXII Collegium Internationale Neuro-Psychopharmacologicum Consensus Workshop that met in Belgium in July 2000. As to this paper:

(i) It begins by making clear that it was referring to Primary Insomnia as I have defined it. The DSM-IV and ICD-10 definitions are set out (as well as the ICSD definition, which I have adverted to, but not described in detail in this judgment).

(ii) It explains the nature of, and importance of, non-pharmacological treatment modalities, going on to say that pharmacotherapy should be the primary therapy for some patients with insomnia and adjunctive for others.

(iii) Moving on to the specifics of pharmacotherapeutic options for the management of symptoms of insomnia, there is detailed consideration of the benzodiazepine-receptor agonists as the "drugs of choice", including consideration of specific drugs in this class. It is unnecessary to set out the detail.

(iv) The paper then goes on to consider other pharmacotherapeutic options apart from the one already discussed. Under the side heading "Melatonin", the paper says this:

> "Melatonin is a hormone secreted by the pineal gland. Its secretion has a circadian rhythm and is inversely related to light exposure. Because peak melatonin secretion is at night, it has received attention as a possible soporific. However, melatonin secretion peaks at night in both diurnal and nocturnal animals, making it unlikely it is fundamentally involved in sleep processes. Although this hormone acts as a chronobiotic and may be useful in treating abnormalities of the circadian rhythm, it is premature to propose a primary role for this hormone in the treatment of insomnia."

So far as sleep disorders are concerned, a role for melatonin was thus not indicated for insomnia, but might be indicated for Circadian Rhythm Sleep Disorder, which (for reasons explained in paragraphs 56*ff* above) is a disorder unrelated to and to be distinguished from Primary Insomnia.

(v) The paper concludes:

> "Insomnia is a common disorder that is associated with significant impairments in quality of life and serious co-morbidities. Despite its prevalence, insomnia is not sufficiently recognised or treated. Patients should be treated only after a complete history and physical examination are conducted to characterise the disorder and detect the presence of associated or complicating conditions. The treatment plan should be tailored to the individual patient but can include a combination of pharmacological and non-pharmacological (e.g., behavioral) therapies. Benzodiazepine-receptor agonists are the drugs of choice in patients with insomnia. The newer benzodiazepine-receptor agonists are important additions to our therapeutic armamentarium. Non-benzodiazepine benzodiazepine-receptor agonists offer the benefits of the older agents and more closely approach the characteristics of the ideal hypnotic (e.g., less

> rebound insomnia and less sleep stage effect). The physician treating the patient with insomnia now has a range of medications that can be used to tailor therapy to the individual patient. The goal of treatment should be to treat in direct response to sleeplessness with medications that minimise residual effects. These consensus recommendations should serve to improve both direct patient care and the response of governmental/regulatory bodies to the management of this disabling condition."

(b) The second such paper is a consensus statement co-ordinated by Professor Josephine Arendt (a leader in the understanding of melatonin, based at the University of Surrey), and endorsed by a number of other researchers/clinicians in this field (the **Arendt Consensus Paper 2000**). The paper, entitled *In what circumstances is melatonin a useful sleep therapy? Consensus statement, WFSRS*[84] *Focus Group, Dresden, November 1999*, was published in (2000) 9 Journal of Sleep Research 397-398. The paper states:

> "Many claims have been made for the efficacy of melatonin as a sleep therapy (and indeed as a treatment for numerous other conditions). Induction of sleepiness by melatonin taken during the day has been known for many years. This focus group was assembled in order to define as far as possible the conditions in which there is good evidence for the usefulness of melatonin, those where evidence is lacking and the dose range for specific objectives. An important objective was to assess any known risks of long-term or short-term treatment.
>
> …
>
> Daily melatonin administration (5 mg) is able to maintain synchronised sleep wake and core temperature rhythms in sighted subjects transferred to a dim light environment conducive to free-running and in some sighted subjects it will resynchronise free-running rhythms…Blind subjects frequently suffer from sleep disorders. There is a clear association between degree of visual loss and the incidence of free-running circadian rhythms with the consequent non-24h sleep-wake disorder…Melatonin (5 mg or less) clearly helps blind subjects to sleep when the internal clock is in antiphase to the 24h day. Most recently, when treatment is timed to the advance portion of the PRC, it has become clear that melatonin will fully synchronise the circadian clock to 24h in some blind subjects, and this can be maintained when the dose of 5-10 mg is reduced…There is positive data concerning the use of timed melatonin in delayed sleep phase syndrome…It has been used to treat sleep disorders in very disabled children, many with visual problems…
>
> Evidence that melatonin can be useful in the treatment of insomnia in older people is inconsistent. Although a 'melatonin deficiency' syndrome associated with poor sleep has been reported in old age (Haimov *et al* 1994; Haimov *et al* 1995) there is inconsistency in the findings and both medication and the health status of older subjects may be partial causes of this apparent melatonin deficiency. In fact, most recent data suggest that nocturnal melatonin concentrations in most healthy older people are comparable to those in young

[84] This is the World Federation of Sleep Research Societies.

> adults (Zeitzer *et al* 1999) and that it is not the amount of melatonin produced, but rather circadian phase, which may be related to sleep quality. There appears to be no point in addressing sleep disorders of unknown origin with melatonin treatment.
>
> All participants considered that care was essential in the use of melatonin. Reports of deleterious effects are rare (e.g., Middleton *et al* 1996). Although no significant side-effects have been reported in normal healthy volunteers, there is no long term safety data and little information on its use with concomitant medication. Of particular concern are its effects on reproductive function, which remain to be fully assessed. Moreover, there is no conclusive information on the residual effects of melatonin. They include exacerbation of epilepsy (but with other data that has shown beneficial effects) and possible withdrawal problems in psychiatric patients. In countries where melatonin is freely available, the uncontrolled use without regard to its functional properties is likely to lead to disillusion in terms of its therapeutic benefit."

(2) Professor Roth's view was that the Consensus Papers set out the common general knowledge of the Skilled Person as at the Priority Date. In particular, he noted:[85]

> "…it was known that melatonin could be useful in the treatment of circadian rhythm disorders, but it was not thought to be useful for the treatment of primary insomnia. In some countries where melatonin was available for sale as an over-the-counter dietary supplement, it was marketed using claims that it could improve sleep generally, but I did not take those claims seriously nor, in my opinion, were they taken seriously in the sleep medicine community generally."

I consider that this is a fair summary of what the Skilled Person would have known or derived from these papers.

(3) The next question that arises is what Professor Morgan made of these papers, since they appear, on their face and according to Professor Roth, to be pertinent (Professor Roth put it more highly than this, and I will express a view in due course) to the question of whether melatonin was implicated in the treatment of Primary Insomnia generally and non-restorative sleep in particular. As to this:

(a) Professor Morgan recognised that these papers had standing and authority. Speaking of the first, he said in the course of his cross-examination:[86]

> "I do not have the expertise of these individuals and I take their consensus as having the authority of people working in this area."

(b) Professor Morgan was aware of both papers at the time of signing Morgan 1, but he made no reference to them in Morgan 1.[87] The obvious question arises as to <u>why</u> no such reference was made. As to this:

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[85] At paragraph 6.63 of Roth 3.

[86] Transcript Day 3/p.442

[87] As to the first, see Transcript Day 3/pp.444 to 445. As to the second, see Transcript Day 3/p.447. Professor Morgan was – unsurprisingly – less clear as to when he became aware of them. He considered that he would have been aware of the second contemporaneously, and the first "maybe sometime afterwards", referring to the date of publication: Transcript Day 3/p.447. At Transcript Day 3/p.449, he said: "…I had no recollection of

(i) Professor Morgan's explanation was as follows:[88]

> "I well knew of their existence and, as I said, I felt the issue raised in both consensus statements I felt had been addressed within the report I had already written. That is how I felt. I could explain which elements of my report I felt appropriately addressed the key features, as I saw them, in the consensus reports, if you wish."

He saw nothing in these papers which detracted from the opinions he expressed in Morgan 1.[89]

(ii) Later on in his cross-examination, Professor Morgan expanded upon this point:[90]

> "I can only return to the answer I gave to your earlier two questions on the issue of why my report was written and focused on the things that it did. I have two paragraphs in my first report that address the melatonin theory of insomnia, and it is stated as at the priority date. This paragraph is principally concerned with the status of the melatonin theory of insomnia virtually as at the priority date. The key references that support Professor Arendt's statement and those of the people in the workshop with her are cited in my first report, they are huge, they are Baskett, they are Youngstedt, all of them saying that the melatonin theory is inconsistent with their findings in well-controlled studies. So I do not have an issue with this statement, but I do not think this statement leads to the conclusion that all attempts to evaluate the potential of melatonin should be suspended. That is not what it is saying."

(c) Professor Morgan's position was, therefore, as follows:

(i) He considered that what he termed the "melatonin theory of insomnia" was a theory that was being challenged by various studies (and so undermined by them) but remained a theory under investigation as at the Priority Date.

(ii) He considered that he had cited the papers relevant to that opinion.

(iii) He considered that the Consensus Papers added nothing to what he had said, and so he had not referred to them.

It is necessary to consider this position in greater detail.

(d) The paragraphs in Morgan 1 where the "melatonin theory of insomnia" is described are paragraphs 4.55*ff* of Morgan 1. Because of the importance of

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taking into my first report these consensus statements, okay, but I was aware of these consensus statements when I submitted my report".

[88] Transcript Day 3/p.451.

[89] Transcript Day 3/p.452. Indeed, as regards the first paper expressly, and the second paper at least by implication, Professor Morgan expressed his agreement and considered that there was nothing inconsistent in his report: Transcript Day 3/pp.458 to 459.

[90] Transcript Day 3/p.461.

the point, I set out all of the paragraphs in Morgan 1 regarding melatonin, and not merely the two paragraphs referencing the prior art regarding the melatonin theory of insomnia:[91]

"Melatonin

4.55 Melatonin is a hormone found naturally in the pineal gland. It helps control an individual's sleep/wake patterns. During the day the pineal is inactive, however, when darkness occurs, the pineal is "turned on" and begins actively to produce melatonin, which is released into the blood. This, in turn, makes an individual feel less alert. In 2001, melatonin was known as a chronobiotic. It was understood to help synchronise the biological rhythms of the 24 hour clock and to signal to the body to prepare for sleep.

4.56 Melatonin was not known to be unsafe in 2001. It was not known to be toxic. Emphasising the 'absence of evidence doesn't mean evidence of absence' principle, Arendt 1997 concluded:

> "There are no published long-term safety data on the use of melatonin for whatever purpose, assuming long-term to mean more than 6 months of daily medication. In the light of its physiological role in animals, the potential deleterious effects include inhibition of reproductive function, delayed timing of puberty, and influence (when taken during pregnancy and lactation) on the circadian status of the fetus and neonate and on future development. Its interactions with other medications are virtually unexplored."

4.57 Melatonin is fairly rapidly metabolised, with an elimination half-life (the time it takes for levels in plasma to diminish by 50%) of approximately 40-60 minutes. Because of this, "controlled release" formulations are necessary to maintain blood concentrations at 'therapeutic' levels.

4.58 As referenced earlier in paragraph 4.3(b), a key textbook in insomnia was Lichstein and Morin (2000). In the chapter "Pharmacological Treatment" (Buysse & Reynolds) melatonin receives about 2 pages of attention (less than benzodiazepines or antidepressants and about the same as antihistamines). In this chapter, the lack of efficacy trials to support melatonin use among older patients is emphasised by Buysse and Reynolds. The authors point out that melatonin was widely used as a sleep-promoting substance, but that its use "…was not preceded by properly controlled empirical clinical trials". They cite the Hughes et al (1998) trial as "…the study with the most rigorous design", and cite Garfinkel et al (1995)…, Haimov, and Wurtman and Zhdanova (1995)…as "actigraphy" studies.

4.59 By 2001, it had been known for many years that melatonin played a key psychological role in circadian mechanisms mediating the regulation and onset of sleep. Arendt et al (1984), for example, had shown melatonin to be a sleep-promoting agent in young adults. Significant (i.e., frequently cited) papers on the role of melatonin in regulating circadian rhythms

[91] Emphasis added.

were subsequently published by Wurtman's group at the Massachusetts Institute of Technology, while a seminal paper on the role of melatonin in treating sleep disturbances in blind people had been published by Arendt's group at the University of Surrey. Both of these groups developed research agendas focussing on endogenous/exogenous melatonin and its relationship with sleep, for example Wurtman and Zhdanova (1995). Melatonin research developed as a specialised area of circadian biology throughout the 1980s and 1990s. Nevertheless, many of the 'headline' findings which related melatonin to the treatment of sleep disorders (such as those mentioned here) would be regarded as common general knowledge even though the skilled person may be less familiar with the detailed content of each study. Therefore, before the Priority Date, dosages of 0.3 – 2 mg of melatonin (both in immediate and slow release formulations) were recognised in the [common general knowledge] as being likely to improve quality of sleep generally.

4.60 The growth of interest in and the spread of knowledge on exogenous melatonin can be estimated from bibliometrics. Taking 2001 as the end point, a search of the scientific literature within Web of Science database identifies 178 papers using the keywords 'melatonin' and 'insomnia', and 182 papers using the keywords 'melatonin' and 'circadian rhythm' and 'disorder'. Not all of these studies involve exogenous melatonin (i.e., melatonin given as a drug), but most do. Up to 2001, melatonin as a therapeutic was the subject of a significant number of papers. The skilled person would have had access to this database at the Priority Date and would have been aware of where to find the relevant papers. The skilled person would not know the exact number of papers linking melatonin and insomnia but would have known there existed a substantial body of work.

