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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LTD. and LUPIN PHARMACEUTICALS, INC.,
Petitioners,

v.

HORIZON THERAPEUTICS, INC.,
Patent Owner.

Case IPR2016-00829
Patent 9,095,559 B2

Before TONI R. SCHEINER, LORA M. GREEN, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

I. Introduction

We instituted a trial under 35 U.S.C. § 314 to review challenges brought by Lupin Ltd. and Lupin Pharmaceuticals, Inc. ("Lupin" or "Petitioner") against claims 1–15 of U.S. Patent No. 9,095,559 B2 (Ex.

1001) ("the '559 patent") in the Petition (Paper 3 ("Pet.")). *See* Paper 13 (Institution Decision ("DI")).

Horizon Therapeutics, Inc. ("Horizon" or "Patent Owner") filed a preliminary response under 37 C.F.R. § 42.107 (Paper 9 ("Prelim. Resp.")) and a response under 37 C.F.R. § 42.120 (Paper 26 ("PO Resp.")) to Lupin's challenges and Lupin filed a Reply (Paper 31 ("Reply")).

Lupin also filed a motion to exclude Horizon Exhibits 2019 and 2041 (Paper 35). *See also* Patent Owner's Opposition to Petitioner's Motion to Exclude (Paper 37) and Petitioner's Reply in Support of Its Motion to Exclude Evidence (Paper 38). These exhibits are discussed in footnotes below.

Horizon does not seek to amend its challenged claims under 37 C.F.R. § 42.121.

A hearing was held on July 28, 2017, and a transcript of the oral argument was made of record (Paper 41).

We conclude that the challenged claims are unpatentable under 35 U.S.C. § 103 over the cited prior art.

A.

Both Lupin and Horizon report that Horizon served Lupin with a complaint in the District Court for the District of New Jersey (Case No. 1:15-cv-07624) alleging that Lupin infringed the '559 patent, as well other related patents. Pet. 7; Prelim. Resp. 2.

Lupin also reports that U.S. Patent No. 8,404,215, which issued from the parent application of the '559 patent, was the subject of IPR2015-01127, filed by Par Pharmaceutical, Inc., and IPR2016-00284, filed by Lupin, which was instituted and joined with the IPR2015-01127 proceeding. The claims

challenged in that review are similar to the claims challenged in the present review, wherein fasting blood ammonia levels are measured, compared to the upper limit of normal, and an adjusted dose of drug is administered if "the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level." *See Par Pharm., Inc. v. Horizon Therapeutics, LLC*, Case IPR2015-01127, slip op. at 6–7 (PTAB September 29, 2016) (Paper 49). Those claims were held to be unpatentable.

Lupin reports further that IPR2015-01117 and IPR2016-00283, involving Horizon's U.S. Patent 8,642,012[1], were instituted and joined. That patent is not related by lineage to the '559 patent and it was held that Petitioner did not show that the challenged claims were unpatentable. *See Par Pharm., Inc. v. Horizon Therapeutics, LLC*, Case IPR2015-01117 (PTAB November 3, 2016) (Paper 53).

We note that Lupin has recently filed petitions for review of the claims of U.S. Patent Nos. 9,254,278 and 9,326,966 (IPR2017-01159 and IPR2017-01160, respectively), which are related as being issued from continuations of the application from the currently challenged '559 patent.

In addition, on July 13, 2017, Par Pharmaceutical, Inc. filed petitions for review of U.S. Patent Nos. 9,095,559, 9,254,278, and 9,326,966 (IPR2017-01768, IPR2017-01767, and IPR2017-01769, respectively).

Decisions on whether to institute trial based on these pending petitions has not yet been issued.

[1] The application that became U.S. Patent 8,642,012 was published as U.S. Patent Publication 2010/0008859, which was cited as prior art in Petitioner's challenges. *See* Ex. 1007.

B.

The claims of the '559 patent are directed to methods of using a drug, glyceryl tri-[4-phenylbutryate] ("HPN-100"), to treat subjects with urea cycle disorders. Individuals suffering from urea cycle disorders ("UCDs") are unable to remove excess nitrogen waste, which is normally excreted in the urine. Ex. 1002 ¶ 30; Ex. 2006 ¶¶ 31–32. When the body functions normally, dietary amino acids are converted first to ammonia and then to urea in the urea cycle and, finally, excreted in the urine. Ex. 1002 ¶ 31; Ex. 2006 ¶ 31. In individuals with UCDs, the enzymes controlling the urea cycle are deficient, leading to high levels of ammonia in the blood. Ex. 1002 ¶ 32; Ex. 2006 ¶¶ 32–33. This accumulation of ammonia at high concentrations in the body is toxic. Ex. 1002 ¶ 32; Ex. 2006 ¶ 33. Patent Owner's witness, Dr. Gregory M. Enns[2], testifies that "[i]ncreased blood ammonia levels manifest mainly as central nervous system dysfunctions such as stupor, convulsions, and coma." Ex. 2006 ¶ 33.

The claims of the '599 patent are directed to methods wherein HPN-100 is administered at an initial or increased dose when a patient's fasting

[2] Dr. Enns testifies that he is a Professor at the Stanford University School of Medicine. Ex. 2006 ¶ 8. Dr. Enns also testifies that he is Board Certified in Clinical Genetics and Clinical Biochemical Genetics by the American Board of Medical Genetics and Genomics. Ex. 2006 ¶ 7. Dr. Enns testifies that he has cared for approximately 70 to 100 UCD patients over the course of his career and that for the UCD patients he manages he prescribes nitrogen scavenging medications on nearly all patients who have not undergone liver transplantation. Ex. 2006 ¶ 11. To manage the care of his patients, Dr. Enns testifies that he adjusts the dose of nitrogen scavenging medication as well as tailors dietary treatment and provides emergency management. Ex. 2006 ¶ 11. We find Dr. Enns to be qualified to provide opinions on the subject matter at issue.

plasma ammonia level is less than the upper limit of the normal range for ammonia, but greater than half that upper limit.

