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Case No: CA-2022-000413

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGHT COURT OF JUSTICE, BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES, INTELLECTUAL PROPERTY LIST (ChD), PATENTS COURT
Marcus Smith J
[2020] EWHC 3270 (Pat), [2022] EWHC 512 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 27 May 2022

Before :

LORD JUSTICE NEWEY
LORD JUSTICE ARNOLD
and
LORD JUSTICE BIRSS

- -

Between :

(1) NEURIM PHARMACEUTICALS (1991) LIMITED **(2) FLYNN PHARMA LIMITED**	**Claimants/ Respondents**
- and -	
(1) GENERICS (UK) LIMITED **(2) VIATRIS UK HEALTHCARE LIMITED**	**Defendants/ Appellants**

- -
- -

Piers Acland QC, Adam Gamsa and **Mitchell Beebe** (instructed by **Taylor Wessing LLP**) for the **Appellants**
Justin Turner QC and **Katherine Moggridge** (instructed by **Gowling WLG (UK) LLP**) for the **First Respondent** and (instructed by **Pinsent Masons LLP**) for the **Second Respondent**

Hearing date : 19 May 2022

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Approved Judgment

This judgment was handed down by the Court remotely by circulation to the parties' representatives by email and release to The National Archives. The date and time for hand-down is deemed to be 10:30 on 27 May 2022.

Lord Justice Arnold:

Introduction

1. In these proceedings the Claimants allege infringement by the Defendants ("Mylan") of European Patent (UK) No. 3 103 443 ("EP443"). EP443 is a second medical use patent which (as unconditionally proposed to be amended) claims the use of a prolonged release formulation of melatonin in a 2 mg dose for improving the restorative quality of sleep in a patient aged 55 years or older suffering from primary insomnia characterised by non-restorative sleep ("NRS"). The First Claimant ("Neurim") is the proprietor of EP443. The Second Claimant markets a product falling within the claims of EP443 under the trade mark Circadin in the United Kingdom pursuant to an exclusive licence granted by Neurim. Mylan market a generic version of Circadin. There is no dispute that Mylan are infringing EP443 if it is valid, but Mylan contend that it is invalid on the ground of insufficiency, or more specifically lack of plausibility.

2. EP443 is a divisional of European Patent (UK) No. 1 441 702 ("EP702"). Accordingly, both EP443 and EP702 have the same priority date, 14 August 2001, and EP443 is due to expire on the same date as EP702 would have expired had it not been revoked, 12 August 2022. There is no material difference between the claims of EP443 and those of EP702 (again, as proposed to be amended) although the wording differs slightly.

3. In previous proceedings brought by the Claimants against Mylan for infringement of EP702, Marcus Smith J dismissed a number of challenges to the validity of EP702 advanced by Mylan for the reasons given in his judgment dated 4 December 2020 [2020] EWHC 3270 (Pat) ("the December Judgment"). Shortly afterwards, however, EP702 was revoked as a result of Neurim's withdrawal of an appeal against an order for revocation by the Opposition Division of the European Patent Office at the conclusion of a hearing before the Board of Appeal.

4. The procedural background to the present appeal is set out in a previous judgment of mine given on 29 March 2022 [2022] EWCA Civ 370 at [2]-[21]. For present purposes it suffices to say that Marcus Smith J rejected Mylan's challenge to the validity of EP443 for the reasons given in the December Judgment as supplemented in a judgment dated 8 March 2022 [2022] EWHC 519 (Pat) ("the March Judgment"). Because most of the judge's reasoning was given in the context of a judgment concerning EP702, but is equally applicable to EP443, I shall use the term "the Patent" to refer to both.

5. Mylan appeal with permission granted by this Court on 16 March 2022. It is convenient to note before proceeding further that, since then, the Claimants have offered a cross-undertaking in damages in the event that Mylan's appeal is dismissed, but EP443 is subsequently revoked by the EPO. In the light of that offer, Mylan no longer pursues its application for a stay of the injunction granted by the judge pending the decision of the EPO (in practice, until expiry of EP443) if the appeal is dismissed. It is therefore unnecessary for this Court to consider the issue identified in my judgment on the Claimants' appeal against two aspects of the judge's order concerning EP702: [2022] EWCA Civ 359 at [55].

The person skilled in art

6. The judge found in the December Judgment that the skilled person to whom the Patent is directed is a sleep medicine clinician with significant expertise in primary insomnia and the guidelines used in the diagnosis of insomnia.