4.61 The doses of melatonin reported to be effective in the treatment of insomnia were reaching agreement by the mid-1990s (i.e., 0.3 – 2 mg). In 2001, the situation was no different. It was recognised that, unmodified, melatonin metabolised quickly after consumption, reducing its impact on sleep throughout the night.

4.62 In 2001, exogenous melatonin for the treatment of insomnia was an active 'work in progress', with broad agreement on dosages (0.3 – 2 mg), formulation (slow release) and the regime likely to impact sleep symptoms. Nevertheless, there were no effectiveness trials, and no specific safety trials.

Melatonin deficiency

4.63 The "melatonin theory of late life insomnia" combines several areas of scientific understanding which would have been common general knowledge among skilled persons at 2001. First, that with increasing age, sleep tends to become shorter (total sleep time reduces), lighter (sleep periods contain less 'deep' sleep, and awakening thresholds are reduced for all sleep stages) and more fragmented (with episodes of wake after sleep onset – "WASO" – becoming more frequent, and longer). Second, that across the human lifespan, sleep was regulated by 2 processes, circadian and homeostatic. Circadian processes reflect the activity of an internal 'body clock' mechanism responsible for a cyclic rhythm of alertness (usually during the day) and sleepiness (strongest at night).

Homeostatic process, on the other hand, reflects the accumulation sleepiness with increasing time awake. And third, that melatonin played a major role in synchronising the circadian rhythm with the light-dark cycles of the 24 hour day. Simply put, the melatonin theory holds that aging-related reductions in the level and rhythmicity of melatonin secretion disturb the circadian regulation of sleep and lead to the increasing levels of insomnia symptoms characteristic of later life.

4.64 It was known that melatonin levels were reduced in later life. Links between ageing, melatonin levels and sleep had been reported, for example, in Baskett et al, 1991…However, it is important to note that melatonin deficiency was not considered a disease such as to cause the skilled person to consider that patients were not suffering from primary insomnia.

4.65 Garfinkel et al (1995), Haimov, and Haimov and Lavie (1995) had all hypothesised that 'later life' insomnia may be the product of a melatonin deficiency which, as shown in the Garfinkel et al (1995) and Haimov studies, could be effectively treated by melatonin replacement. Haimov promoted the assertion that insomnias in older people can result from melatonin deficiency which, in turn, can be rectified by exogenous melatonin. The impact of Haimov and Garfinkel et al (1995) studies is reflected in the bibliometrics. Between 1995 and 2001, the Garfinkel et al (1995) paper was cited (i.e., appeared in the reference lists of subsequently published papers) 156 times, while Haimov was cited 131 times. This is high impact. The skilled person would be aware of the hypothesis and the use of exogenous melatonin to rectify the deficiency but would not be familiar with every line of these papers.

4.66 The melatonin theory proposed by Garfinkel et al (1995) and Haimov and Lavie (1995) assumed: 1) that lower melatonin levels predicted insomnia symptoms in later life, and that, as a result 2) insomnia symptoms associated with low melatonin deficiency could be effectively treated with melatonin replacement therapy.

4.67 Toward the end of the period 1995-2001, both of these predictions had been tested in high-quality studies. For example, Youngstedt et al (1998)…had shown that 6-sulphatoxymelatonin (6-SMT, a metabolite of plasma melatonin) did not independently predict sleep outcomes in elderly people, and concluded "…low melatonin production may not be an important factor in insomnia among the elderly". Hughes et al (1998), in a controlled trial among older patients with age-related insomnia, found that melatonin 0.5 mgs did not improve objective measures of total sleep time, sleep efficiency, or wake after sleep onset, or subjective measures of nighttime sleep and daytime alertness. It was also found that melatonin levels were unrelated to sleep, and that 'low melatonin producers' were not preferentially responsive to melatonin replacement. In a study conducted in June 2001, Baskett et al compared 6-SMT excretion in 2 well-defined groups of elderly people with, and without, (primary) sleep maintenance insomnia. The results showed no differences in 6-SMT levels, allowing the conclusion "Older people with age-related sleep maintenance problems do not have lower melatonin levels than older people reporting normal sleep". Again, I would expect the skilled person to be aware of the results of these studies as part of his common general knowledge, but not the details of the papers.

> 4.68 By 2001, therefore, evidence was accumulating which suggested that the pathway connecting insomnia, ageing and melatonin was unlikely to be linear. Nevertheless, the skilled person understood that melatonin (in the dose of 1 and 2 mg (slow release)) had been shown in some studies To have had a positive effect on the sleep of elderly insomniac patients and, as a result, remained a promising treatment. In the light of results cited in [paragraph] 4.67…the skilled person would have considered that the original theoretical position of Garfinkel et al (1995) and Haimov (a melatonin deficiency) was not fully supported, but that this area of research was worth pursuing further and should not be foreclosed by the results of other studies."

(e) It is necessary to be absolutely clear what these paragraphs are going to. They are written in support of the proposition that, in advance of the Priority Date, it was well known that the administration of slow release melatonin in dosages around 2mg would – at least in older people – improve quality of sleep.[92] Obviously, this is a, if not the, central point going to the Patent's validity, and in consequence this is a proposition to which I have, unsurprisingly, paid considerable attention. Unfortunately, Professor Morgan's assertion is supported not by evidence but by a melange of irrelevance and, frankly, misdirection. More specifically:

(i) Professor Morgan is extremely careful, in these paragraphs, <u>not</u> to define his terms. I have set out above what I consider these paragraphs are directed to. When, however, the paragraphs are parsed with care, it is not clear whether Professor Morgan is talking about "non-restorative sleep" or the "quality of sleep" in the technical senses I have described or whether he is using the term altogether more generally.[93]

(ii) Professor Morgan has deployed at least two irrelevant "red-herrings". The first is his persistent reference to material going to Circadian Sleep Rhythm Disorder. As I have described, this is a real issue for individuals whose sleep clock is out of synchronisation with their external environment, and melatonin is indicated as a means of re-setting the clock. But that has nothing to do with Primary Insomnia nor Primary Insomnia characterised by non-restorative sleep. Yet Professor Morgan weaves references to melatonin and Circadian Sleep Rhythm Disorder throughout these paragraphs,[94] without justifying those references. As I have said, my understanding on the totality of the evidence is that these references are not justified.

(iii) The second is the "melatonin theory of late life insomnia". I am completely at a loss to understand why Professor Morgan has

[92] See the underlined parts of paragraphs 4.59, 4.61, 4.62 in Morgan 1.

[93] In particular, I note the use of terms that are more or less meaningless: "likely to impact on sleep symptoms" in paragraph 4.62; "treatment of insomnia" in paragraph 4.61; even "quality of sleep" in paragraph 4.59 is made less clear by the addition of "generally".

[94] See paragraphs 4.55 and 4.59.

referred to this theory, because it is both irrelevant and discredited. It is irrelevant because, as Professor Morgan does say in paragraph 4.64,[95] melatonin deficiency was not considered a disease related to Primary Insomnia. When one considers the papers referenced by Professor Morgan, it becomes clear that none of the studies was actually considering Primary Insomnia. They were considering the effects of the natural process of aging, and the ameliorative effect of melatonin in this context.[96] It is discredited (and I say this meaning no disrespect: it is simply the way science works – propositions are tested until they are disproved) for the reasons given by Professor Morgan in his report. It may very well be – as Professor Morgan suggests – that further research into melatonin levels and the elderly is indicated or desirable. But that says nothing about the effect of melatonin on an individual aged 55 and over diagnosed as suffering from Primary Insomnia indicated by non-restorative sleep.

(iv) Professor Morgan buttresses his analysis by the use of pseudo-scientific word searches. Thus, in paragraphs 4.60 and 4.65 of Morgan 1 he refers to the significance of "bibliometrics". By this, he means either the extent to which certain words are used in the literature or the number of times certain articles or studies are cited. I certainly do not intend to deprecate the use of search engines like the Web of Science to find significant materials for someone to consider. But that is the beginning, not the end, of the process of building or extending knowledge. The process serves to identify material to be further digested, to see what they teach. Significantly, when Professor Morgan refers to bibliometrics, he is remarkably vague as to what – precisely – this material teaches.[97]

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[95] At least, that is what I take the Professor to be saying in paragraph 4.64. The double negative makes the paragraph hard to follow.

[96] Thus:

(1) Baskett, Cockrem and Todd, *Melatonin Levels in Hospitalized Elderly Patients: A Comparison with Community Based Volunteers*, (1991) 20 Age and Aging 430-434 (**Baskett et al 1991**, cited at paragraph 4.64 of Morgan 1) concerned twenty one-hour melatonin plasma profiles studied in 15 normal elderly volunteers from the community.

(2) Garfinkel, Laudon, Nof and Zisapel, *Improvement of sleep quality in elderly people by controlled-release melatonin*, (1995) 346 The Lancet 541-544 (**Garfinkel et al 1995**, cited at paragraph 4.65 of Morgan 1) concerned 12 elderly subjects "who were receiving various medications for chronic illnesses and who complained of insomnia". Although all subjects complained of "long term insomnia", this was not further specified. (That is not, I stress, a criticism of the study: it merely highlights that the study was focussed not on primary insomnia but sleep more generally in old people.)

(3) Haimov and Lavie, *Potential of Melatonin Replacement Therapy in Older Patients with Sleep Disorders*, (1995) 7(2) Drugs & Aging 75-78 (**Haimov and Lavie 1995**, cited at paragraph 4.65 of Morgan 1) concerned the use of a "sustained-release melatonin formulation to effectively restore melatonin levels in the elderly to those present in younger individuals throughout the night, in comparison with conventional-release tablets and placebo."

[97] Thus, in paragraph 4.60, Professor Morgan refers to the skilled person knowing of "a substantial body of work": but to what end? Again, in paragraph 4.65, the volume of citation is stated to be "high impact": but impact on what?

(v) Professor Morgan is guilty of what can only be described as misleading citation of material. In paragraph 4.56 of Morgan 1, he cited a paper by Arendt, *Safety of Melatonin in Long Term Use* (**Arendt 1997**),[98] in support of the proposition that melatonin was not known to be unsafe in 2001. The quotation from Arendt 1997 is partial:[99]

> "There are no published long-term safety data on the use of melatonin for whatever purpose, assuming long-term to mean more than 6 months of daily medication. In the light of its physiological role in animals, the potential deleterious effects include inhibition of reproductive function, delayed timing of puberty, and influence (when taken during pregnancy and lactation) on the circadian status of the fetus and neonate and on future development. Its interactions with other medications are virtually unexplored. **For most positive effects published, there also exist negative reports. There are insufficient data on its use in organic or psychiatric disease for any evaluations to be made. There are insufficient data on dose, formulation, and consequent relationships of individual pharmacokinetics and pharmacodynamics for recommendations at present. However, in normal healthy adults over 18 years old, not pregnant or lactating, with no personal or family histories of psychiatric disorder, and unmedicated except for oral contraceptives and minor analgesics (if necessary), the only significant short-term side effect in the author's experience has been sleepiness following oral ingestion of synthetic melatonin (5 mg or less, oral fast release), licenced for human experimental use and for prescription on a named-patient basis.**"

Moreover, there is no reference to the rather more stark concerns about safety expressed in the Arendt Consensus Paper 2000.

In paragraph 4.59 of Morgan 1, Professor Morgan refers to "a seminal paper on the role of melatonin in treating sleep disturbances in blind people". This is in fact a reference to a letter in The Lancet referring to the effect of melatonin on the daily sleep rhythm in a blind man "with a history of desynchronised sleep-wake cycles".[100] The letter – no doubt interesting – cannot be described as seminal and (if it is) is seminal in an area irrelevant for the purposes of Professor Morgan's report.

Finally, there is – to the reader of Morgan 1 – a natural implication that the conclusions expressed by Professor Morgan in paragraph 4.61 of Morgan 1 are supported by the statements and the material referenced in paragraph 4.60. In cross-examination, Professor Morgan disavowed this:[101]

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[98] (1997) 12(6) Journal of Biological Rhythms 673-681.

[99] The text in **bold** is that which is not quoted by Professor Morgan.

[100] Arendt, Aldous, Wright, *Synchronisation of a disturbed sleep-wake rhythm in a blind man by melatonin treatment*, (1988) The Lancet 772-773 (**Arendt *et al* 1988**, cited in Morgan 1 at paragraph 4.59).

[101] Transcript Day 3/pp.588*ff*.

> **A (Professor Morgan)** …What paragraph 4.60 set out to do was just develop a purview of the area and the literature, just to get a feel of the volume of work going on in this area. It was not part of another strategy for a literature search. It was exactly what is described here – to quantify the work going on in this area.
>
> **Q (Mr Waugh, QC)** With great respect, Professor, that is not what paragraph 4.61, which immediately follows on from this, says:
>
> > "4.60 ...Not all of these studies involve exogenous melatonin (i.e., melatonin given as a drug), but most do…
> >
> > 4.61 The doses of melatonin reported to be effective in the treatment of insomnia were reaching agreement by the mid 1990s (i.e., 0.3 – 2 mg)"
>
> **A (Professor Morgan)** Yes.
>
> **Q (Mr Waugh, QC)** You are suggesting that these papers reported that these doses were effective by the mid-1990s?
>
> **A (Professor Morgan)** That was not my intention. That is a coincidence of proximity.
>
> **Q (Mr Waugh, QC)** You say how many papers involved melatonin, exogenous melatonin, and then immediately say that the doses of melatonin reported to be effective were X. The clear inference is that the papers reported the effectiveness of melatonin in the treatment of insomnia, reaching agreement – you are saying there is a consensus by the mid-1990s that there were doses effective in the treatment of insomnia?
>
> **A (Professor Morgan)** That is my view of how things were, but the statement is not directly connected to the paragraph above it.