Claim 1 of the '559 patent is representative of the claims challenged in Petitioner's Ground 1 and recites:

> A method for adjusting the dosage of glyceryl tri-[4-phenylbutyrate] in a subject being treated for a urea cycle disorder who has previously been administered an initial dosage of glyceryl tri-[4-phenylbutyrate] and *who has a fasting plasma ammonia level less than the upper limit of normal for plasma ammonia level*, the method comprising:
>
> (a) measuring a fasting plasma ammonia level for the subject;
>
> (b) comparing the fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and
>
> (c) administering an adjusted dosage of glyceryl tri-[4-phenylbutyrate], wherein the adjusted dosage is greater than the initial dosage *if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level*.

Ex. 1001, 24:28–39 (emphasis added). Independent claim 2, the only other independent claim challenged in Ground 1, is similar to claim 1, differing in the preamble among other small differences.

Claim 3 is challenged in Petitioner's Ground 2 and recites:

> A method of administering glyceryl tri-[4-phenylbutyrate] to a subject having a urea cycle disorder, the method comprising:
>
> (a) measuring a first fasting plasma ammonia level for the subject:
>
> (b) comparing the first fasting plasma ammonia level to the upper limit of normal for plasma ammonia level; and
>
> (c) administering an initial dosage of glyceryl tri-[4-phenylbutyrate] to the subject if the fasting plasma ammonia level is greater than half the upper limit of normal for plasma ammonia level and less than the upper limit of normal for plasma ammonia level.

Ex. 1001 at 24:49–60. Claim 3 requires administering an *initial* dosage of HPN-100 to a subject if the fasting plasma ammonia level is greater than half, but less than the upper limit of normal for plasma ammonia.

C.

We instituted trial on the grounds of unpatentability asserted by Petitioner. Both grounds were on the basis of obviousness under 35 U.S.C. § 103 and are as follows:

Ground	References	Claims
1	Blau (Ex. 1006)[3], Simell (Ex. 1005)[4], and the '859 Publication (Ex. 1007)[5]	1, 2, 4, 5, 7–10, 12, and 13
2	Blau, Simell, the '859 publication, and Brusilow '84 (Ex. 1004)[6]	3, 6, 11, 14, and 15

II. Analysis

Under 35 U.S.C. § 103, subject matter is unpatentable

> if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

[3] PHYSICIAN'S GUIDE TO THE LABORATORY DIAGNOSIS OF METABOLIC DISEASES, 261–76 (Nenad Blau et al. eds., 2d ed. 1996).
[4] Simell et al., *Waste Nitrogen Excretion Via Amino Acid Acylation: Benzoate and Phenylacetate in Lysinuric Protein Intolerance*, 20 PEDIATRIC RESEARCH 1117–21 (1986).
[5] U.S. Patent Publication 2010/0008859 A1 was filed on January 7, 2009, and published on January 14, 2010.
[6] Brusilow et al., *Treatment of Episodic Hyperammonemia in Children with Inborn Errors of Urea Synthesis*, 310 THE NEW ENGLAND JOURNAL OF MEDICINE 1630–34 (1984).

The Supreme Court explains that if the person of ordinary skill could have arrived at the claimed subject matter using common sense to combine different teachings of the prior art, that subject matter is likely obvious, not innovative. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

To determine obviousness,

> [o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. . . . As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

Id. at 418. We analyze the evidence presented by Petitioner and Patent Owner in light of the Supreme Court's guidance.

A.

The following findings of fact, like others in this opinion, are supported by a preponderance of the evidence.

Petitioner points to the '859 publication for its teaching that nitrogen scavenging drugs, including HPN-100, were known to treat UCDs. *See* Pet. 22–23; Ex. 1007 ¶¶ 88–91, 95–99, 107–108, 226, and 232; Ex. 1002 ¶ 53. The '859 publication provides that HPN-100 is a phenylbutyric acid ("PBA") pro-drug of choice for individual management of patients with these disorders. Ex. 1007 ¶ 108; *see* Pet. 21–22 (citing Ex. 1002 ¶ 53). The '859 publication also teaches that increased dosages of nitrogen scavenging drugs could be used to control plasma ammonia levels. Ex. 1007 ¶ 83; *see*

Pet. 21–22. Thus, we agree with Petitioner and find that those of skill in the art[7] would have known to use the drug recited in the challenged claims to treat subjects with a UCD.

Petitioner also cites to the '859 publication for its teaching that measuring plasma or blood levels of ammonia was known to be useful for determining the effectiveness of the overall drug and dietary regimen for a particular patient. Ex. 1007 ¶¶ 88–91; *see* Pet. 22, citing Ex. 1002 ¶ 53. Specifically, the '859 publication teaches

> The plasma or blood level of ammonia is optionally also determined, in addition to measuring urinary PAGN, to assess the effectiveness of the overall drug and dietary regimen for a particular patient. If the ammonia control is inadequate, the dosage of the nitrogen scavenging drug may need to be increased if that can be done, or the patient's dietary protein intake can be decreased if that is feasible.

Ex. 1007 ¶ 83. Furthermore, the '859 publication teaches a method of individually adjusting the dose of a nitrogen scavenging drug, including HPN-100, for a patient who had previously been treated with a drug, including a) administering drug, b) measuring the amount of nitrogen waste excreted, and

> c) optionally measuring blood ammonia to determine if the initial dosage is sufficient to control blood ammonia levels, or to establish a suitable average ammonia level: and
>
> d) adjusting the initial dosage of the new drug as needed to provide an adjusted dosage based upon ammonia control, dietary protein, and the amount of total waste nitrogen excreted by the patient.

[7] The level of ordinary skill in the art is discussed on pages 14–15.

Ex. 1007 ¶¶ 95–99. *See also id.* at ¶ 226 ("The physician may also monitor the plasma ammonia levels and dietary protein intake in the patient to ascertain whether the patient's dietary protein intake and drug treatment combined are producing the appropriate therapeutic effect") and ¶ 232 ("Subsequent dose adjustment would be based on repeated measurement of urinary PAGN as well as assessment of dietary protein and plasma ammonia."). *See* Pet. 22–23, citing Ex. 1002 ¶ 53. From these teachings, we agree with the Petitioner and find that the '859 publication teaches using plasma ammonia levels to make adjustments in nitrogen scavenging drug levels.