The expert evidence

7. The judge received expert evidence from Professor Thomas Roth (called by the Claimants) and Professor Kevin Morgan (called by Mylan). The judge described Prof Roth in the December Judgment at [13(1)(f)] as "one of the foremost sleep medicine experts in the world" and considered that Prof Roth had done his absolute best to assist to court. The judge explained that Prof Morgan's expertise was both more general than that of Prof Roth, in that his work covered human ageing generally, and more specific, in that the effect of ageing on sleep was an important aspect of his work. The judge rejected the Claimants' submission that Prof Morgan was not appropriately qualified. The judge was, however, highly critical of Prof Morgan's evidence in his first and second reports, describing them at [13(3)(h)] as "in critical respects, disingenuous documents … calculated, not to assist, but to mislead, the court". Accordingly, the judge was "not confident" that he could "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".

The common general knowledge

8. The judge made detailed findings as to the common general knowledge of the skilled person in the December Judgment at [33]-[36] and [50]-[67]. The findings which are relevant for the purposes of the appeal may be summarised, using the judge's headings, as follows.

The nature of primary insomnia and the position of NRS within primary insomnia

9. The term "primary insomnia" derives from the *Diagnostic and Statistical Manual of Mental Disorders*, the 4th edition of which ("DSM-IV") distinguishes between "primary sleep disorders" and "secondary sleep disorders". In broad terms, secondary sleep disorders are linked to another medical or psychological condition, whereas primary sleep disorders are not.

10. According to DSM-IV, primary insomnia is indicated where the predominant complaint is one or more of the following:

    (i) difficulty initiating sleep (sometimes referred to as "sleep latency");

    (ii) difficulty maintaining sleep; or

    (iii) NRS, which is explained as meaning: "individuals … feeling that their sleep was restless, light or of poor quality".

11. The 10th revision of the *International Classification of Mental and Behavioural Diseases* ("ICD-10") describes primary insomnia as "nonorganic insomnia", but uses similar diagnostic criteria to those in DSM-IV, although ICD-10 uses the term "poor

quality of sleep" to denote NRS. I shall concentrate on the DSM-IV terminology, as did the judge.

12. The three characteristics of primary insomnia referred to above can co-exist or exist separately. According to DSM-IV and ICD-10, the most prevalent complaints are difficulty initiating sleep and/or difficulty maintaining sleep.

13. As the judge found at [53]:

> "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 …"

Accordingly, as the judge noted at [54(2)(a)], "it is necessary to avoid terminological traps".

The co-existence (or otherwise) of NRS with other indications of primary insomnia

14. The skilled person would expect NRS to present either as a solitary indicator of primary insomnia or in conjunction with other diagnostic indicators (i.e. difficulty initiating sleep and maintaining sleep).

Diagnosing NRS

15. Primary insomnia characterised by NRS is a purely subjective phenomenon because only the individual in question can say whether their sleep has been restorative. At [62(2)], the Judge accepted as accurate the following explanation given in a book co-authored by Prof Morgan in 1999:

> "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)."

16. Objective methods for monitoring sleep such as polysomnography (electrophysiological monitoring of brain waves etc) and actigraphy (monitoring of the patient's movements) are not used in the diagnosis of NRS. Instead, primary

insomnia characterised by NRS is diagnosed by ascertaining how, subjectively, the patient considers their quality of sleep, typically by taking a history.

17. Questionnaires may be used to ascertain how, subjectively, the patient considers their quality of sleep. One such questionnaire is the Leeds Sleep Evaluation Questionnaire ("LSEQ") which was published in Parrott and Hindmarch, "Factor analysis of a sleep evaluation questionnaire", *Psychological Medicine*, 8, 325-329 (1978) ("Parrott and Hindmarch").

18. As Parrott and Hindmarch explains, the LSEQ comprises 10 questions, grouped into four chronological areas: (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; and (4) the integrity of behaviour following wakefulness (BFW): questions 8, 9 and 10.

19. The LSEQ is as follows:

> "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."

20. The judge made the following findings at [64] concerning the skilled person's understanding of questions 4 and 5 (emphasis in the original, footnotes omitted):

> "(3) There was a good deal of debate before me about what these questions - in particular, questions 4 and 5 - were getting at. [Counsel for Mylan] 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 [Parrott and Hindmarch] that that is exactly how the authors perceive the questions [the judge quoted a passage describing the chronological grouping of the questions].
>
> (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."