(f) I do not consider that Professor Morgan's failure to cite the Consensus Papers can be justified, certainly not for the reasons he has given. These papers are <u>not</u> concerned with the melatonin theory of late life insomnia, discussed by Professor Morgan, and which (for the reasons I have given) I regard as essentially irrelevant. They are concerned with the medical usefulness – or otherwise (and in this case it <u>was</u> otherwise) – of melatonin generally in cases of insomnia. The fact that the effect of melatonin on non-restorative sleep is not noted in these papers seems to me – given the purpose of these papers and the persons by whom they were authored – to be extremely significant, and to support the conclusion of Professor Roth, which I have cited at the beginning of this paragraph.

(g) Given Professor Roth's treatment of the Consensus Papers in Roth 3,[102] Professor Morgan could hardly avoid referencing them in Morgan 2, which was responsive to Roth 3. Morgan 2 contains a number of paragraphs dealing with the consensus papers, but the significance of these papers is side-stepped in what can only be described as a most unsatisfactory manner, without engaging in the substance of what Professor Roth was saying. Equally, in cross-examination, Professor Morgan was invited to articulate precisely where he agreed and where he disagreed with Professor Roth. In my judgment, he did not do so. I do not consider that it is necessary to quote from either Morgan 2 or the transcript. The relevant passages are paragraphs 3.25, 3.27, 3.31 and 3.33 of Morgan 2 and Transcript Day 2/pp.453ff. I do not cite these passages simply because I do not consider that Professor Morgan either agreed with or sought to refute the points made by Professor Roth regarding the Consensus Papers, but merely rehashed the points he made in Morgan 1, which – for the reasons I have given – I regard as fundamentally unsatisfactory and not to be relied upon.

D. THE TRUE CONSTRUCTION OF THE PATENT

68. The person skilled in the art and his or her common general knowledge is, as I have said, relevant to various of the matters before me. The first of these is the true construction of the Patent. I must construe the Patent through the notional addressee, who is the Skilled Person described above, with the common general knowledge that I have also described.[103]

69. In this case, it is very clear that the Patent claims by way of Claims 1 and 4 the use of melatonin (in the form described) for improving the restorative quality of sleep in a patient suffering from Primary Pnsomnia characterised by non-restorative sleep.[104]

70. The Skilled Person would appreciate the references in Patent/[0001] to DSM-IV and ICD-10, and would, as a result, understand that the terms "primary insomnia", "non-organic insomnia" and "non-restorative sleep" would bear the technical meanings that I have described in Section C above. Patent/[0001] does not, itself, refer to "quality of sleep" or "sleep quality", but there are other, multiple references in later paragraphs of the Patent to quality of sleep. The Skilled Person would, inevitably, understand such terms in their technical sense. Specifically, the Skilled Person would understand that "quality of sleep" was the ICD-10 equivalent of "non-restorative sleep" and would understand the Patent to be using these terms in this way.

71. Claims 1 and 4 both refer to the invention "improving the restorative quality of sleep". Professor Morgan had an issue with the phrase "improving the restorative quality of sleep", which appears in Claims 1 and 4 of the Patent.[105] In Morgan 1/§6.40, Professor Morgan said:

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[102] Which I have described in paragraph 67(2) above.

[103] See, generally, Terrell, ch 9.

[104] I am using the formulation in Claim 1; Claim 4 is to similar effect.

[105] Set out in paragraph 43 above.

"The invention is said to "improve the restorative quality of sleep". "Restorative quality of sleep" was not a term of art used in sleep research and medicine in 2001. It is not a term I was familiar with before reading the Patent and the skilled person would not be familiar with it either. It is not a term of art and no definition is given in the Patent."

72. I reject this evidence as fanciful. Both Claims 1 and 4 refer to a patient "suffering from primary insomnia characterised by non-restorative sleep". The Skilled Person would understand this to mean an individual suffering from the sort of insomnia that I have described in Section C above. Absent the words in **bold** that I have highlighted in paragraph 39 above, which confuse and distract from what the Patent claims to teach, there is no room for any misunderstanding or alternative meaning within the terms of the Patent. On the whole, the Patent is clear. The phrase "improve the restorative quality of sleep" is coloured by the nature of the symptoms of this individual and the Skilled Person would understand that the invention was claiming to ameliorate or eliminate this particular symptom. The meaning of the phrase is clear from the Patent.

E. LACK OF NOVELTY OR ANTICIPATION

(1) Introduction

73. I turn, then, to the question of whether the Patent lacks novelty or whether the Patent has been anticipated by prior art. The basis on which it is suggested by Mylan that the Patent lacks novelty is Haimov 1995.[106] It is necessary for me to consider first the relevant law (Section E(2)) and then Haimov 1995 (Section E(3)). My conclusions are stated in Section E(4).

(2) The law

74. The law on novelty – in particular in the context of second medical use patents – was set out by Floyd J in *Regeneron Pharmaceuticals Inc v. Genentech Inc*:[107]

> "96. Section 2(1) of the Patents Act 1977 provides:
>
> > "(1) An invention shall be taken to be new if it does not form part of the state of the art.
> >
> > (2) The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way."
>
> 97. This part of the law of patents was reviewed by the House of Lords in *Synthon v. SKB*, [2006] RPC 10. There are two requirements for a claim to be anticipated by a prior document: disclosure and enablement. As to disclosure, Lord Hoffmann, who gave the leading judgment, began by citing passages from what he described as two judgments of "unquestionable authority": the speech of Lord Westbury LC in *Hills v. Evans*, (1862) 31 LJ Ch (NS) 457 at 463 and the judgment of the Court of Appeal in *General*

[106] See paragraph 8(1) above.

[107] [2012] EWHC 657 (Pat).

Tire and Rubber Co v. Firestone Tyre and Rubber Co Ltd, [1972] RPC 457 at 485–486. In the latter case the Court of Appeal said:

> "If the prior inventor's publication contains a clear description of, or clear instructions to do or make, something that would infringe the patentee's claim if carried out after the grant of the patentee's patent, the patentee's claim will be shown to lack the necessary novelty. The prior inventor, however, and the patentee may have approached the same device from different starting points and may for this reason, or it may be for other reasons, have so described their devices that it cannot be immediately discerned from a reading of the language which they have respectively used that they have discovered in truth the same device; but if carrying out the directions contained in the prior inventor's publication will inevitably result in something being made or done which, if the patentee's claim were valid, would constitute an infringement of the patentee's claim, this circumstance demonstrates that the patentee's claim has in fact been anticipated.
>
> If, on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the ground of obviousness. To anticipate the patentee's claim the prior publication must contain clear and unmistakeable directions to do what the patentee claims to have invented…A signpost, however clear, upon the road to the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee."

98. At [22], Lord Hoffmann says this:

> "If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent. That may be because the prior art discloses the same invention. In that case there will be no question that performance of the earlier invention would infringe and usually it will be apparent to someone who is aware of both the prior art and the patent that it will do so. But patent infringement does not require that one should be aware that one is infringing: "whether or not a person is working [an]…invention is an objective fact independent of what he knows or thinks about what he is doing": *Merrell Dow Pharmaceuticals Inc v. HN Norton & Co Ltd*, [1996] RPC 76, 90. It follows that, whether or not it would be apparent to anyone at the time, whenever subject-matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied. The flag has been planted, even though the author or maker of the prior art was not aware that he was doing so."

99. The claims in the present case specify a medical use for a product either in the so called Swiss form ("use of compound X in the manufacture of a medicament to treat disease Y") or in the form permitted by the European Patent Convention 2000 ("compound X for use in treating disease Y"). In the European Patent Office the view is taken that, with claims in either form, the actual achievement of the therapeutic effect is a functional technical feature of the claim, as opposed to a mere statement of purpose or intention. That this is so can be seen from decision T 0609/02 *The Salk Institute for Biological Studies*, at [9] of the Reasons and the cases cited there, which include, in the non-medical field, the well known *Mobil* decision G2/88. The claimants did not have any convincing reason why that should not apply here.

100. Mr Waugh reminded me that novelty is not created merely by describing something old in different language, or merely by providing new information about what is old. He had in mind, no doubt, cases such as *Bristol Myers Squibb v. Baker Norton Pharmaceuticals*, [2001] RPC 1. That submission is correct."

75. The law is also clearly set out in *Terrell*, which states:

"11-03 The current law was concisely summarised by Lord Hoffmann sitting in the Court of Appeal in *H Lundbeck A/S v. Generics (UK) Ltd* as follows:

> "In order to anticipate a patent, the prior art must disclose the claimed invention and (together with common general knowledge) enable the ordinary skilled person to perform it.

11-04 To "disclose the claimed invention" as here required, the prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent.

11-05 The need for an "enabling disclosure" is equally important. A disclosure of, e.g. the existence of a chemical substance is not enabling (and therefore not an anticipation) if the skilled reader would not know from the information given how to produce or obtain it, or how to obtain or to make the required starting materials. Merely being told it exists is not of itself enough."

76. Enablement is of particular importance in the case of the anticipation of second medical use patents, such as this. It is the second medical use that must be anticipated – not the medicament itself nor some other use:[108]

"Medical use claims owe their novelty to the discovery of the new therapeutic use of the medicament. The actual achievement of the therapeutic effect is a functional technical feature of such a claim. This is true for Swiss-style claims and EPC 2000 claims. Therefore, in order for prior art to deprive a medical use claim of novelty, there must be an enabling disclosure of the claimed therapeutic effect. So if and to the extent that plausibility forms part of the requirement for enablement in the context of sufficiency (so held in *Regeneron*), logically it must play the same role in the context of novelty."

(3) Haimov 1995

77. The summary in Haimov 1995 states:

"Changes in sleep-wake patterns are among the hallmarks of biological ageing. Previously, we reported that impaired melatonin secretion is associated with sleep disorders in old age. In this study we investigated the effects of melatonin replacement therapy on melatonin-deficient elderly insomniacs. The study comprised a running-in, no-treatment period and four experimental periods. During the second, third and fourth periods, subjects were administered tablets for 7 consecutive days, 2 hours before desired bedtime. The tablets were either 2 mg melatonin administered as sustained-release or fast-release formulations, or an identical-looking placebo. The fifth period, which concluded the study, was a 2-month period of daily administration of 1 mg sustained-release melatonin 2 hours before desired bedtime. During each of these five experimental periods, sleep-wake patterns were monitored by wrist-worn actigraphs. Analysis of the first three 1-week periods revealed that a 1-week treatment with 2

[108] *Terrell* at [11-97].

mg sustained-release melatonin was effective for sleep maintenance (i.e. sleep efficiency and activity level) of elderly insomniacs, while sleep initiation was improved by the fast-release melatonin treatment. Sleep maintenance and initiation were further improved following the 2-month 1-mg sustained-release melatonin treatment, indicating that tolerance had not developed. After cessation of treatment, sleep quality deteriorated. Our findings suggest that for melatonin-deficient elderly insomniacs, melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep."

78. As is clear from this summary, Haimov 1995 is concerned with what Professor Morgan would call the "melatonin theory of insomnia", where poor sleep was attributed to a melatonin deficiency that increased as a function of age (i.e., the older a person, the lower the levels of melatonin). That explains the broad-brush approach taken in the selection of the individuals participating in the study. The subjects of the study were described in the following terms:[109]

"The study population comprised three groups: i) independently living insomniacs (eight patients: four male, four female; aged 73.1 ± 3.9 years); ii) institutionalised insomniacs (18 patients: six male, 12 female; aged 81.1 ± 8.9 years) living a minimum of 6 months in a nursing home; iii) elderly without sleep disorders (25 patients: 19 male, six female; aged 71.4 ± 5.2 years) living independently in the community. The purpose of recording the elderly group without sleep disorders was to validate the subjective complaints of insomnia. This group was not included in the treatment part of the study. These subjects overlap with those in our previous report of sleep disorders and melatonin rhythm in the elderly. The insomnia patients (the independently living insomniacs and the institutionalised insomniacs) were considered "melatonin-deficient" because they had significantly lower peaks of secretion than did the elderly without sleep disorders…All subjects were in good clinical condition, and none met any criteria for dementia or depression according to the Mini-Mental State Examination or the Hamilton rating scale. Subjects were personally interviewed by an experienced physician to rule out significant sleep apnea syndromes which could be related to physiologically based insomnia, or any medical illness that might interfere with sleep. None of the subjects used any medication that could affect sleep or the noradrenergic system for at least 1 month prior to the study. Because in the International Classification of Sleep Disorders (ICSD) there is no diagnosis of insomnia in the elderly, we accepted volunteers if they reported sleeping poorly on at least 3 nights per week and if their insomnia had lasted for a minimum of 6 months. Volunteers also had to report that their insomnia clearly affected their daytime functioning, that it was not caused by chronic pain or any known medical disease and that the volunteer did not use either alcohol or drugs that might affect sleep. Volunteers were then sent a number of questionnaires, including a one-week sleep log, a mini-sleep questionnaire (MSQ) and the Technion Sleep Questionnaire."

79. As can be seen from the summary, the effect of melatonin on the group was beneficial. The study concluded:

"This study suggests two important principles of melatonin replacement therapy of melatonin-deficient, elderly insomniacs: i) melatonin appears to have a beneficial effect when administered in the form of sustained-release tablets and ii) to ensure efficacy, long-term treatment is recommended.