Petitioner also argues that the '859 publication indicates that maintaining stable plasma ammonia levels is desirable. For example, Petitioner cites to the teaching in the '859 publication that "when the subject is treated with the prodrug, which can be HPN-100, the subject will typically achieve and maintain normal plasma ammonia levels." Ex. 1007 ¶ 182; *see* Reply 3. Similarly, the '859 publication teaches that only 2–3 doses of HPN-100 can provide "a stable level of plasma ammonia," and compares this number to the 3–6 doses necessary with a different drug, PBA. *See* Ex. 1007 ¶ 46; Reply 3. From these teachings, we agree with the Petitioner and find that maintenance of normal plasma ammonia levels was a goal for those of ordinary skill in the art.

The '859 publication discusses normal plasma ammonia levels. For example, the '859 publication teaches

> that for patients having ammonia levels above about 40 µmol/L when treated with sodium PBA, HPN-100 at equimolar dosages provided superior control of ammonia, and consistently reduced ammonia levels to below about 40 µmol/L. Thus for patients whose ammonia levels are abnormal (e.g. above about 40

> µmol/L) when treated with sodium PBA, it is expected that better ammonia control can be achieved with an equimolar amount of HPN-100.

Ex. 1007 ¶ 209; *see* Pet. 18. Similarly, the '859 publication teaches that "plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject, and commonly this would mean plasma ammonia level is below about 40 µmol/L." Ex. 1007 ¶ 94. *See* Pet. 18; *see also* Ex. 1007 ¶ 226 ("Dietary protein intake or drug dosage or both could be adjusted to attain a normal or desired plasma ammonia level, e.g., a level below about 40 µmol/L."). Based on these teachings we agree with Petitioner and find that those of ordinary skill in the art knew plasma ammonia levels below a level considered to be normal were acceptable, even desirable.

The '859 publication refers to plasma ammonia levels at the upper limits of normal, stating that "[i]n certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 µmol/L, and it is recognized in the art that a normal ammonia level will vary depending upon exactly how it is measured . . . ." Ex. 1007 ¶ 94. Elsewhere, the '859 publication provides that a normal plasma ammonia level is "a level of less than about 40 µmol/L, or of not greater than 35 µmol/L . . . ." Ex. 1007 ¶ 85; *see* PO Resp. 16–17. These teachings indicate to us that recitation of specific plasma ammonia levels are not necessarily useful in determining the upper limit of normal because reported plasma ammonia levels may vary depending on how they are measured.

Nevertheless, we agree with the parties[8] that the claim term "upper limit of normal" ("ULN") means the highest value in a range of normal values. *See* Pet. 10; PO Resp. 21. We determine that the plain meaning and the broadest reasonable interpretation of the claim term "*less than* the upper limit of normal" is any value less than the highest value in the range of normal values. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard); *see* 37 C.F.R. § 42.100(b).

We also find, from the statement "a plasma ammonia level of less than about 40 μmol/L, or of not greater than 35 μmol/L would indicate the treatment was effective" (Ex. 1007 ¶ 74; *see also id.* ¶ 85), that treatment would be considered effective by those in the art when plasma ammonia levels are below a level considered to be the upper limit of normal.

In summary, the '859 publication teaches that those of skill in the art would have known to use HPN-100 to treat subjects with UCDs. It also teaches that measuring plasma or blood level of ammonia was known to be useful in determining the effectiveness of a drug regimen for a particular patient and that measuring blood ammonia was a known step in adjusting drug dosages. The '859 publication teaches that maintaining normal plasma ammonia levels was desirable in the art. Although specific measurements of

[8] Patent Owner notes that the parties do not dispute the meaning of any of the claim terms. PO Resp. 2. Because the meaning of the terms in the challenged claims are evident from their ordinary meaning and not controversial, we need not provide a separate analysis of them. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("claim terms need only be construed 'to the extent necessary to resolve the controversy.' *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).").

plasma ammonia do not necessarily indicate the upper limit of normal consistently across different ways of measuring it, the ’859 publication teaches that treatment would have been considered to be effective when plasma ammonia levels were less than what is determined to be the upper limit of normal in a given case.

In addition to the ’859 publication, Petitioner relies on Blau and Simell for the teaching to collect blood from UCD patients after a fast in order to measure plasma ammonia levels. Ex. 1006 at 273 (Table 11.9); Ex. 1005 at 1118; *see* Pet. 25–26 (citing Ex. 1002 ¶¶ 58, 59); *see also id*. 1002 ¶ 46, n.2 (citing Ex. 1015 at S11). Anticipating Patent Owner’s argument that Blau relates to diagnosis not treatment of UCDs, Petitioner also cites to Exhibits 1010 and 1015 as evidence that it was generally recommended to measure plasma ammonia after a fast. *See* Pet. 16, n.2. Exhibit 1010 is a “Lab Update” about measurement in ammonia in blood, and Exhibit 1015 is a publication entitled “Measurement of ammonia in blood.” Both state that most methods recommend collecting a sample from patients who have fasted for at least 6 hours. *See* Ex. 1010, 4; Ex. 1015, 1. From this evidence, we agree with Petitioner that those of skill in the art would have known that measuring fasting serum ammonia levels, as taught in at least Simell and Blau, was known to be useful with the methods taught in the ’859 publication.

In regard to Ground 2, which challenges claim 3 and the claims that depend on it, Petitioner cites Brusilow ’84 for its teaching of measuring a patient’s fasting plasma ammonia level when he or she is admitted, presumably to a hospital, and, in response to elevated levels, treating with the nitrogen scavenging drugs sodium benzoate and phenylacetate. *See* Pet.

35–36, citing Ex. 1004 at 1631; *see* Ex. 1002 ¶ 77. We agree with Petitioner and find that Brusilow '84 teaches it was known to initiate drug therapy when a patient presented with plasma ammonia levels above the upper limit of normal. Pet. 39–41, citing Ex. 1002 ¶ 83.

B.