21. In footnote 76 to [64(6)(b)] the judge stated:

> "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."

Methods of treatment for primary insomnia in general, and NRS in particular

22. There was no treatment for NRS in 2001. It was known that melatonin could be useful in the treatment of circadian rhythm disorders, but it was not thought to be useful in the treatment of primary insomnia.

The Patent

23. The specification begins at [0001] by stating that the invention "relates to the use of melatonin for the manufacture of a medicament for treating primary insomnia (as defined by DSM-IV) or nonorganic insomnia (as defined by ICD-10) when characterized by non-restorative sleep". The specification proceeds to outline the nature of primary insomnia at [0002] to [0005].

24. At [0006] the specification notes that the possibility of administering exogenous melatonin to ameliorate sleep disorders is the subject of many scientific papers, some of which are described briefly in [0007] to [0012], and at [0013] it notes that there appears to be little or no evidence from published articles that the administration of melatonin in the dosage contemplated by the invention would be likely to improve the restorative quality of sleep in subjects affected by primary insomnia characterised by NRS. At [0014] the specification states that the inventors have surprisingly found that melatonin improves the restorative quality of sleep in patients suffering from primary insomnia.

25. After a summary of the invention at [0015] to [0018], there is a detailed description of the invention at [0019] and following. At [0027] the invention is said to be illustrated by five Examples. Examples 1 and 4 are both "reference" examples, which the skilled person would appreciate do not purport to describe something falling within the claims. Example 5 concerns the preparation of the prolonged release melatonin formulation and is not relevant for present purposes.

26. Example 2 is described as follows:

> "[0032] 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.
>
> [0033] 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.
>
> [0034] Table 1: Effects of melatonin and placebo on subjectively assessed quality of sleep and daytime alertness in primary insomnia patients.

Table 1: Effects of melatonin and placebo on subjectively assessed quality of sleep and daytime alertness in primary insomnia patients.

Response	Melatonin, change in mm mean (SE)	Placebo, change in mm mean (SE)
Change in perceived quality of sleep	-24.3 (2.6)*	-17.6(2.1)
Change in perceived daytime alertness	-16.8 (2.7)*	-6.6 (2.0)
*The difference from placebo is significant (p<0.05).		

[0035] Conclusions. These results show that melatonin enhanced the restorative value of sleep in these primary insomnia patients."

27. The questions set out in [0032] correspond to questions 4 and 9 in the LSEQ. There is no reference in Example 2, or anywhere else in the specification, to any of the other questions in the LSEQ.

28. Example 3 is described as follows:

"[0036] 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.

[0037] 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 a significant worsening of the quality of sleep and daytime alertness compared to placebo. The results are tabulated in Table 2.

[0038] Table 2: Effects of melatonin and placebo on subjectively assessed quality of sleep and daytime alertness in primary insomnia patients aged 55 and higher.

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)

> [0039] 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)."

29. By contrast with the results in Example 2, there is no claim to statistical significance for the results in Example 3.

The claims

30. It is sufficient for the purposes of the appeal to refer to claim 1 of EP443 as proposed to be amended. This claim is in "Swiss" form, but there is a parallel claim in EPC 2000 form:

> "Use of at least one compound selected from melatonin in an effective amount ~~within the range~~ of ~~0.025 to 50~~ 2 mg, 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 **characterized by** non-restorative sleep, wherein the medicament is a prolonged release formulation and comprises also at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers, adjuvant or carrier."

The law

31. There is no dispute as to the applicable legal principles. 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. The criterion for plausibility was stated by Lord Sumption in *Warner-Lambert Co LLC v Generics (UK) Ltd* [2018] UKSC 56, [2019] Bus LR 360 at [36]-[37] as follows:

> "36. … The principle is that the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true. Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. It reflects the practical difficulty of demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding. But it cannot be deprived of all meaning or reduced … to little more than a test of good faith. …
>
> 37. 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. 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. As Lord Hoffmann observed in *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] 4 All ER 621, para 28, 'it is hard to see how the notion that something is worth trying or might have some effect can be described as an invention in respect of which anyone would be entitled to a monopoly'. But, third, the claimed therapeutic effect may well be rendered plausible by a specification showing that something was worth trying for a reason, i.e. 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* (T-609/02), 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* (T-609/02) 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."