In conclusion, melatonin deficiency seems to be a key variable in the incidence of sleep disorders in the elderly. From the results of the present study, it seems likely that melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep in this

[109] Emphasis added.

population. Further studies employing the chronic administration of melatonin, in varying dosages of different preparations, and the investigation of their effects by segmenting the long-term treatment into intervals must be pursued before determining the most efficient melatonin replacement therapy for elderly insomniacs."

80. Both Professor Roth and Professor Morgan considered Haimov 1995 in their evidence. As to their evidence:

(1) Professor Roth articulated a series of concerns in relation to the method and design, methodology and tabulation of results in the study.[110] If the purpose of the study had indeed been to assess the effects of melatonin on Primary Insomniacs characterised by non-restorative sleep, then there might well be force in these points. Had that been the objective of the study, then I have no doubt that the population of the study would have been very different. As Professor Roth puts it:[111]

> "…if the authors of Haimov had intended to test a hypothesis for treating patients suffering from primary insomnia or patients suffering from primary insomnia characterised by non-restorative sleep, they would have carefully diagnosed the patients so to include only such patients and specified that they had done so. However, none of the patients in the study populations are described as having been diagnosed with primary insomnia characterised by non-restorative sleep or nonorganic insomnia characterised by poor quality of sleep…"

(2) But the focus of the study was very different. The focus was on "melatonin-deficient" individuals, because the aim of the study was to see if the curing of such a deficiency would improve sleep. The study was concerned with sleep issues in the old for that reason – melatonin deficiency is, typically, a function of age. Obviously, the study was concerned with identifying insomnia in the old, that was "primary" in the sense that the cause being investigated was insomnia due to melatonin deficiency. It was noted that there were no criteria in the International Classification of Sleep Disorders for diagnosing insomnia in the elderly. Quite rightly, given what was being assessed, the authors of the study eschewed the ICD-10 and DSM-IV diagnostic criteria,[112] focussing instead on those who had persistent sleep complaints without any other overt explanation for their insomnia other than melatonin deficiency. Once again, terminology can mislead, rather than assist. I have no doubt that the study was not seeking to isolate and study "Primary Insomniacs" in the sense that Professor Roth would use that term and in the sense that I have defined it in paragraph 34(4) above (and, significantly, the study did not particularly use that term). But, equally, the term "primary insomnia" (emphatically using the lower case) would not be inapposite, given that the study was focussing on those with sleep issues and a melatonin deficiency, with a view to assessing the relationship between these two characteristics.

[110] Paragraphs 9.5*ff* of Roth 3.

[111] Paragraph 10.3 of Roth 3.

[112] A point noted by Professor Roth in paragraph 10.3 of Roth 3.

(3) In short, whilst the study unquestionably focussed on primary insomnias (using the term in the looser sense that I have described), the critieria that informed the selection of the individuals the subject of the study was not that contained in either ICD-10 or DSM-IV. Rather, the study was considering whether a melatonin deficiency was causing insomnia, and the individuals the subject of the study was identified by reference to this criterion. There was certainly no focus whatsoever on restorative sleep or quality of sleep in the technical sense. I accept Professor Roth's point that it is clear that Haimov 1995 was using the term "sleep quality" in what to Professor Roth would be a non-technical sense.[113] More accurately, "sleep quality" was not being used in the ICD-10 sense.

(4) Professor Morgan defends the study, suggesting that it was focussed on individuals suffering from Primary Insomnia.[114] He is unable to explain – and, indeed, does not discuss – the failure on the part of the authors to apply the ICD-10/DSM-IV diagnostic criteria. Professor Morgan concludes:[115]

"The study concludes:

> "From the results of the present study, it seems likely that melatonin replacement therapy may be beneficial in the initiation and maintenance of sleep."

It is my view that the skilled person would agree with this conclusion based on the results reported. The skilled person would also recognise that "maintenance of sleep" was used in the article to refer to both sleep efficiency and activity levels, as reflective of subjective sleep quality. The study supports the conclusion that sleep quality, in a general sense, was improved with a 1 or 2 mg sustained release melatonin formulation. As noted above, the skilled person would also understand that activity levels during sleep could be used as a proxy for experiences of non-restorative sleep (or poor quality sleep in the context of the ICD-10 diagnostic guidelines). The reduction in the activity level (i.e., more restful sleep) reported in table 2 [of the study] would have been recognised by the skilled person as proxy for or reflective of an improvement in non-restorative sleep experienced by the subjects."

I do not accept this evidence:

(a) For the reasons already given in paragraph 62 above, I do not accept Professor Morgan's view that actigraphic or other "objective" measures can measure sleep quality, using that term in the technical sense.

(b) I fail to see how the Skilled Person could understand that the study had anything to do with Primary Insomnia in the ICD-10 / DSM-IV sense, still less with quality of sleep / non-restorative sleep. The study was, quite obviously on its face, concerned with something altogether different.

(c) Quite why Professor Morgan did not – in these paragraphs – place this study in context as part of the "melatonin theory of insomnia" is

[113] Paragraph 9.22 of Roth 3. I do not understand this to be a criticism on the part of Professor Roth; and I certainly do not intend any such criticism myself.

[114] Paragraphs 5.*2ff* of Morgan 1.

[115] Paragraph 5.35 of Morgan 1.

surprising. The study is express in its terms and scope: it is looking at the effects of melatonin on those with *(i)* an insomnia complaint, which *(ii)* appears to be primary[116] in that *(iii)* there is no other overt indicator for the insomnia other than melatonin deficiency. As such, it belongs to the research that Professor Morgan made so much of in paragraphs 4.55 to 4.68 of Morgan 1. Indeed, Haimov 1995 is expressly referenced in these paragraphs: see paragraph 4.65 of Morgan 1.

(4) Conclusion on novelty

81. I conclude that Haimov 1995 in no way anticipates the Patent and that the Patent is novel over Haimov 1995. Haimov 1995 simply does not address the inventive step which is taught in the Patent. That is not surprising, since the study was directed to a completely different matter. However, to be clear, the Patent was not even "accidentally" anticipated by Haimov 1995: the Skilled Person would have learned nothing about the effect of melatonin on Primary Insomnia characterised by non-restorative sleep from Haimov 1995.

F. LACK OF INVENTIVE STEP OR OBVIOUSNESS

(1) Introduction

82. As I have described in paragraph 8(2) above, Mylan contends that Patent does not disclose an inventive step and is obvious in light of Haimov 1995, Melatonex and the Melatonex Webpage and Zisapel 1999.

83. What is obvious – and what is not obvious – is not a matter that can further be deconstructed or defined. The word means what is says.[117] The question of obviousness is approached in the following way. In light of the common general knowledge of the person skilled in the art, and having construed the inventive concept of the claim in question:

(1) 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?

(2) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

84. Unless the prior art can properly be seen as part of a mosaic, each piece of prior art must be considered separately, to see if the invention claimed by the patent is actually inventive or whether it is, in light of the prior art, obvious.

85. Although these matters have already been traversed in this judgment, I should be clear that the inventive step claimed by the Patent is that the use of melatonin (in the form described) improves the restorative quality of sleep in a patient suffering from Primary

[116] Quite clearly, the authors of Haimov 1995 would regard "primary insomnia" as insomnia due to melatonin deficiency (the point under examination). That is very different from the "Primary Insomnia" in Professor Roth's lexicon.

[117] See *Windsurfing International Inc v. Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 at 73 to 74.

Insomnia characterised by non-restorative sleep.[118] The question is whether the three items of prior art pleaded by Mylan render this obvious in the manner that I have described. I consider these three items in turn below.

(2) Haimov 1995

86. It is unnecessary for me to repeat the description of the content of Haimov 1995 contained in paragraphs 77*ff* above. I fully recognise that the test for novelty/anticipation is a materially higher one than that of obviousness/lack of inventive step, and the mere fact that the invention disclosed by the Patent has not been anticipated by Haimov 1995 does not mean that Haimov 1995 does not render the claims in the Patent not inventive.

87. However, in this case, I conclude that Claims 1 and 4 are original and are inventive over Haimov 1995. The Skilled Person, having the common general knowledge that I have described, but lacking inventive capacity, would draw nothing from Haimov 1995 to render the invention of the Patent obvious. As I have described, Haimov 1995 suggests that the administration of melatonin may have beneficial effects on aged persons suffering from a deficiency in melatonin. Haimov 1995 says literally nothing about the effect of melatonin on an individual (of whatever age) suffering from Primary Insomnia characterised by non-restorative sleep.

88. The Patent is not obvious over Haimov 1995.

(3) Melatonex and the Melatonex Webpage

89. As I have described, melatonin is available on a non-prescription basis in the United States, but not in the United Kingdom. It is, therefore, possible to purchase melatonin or products containing melatonin in the United States in a manner that is not possible in the United Kingdom. I am prepared to assume that this is something that the Skilled Person would know, and I proceed on that basis.

90. The Melatonex Webpage describes Melatonex in the following terms:

> "**Sleep better to feel better**
>
> MELATONEX is a dietary supplement containing melatonin, a substance produced by our own bodies that regulates the body's natural sleep/wake cycle. After we reach maturity, melatonin production declines with age which can make restful sleep more difficult to achieve. Melatonin production can also diminish through our use of substances like alcohol, tobacco, caffeine, aspirin and many common medications. MELATONEX supplementation can help to restore the melatonin we need for a restful, natural sleep.[*]"

Pausing there, the webpage – by way of the asterisk footnote – then refers to a warning in bold type in a box:

> "**These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.**"

[118] I am using the formulation in Claim 1, but Claim 4 I find is to similar effect.

The text then continues:

"**Unique time release delivery**

MELATONEX uses a unique time-release delivery system that releases melatonin the way the body does, gradually while you sleep.

Antioxidant action

Research shows melatonin to be a highly effective antioxidant against hydroxyl free radicals, toxic by-products or normal metabolism that can cause cell damage.*"

The asterisk refers to the same warning as above. The rest of the webpage contains suggestions as to use, supplement facts and cautions as to use, which it is unnecessary to set out.

91. In Roth 3, Professor Roth makes the point that the Skilled Person would view Melatonex and the Melatonex Webpage with a degree of scepticism:[119]

"The skilled person would not have considered a webpage such as the Melatonex Webpage to provide any legitimate information relevant to their clinical practice, including to treating a patient suffering from primary insomnia whether or not characterised by non-restorative sleep, or to the field of primary insomnia generally…I note that the webpage provides no scientific data, or any other form of support, for the claims made. At the Priority Date, I would have been highly sceptical of any claims or information provided on the Melatonex Webpage (or on the Melatonex product itself) and would not have given this document any weight."

Later on in Roth 3, Professor Roth goes on:[120]

"The Melatonex Webpage contains no data. The Melatonex Webpage would be regarded by the skilled person as a mere advertising "puff"."

92. Professor Morgan appeared to share Professor Roth's view that the Melatonex Webpage amounted to no more than advertising copy, but he considered that this would nevertheless motivate the Skilled Person to "conduct further research":[121]

"8.16 The skilled person, given what was known in 2001, would expect the product being advertised here to share the same qualities and impact as what was known in 2001 about slow release melatonin. Melatonin's role in inducing sleep was well-known, albeit that its mechanism of action was not.

8.17 The difference between Melatonex and the claim of the Patent is therefore a disclosure that prolonged release melatonin is effective in improving the restorative quality of sleep in this patient population. There is no data presented in the label, but Melatonex refers to achieving a "restful, natural sleep". In light of what was known about melatonin in 2001 and the potential of melatonin replacement therapy, the skilled person would be motivated to conduct further research. The skilled person would conduct a trial to test melatonin doses, including the 3 mg used within the Melatonex

[119] Paragraph 14.14 of Roth 3.

[120] Paragraph 15.6 of Roth 3.

[121] Morgan 1.

formulation, with a reasonable expectation of showing an improvement in the subject's experience of getting to sleep, maintaining sleep and non-restorative sleep."

93. In my judgment, the Patent is plainly not obvious over Melatonex and the Melatonex Webpage:

(1) The Melatonex Webpage does no more than re-hash the putative benefits of melatonin for sleep problems, with loose reference to circadian rhythm issues and the theory that melatonin levels need to be "topped up" in some people. There is no suggestion that the product would be of benefit to those suffering from Primary Insomnia, and there is no reference whatsoever to non-restorative sleep.

(2) There is, of course, reference to the quality of sleep ("better sleep"), but this is plainly using the term in the non-technical sense that I have described. Professor Morgan's suggestion that the wording could be construed as having a technical meaning in this non-technical "puff" of an advertisement is fanciful.

(3) The notion that the Melatonex Webpage could motivate the Skilled Person to conduct further research is similarly fanciful. Even if the content of the Melatonex Website had appeared in a respected journal – and, of course, it would not have done, given its content – I see nothing in it to make the invention disclosed in the Patent in any way obvious.

(4) More to the point, I do have to take account of the fact that this emphatically was not a respected publication: it was an advertisement for a non-medicament. Even if the language had been more technical and the text more overt in its reference to the invention – suppose, for instance, it had gone so far as to say that melatonin made sleep more restorative in insomniacs suffering from Primary Insomnia – even then I doubt whether the Skilled Person would have paid any regard to this, simply because the webpage carries with it all the puffery of the Carbolic Smoke Ball.[122]

(4) Zisapel 1999

94. I referenced this publication in paragraph 8(2)(c) above. The article is characterised by the keywords "Melatonin – Insomnia – Sleep – Circadian Rhythms – Therapy". The abstract for the article provides:

"The pineal product melatonin is involved in the regulation of the sleep/wake cycle in humans. In blind individuals and in people travelling through time zones, melatonin rhythms are sometimes unsynchronised with the diel cycle, and nocturnal sleep may be disturbed. Low or distorted melatonin rhythms have repeatedly been reported in middle aged and elderly insomniacs. Melatonin administration effectively synchronised the sleep wake cycle in blind individuals and in subjects suffering from jet lag and advanced sleep onset in subjects suffering from delayed sleep phase syndrome. In elderly insomniacs, melatonin replacement therapy significantly decreased sleep latency, and/or increased sleep efficiency and decreased wake time after sleep onset. In addition, melatonin substitution facilitated benzodiazepine discontinuation in chronic users. These data show an association between melatonin rhythm

[122] Although it must be noted that the Court of Appeal found that the advertisement in *Carlill v. Carbolic Smoke Ball Company*, [1893] 1 QB 256 was not a "mere puff" (Lindley LJ at 261).

disturbances and difficulties to promote or maintain sleep at night. Specific melatonin formulations may be useful to treat circadian-rhythm-related sleep disorders and age-related insomnia."