Petitioner also relies on the testimony of Dr. Vaux to demonstrate the obviousness of the challenged claims. Dr. Vaux testifies that the objective of therapy with nitrogen scavenging drugs was known to be maintenance of ammonia levels within normal limits. Ex. 1002 ¶ 54; *see* Pet. 24. This testimony is reflected in the prior art, which teaches: "The goal of treatment is to maintain normal levels of plasma ammonia through the use of low protein diet and medication while allowing for normal growth." Ex. 1016 at S58.

Petitioner also relies on Dr. Vaux's testimony that ammonia levels were known to vary during the day, for example after eating or because of the time. *See* Pet. 24–25, citing Ex. 1002 ¶ 55. We credit Dr. Vaux's testimony on this issue because it is supported by the prior art. Specifically, the prior art teaches that "postprandial" ammonia levels were known to be "30-60 µmol/L higher depending on time and N load." Ex. 1006, 268, Table 11.5; *see* Ex. 1002 ¶ 55. Similarly, it was reported in the prior art that the circadian rhythm has an effect on plasma ammonia levels. Ex. 1012, 213, abstract. *See also* Ex. 1017, 164, Table II (providing plasma ammonia levels after protein ingestion at different hours after protein load) and Ex. 1016 at S58.

In light of this knowledge, Dr. Vaux testifies:

> In order to maintain plasma ammonia levels within normal limits, a person of ordinary skill in the art would have been

> motivated to administer more drug to reduce the ammonia levels, even in cases where the fasting plasma ammonia level was above half the ULN but below the ULN. A person of ordinary skill in the art would have been motivated to maintain a patient at normal plasma ammonia levels, and would have known that variation of ammonia levels due to time of day and/or ingestion of food would risk taking the patient outside of normal levels. (Ex. 1006 at 268, Table 11.5.) *For example, for a patient with fasting plasma ammonia levels approaching the ULN, a person of ordinary skill in the art would have desired to maintain the patient at normal ammonia levels, and would have known that variation in ammonia levels due to time of day and/or ingestion of food would potentially take the patient outside of normal levels.* Thus, even though the patient's fasting plasma ammonia level was already below the ULN, a person of ordinary skill in the art would have been motivated to increase the dose of drug to lower the patient's baseline ammonia and to help ensure that the patient routinely stayed within normal plasma ammonia limits.

Ex. 1002 ¶ 55 (emphasis added); *see also id.* ¶¶ 51, 65; Pet. 24–25, 28–29. Dr. Vaux's testimony indicates there would have been a reason for those of ordinary skill in the art to have modified prior art methods of increasing nitrogen scavenging drug dosage when a patient's plasma ammonia levels were approaching the upper limit of normal but had not yet exceeded it. According to Dr. Vaux, those of ordinary skill in the art would have understood that increasing the dosage would maintain ammonia levels in the normal range after a meal or when influenced by daily rhythms.

Patent Owner argues that Dr. Vaux's testimony should be given little weight because Dr. Vaux is not board certified in clinical genetics or clinical biochemical genetics and has not published or spoken publicly about the treatment of UCDs. According to Patent Owner, Dr. Vaux is not qualified

as one of ordinary skill in the art on the subject matter of this review. PO Resp. 20, 36.

Patent Owner and Petitioner define a person of ordinary skill in the art as having similar qualifications (*compare* Pet. 8–9, citing Ex. 1002 ¶ 19 with PO Resp. 15–16, citing Ex. 2006 ¶ 26), but Patent Owner argues that the ordinarily skilled artisan must additionally have "at least three years of residency/fellowship training in Medical Genetics, including Biochemical Genetics, followed by certification in Clinical Genetics and Clinical Biochemical Genetics by the American Board of Medical Genetics and Genomics." PO Resp. 15–16, citing Ex. 2006 ¶ 26. We agree with the qualifications on which the parties agree and find that one of ordinary skill in the art would have an M.D. or equivalent degree, with a residency and specialized training in the diagnosis or treatment of inherited metabolic disorders, such as UCDs and other nitrogen retention disorders. *See* Pet. 8–9; PO Resp. 15–16. We also agree with Patent Owner that one of ordinary skill in the art would have experience treating patients with nitrogen retention disorders, including UCDs. *See* PO Resp. 16.

We are not persuaded by Patent Owner's argument that the lack of specific residency/fellowship training or certification, disqualifies Dr. Vaux from providing opinion testimony on the motivations, understandings, and actions of those of ordinary skill in the art. Dr. Vaux testifies that he is "a medical doctor with specialty training in Pediatrics and Clinical Genetics" and is currently Professor and Clinical Chief of the Division of Medical Genetics in the Department of Medicine at UC San Diego. Ex. 1002 ¶ 1. He also testifies:

> Since 1994, I have regularly diagnosed and treated patients with urea cycle disorders ("UCD"), and continue to do so today. In

> treating UCD patients, I regularly prescribe nitrogen scavenging drugs and treat patients who are maintained on therapy with nitrogen scavenging drugs.

Ex. 1002 ¶ 1. Thus, Dr. Vaux has actually treated UCD patients for at least five years (a requirement recited by Patent Owner, *see* PO Resp. 16), including prescribing drugs. Patent Owner does not direct us to evidence that Dr. Vaux's testimony is untruthful or that his treatment of UCD patients is ineffective, indicating that he does not understand how to treat them. Accordingly, even if Dr. Vaux does not have the specialized certificates or particular training that Patent Owner argues are necessary, he has done the job for over twenty years of one who would carry out the claimed methods. We consider this experience more relevant than certificates or training. Thus, we determine that Dr. Vaux is qualified to provide opinions about the motivations, understandings, and actions of one of ordinary skill in the art.

C.