The lay-patient argument

32. Mylan contend that the Patent does not plausibly disclose the effect that it claims because of what has come to be called "the lay-patient argument". As is common ground, the plausibility of the claimed effect depends on what is disclosed by

Examples 2 and 3 read in the context of the specification as a whole. As is also common ground, the key data in both Examples are those generated by the responses to the question concerning "quality of sleep".

33. For convenience, I shall set out the question and the criteria for answering it again:

> Question: "How would you compare the quality of sleep using the medication with nonmedicated (your usual) sleep?"
>
> Answer: [on a scale between] "more restless than usual" and "more restful than usual"

34. Mylan contend that there is nothing in this question or the responsive criteria which bears any relation to NRS. Mylan say that this is hardly surprising given that the LSEQ, from which the question is taken, was published nearly ten years before NRS was recognised as a diagnostic indicator of primary insomnia in the third edition of the DSM in 1987.

35. Furthermore, Mylan contend that the responsive criteria are plainly capable of invoking the non-NRS indicators of primary insomnia. For example, a patient who has difficulty maintaining sleep may well describe the quality of their sleep as "more restless than usual". Likewise, a patient whose sleep initiation is improved might well conclude that the quality of their sleep is "more restful than usual".

36. Mylan do not dispute that the skilled person would attach a technical meaning to "quality of sleep" when used in the context of ICD-10, namely as a reference to NRS. Mylan contend, however, that that is irrelevant when it comes to the critical issue in relation to plausibility, namely how the skilled person would understand the data in the Examples. This depends on how the patients would have answered the question, which in turn depends on how the patients would understand the question. As is common ground, the patients in the Examples would have been laypeople, not skilled persons.

37. Mylan point out that the stated purpose of Examples 2 and 3 is to investigate the effect of melatonin on "subjectively assessed sleep quality": see [0032] and [0036]. Consistently with this purpose, the specification explains that the data were generated by asking patients to mark the level of their "perceived quality of sleep". There is no suggestion in [0032] or [0036] that the patients were instructed to answer the "quality of sleep" question in any particular way or with any special meaning in mind. Mylan argue that, in order to single out NRS, such instructions would have needed to be highly exacting. In particular, when assessing whether the quality of their sleep had been "more restless" or "more restful" than usual, the patients would need to be instructed to exclude from their consideration (i) how long it took to get to sleep and (ii) any periods of waking in the night and (iii) any other aspect of their sleep except its restorative quality.

38. Accordingly, Mylan argue, the data in the Patent could only render the claimed effect plausible if it was common general knowledge that patients were so instructed in studies of the kind described in Example 2 and Example 3. Mylan point out that the judge made no finding that this was common general knowledge, nor was there any evidence before him to that effect.

39. Mylan submit that it follows that the responses to the "quality of sleep" question reported in Examples 2 and 3 cannot plausibly demonstrate that melatonin has an effect on NRS. Since the data themselves do not distinguish between NRS and other forms of insomnia, it is immaterial that the reader of the Patent is a skilled person who has a technical understanding of "quality of sleep" in the context of ICD-10.

40. Furthermore, Mylan argue that, even if the skilled person might think that the question was intended to be specific to NRS, the specification itself contradicts such a reading when it states at [0039]:

> "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)."

Mylan say that this must be a reference to the data showing that, as the specification puts it at [0037], "[s]urprisingly, it was found that in patients <55 years of age there was a significant worsening of the quality of sleep … compared to placebo". Thus the statement in [0039] assumes that the answers to the question are referrable to "other aetiologies" such as "inability to initiate sleep", and not just NRS.

The judge's reasoning

41. It is important to note two points before considering the judge's reasoning. First, as Mylan accept, the lay-patient argument was not articulated very clearly by Mylan at trial. No doubt for that reason, the lay-patient argument was not squarely addressed by the judge in the December Judgment. It was, however, considered by the judge in the March Judgment on the basis of the evidence at trial and his findings in the December Judgment. Secondly, as Mylan also accept, the point about the last sentence of [0039] in the Patent was not advanced at trial. More specifically, it was not a point made by Prof Morgan, nor was it put to Prof Roth.