95. The article concludes:

"Based on the current scientific and clinical knowledge, there seem to be at least three distinct clinical indications for melatonin therapy in insomnia: (a) replacement therapy in case of low or absent nocturnal melatonin concentrations. In these patients regaining of a robust melatonin rhythm may be better met with the controlled-release melatonin formulation. (b) Phase-shifting of the circadian clock for phase resetting in blind people, jet lag or delayed sleep phase syndrome, regular release melatonin has proven efficacy. (c) Benzodiazepine discontinuation. Presently, no melatonin formulation has been approved for clinical use by any regulatory authority. The decisions of whether to use melatonin therapy, when to use it and for what period of time, and what formulation to use await further scientific attention."

96. Professor Roth regarded Zisapel 1999 as a review of the literature in the area of melatonin treatment. It neither reported any original research nor did it give any meta-analysis of the data reviewed.[123] *Per se*, therefore, Zisapel 1999 is an unpromising piece of prior art from the point of view of demonstrating obviousness in the Patent, since one would expect the relevant prior art to appear elsewhere than what is purely a review article. To this end, Professor Roth reviewed the references in Zisapel 1999 in the way that he considered the Skilled Person would have done.

97. Professor Roth concluded that the paper – whilst obviously directed at the effects of melatonin on insomniacs, including what the paper called primary insomniacs – did not render the inventive concept in the Patent obvious:[124]

"13.2 Zisapel 1999 is not concerned with primary insomnia as defined by DSM-IV (or nonorganic insomnia as defined by ICD-10) characterised by non-restorative sleep. While there are references to primary insomnia, Zisapel 1999 does not address the therapeutic use of melatonin for treating primary insomnia (whether characterised by non-restorative sleep or otherwise).

13.3 A number of observations are reported by Zisapel 1999 on melatonin rhythms or levels in patients which it incorrectly asserts have primary insomnia. The observations also do not always match up with the data cited in the underlying paper, see for example my comments on Rodenbeck and Pollak above. Zisapel 1999 does not report any relationship between melatonin and the restorative quality of sleep of patients.

13.4 Zisapel 1999 does not mention non-restorative sleep. If the skilled person was interested specifically in the sub-population of primary insomnia patients with non restorative sleep, Zisapel 1999 provides nothing about how to treat that population.

13.5 Zisapel 1999 does not assess whether a patient's restorative quality of sleep is improved by melatonin, other than in benzodiazepine-dependent patients, and even there infrequently.

[123] Paragraph 12.2 of Roth 3.

[124] Roth 3.

13.6 Moreover, those papers reviewed in Zisapel 1999 in which the effect of melatonin on the patients' subjective assessment of their "sleep quality" was assessed…, tend to point away from melatonin being of use in patients with primary insomnia."

98. Professor Morgan's views were as follows:[125]

"8.18 The skilled person would understand from Zisapel that prolonged release melatonin doses within the range claimed specific 1-2 mg in the Patent may effectively improve sleep quality in elderly insomnia patients.

8.19 The difference between Zisapel and the claim of the Patent is that Zisapel does not expressly discuss the use of slow-release melatonin in relation to primary insomnia characterised by non-restorative sleep and its impact on "restorative quality of sleep". Sleep onset and maintenance problems expressly mentioned in relation to the cited studies, but there is no mention of non-restorative sleep. For the reasons given in paragraph 5.51, the skilled person would understand that the conclusions of Zisapel are applicable to primary insomnia, and this would include patients complaining of non-restorative sleep.

8.20 The skilled person would understand that improvement of sleep quality (when used in a general sense) would be reasonably expected to improve a patient's responses on aspects of sleep that would lead to a complaint of non-restorative sleep. If the skilled person were to incorporate such testing into a subsequent trial, they would reasonably expect improvements in the subject's quality of sleep, demonstrating improvements in the subject's experience in getting to sleep, maintaining sleep and non-restorative sleep."

99. I conclude that the views of Professor Roth are to be preferred over those of Professor Morgan. Zisapel 1999 goes nowhere close to exploring any relationship between non-restorative sleep in Primary Insomniacs and melatonin. The point is neither mentioned in the article itself, nor adverted to in the prior art referenced. There is nothing to render the invention in the Patent obvious to the Skilled Person.

G. INSUFFICIENCY

(1) Introduction

100. The various aspects of insufficiency were described in paragraph 8(3) above. By the time of closing submissions, Mylan ran insufficiency on two different grounds:

(1) First, on a stand-alone basis: Mylan contended that there was no data in the Patent which evidenced the claimed effect, namely an improvement in the restorative quality of sleep in a patient suffering from Primary Insomnia characterised by non-restorative sleep.[126]

(2) Secondly, as a "squeeze" with anticipation on Haimov 1995.[127] That "squeeze" was described in Mylan's written closing submissions as follows:

[125] Morgan 1.

[126] Mylan's written closing submissions at paragraph 267(a).

[127] Mylan's written closing submissions at paragraph 267(b).

> "12. For the purposes of anticipation of the claims of the Patent, the issues are whether:
>
> (a) the Haimov [1995] patient population was suffering from [non-restorative sleep]; and
>
> (b) whether the demonstrated improvement was in respect of "the restorative quality of sleep" in such a patient.
>
> 13. As to (a), if the Court were to accept Professor Roth's logic which he applied to the patient groups in Examples 1-3 of the Patent (namely, the patient population must have included primary insomniacs suffering from [non-restorative sleep] because there is a reported improvement in the quality of sleep measurement as assessed by the [Leeds Sleep Evaluation Questionnaire Question 4], then that logic applies equally to Haimov which similarly discloses a primary insomnia group characterised as suffering from [non-restorative sleep].
>
> 14. If the Court were not to accept Professor Roth's logic (which is not accepted by Professor Morgan, as his view is that responses to [the Leeds Sleep Evaluation Questionnaire Question 4] alone are not capable of being used to identify only primary insomniacs suffering from [non-restorative sleep], rather they are merely recording the quality of sleep that the patient experienced during the night), then Haimov [1995] does not anticipate the Patent, but that the Patent is insufficient on the further ground that there is no data in the Patent showing an improvement in respect of any quality of sleep measure, in relation to a group of primary insomniacs suffering from [non-restorative sleep]."

I have, of course, not forgotten how insufficiency was pleaded in the Grounds of Invalidity, and I read these submissions in light of Mylan's pleaded case.[128]

(2) Insufficiency on a stand-alone basis

(a) Type of insufficiency alleged

101. The insufficiency alleged by Mylan appears to be a combination of uncertainty insufficiency[129] and lack of plausibility insufficiency.[130] It is logical to begin with uncertainty insufficiency and then move on to lack of plausibility insufficiency.

(b) Uncertainty insufficiency

102. Paragraphs 4 and 5 of Mylan's Grounds of Invalidity suggest that the meaning of the term "restorative quality of sleep" is both *(i)* ambiguous and uncertain and *(ii)* incapable of measurement such that the Skilled Person would not be enabled to work the invention of the claims.

103. I have, in effect, dealt with both of these points when considering the true meaning of the Patent (in Section D above) and the nature of non-restorative sleep (in Section C

[128] The relevant Grounds of Invalidity are set out in paragraph 8(3)(d) above.

[129] Described in paragraph 8(3)(c) above.

[130] Described in paragraph 8(3)(d) above.

above). I can therefore state my conclusions on uncertainty insufficiency relatively briefly:

(1) For the reasons given in Section D above, I consider the phrase "improving the restorative quality of sleep" to be clear and unambiguous to the Skilled Person. The Patent is concerned with individuals suffering from Primary Insomnia (in the DSM-IV sense), which insomnia is characterised by non-restorative sleep (again, in the DSM-IV sense). One might equally say that the Patent is concerned with individuals suffering from nonorganic insomnia (in the ICD-10 sense), which insomnia is characterised by poor quality of sleep (again, in the ICD-10 sense).[131] Reading the Patent as a whole, it is absolutely clear that what the Patent is claiming is an invention that improves the sleep of:

(a) An individual suffering from Primary Insomnia characterised by non-restorative sleep;

and/or (which is the same thing)

(b) An individual suffering from inorganic insomnia characterised by poor quality of sleep.

That is what the phrase "improving the restorative quality of sleep" clearly means. I reject the suggestion that the phrase is in any way ambiguous or uncertain.

(2) Turning to the question of measurement and enablement, this is closely tied to the manner in which Primary Insomnia characterised by non-restorative sleep is diagnosed and assessed. As has been described in Section C above, the complaint is diagnosed and the patient's condition (whether it improves or gets worse) assessed through the subjective input of the patient (by taking a history, including a sleep history, and by using questionnaires like the Leeds Sleep Evaluation Questionnaire). There is (as yet, at least, and certainly as at the Priority Date) no objective or external means of reaching such a diagnosis or of assessing whether the individual's condition is getting better or worse.

(3) In these circumstances, the measure of whether the restorative quality of sleep has been improved will turn on the effective interrogation of the individuals suffering from Primary Insomnia characterised by non-restorative sleep both before and after treatment in accordance with the invention described in the Patent. In short, do individuals suffering from non-restorative sleep report an improvement after receiving 2mg slow-release melatonin? The Skilled Person will obviously be capable of assessing this contended for effect. I reject the suggestion that the Skilled Person is not enabled to work the invention of the claims.

[131] See, generally, Section C above.

(c) Lack of plausibility insufficiency

(i) Approach

104. Since the Patent is a patent for a second medical use of a known medicinal compound, the Patent must plausibly disclose the effect that it claims. I have described, in the preceding paragraphs, the effect that the Patent claims: see, in particular, paragraph 103(1) above.

105. The answer to this question depends upon the data contained in the Examples set out in the Patent. That is trite: it was common ground between the parties that bare assertion was not enough to found plausibility and (self-evidently) if the data was not disclosed in the Patent, but had been published elsewhere then, whilst the Patent might be plausible, it would likely be unoriginal.

106. I have already considered Professor Morgan's approach to the Examples in the Patent, and given my reasons for rejecting his approach to construing or understanding these Examples.[132] Of course, the meaning of the Patent, the nature of the Skilled Person, that person's common general knowledge and the nature of that common general knowledge are all matters for me, assisted by the expert (and other) evidence adduced. In providing me with such assistance, it is almost inevitable that experts will stray into what is properly judicial territory when explaining their understanding, for example, of what the Patent teaches. Questions of construction and interpretation are inevitably a part of this, and I have benefitted from the experts' explanation as to how they regarded the materials that were adduced in evidence before me.

107. Whilst I have not accepted Professor Morgan's approach to interpreting the Examples, I have certainly been assisted by his explanation of his approach. The same is true of Professor Roth, who gave the following explanation as to how he viewed the materials that he had considered:[133]

> **A (Professor Roth)** …I am going to take this opportunity to address this thing which you have repeated on multiple occasions. There is not a single standard – my Lord, there is not a single standard of evidence. The standard of evidence in a patent is not the same as a standard of evidence in a scientific publication. Nor is it the same standard of evidence that is given for a regulatory study submitted to a regulatory body, such as the EMEA or the FDA. I have read patents where we do not have any data, we just have a single case report. That is not the standard which a journal has. You are 100% right, and I said that. I said in none of these three studies do I accept their assertion of primary insomnia, if this was a journal article. If I was sitting on an advisory board for the FDA, which I have done, I would not have accepted that.
>
> In reading the patent, I would accept that, because there is very different rules of evidence for scientific journals, and very different rules of evidence for regulatory bodies.
>
> So to apply the same rules of evidence across all three of those

[132] See paragraph 42(2) above.

[133] Transcript Day 2/pp.353*ff*.

> domains is not viable.
>
> So, for example, many of the studies we talked about on melatonin were cross-over studies. Well, an FDA or an EMEA would have rejected those out of hand, because they want parallel group studies, not cross-over studies.
>
> So to your question…did I treat patent data differently than I treat journal article data? Yes, I did and I do, and I think that is accepted in the field.
>
> …
>
> **Q (Marcus Smith J)** Professor, just to follow up on that, when you are describing what you extract or derive from statements in a patent, as opposed to statements in a peer reviewed publication, and describe what you derive from those different documents in a report, you, for the reasons you have given, read them in a slightly different way?
>
> **A (Professor Roth)** Yes, my Lord. I see these patents – if I can get on to that, my Lord. I see these patents as reason to believe. I see publications as demonstrations of the belief, and I see regulatory bodies as systematic demonstrations of that and very specific methodologies.
>
> **Q (Marcus Smith J)** That is very clear, Professor, and just to follow through on that, I entirely understand what you are saying, but I think that that approach to reading these three different classes of document is something that feeds into the way you describe what you derive from these documents in your report?
>
> **A (Professor Roth)** Yes, my Lord.

Professor Roth was criticised for this approach,[134] on the basis that Professor Roth was reading both the prior art and the Patent according to different standards:

> "This is a totally inappropriate approach – the Skilled Person should read both the prior art and the Patent with the same degree of expertise and the same common general knowledge."