Even if Dr. Vaux were not qualified as one of ordinary skill in the art about the subject matter of this proceeding, we still would accord weight to his testimony because we find it to be supported by the prior art. For example, despite Patent Owner's arguments that "no support exists for Dr. Vaux's contention that a goal of nitrogen scavenging therapy is to maintain a *stable* plasma ammonia level" (*see* PO Resp. 34), the '859 publication teaches that when treating with HPN-100 "the subject will typically achieve and maintain normal plasma ammonia levels." Ex. 1007 ¶ 182. Similarly, Berry (Ex. 1016) cited by Dr. Vaux, teaches that "[t]he goal of treatment is to maintain normal levels of plasma ammonia through the use of low-protein diet and medication while allowing for normal growth." Ex. 1016, S58. We find that these prior art references support Dr. Vaux's testimony that

"[m]aintenance of plasma ammonia levels within normal limits is one of the objectives of therapy with nitrogen scavenging drugs." Ex. 1002 ¶ 54. We note that even Dr. Enns, Patent Owner's witness, testifies that "a number of references repeat the idea that the goal is to maintain plasma ammonia within normal limits." Ex. 2006 ¶ 114, citing Ex. 1020 at 3328; Ex. 1016 at S58; Ex. 2021 at 33.

Patent Owner argues that Dr. Vaux's testimony is not supported because "the prior art does not state that the goal of maintaining a normal plasma ammonia level means staying within normal during the entire course of every day." PO Resp. 34. We disagree that this accurately characterizes Dr. Vaux's testimony or that the invention as recited in the'559 patent claims would have been obvious only if skilled artisans had a goal of constant maintenance throughout the "entire course of every day." Instead, the challenged claims merely recite administering an adjusted dosage of drug.

We are also not persuaded by Dr. Enns's testimony that the known variability in plasma ammonia levels made it too difficult to try to achieve stability in plasma ammonia levels when treating UCDs. PO Resp. 34, citing Ex. 2006 ¶¶ 41, 43, 86–87. Because the prior art expressly provides for a goal of maintaining normal levels of plasma ammonia at least in part with medication (*see* Ex. 1016, S58), we are not persuaded that Dr. Vaux's testimony lacks support.

Patent Owner argues further that there is no support for Dr. Vaux's assumption that a physician would have taken any action when a patient had a normal plasma ammonia level or that the action would have been to increase drug dosage. PO Resp. 34, citing Ex. 2006 ¶¶ 86–87; *see also* PO

Resp. 39–41 (citing Ex. 2006 ¶¶ 13–14). We disagree because the '859 publication teaches that "plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject . . . ." Ex. 1007 ¶ 94. Thus, the '859 publication teaches that a known goal of treatment is plasma levels that are below normal, not just below the upper limit of normal.

Patent Owner argues that the prior art teaches only adjusting drug dosages when plasma ammonia levels are far above the upper limit of normal, not within the normal range, citing several references in support. PO Resp. 38–46. For example, Patent Owner cites to Brusilow '84 (Ex. 1004) to show that ordinarily skilled artisans were concerned only when plasma ammonia levels were three times normal or higher. PO Resp. 41 (citing Ex. 1004, 1631 and Ex. 2006 ¶¶ 67–68). We do not consider Brusilow '84 to support Patent Owner's argument because treatment of one or several patients with high plasma levels of ammonia does not indicate skilled artisans would always wait until plasma ammonia reached those levels.

Patent Owner also cites to Berry (Ex. 1016) for its discussion of adjusting the dose of nitrogen scavenging drugs only when plasma ammonia levels are more than three times the upper range of normal. PO Resp. 43 (citing Ex. 1016, S58–S59); Ex. 2006 ¶¶ 80, 114, and 119. The portion of Berry cited by Patent Owner, though, refers to prophylactic treatment when a patient is ill and therefore may not be indicative of all dosing decisions. *See* Reply 7–8. In addition, Berry includes teachings to adjust drug dosage at plasma levels within the claimed range because it applies to any plasma level *below* three times the upper range of normal, a range that includes below the upper limit of normal. Reply 7–8. Accordingly, we are not

persuaded, based on Berry's teachings, that those of ordinary skill in the art would not have had a reason to adjust drug dosage when plasma ammonia levels were below the upper limit of normal.

For similar reasons, we are not persuaded by Patent Owner's citations to Batshaw (Ex. 2009), Feillet (Ex. 2018), and Barsotti (Ex. 1015). *See* PO Resp. 44 (citing Ex. 2006 ¶¶ 116, 119). Batshaw states: "The aim of long-term therapy has been to maintain metabolic control with plasma ammonia concentrations *less than* twice normal . . . ." Ex. 2009, S51 (emphasis added). Feillet states: "The aim should be to maintain good metabolic control with plasma ammonia concentrations *less than* 80 μmol/L (normal < 50 μmol/L) . . . ." Ex. 2018, 109 (emphasis added). Barsotti states: "In the venous blood of healthy adults and children, blood ammonia levels are approximately 30 μmol/L, and levels exceeding l mmol/L occur under conditions of acute hyperammonemia." Ex. 1015, S11. Each of these references teaches that a range of less than the upper limit of normal is included in the targeted range. We agree with Petitioner that setting an upper limit on tolerable plasma ammonia levels does not mean that those of ordinary skill in the art would not have had a reason to adjust drug dosage at lower plasma ammonia levels. *See* Reply 8.

Patent Owner also cites to a publication entitled "Consensus statement from a Conference for the Management of Patients With Urea Cycle Disorders" (Ex. 2025). PO Resp. 44. This publication teaches there was no agreement on whether plasma ammonia levels greater than three times normal require intravenous drug administration. Ex. 2025 at S3. Although this may support Patent Owner's argument to some extent, immediately after this teaching, the publication states: "Ammonia levels change rapidly. An

elevated ammonia level during a clinic visit in a patient without symptoms, however, does require adjustment of therapy or better compliance with the recommended treatment regimen." Ex. 2025, S3; *see* Reply 8. We find this passage to be in tension with the passage relied on by Patent Owner. The second passage is more supportive of Dr. Vaux's testimony about the reasons why ordinarily skilled artisans would have adjusted drug dosages when plasma ammonia levels are approaching the upper limit of normal because it refers to "elevated ammonia levels" in patients without symptoms, without specifying that these levels would be above the upper limit of normal. We give the second passage more weight because it expressly supports Dr. Vaux's testimony, whereas the passage relied upon by Patent Owner indicates only that there was disagreement in the art.