42. In the December Judgment the judge held that the Patent did plausibly disclose the effect that it claimed for the following reasons (so far as relevant, footnotes omitted):

> "111. The test of plausibility is obviously met. [Example 2] 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:
>
> …
>
> (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, and to the extent that Professor Morgan sought to suggest that they were not, I reject that evidence.
>
> …
>
> 113. I conclude that, by reason of Example 2 alone, the Patent is sufficiently plausible.
>
> …
>
> 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 - 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. 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."

43. In the March Judgment the judge rejected the lay-patient argument for the following reasons (original emphasis, footnotes omitted):

> "6. The lay-patient argument turned on the contention that Examples 2 and 3 were insufficient to render the Patent … plausible. This was because the questionnaire that may have been used to interrogate the patients as to their sleep referred only to the 'quality of sleep'. As is clear from the Main Judgment, the term '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". Which meaning is intended is a question of context and construction to which I shall have to pay attention in this judgment'.
>
> 7. At the Trial, the expert evidence of Professor Morgan was that the Skilled Person would not understand the questionnaire in this way, and the contention was that the questions in the questionnaire 'were directed at quality of sleep in the non-technical sense'. If that contention had succeeded, the force of the Examples in the Patent would have been undermined.
>
> 8. I rejected the contention in no uncertain terms at [64(6)] of the Judgment, concluding that 'I have no doubt that the Skilled Person would attach a technical meaning to the term "quality of sleep"'.

> 9. The lay-patient argument contends that – notwithstanding the finding I have made as regards the Skilled Person's understanding of the questionnaire – the patient and the clinicians the subject of the trials recorded in the Examples were not the Skilled Person and might understand the term 'quality of sleep' in the non-technical sense. The Examples would, for that reason, 'not be worth the paper they were written on': …
>
> 10. The point is that notwithstanding the Skilled Person's understanding of the terms of the questionnaire, the Skilled Person would expect the clinicians in charge of the trials recorded in the Examples so to botch the trials that they produced meaningless data. Put this way – and [counsel] put it far more elegantly for Mylan – the point is hopeless. The Skilled Person would expect the trials to be conducted in line with the Skilled Person's understanding of what was under investigation (i.e., quality of sleep in the technical sense) and – more to the point – the presumption has to be that clinicians conducting trials intended to evaluate quality of sleep in this technical sense would do their job competently."
>
> The judge went on to refer to what he had said at [64(4)] of the December Judgment and to quote a passage from the cross-examination of Prof Roth which supported his summary of the witness' evidence at [64(3)].

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44. The judge's decision that the Patent plausibly discloses the effect that it claims is an evaluative assessment. It follows that Mylan must establish that the judge made an error of principle in his assessment. The only error suggested is that the judge was wrong to reject the lay-patient argument.

45. Mylan make five main criticisms of the judge's reasoning on this issue. First, Mylan criticise the judge's reasoning in the December Judgment at [64(3)-(6)] (quoted in paragraph 20 above). Mylan argue that the judge was correct to distinguish between the way in which a skilled person would understand "quality of sleep" in the context of ICD-10 and the way in which a layperson would understand that expression, but failed to apply that distinction when considering how questions 4 and 5 of the LSEQ would be understood. The judge concentrated on how "the Skilled Person using the questionnaire" in 2001 would understand the questions, not on how the layperson answering the questions would understand them. Mylan go on to argue that the judge was therefore wrong to reject Prof Morgan's evidence on this point in footnote 76 (quoted in paragraph 21 above).

46. Secondly, Mylan contend that, even if the judge was correct as to how questions 4 and 5 of the LSEQ would be understood in that context, he was wrong to treat that finding as applicable to the "quality of sleep" question in the Patent in the December Judgment at [112(3)]. Mylan point out that in [64(6)(c)] the judge relied upon the chronological sequence of the questions in the LSEQ, but as noted above there is no indication in the specification that any questions other than questions 4 and 9 were asked. Again, therefore, Mylan argue that the judge was wrong to reject Prof Morgan's evidence on this point.

47. Thirdly, Mylan contend that the judge made the same errors in the March Judgment. Again, he focused on "the Skilled Person's understanding of the terms of the questionnaire", rather than upon how the layperson would understand the single "quality of sleep" question.

48. Fourthly, Mylan contend that the judge's reasoning at [10] in the March Judgment (quoted in paragraph 43 above) involves assuming that the results support the conclusions drawn from them and therefore assuming that either the entire LSEQ was administered or the patients were instructed as to the meaning of "quality of sleep" when neither is disclosed. Mylan argue that this is to reduce plausibility to a mere test of good faith.