This criticism misses the point. I do not consider that Professor Roth was applying different levels of expertise or common general knowledge according to the document the Skilled Person was hypothetically considering or hypothetically had in mind. Rather, he was noting that the meaning that the Skilled Person with the same common general knowledge in all cases would attach to different types of document would be different. At the end of the day, what these documents say is for me, based upon the expert evidence before me. But it is fundamental to understanding that evidence that I know how the expert before me reads such documents. Whether that reading is ultimately justified or not is an altogether different question.

108. With that introduction, I turn to the Examples in the Patent. As I noted in paragraph 41 above, the Patent identified five examples, but only two are material for present purposes. Examples 1 and 4 are both "reference" examples, which the Skilled Person

[134] See, in particular, paragraphs 35(c) and (d) of Mylan's written closing submissions.

would appreciate were not purporting to describe something within the Claims.[135] Example 5 concerns the preparation of the prolonged release melatonin formulation and is irrelevant for present purposes.

109. I therefore focus on Examples 2 and 3 and consider whether they render the Patent plausible.

(ii) Example 2

110. The Patent states:[136]

> "[0026] Method. The effect of a prolonged-release formulation of melatonin on **subjectively assessed sleep quality** and daytime vigilance in 170 elderly **primary insomnia patients** (aged 68.5 [SD 8.3] years) were studied in a randomised, double-blind, two parallel group study. The subjects were treated for 2 weeks with placebo to establish baseline characteristics and then for 3 weeks with melatonin (2 mg per night of prolonged-release formulation) or placebo. On the last three days of the baseline and treatment periods patients were asked to assess **the quality of their sleep** the previous night and their feeling in the morning. The quality of sleep question was "How would you compare the quality of sleep using the medication with non-medicated (your usual) sleep?" The patients marked the level of **their perceived quality of sleep** on a 100mm, non-hatched horizontal line with two endpoints. The left endpoint was labelled "more restless than usual"and the right endpoint was labelled "more restful than usual". The waking state question was "How do you feel now?" The patients marked the level of their perceived waking state on a 100mm, non hatched horizontal line with two endpoints. The left endpoint was labelled "tired" and the right endpoint was labelled "alert". The distance of the patient mark from the right endpoint in mm was measured (a reduction in value therefore indicates a **better sleep or less tired state**). The mean distance across the three nights was calculated.
>
> [0027] Results. It was found that **both quality of sleep and daytime alertness significantly improved** with melatonin compared to placebo (Table 1) showing a link between improved restful sleep and less fatigue in the morning.

111. The test of plausibility is obviously met. This was a reasonably large study (of 170 elderly individuals) who were Primary Insomniacs at least some of whose sleep was characterised by its non-restorative quality. The study was conducted on established lines (use of placebos and blind testing) and resulted in a statistically significant outcome in that it enabled the conclusion that melatonin enhanced the restorative value of sleep.

112. Professor Morgan made the following points regarding the plausibility of Example 2, which it is necessary to consider:

(1) He noted that no information was provided as to how the subjects of the study were diagnosed with Primary Insomnia.[137] He is, of course, right about this, and – if this were a peer-reviewed article – his criticism might have some force in terms of the sustainability of the contention that melatonin improved the restorative

[135] See paragraph 42(3) above.

[136] Emphasis added in **bold**. The underlinings are as in the original.

[137] Paragraph 6.16 of Morgan 1.

quality of sleep. But the test is not what would satisfy a peer-reviewed article, but whether the standard of plausibility is met. In my judgment, the phrase "primary insomnia patients" in Example 2 is clearly and unambiguously used in its technical sense, and it would be entirely wrong to disregard this statement simply because the precise criteria for selecting the subjects of the study were not set out in terms.

(2) Equally, the language used in Example 2 makes clear that not only were these individuals diagnosed as Primary Insomniacs, they were Primary Insomniacs whose sleep was characterised as non-restorative or (in the technical sense) of poor quality. Professor Morgan's suggestion that this was not the case because detailed evidence was not provided as to diagnosis is unsustainable.[138]

(3) The questions that were asked of the patients are similar to (although not absolutely identical with) those used in the Leeds Sleep Evaluation Questionnaire. For the reasons I have given, such questions (including, to be clear, as framed in Example 2) are directed to quality of sleep in the technical sense,[139] and to the extent that Professor Morgan sought to suggest that they were not, I reject that evidence.[140]

(4) In Morgan 3, Professor Morgan makes the point that a number of the patients in the study may have been 55 years or younger, thus rendering the claims of the Patent – which, as amended, claims the second medical use in relation to patients aged 55 and over – less plausible. So far as it goes, I take the point. But the point does not go very far. Example 2 shows that the Skilled Person would expect to see some benefit in the use of prolonged release melatonin in the over 55s, and the fact that the study included some under 55s would not materially undermine this expectation.

113. I conclude that, by reason of Example 2 alone, the Patent is sufficiently plausible.

(iii) Example 3

114. The Patent states:[141]

"[0029] Method. The effect of melatonin on **subjectively assessed sleep quality and daytime vigilance** in 131 **primary insomnia patients** (aged 20-80 years) were studied in a randomised, double-blind, parallel group study. The subjects were treated for 1 week with placebo to establish baseline characteristics and then for 3 weeks with melatonin (2mg per night of prolonged-release formulation) or placebo. On the last three days of the baseline and treatment periods patients were asked to assess the quality of their sleep the previous night and their feeling at daytime as described in Example 2.

[0030] Results. **In the 55 years and older patients, there was an improvement of quality of sleep and daytime alertness as found in the other studies in the elderly (see Example 2). Surprisingly, it was found that in patients <55 years of age there was**

[138] Paragraph 6.16 of Morgan 1.

[139] See paragraph 62 above. The questions in Example 2 are obviously similarly directed.

[140] See paragraphs 6.17 to 6.20 of Morgan 1.

[141] Emphasis added in **bold**. The underlinings are as in the original.

a significant worsening of the quality of sleep and daytime alertness compared to placebo. The results are tabulated in Table 2.

Table 2: Effects of melatonin and placebo on subjectively assessed quality of sleep and daytime alertness in primary insomnia patients aged 55 and higher and patients aged less than 55 years (mean in mm (SE)).

Response	Melatonin	Placebo
Change in perceived quality of sleep Patients aged 55 and over	-13.1 (4)	-7.4 (3)
Change in perceived daytime alertness Patients aged 55 and over	-16.3 (3.7)	-7.5 (3.3.)
Change in perceived quality of sleep Patients aged less than 55	-1.6 (2)	-13.7 (5)
Change in perceived daytime alertness Patients aged less than 55	+2.9 (3)	-4.0 (4)

[0031] Conclusions. The elderly are more likely to have maintenance and **non-restorative sleep** problems, as 40% of older individuals complain about sleep problems, including disturbed or "light" sleep, and undesired daytime sleepiness (Vitiello, Michael Geriatrics Vol 54(11):47-52 1999). Younger people typically have sleep onset problems (Roth, Thomas and Roehrs, Timothy Sleep Vol 19(8): S48-49 1996), and their main problem may be due to sleep deficit not non-restorative sleep. These results (Table 2) clearly indicate that melatonin was effective in primary insomnia related to non-restorative sleep, but can be detrimental to insomnia related to other aetiologies (e.g., sleep deficit due to inability to initiate sleep)."

115. I consider that Example 3 (as with Example 2) of itself enables the Patent to demonstrate that the invention is plausible. Again, the language used in Example 3 makes clear that the focus of the study was the effect of melatonin on non-restorative sleep in Primary Insomniacs. Although the results are not statistically significant[142] – obviously a relevant factor – the fact is that the study shows that there is "something in" the invention. Example 3 goes well-beyond mere assertion.

116. Professor Morgan's points regarding Example 3 are similar to those that he makes in relation to Example 2: the selection criteria for the study group are unclear, and the outcome not clearly consistent with the invention claimed.[143] I accept that there is some force in these points: but they have nothing like the force needed to render the Patent invalid for a lack of plausibility insufficiency.

[142] Paragraph 6.25 of Morgan 1.

[143] Paragraphs 6.22*ff* of Morgan 1.

(d) Conclusion

117. For all these reasons, I reject the contention that the Patent is invalid by reason of insufficiency.

(3) The "squeeze"

118. I do not consider that the "squeeze" argument advanced by Mylan to be soundly based, and I reject it. That is because the logic that underpins the argument is based upon the existence of a terminological equivalence between Haimov 1995 and the Patent. But – for the reasons set out in detail in paragraphs 77 to 81 above – there is no such equivalence. A "squeeze", in order to work, requires the two opposing elements of the squeeze to meet, as it were, in the middle, with the result that there is no "validity" gap between the two elements in which the patent in question can exist. In such a case, the patent is either invalid for one reason (here: because it is anticipated) or invalid for another (here: because it is insufficient).

119. In this case, there is quite simply no "squeeze" argument because Haimov 1995 and the Patent are, if I may change the metaphor, "ships passing in the night", and they never meet.

H. EXCLUSIVE LICENCE

(1) Introduction

120. Paragraph 3 of the Re-Amended Particulars of Claim provides:

> "[Flynn] is the exclusive licensee under the Patent pursuant to a licence agreement dated 22 January 2020 (the "Agreement") (as clarified and varied by the 19 May 2020 Clarification Agreement). The Agreement was registered and recorded at the UK Intellectual Property Office on 18 February 2020."

121. Mylan's Re-Amended Defence and Counterclaim pleads as follows in response:

> "As to paragraph 3, it is denied that the Agreement (as varied by the agreement dated 19 May 2020 between Neurim Pharmaceuticals (1991) Ltd, Rad-Neurim Pharmaceuticals EEC Limited and Flynn Pharma Ltd) is an exclusive licence under the Patent because it is not a licence for [Flynn] to carry out any relevant act in respect of the claimed invention to the exclusion of all others. It is admitted that the Agreement was registered at the UK Intellectual Property Office on 18 February 2020. Paragraph 3 is otherwise not admitted."

122. As was common ground, the question of whether Flynn was an exclusive licensee was determinative of the question of Flynn's standing as a claimant in these proceedings. Section 67(1) of the Patents Act 1977 provides:

> "Subject to the provisions of this section, the holder of an exclusive licence under a patent shall have the same right as the proprietor of the patent to bring proceedings in respect of any infringement of the patent committed after the date of the licence; and references to the proprietor of the patent in the provisions of this Act relating to infringement shall be construed accordingly."

123. Section 130(1) of the Patents Act 1977 – the interpretation section – defines an exclusive licence as meaning:

"…a licence from the proprietor of or applicant for a patent conferring on the licensee, or on him and persons authorised by him, to the exclusion of all other persons (including the proprietor or applicant), any right in respect of the invention to which the patent or application relates…"

124. Since the nature of an exclusive licence under this definition is central to this issue, in particular the ability for the interests in a patent to be sliced many ways, with each slice maintaining its aliquot of "exclusivity", it is as well to set out what *Terrell* says about the definition of exclusivity:

"16-25 There may, therefore, be several exclusive licensees, each having an exclusive licence in their own field and each may sue in respect of an infringement committed in contravention of their particular right. The definition of an exclusive licence may not prevent the proprietor retaining some measure of control of sub-licences, perhaps through an agency relationship.

16-26 An exclusive licensee who has the right to grant sub-licences may grant an exclusive licence to another and such a licence will fall within the definition of section 130(1) if it deprives the first exclusive licensee of rights in respect of the invention to which the patent relates. However, a person who merely has the exclusive right to manufacture to an exclusive licensee's specification is not an exclusive licensee within the definition of section 130(1) because an exclusive right to manufacture to another's specification does not constitute an exclusive licence of a right "in respect of the invention to which the patent…relates."

16.27 In the absence of evidence establishing that the claimant is an exclusive licensee their claim will be struck out but there should be no additional finding to the effect that they are not in fact an exclusive licensee unless there is evidence to justify that finding."

125. This section considers the following matters in the following way:

(1) Section H(2) set out the terms of the relevant contractual provisions. According to Neurim and Flynn, these provisions were provisions of extreme commercial sensitivity, and I have endeavoured to respect that sensitivity in this judgment. However, Neurim and Flynn both failed to appreciate that it is for the exclusive licensee to establish that status of exclusivity, where it is disputed, and that it is a necessary part of that burden to put the licence into evidence, so that the court may consider it. Neurim and Flynn's disinclination to make good their case by producing, in unredacted form, the contractual documentation on which Flynn relied until the eleventh hour, meant that the points that Mylan took in relation to exclusivity were inevitably framed late and that the issues were not – for that reason – as clearly articulated as they might have been.

(2) Section H(3) considers whether, in light of these provisions, and in light of the claims in the Patent, Flynn can properly be said to be within the meaning of "exclusive licensee" in the sense of the Patents Act 1977.

(2) The contractual provisions

126. The contractual relations between Neurim and Flynn are set out in the following documents:

(1) A Licence and Distribution Agreement between Neurim, RAD-Neurim Pharmaceuticals EEC Limited and Flynn dated 26 November 2011.

(2) An Amendment and Common Interest Agreement between the same parties dated 22 January 2020.

(3) A Clarification Agreement between the same parties dated 19 May 2020.

I shall refer to these agreements as, respectively, the **November 2011 Agreement**, the **January 2020 Agreement** and the **May 2020 Agreement**. They are closely related, in that the January 2020 Agreement amends the November 2011 Agreement, and the May 2020 Agreement "clarifies" (it will be necessary to consider what that means) the January 2020 Agreement.