Patent Owner also cites to the '157 publication (Ex. 2012) to show that ordinarily skilled artisans would not have had any reason to adjust drug dosages until plasma levels were above the upper limit of normal. PO Resp. 42. Patent Owner asserts that the '157 patent teaches that no dosage adjustments were needed for patients with ammonia levels under 30 µmol/L (reportedly below the average upper limit of normal). This does not persuade us that the '157 publication demonstrates those of skill in the art would not have considered adjusting the dose of drug when plasma ammonia levels are below the upper limit of normal. Instead, as Petitioner notes, the '157 publication also teaches adjusting drug dosage to attain "a normal or desired plasma ammonia level, e.g. a level below about 40 µmol/L." Ex. 2012 ¶ 299; *see* Reply 7.

Patent Owner cites to other prior art references to show that above normal plasma ammonia levels were acceptable. For example, Patent

Owner argues that Table 4 of Häberle[9] teaches increasing the dosage of nitrogen scavenging drugs only when plasma ammonia is at a level above the upper limit of normal, but not when it is within the normal range. PO Resp. 42–43 (citing Ex. 2019, 1975, Table 4). Table 4 of Häberle indicates that its recommendations are for action in "symptomatic" patients with increased levels of ammonia in their blood ("hyperammonemia"). *See* Ex. 2019, 1975, Table 4; Ex. 2006 ¶ 118 (noting that Table 4 of Häberle provides suggestions for action in symptomatic patients).

When we read Table 4 in the context of the rest of Häberle, we find that it is referred to only in the context of "[m]anagement of acute hyperammonemia" when a patient is in "hyperammonemic crisis" and being transferred to a "specialist centre" with the possibility of coma. *See* Ex. 2019, 1974. We are not persuaded that these conditions are necessarily relevant to the treatment discussed by Dr. Vaux in his testimony. That is, Dr. Vaux refers to determination of drug dosage "to help insure that the patient routinely stayed with normal plasma ammonia limits." Ex. 1002 ¶¶ 51, 55. Thus, whereas Häberle relates to crisis situations, Dr. Vaux's testimony relates to routine management of UCD patients, who are not necessarily symptomatic. Patent Owner has not directed us to evidence showing how ordinarily skilled artisans would determine drug dosage in other situations, for example when attempting to maintain normal levels of plasma ammonia in non-symptomatic patients partaking in usual activities, such as eating, over the course of a day.

[9] Petitioner disputes the admissibility of Häberle as prior art in its Motion to Exclude. Paper 35 at 3–9. As discussed in the main text, above, we do not consider Häberle to be persuasive of the non-obviousness of the challenged claims. Accordingly, Petitioner's arguments are moot.

Patent Owner argues that clinicians typically use the lowest dosage possible of medication to avoid side effects, indicating that there would not have been motivation to increase drug dosage when a patient's plasma ammonia levels were not above the upper limit of normal. PO Resp. 44–45 (citing Ex. 2006 ¶ 121). Patent Owner and Dr. Enns cite to the severe toxicity that can result from massive overdosing in response to prescription or pharmacy errors. PO Resp. 44–45. The references Patent Owner cites[10] do not report such problems with HPN-100 overdosing. *See* Ex. 1006 at 262 (regarding phenylbutyrate); Ex. 2031 at S64 (regarding phenylbutyrate); Ex. 2032 at S79–S85 (regarding sodium phenylbutyrate and sodium phenylacetate); Ex. 1014, 10–19 (regarding phenylbutyrate). *See* Reply 9. Instead, the '859 publication teaches:

> [I]t has also been found that HPN-100 exhibits no indications of toxicity at equimolar doses when compared to the approved PBA [phenylbutyric acid] dosage of 20 g/day and a dose 2-3 times the equivalent of 20 grams of PBA is unlikely to produce PAA blood levels leading to [adverse effects]. Moreover, tolerability of taking HPN-100 is much higher than for PBA . . . . In some patients or clinical settings, HPN-100 doses well above the approved PBA dosage are expected to be beneficial[.]

Ex. 1007 ¶ 86.

Furthermore, although Patent Owner argues that artisans would have wanted to avoid the risks of "massive overdoses" (PO Resp. 44–45), the challenged claims encompass only slight drug dosage adjustments. Patent Owner has not directed us to evidence that slight increases in HPN-100

[10] Patent Owner argues that the '859 publication at paragraph 83 teaches limiting the dosage of HPN-100 to not exceed that of phenylbutyrate at paragraph 83 (PO Resp. 45), but this paragraph does not mention dosing of either drug specifically.

would have been considered to be dangerous. Accordingly, we are not persuaded by Patent Owner's arguments regarding the risks of toxicity of nitrogen scavenging drugs.

Patent Owner relies on Dr. Enns's testimony to argue that those of ordinary skill in the art would not have relied on a normal plasma ammonia level to adjust a patient's drug dosage because such plasma ammonia levels were known to be variable. PO Resp. 46 (citing Ex. 2006 ¶¶ 100–101). According to Dr. Enns, plasma ammonia levels were not used as the basis of adjusting drug dosage. *See* Ex. 2006 ¶ 101. The '859 publication teaches otherwise. Specifically, the '859 publication expressly provides a method to individually adjust the dose of a nitrogen scavenging drug, including "optionally measuring blood ammonia to determine if the initial dosage is sufficient to control blood ammonia levels, or to establish a suitable average ammonia level" and then "adjusting the dosage of the new drug as needed . . . ." Ex. 1007 ¶¶ 95–99; *see also id.* ¶¶ 88–91. Although the method taught in the '859 publication also teaches measuring the amount of total waste nitrogen and/or PAGN excreted, Patent Owner's challenged claims are open to additional steps because of the "comprising" transitional language. In contrast to Dr. Enns's testimony, we find that the prior art taught using plasma ammonia levels as the basis, at least in part, for adjusting nitrogen scavenging drug dosages.

Patent Owner argues further that the variability of plasma ammonia levels throughout the day counsels against relying on them to adjust drug dosage. PO Resp. 47–48, citing Ex. 2006 ¶ 102. Instead, because high ammonia levels are toxic to the patient and can lead to coma (*see* Ex. 1002 ¶ 32; Ex. 2006 ¶ 33), we are more persuaded by Dr. Vaux's testimony (*see*

Ex. 1002 ¶¶ 51, 55) that ordinarily skilled artisans would consider this variability to be a reason to increase drug dosage when plasma ammonia levels approach the upper limit of normal.