49. Fifthly, Mylan point out that, even in the March Judgment, the judge does not take into account the statement made in the last sentence of [0039].

50. I do not accept these arguments for the following reasons. First, while it is common ground, as noted above, that the patients in Examples 2 and 3 were laypeople and not skilled persons, I consider that the judge was right to focus on the purpose for which the "quality of sleep" question was being asked. Although Mylan are correct that [0032] and [0036] simply refer to "subjectively assessed sleep quality", the skilled reader of the Patent reads those statements in their context in the specification as whole. Read in context, it would be clear to the skilled person that the purpose of Examples 2 and 3 is to demonstrate that melatonin is effective in enhancing the restorative value of sleep in primary insomnia patients i.e. treating NRS.

51. Secondly, I consider that the judge was also right to say that the skilled person would assume that the trials reported in Examples 2 and 3 were competently conducted unless there was some reason to think otherwise. Accordingly, the skilled person would presume, unless there was some reason to think otherwise, that the "quality of sleep" question had been administered in a way which was capable of producing meaningful data. This is not to reduce plausibility to a mere test of good faith, because plausibility depends on the reported results of the trials. Nor is it to assume that the results do support the conclusions drawn in the Patent, which is a separate question. Even if it is correct that the "quality of sleep" question is not without more specific to NRS, there are two ways in which it could have been administered so as to produce meaningful data.

52. The first is that the entirety of the LSEQ was administered, thereby ensuring that patients answered the questions in chronological sequence. This is inherently probable given that the use of the LSEQ was well established in the field and that questions 4 and 9 were asked. Moreover, Prof Morgan's evidence was that, given the expense of conducting a trial of this size, he "would expect further data to have been collected from the 301 patients". There would be nothing unusual in what is evidently a compressed report of the trials omitting some of the experimental details and results. The judge found, and was entitled to find, that, if all the questions in the LSEQ were asked in chronological sequence, the answers to questions 4 and 5 would be specific to NRS.

53. The second way in which this could have been done even if questions 4 and 9 were asked in isolation was to give the patients appropriate instructions, as Mylan accept could be done. Again, it would not be surprising if this was omitted from the report.

Contrary to Mylan's argument, this does not require a finding that it was common practice to educate patients in this way. It is sufficient that it is a possible way in which the Examples could have been competently performed in the absence of anything to indicate that they were not competently performed.

54. Thirdly, it is not necessarily correct that, even if administered in isolation and without further instructions, the "quality of sleep" question would not be specific to NRS. Prof Roth gave evidence in paragraph 7.20 of his third report that:

> "… The question asked is within the range of questions one would typically expect to see used in the field of sleep medicine. The skilled person would understand it to be an acceptable way to assess a patient's subjective restorative quality of sleep. It is important to understand that the terms 'restful' and 'restless' used in the context of a patient's subjective report about the quality of their sleep such as this are not terms concerned with the patient's sleep onset or sleep maintenance (i.e. parameters that can be assessed objectively, such as by actigraphy). If I had been presented with this question and endpoints in a draft paper for peer review at the Priority Date, I would have accepted them as suitable measures of a patient's subjective restorative quality of sleep."

55. Fourthly, the judge was entitled to reject Prof Morgan's evidence for the reasons he gave. In any event, the judge was entitled to prefer the evidence of Prof Roth, including the evidence I have quoted in the preceding paragraph.

56. Fifthly, Mylan's best point is the point concerning the last sentence of [0039]. I agree with Mylan that the natural interpretation of this sentence is that set out in paragraph 40 above. But, read in that way, the skilled person would appreciate that there was an apparent contradiction between that statement and the remainder of the description of Examples 2 and 3. The question then is how the skilled reader would resolve that apparent contradiction. Given that it is a question of the skilled reader's technical understanding, expert evidence is required before the court can draw a conclusion. For example, one possibility is that the skilled reader would consider that, notwithstanding the wording of the sentence in question, the conclusion was likely to have been informed by answers to questions 1-3 in the LSEQ. As noted above, Mylan failed either to adduce evidence from Prof Morgan about this or to put the point to Prof Roth. In those circumstances it is not open to Mylan to rely upon this point.

Conclusion

57. For the reasons given above I would dismiss the appeal.

Lord Justice Birss:

58. I agree.

Lord Justice Newey:

59. I also agree.