127. Neurim and Flynn only provided unredacted forms of the totality of the agreements setting out their legal relationship at the last minute and only after a very clear indication from me that they would be most unlikely to succeed in demonstrating an exclusive licence within the meaning of section 130(1) of the Patents Act 1977 unless they did so. Given that instruments like contracts must be construed as a whole, taking into account all their provisions, as well as the "factual matrix" surrounding such agreement, I do not consider that redaction of such instruments on the basis that the redacted provisions are "confidential and irrelevant" is permissible. A party may very well take the view that certain sensitive provisions add nothing to the construction of the contract: but that is not something that one party can simply assert as against its litigation counterparty. If the point is in issue – as it was here – the document must be disclosed to the other side and to the court.[144] If the document can be disclosed,[145] but is not, then the disclosing party is not entitled to an inference that what that party asserts is correct. To the contrary.[146]

128. Ultimately, all of the relevant agreements were disclosed to nominated lawyers in Mylan and to the court, and Mylan was able to state by reference to the contracts why the licence granted to Flynn was not exclusive.[147]

129. Clause 3 of the November 2011 Agreement provides:

> "3.1 Neurim grants Flynn which accepts, under the Neurim Patents, the Neurim Confidential Information, the Existing Marketing Authorisation and the Trademark, a licence to Distribute the Product in the Territory for use in the Field during the Term.

[144] Of course, where parts of the same document deal with entirely different subject matters, one relevant and one irrelevant, the relevant part can be disclosed and the irrelevant redacted: see, for example (albeit in the context of privilege), *Great Atlantic Insurance Co v. Home Insurance Co*, [1981] 1 WLR 529at 536. But that is a test that is difficult to meet in the context of a contract to be construed as a whole.

[145] Matters are, of course, different where the document has been destroyed, for example.

[146] *Promontoria (Oak) Ltd v. Emanuel*, [2020] EWHC 104 (Ch).

[147] The complete, unredacted, January 2020 Agreement was disclosed on the basis that it was "Privileged & Confidential – External Lawyers' Eyes Only". The assertion of privilege was rightly not pursued by Neurim and Flynn. Even before the document was disclosed, it was difficult to understand the claim to privilege. Having seen the document, the assertion of privilege was obviously untenable.

3.2 Flynn shall not have any right to grant sub-licences rights under or in respect of the rights granted in clause 3.1. Flynn may use a pre-wholesaler.

3.3 The licence to use the Existing Marketing Authorisation shall not include any extensions and amendments to the Existing Marketing Authorisation.

3.4 For the avoidance of any doubt:

3.4.1 Combination Products are expressly excluded from this Agreement and shall at all times be the subject of separate discussion and agreement between the parties provided that neither party shall be obliged to enter any discussions with the other party in respect of Combination Products. Notwithstanding the foregoing, each Party shall keep the other Party informed of its plans for any Combination Products prior to starting any development of such Combination Products. In case of such project or development, Neurim grants to Flynn a right of first notice and negotiations in the Territory when the Combination Product is based on Melatonin.

3.4.2 This Agreement does not grant Flynn distribution or other rights in relation to melatonin products other than the Product."

130. Clause 3 contains a number of defined terms. Not all are material, but the following are:

(1) "Neurim Patents" means the "Patent Rights" owned by Neurim as more specifically set out in schedule 1 to the agreement. The Patent – then an application – is the only patent listed in schedule 1. "Patent Rights" are broadly defined to mean "all patents and patent applications including divisionals, continuations, continuations-in-part, reissues, re-examinations, renewals, extensions (including patent term extensions), supplementary protection certificates and any similar or analogous rights related to the Product".

(2) "Product" is defined as "the prolonged release prescription product containing 2mg Melatonin known as Circadin for use in the Field as covered by the Existing Marketing Authorisation namely, for the treatment of primary insomnia patients aged 55 and older."

(3) "Field" means "insomnia and circadian rhythm sleep disorders, subject to clause 3".

(4) "Distribute" – defined in the agreement as "Distribution" – means "to import, distribute, promote, market, sell or offer for sale the Product, and 'Distribute' has a corresponding meaning".

(5) "Combination Products" do not appear to be defined in the agreement.

(6) "Territory" means the United Kingdom of Great Britain and Northern Ireland and the Republic of Ireland.

131. Clause 17 concerns litigation regarding the Patent. Clause 17.3 provides:

"Neurim shall have the sole right to bring an infringement action or any other appropriate action directly related to infringement of that Neurim Patent or misuse of Neurim Confidential Information at Neurim's expense. Flynn shall, and shall procure that its [*sic*], cooperate

reasonably with Neurim at Neurim's expense in any such action where it relates to the Territory. To the extent that the infringement or misuse takes place in the Territory and Neurim elects not to take action within ninety (90) days of notification thereof to or by Flynn may do so [*sic*] at its expense, provided that Flynn shall keep Neurim informed of any legal proceedings or settlement negotiations in relation thereto and the terms of any settlement Flynn proposes to enter into shall be subject to Neurim's prior written approval, not to be unreasonably withheld. Neurim shall cooperate with Flynn reasonably at Flynn's expense in any such action."

132. In his evidence, Dr Fakes expressed the view that the November 2011 Agreement gave Flynn "the exclusive right and licence under the Neurim Patents".[148] Strictly, such views are irrelevant to questions of contractual interpretation – although I shall consider what Dr Fakes' says, in case this sheds light on the "factual matrix". In this case, Dr Fakes' evidence does not. Moreover, his subjective view as to the meaning of the licence in clause 3.1 is unsustainable. I can see no basis for the view that the November 2011 Agreement precludes Neurim from working the invention itself or granting other licences in the jurisdiction. The only contrary indicator is clause 17.3, which confers on Flynn a contingent right to commence an infringement action – which Flynn could only do if it were an exclusive licensee. However, I do not consider that clause 17.3 can permit me to import exclusivity into clause 3.1, when there is no other indication in the agreement that this was the intention of the parties. It seems to me that clause 17.3 is simply a case where the agreement has sought to confer on Flynn a standing to pursue a claim which does not exist as a matter of law, Flynn not otherwise being an exclusive licensee.

133. I turn then to the January 2020 Agreement. This agreement expressly modifies the November 2011 Agreement, which otherwise remains in full force and effect.[149] Defined words and expressions in the November 2011 Agreement bear the same meaning in the January 2020 Agreement, unless the context specifically requires otherwise.[150] However, if there is any conflict between the January 2020 Agreement and the November 2011 Agreement, the former (the January 2020 Agreement) prevails.[151]

134. By clause 3.6 of the January 2020 Agreement, clause 3.1 of the November 2011 Agreement was deleted and replaced as follows:[152]

"Neurim grants Flynn which accepts, under the Neurim Patents, the Neurim Confidential Information, the Existing Marketing Authorisation and the Trademark, an exclusive licence to Distribute the Product in the Territory for use in the Field during the Term."

135. By clause 3.7 of the January 2020 Agreement, clauses 17.2 to 17.4 of the November 2011 Agreement were deleted and different clauses regarding the prosecution of infringers inserted. It is unnecessary – and, in view of their confidentiality, undesirable – to set these out in full. It is sufficient to note that Flynn's ability to maintain infringement proceedings like the present independent of Neurim are even more

[148] Paragraph 11 of Fakes 4.

[149] Clause 3.2.

[150] Clause 3.3.

[151] Clause 3.4.

[152] Differences in wording are indicated by my underlinings and ~~strikeout~~.

circumscribed than under the old clause 17. Clause 17 makes provision for joint proceedings, with Neurim very much taking the lead. If Neurim does not seek to vindicate its rights, the January 2020 Agreement is silent, and it would appear that the agreement contemplates no independent action on the part of Flynn being commenced in these circumstances.

136. Finally, the May 2020 Agreement provides that the parties to it "wish to confirm and give effect to their understanding of the meaning of the term "Product"" in the preceding two agreements that I have already described. In substance, this agreement deletes and replaces the definition of "Product" in the November 2011 Agreement. "Product" is now defined as "the prolonged release prescription product containing 2mg Melatonin known as Circadin including any generic equivalent or version thereof ~~for use in the Field as covered by the Existing Marketing Authorisation namely, for the treatment of primary insomnia patients aged 55 and older~~."[153]

(3) Exclusivity

(a) Points taken by Mylan

137. Mylan contends that the licence between Neurim and Flynn was not exclusive for two reasons:

(1) First, Neurim was entitled – even under the agreement as revised, twice – to "work the residual part of the claim of the invention and is free to exploit and/or licence other third parties to work that part of the claim".[154] In its submissions, Mylan provided the following examples of what is called the "salami slicing" of the property rights in the Patent:[155]

> "(i) a prolonged release tablet containing 2 mg melatonin with any "pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifier, adjuvant or carrier" which is not bioequivalent to Circadin;
>
> (ii) a medicament adapted for rectal, parenteral, transbuccal, intrapulmonary (e.g., by inhalation) or transdermal administration (which is a subset of Claim 1, as can be seen from the limitation to claim 1 specified in claim 2) which is not in the same pharmaceutical form or route of administration as Circadin; and/or
>
> (iii) any medicament comprising prolonged release formulation comprising 2 mg melatonin and at least one additional therapeutic agent (including, by way of example, one or more of those listed in paragraph [0014] of the Patent."

(2) Secondly: [156]

> "The unredacted clauses [in the January 2020 Agreement] (including in particular clause 3.7 sub-heading 17.2.2 "Enforcement Actions" and the sub-headings referred to therein)

[153] Differences in wording are indicated by my underlinings and ~~strikeout~~.

[154] See paragraph 184 of Mylan's written opening submissions and paragraph 293 of Mylan's written closing submissions, which put the point in materially the same way.

[155] Paragraph 293 of Mylan's written closing submissions.

[156] See paragraph 189 of Mylan's written opening submissions and paragraph 306 of Mylan's written closing submissions, which put the point in materially the same way.

> are inconsistent with the grant of an exclusive licence because they do not allow [Flynn] to initiate proceedings for infringement of the Patent in the UK without [Neurim] and therefore do not provide that [Flynn] has the same right to bring proceedings as [Neurim], within the meaning of the Patents Act 1977…"

138. It is necessary to consider these two points in turn.

(b) "Salami slicing"

139. Whether the licence granted by Neurim to Flynn is exclusive or non-exclusive is, essentially, one of construction. Drawing on the decisions of Pumfrey J in *Dendron v. University of California*[157] and Henry Carr J in *Illumina Inc v. Premaitha Health plc*,[158] Mr David Stone (sitting as a Deputy High Court Judge) helpfully summarised the law in the following propositions in *Oxford Nanopore Technologies Ltd v. Pacific Biosciences of California Inc* at [44]:[159]

> "(i) Whether or not a licence is an exclusive licence for the purposes of section 67(1) of the Patents Act is a matter for English law: *Dendron*…at [9];
>
> (ii) A licence which purports to be an exclusive licence may not necessarily be so. Identifying an exclusive licence depends on a proper construction of the document or documents: *Dendron* at [9]. An exclusive licence will be expressly so: circumstances in which an exclusive licence will be implied will be rare, if they exist at all;
>
> (iii) It is for the party asserting that it is an exclusive licensee to demonstrate that it is: *Dendron* at [9];
>
> (iv) The assessment of whether or not a licence is exclusive is not a "once and for all assessment": *Dendron* at [11]. An exclusive licence may confer upon the patentee a power to convert the licence into a non-exclusive licence: *Dendron* at [11];
>
> (v) The "essential element" of an exclusive licence is that it is a licence to the exclusion of all other person, including the patentee or applicant: *Dendron* at [11];
>
> (vi) It is possible to have a plurality of exclusive licences in respect of any one patent: *Courtauld*, [1956] RPC 208 at [210]; *Illumina* at [475];
>
> (vii) But each exclusive licence may only be granted to one person – a licence will not be exclusive if granted to a number of entities, even if they are under the same control: *Illumina* at [254];
>
> (viii) An exclusive licensee may grant sub-licences to "persons authorised by him": *Dendron* at [11]; *Illumina* at [254];
>
> …"

140. In this case, I conclude that Neurim, having originally retained a right itself to work the Patent – see paragraph 132 above –, has successfully managed to divest itself of that

[157] [2004] EWHC 1163 (Pat).

[158] [2017] EWHC 2930 (Pat).

[159] [2017] EWHC 3190 (Pat).

ability and has not retained a "slice" of the action that renders Flynn's rights non-exclusive. As to this:

(1) The replacement of clause 3.1 with a new clause 3.1 makes it clear that the licence is in terms intended to be exclusive,[160] and the terms "Field", "Distribute", "Patent Rights" are broadly defined. Bearing in mind that this is a second medical use Patent – in that what is patented is a specific use of an existing medicament – it is difficult to see what could lie outside the scope of the grant by Neurim that would render it non-exclusive.

(2) I have considered each of the examples put forward by Mylan, and I am unpersuaded that they amount to second medical uses within the Patent that are at the same time not within the exclusive grant to Flynn.

(3) I was troubled by the mismatch – or apparent mismatch – between the scope of Claims 1 and 4 in the unamended Patent and the scope of the licence granted by Neurim to Flynn. It is fortunate that the amendments proposed to the Patent render this question academic for, absent these amendments, I consider that Mylan's case would have been more compelling:

(a) "Product", as we have seen, was defined as "the prolonged release prescription product containing 2mg Melatonin known as Circadin for use in the Field as covered by the Existing Marketing Authorisation namely, for the treatment of primary insomnia patients aged 55 and older."

(b) As originally framed in the Patent, however, the patented use was for unit dosages comprising 0.025 to 10 mg (not just 2 mg) for use in patients of any age, not just 55 and over.