In general, Patent Owner argues there is no teaching in the prior art to increase drug dosage for subjects whose plasma ammonia levels are less than the upper limit of normal. *See* PO Resp. 51–54 (citing Ex. 2006 ¶¶ 59–84). We are not persuaded by this argument. The prior art need not expressly teach what is recited in the challenged claims. Instead, Petitioner need only show that there would have been a reason for ordinarily skilled artisans to modify what was taught in the prior art and that there would have been a reasonable expectation of success in doing so. As the Supreme Court noted, "[i]n many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends." *KSR*, 550 U.S. at 419. In light of the teachings in the prior art regarding measuring plasma ammonia levels in a fasting state and using this information to adjust drug doses, along with Dr. Vaux's testimony, we are persuaded that Petitioner has established that one of ordinary skill in the art would have had a reason to increase drug dosage for subjects whose plasma ammonia levels are less than the upper limit of normal.

D.

Patent Owner also argues that there would not have been a reason to combine the teachings of the '859 publication with those of Simell, Blau, or Brusilow '84 to achieve the claimed invention. PO Resp. 24–33. Petitioner asserts that one of ordinary skill in the art would have combined the teachings of these references based on Dr. Vaux's testimony that each

contributes to beneficial aspects of adjusting the dosage of a nitrogen scavenging drug. *See* Pet. 19–20 (citing Ex. 1002 ¶¶ 47–50). Specifically, Dr. Vaux explains that the '859 publication provides guidance on choosing a dosage of nitrogen scavenging drug, while Simell and Blau provide guidance on measuring plasma ammonia levels. *See id.*

Patent Owner challenges Dr. Vaux's assertions by arguing that Simell measured fasting blood ammonia for reasons unrelated to the treatment of UCD patients with nitrogen scavenging drugs. *See* PO Resp. 26–30 (citing Ex. 2006 ¶¶ 8, 91–92). Specifically, Patent Owner argues that Simell teaches administering drugs other than HPN-100 and administering them intravenously in patients with artificially induced hyperammonemia, in contrast to the '859 publication, which teaches oral HPN-100 for long-term management of UCD patients. *See* PO Resp. 26–27. Patent Owner argues further that Simell refers to a different condition, lysinuric protein intolerance, which Patent Owner asserts is not a type of UCD. *See* PO Resp. 27–29 (citing Ex. 2006 at ¶¶ 93–94).

Patent Owner argues further that Blau teaches only methods of diagnosis of metabolic diseases, rather than treatment of UCDs. PO Resp. 32 (citing Ex. 2006 ¶ 96). Regarding Brusilow '84, Patent Owner argues that the reference teaches a different drug to treat episodic hyperammonemia in UCD and does not emphasize measuring fasting plasma ammonia levels. PO Resp. 30–31 (citing Ex. 2006 ¶ 97).

We are not persuaded by Patent Owner's arguments because even if Simell, Blau, and Brusilow '84 are not directed to the exact same aspects of UCDs as the '859 publication, they reflect the knowledge of those with ordinary skill in the art with respect to measuring plasma ammonia levels

after a fast.[11] As discussed above, Exhibits 1010 and 1015 provide further evidence that the use of fasting ammonia levels in Simell, Blau, and Brusilow '84 was not limited to the exact circumstances reported in these references. *See* Pet. 16, n.2. Accordingly, we are persuaded that the preponderance of the evidence supports the finding that those of skill in the art would have considered it obvious to modify the teachings of the '859 publication by using fasting serum ammonia levels as taught in at least Simell and Blau.

E.

According to Patent Owner, the skilled artisan would have considered a successful outcome to be "reducing the incidence and frequency of hyperammonemia." PO Resp. 56. Patent Owner argues that Petitioner fails to prove that one of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of the cited references to achieve the claimed invention, specifically in treating UCDs with the claimed methods. PO Resp. 55–57. Specifically, Patent Owner argues that before the data in the '859 patent was known, a skilled artisan would not have expected that an increased dosage of nitrogen scavenging drug would lower a patient's baseline when the plasma ammonia level was already within normal limits. PO Resp. 57. The challenged claims do not require that the recited methods result in any specific efficacy or any specific level

[11] Petitioner argues that Exhibit 2041, which Patent Owner cites in support of its arguments about the inapplicability of Simell (*see* PO Resp. 26), should be excluded because it does not qualify as prior art. *See* Paper 35 at 9–10. Even if we found Ex. 2041 to be admissible, we are not persuaded by the argument Patent Owner presents in reliance on it. Accordingly, Petitioner's arguments regarding Ex. 2041 are moot.

of reduction of the incidence or frequency of high plasma ammonia levels. Thus Petitioner need not show that any specific result, such as lowering a "baseline," would have been expected.

Patent Owner argues further that Dr. Vaux's testimony regarding the knowledge to administer HPN-100 to lower plasma ammonia levels is not sufficient evidence of a reasonable expectation of success. *See* PO Resp. 55, citing Ex. 1002 ¶ 67. In contrast, Patent Owner asserts that "Dr. Enns has observed plasma ammonia levels increasing or remaining unchanged with increased drug dosage." *See* PO Resp. 56 (citing Ex. 2006 ¶ 119).

We credit Dr. Vaux's testimony over Dr. Enns's on this point because Dr. Vaux supports his testimony with reference to the prior art. For example, Dr. Vaux cites the portion of '859 publication that explains how nitrogen scavenging drugs, such as HPN-100, act to reduce high levels of endogenous ammonia by providing phenylacetic acid in vivo, which is metabolized efficiently to form phenylacetyl glutamine, a compound that removes nitrogen from ammonia and allows it to be excreted in the urine. *See* Ex. 1002 ¶ 67 (citing Ex. 1007 ¶¶ 21–23).