(c) Given the narrower definition of "Product", effectively a subset of the claims in the Patent, Neurim clearly retained to itself the ability to work the Patent outside the grant to Neurim because (in the respects I have identified) the scope of the second medical use was wider than the grant to Flynn pursuant to the licence.

(d) In these circumstances, the question of whether Neurim granted Flynn an exclusive licence as defined by section 130(1) of the Patents Act 1977 is a very difficult one.

(e) I accept, of course, that it is possible to subdivide the monopoly conferred on the proprietor of a patent.[161] However, where it is proposed to split the monopoly contained in a single claim in a patent, such that each segment of that split is exclusive, the drafting must be pellucid. Whilst I appreciate that Robert Walker J was merely considering the point at an interlocutory stage in *Peaudouce SA v. Kimberly Clark Ltd*,[162] I consider that his

[160] See paragraph 134 above.

[161] See, for instance, Pumphrey J in *Spring Form Inc v. Toy Brokers Ltd*, [2002] FSR 17 at [20].

[162] [1996] FSR 680.

concern about the "unreality" of "salami-slicing of rights under different claims" is a warning that is well made.[163]

(f) The critical language in section 130(1) is "conferring…any right in respect of the invention". Provided that right is exclusive, even if it is only a sliver of a claim of a patent, it seems that the requirements of section 130(1) are met. In this case, therefore, I conclude that Flynn has been granted an exclusive licence in relation to 2 mg doses of melatonin in those aged 55 and over, and that even though the unamended Patent claims unit dosages between 0.025 and 10 mg, so far as 2 mg does are concerned, Flynn has the exclusive right to work the Patent, to the exclusion of Neurim. However, I have to say, in reaching this conclusion, I have felt in full measure the unreality articulated by Robert Walker J in *Peaudouce*.[164]

141. For these reasons, I find that Mylan's first attack on the exclusivity of Flynn's licence fails.

(c) An inability in Flynn to vindicate its own rights

142. Section 67(1) of the Patents Act 1977 provides that the holder of an exclusive licence under a patent shall have the same right as the proprietor of the patent to bring proceedings in respect of any infringement of the patent committed after the date of the licence. This is expressed to be a consequence of the grant of an exclusive licence as defined by section 130(1). The right to bring proceedings for infringement is not expressed to be a necessary condition for "exclusivity".

143. However, an essential part of the grant of a right is the ability to vindicate it. The 1977 Act confers on an exclusive licensee the ability to enforce another's rights, namely those of the patent holder. What if, as here, the licence itself takes away the very rights conferred in such a case by section 67 of the 1977 Act?

144. It seems to me – and the point is not covered by authority – that this has the effect of rendering the licence non-exclusive. The whole point of the section is to confer an additional right to claim for infringement on the licence-holder, and not to deprive the patent-holder of its rights.[165] There is, therefore, created by section 67, an additional cause of action, vesting in the licence-holder.[166]

145. The provisions of the licence in this case, as it seems to me, essentially take away Flynn's ability to prosecute such a claim. Referring to the new clause 17.2, inserted by the January 2020 Agreement:

(1) As I have noted, Flynn has no right to bring a claim independent of Neurim.

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[163] At 691.

[164] I should say that I do not consider the fact that the 2mg dose was the only dose that had marketing authorisation to be in any way relevant. The licence is in relation to claims in the Patent: the fact that the 2mg dose was the most valuable, because a marketing authorisation existed in relation to it, is immaterial.

[165] *Optical Coating Laboratory Inc v. Pilkington PE Ltd*, [1993] FSR 310 at 313 (reversed, but not on this ground, [1995] RPC 145).

[166] The wording of section 67(1) is very clear on this point: "…the holder of an exclusive licence under a patent shall have the same right as the proprietor…" (emphasis added).

(2) Where the rights under the Patent are to be enforced, Neurim and Flynn are jointly to take the appropriate steps (clause 17.2.2), with Neurim taking the lead and with Flynn playing an essentially supporting role:[167]

> "If the Parties jointly bring any suit, action or proceeding under clause 17.2.2, then Flynn agrees to be joined as party plaintiff or defendant (as appropriate to the relevant jurisdiction) if necessary to prosecute the suit, action or proceeding, claim the maximum amount of damages, to give Neurim reasonable authority to file and prosecute the suit, action or proceeding, and/or to avoid Neurim having to provide security for costs; provided, however, that neither Party will be required to transfer any rights, title, or interests in or to any property to Flynn or any other Party to confer standing on a Party. Flynn shall immediately execute all documents provided by Neurim in order for Neurim to initiate and maintain any action, claim the maximum amount of damages in such action and for Flynn to be named as a party in an action and to avoid Neurim having to provide security for costs in such action."

(3) Clause 17.2.3.2 makes clear that in any litigation, "Neurim shall take the lead";[168] by clause 17.2.3.2.4, Neurim and Flynn will jointly instruct barristers to act on their behalves; and by clause 17.2.3.3, Flynn "will provide reasonable assistance to Neurim".

(4) Flynn does have the right to have a say in any settlement. Clause 17.2.3.4 provides:

> "Neurim will not settle any claim, suit or action that it brought under clause 17.2.2.1 without the prior written consent of Flynn, not to be unreasonably withheld."

However, any damages or monetary awards recovered in the action are strictly apportioned as between Neurim and Flynn in accordance with a pre-determined formula, with no reference to their actual losses or the value of their respective claims. (Out of deference to the confidentiality insisted upon by Neurim and Flynn, I shall not quote clause 17.2.3.5, but that is its effect.)

146. The upshot is that what appears, on its face, to be an exclusive licence to Flynn, is actually no such thing when the provisions regarding the enforcement of Flynn's rights under the licence are taken into account. These provisions make absolutely clear that Flynn has no rights independent of Neurim, and that an infringement action such as this is in reality being prosecuted as a single cause of action by Neurim, with Flynn as little more than a cypher. I do not need to consider whether the exclusivity conferred by the new clause 3.1 amounts to a "sham" within the meaning of *Snook v. London- and West Riding Investments Ltd*,[169] simply because the effect of clause 17, also as amended, deprives clause 3.1 of substantially all meaning. Viewing clause 3.1 on its own – without considering clause 17 – an entirely misleading view of Flynn's rights is obtained. Viewing the licence agreement between Neurim and Flynn as a whole, this is not a case where two interested persons can separately prosecute separate rights. Rather, this is a case where the apparently separate and exclusive rights of Flynn are

[167] Clause 17.2.3.

[168] Including in the instruction of experts: clause 17.2.3.2.5.

[169] [1967] 2 QB 786.

eliminated by the ostensibly procedural, but in truth substantive, provisions of clause 17.

147. Accordingly, I conclude that, construing the agreement as a whole, Flynn is not Neurim's exclusive licensee, and that it has no standing in these proceedings.

I. CONCLUSIONS AND DISPOSITION

148. For the reasons given in this judgment, I find that:

(1) The challenges to the validity of the Patent all fail, and that Mylan is either threatening to, or is, infringing the Patent.

(2) The only proper person capable of bringing this action for infringement is, however, Neurim. Flynn is not an exclusive licensee within the meaning of sections 67 and 130 of the Patents Act 1977, and has no standing to bring an action for the infringement of the Patent.

149. I invite the parties to draw up an order reflecting the conclusions that I have reached. I should conclude by making two points:

(1) First, I must express my gratitude to the legal teams on both sides for the efficient, effective and courteous way in which the proceedings were conducted.

(2) Secondly, this is a long judgment, and it deals with the material points as I consider them to be. A number of points were made in the (very detailed and inevitably long) written submissions of the parties. The fact that not all of these points have been specifically set out and dealt with should in no way be taken as an indication that they have not been considered. They have been – but I simply did not find them material in light of my assessment of the evidence as a whole, and as set out in this judgment.

ANNEX 1

TERMS AND ABBREVIATIONS USED IN THE JUDGMENT

(paragraph 1, footnote 1)

TERM/ABBREVIATION	FIRST USE IN THE JUDGMENT
Arendt 1997	§67(3)(e)(v)
Arendt Consensus Paper 2000	§67(1)(b)
Arendt *et al* 1988	§67(3)(e)(v) footnote 100
ASDA 1995	§62(3) footnote 72
Baskett *et al* 1999	§67(3)(e)(iii) footnote 96
Circadian Rhythm Sleep Disorder	§34(7)
Circadin	§3
Claimants	§1
classical insufficiency	§8(3)(a)
Consensus Papers	§67(1)
Dyssomnias	§34(1) in quote
EPC 2000	§44(2)
Examples	§41
Example 2	§41(2)
Example 3	§41(3)
Example 5	§41(5)
excessive claim breath insufficiency	§8(3)(b)
DSM-IV	§33
Fakes 4	§13(2)(b)
Flynn	§1
Garfinkel *et al* 1995	§67(3)(e)(iii) footnote 96
Haimov 1995	§8(1)
Haimov and Lavie 1995	§67(3)(e)(iii) footnote 96
Horne 1994	§62(3)(a)
ICD-10	§35
January 2020 Agreement	§126
lack of plausibility insufficiency	§8(3)(d)
Leeds Sleep Evaluation Questionnaire	§64
Lichstein and Morin 2000	§62(3)(a)
May 2020 Agreement	§126

Melatonex	§8(2)(b)
Melatonex Webpage	§8(2)(b)
Morgan 1	§13(3)(b)
Morgan 2	§13(3)(c)(ii)
Morgan 3	§13(30(c)(iii)
Morgan and Closs 1999	§62(2) footnote 69
Mylan	§5
Neurim	§1
November 2011 Agreement	§126
Ohayon 1997	§55
Patent	§1
Parasomnias	§34(1) in quote
Parrott and Hindmarch 1978	§64(1)
Primary Insomnia	§34(4)
Primary Sleep Disorders	§34(1) in quote
Priority Date	§4
RAD Neurim	§3
Reference Example 1	§41(1)
Reference Example 4	§41(4)
Roth 1	§13(1)(b)(i)
Roth 2	§13(1)(b)(i)
Roth 3	§13(1)(a)
Roth 4	§13(1)(b)(ii)
Roth Consensus Paper 2001	§67(1)(a)
Sadeh *et al* 1995	§62(3) in quote
Secondary Sleep Disorder	§34(2)
Skilled Person	§48
Short sleepers	§34(7) in quote
Terrell	§19 footnote 23
uncertainty insufficiency	§8(3)(c)
Zisapel 1999	§8(3)

ANNEX 2

CHRONOLOGY OF RELEVANT MATERIALS

(paragraph 8(1) footnote 7)

DATE	EVENT	REFERENCE IN THE JUDGMENT
1978	Publication of Parrott and Hindmarsh 1978	§64(1)
1991	Baskett *et al*	§67(3)(e)(iii) footnote 96
1992	Publication of ICD-10	§35
1994	Publication of DSM-IV	§33
1994	Publication of Haimov 1994	C3/37
1994	Publication of Horne 1994	§62(3)(a)
1995	Publication of Haimov 1995	§8(1)
1995	Publication of Sadeh *et al* 1995	§62(3) in quotation
1995	Publication of ASDA 1995	§62(3) footnote 72
1995	Haimov and Lavie 1995	§67(3)(e)(iii) footnote 96
1995	Garfinkel *et al* 1995	§67(3)(e)(iii) footnote 96
1997	Publication of Ohayon 1997	§55
1997	Publication of Arendt 1997	§67(3)(e)(v)
1999	Publication of Zisapel 1999	§8(2)(c)
2000	Publication of Lichstein and Morin 2000	§62(3)(a)
2000	Publication of the Arendt Consensus Paper 2000	§67(1)(b)
2001	Publication of the Roth Consensus Paper 2001	§67(1)(a)
1 August 2001	Publication of Melatonex Webpage	§8(2)(b)
14 August 2001	Priority Date of the Patent.	§4

HP-2020-000005

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT
Before: Mr Justice Marcus Smith Date: 4 December 2020

Claim No. HP-2020-000005

B E T W E E N:

(1) NEURIM PHARMACEUTICALS (1991) LIMITED
(a company incorporated under the laws of Israel)
(2) FLYNN PHARMA LIMITED
(a company incorporated under the laws of the Republic of Ireland)

Claimants

-and-

(1) GENERICS UK LIMITED T/A MYLAN
(2) MYLAN UK HEALTHCARE LIMITED

Defendants

O R D E R

UPON this action having been heard by the Honourable Mr Justice Marcus Smith on 29-30 October, and 2 and 5 November 2020

AND UPON the Court handing down Judgment on 4 December 2020

IT IS ORDERED THAT:

1. The hearing to determine the appropriate form of Order following the handing-down of the Judgment in these proceedings (the "Form of Order Hearing") be adjourned to the week commencing 14 December 2020. Unless the parties notify the court in a communication signed by all solicitors by no later than 2:00pm on 4 December 2020 as to which day in that week the Form of Order Hearing shall take place, the hearing will take place at 10:30am on Monday 14 December 2020.

2. Such adjournment is an adjournment within paragraph 4.1(a) of Practice Direction 52A to Part 52 and accordingly the time for making any application for permission to appeal be extended until the Form of Order Hearing. Pending that hearing the time for service of any Appellants' Notice shall not run.

3. Until the Form of Order Hearing the documents referred to in the Order dated 21 November 2020 shall remain confidential and shall only be used for the purpose of these proceedings notwithstanding that they have been, or may have been, disclosed, read to or by the Court or referred to at a hearing which has been held in public.

Service of the Order

The Court has provided a sealed copy of this order to the serving party:

Gowling WLG (UK) LLP

4 More London Riverside

London

SE1 2AU

Ref: 2699386/PMI/CFJ2

Solicitors for the First Claimant