In contrast, the paragraph of Dr. Enns's testimony to which Patent Owner directs us discusses only the teachings of the prior art regarding drug dosages determinations when plasma ammonia levels are higher than the upper limit of normal. *See* Ex. 2006 ¶ 119. We note that in paragraph 123 of his declaration (Ex. 2006), Dr. Enns testifies that "[i]t is all too possible that administration of nitrogen scavenging drugs will increase or remain unchanged with increased drug dosage—it is not an easy linear relationship." This testimony appears to be merely speculative and conflicts with the teachings of the prior art.

Patent Owner also cites Dr. Enns's testimony to argue that one of ordinary skill in the art would not have understood the correlation between a specific fasting plasma ammonia level and daily average ammonia levels and maximum plasma ammonia levels without the detailed statistical analysis presented in the '559 patent. *See* PO Resp. 56 (citing Ex. 2006 ¶ 124). According to Dr. Enns,

> [w]ithout this data, one of ordinary skill would have no expectation that an increased dosage of nitrogen scavenging drug would lower a patient's baseline when their plasma ammonia level was already within normal limits. In addition, given the known variability and unreliability of plasma ammonia values, one would not have had any expectation that an increased dosage of nitrogen scavenging drug would ensure they stayed within the normal limits.

Ex. 2006 ¶ 124. We are not persuaded by either Patent Owner's argument or Dr. Enns's testimony because the challenged claims do not require that the subject's "baseline" plasma ammonia levels be lowered or that plasma ammonia levels stay within normal limits for any specific amount of time. Thus, we are not persuaded that the statistical analysis presented in the '559 patent was necessary to carry out the methods of the challenged claims.

To the extent the methods of the challenged claims require any efficacy in treating a subject, they would encompass reducing plasma ammonia levels to some minimal extent. Because Dr. Vaux testifies, based on the '859 publication teaching that the action of HPN-100 is to remove endogenous ammonia by providing a pathway for its excretion, we are persuaded that one of ordinary skill in the art would have had a reasonable expectation of success in reducing plasma ammonia levels using an administering step as recited in the claims. Indeed, the '859 publication is directed to using HPN-100 to treat patients with UCDs. Furthermore, as

Petitioner notes, reduction of plasma ammonia levels below half the upper limit of normal after administration of HPN-100 is exemplified in Figure 12 of the '859 publication. *See* Reply 23.

Accordingly, we are persuaded that the ordinary artisan would have had a reasonable expectation of success in combining the prior art teachings to achieve the claimed methods.

F.

We are persuaded by the arguments and supporting evidence presented by Petitioner that independent claims 1, 2, and 3 of the '559 patent would have been obvious over the prior art.

G.

Claim 5 of the '559 patent recites the methods of claim 1 or 2 further comprising repeating the measuring, comparing, and administering steps until the subject exhibits a fasting plasma ammonia level at or below half the upper limit of normal. *See* Ex. 1001 at 24:64–67. Petitioner challenges claim 5 of the '559 patent based on the cited prior art discussed above and Dr. Vaux's testimony that there is no minimum level of blood ammonia that must be maintained for normal body function. Pet. 31 (citing Ex. 1002 ¶ 68).

With respect to claim 5, Patent Owner contends there is no prior art that suggests targeting an ammonia level below half of the upper limit of normal and that normal ranges were considered to be acceptable. PO Resp. 58.

We are not persuaded by these arguments because, as Petitioner argues, the '859 publication and other prior art teach that maintaining plasma ammonia levels *below* ranges considered to be normal was desirable.

See Reply 10–11; *see, e.g.*, Ex. 1007 ¶ 74 ("a plasma ammonia level of less than about 40 μmol/L, or of not greater than 35 μmol/L would indicate the treatment was effective."). These teachings conflict with Dr. Enns's testimony that those of ordinary skill in the art would not have had any motivation to target plasma levels below half of the upper limit of normal. *See* Ex. 2006 ¶¶ 125–27. Even if the prior art does not expressly teach the limitations of the challenged claims, we are persuaded that it supports Petitioner's argument that ordinarily skilled artisans would have had reason to target any level below the upper limit of normal. As Petitioner argues, Patent Owner "has not submitted any evidence that the claimed ammonia value exhibits unexpected results over the prior art disclosure of ammonia values that are less than the ULN." Reply 11.

H.

Petitioner includes the claims dependent on claims 1, 2, and 3 in the patentability challenges. *See* Pet. 30–35 and 44–46.

Dependent claim 4 recites the method of claim 1 or 2 and requires that the administered dose of HPN-100 "produces a normal average daily ammonia level in the subject." Ex. 1001 at 24:61–63. We find that, as Petitioner argues, it was known to administer HPN-100 to lower plasma ammonia levels (*see* Ex. 1007 ¶¶ 21–23) and maintenance of plasma ammonia levels within the normal limits was a goal of drug therapy (*see id.* ¶ 83; Ex. 1016, S58). Accordingly, we agree with Petitioner that those of skill in the art would have had reason to administer HPN-100 to achieve a normal average daily ammonia level in the subject and would have considered the method of claim 4 to have been obvious. *See* Pet. 30. Patent Owner does not argue to the contrary in regard to claim 4.

Dependent claim 6 recites the method of claim 3, further comprising repeating the steps of claim 3 a second time and administering an adjusted dosage of HPN-100 that is greater than the initial dosage recited in claim 3. Ex. 1001 at 25:1–11. We agree with Petitioner that claim 6 would have been considered obvious by those of ordinary skill in the art for the same reasons claim 3 would have been considered to be obvious. *See* Pet. 44. Patent Owner does not argue to the contrary in regard to claim 6.

Claims 7, 8, and 9 recite the methods of claims 1–3 wherein the upper level of normal is "35 µmol/L," is "specific to the laboratory in which the fasting plasma ammonia level is measured," or is determined in an extra method step prior to step (b) of the dependent claim. *See* Ex. 1001 at 25:12–18. We agree with Petitioner that the '859 publication teaches that 35 µmol/L was considered to be an upper limit of normal under some testing, but that such levels could vary with different laboratories. *See* Pet. 32–33 (citing Ex. 1007 ¶ 94). We also agree that the prior art teaches that it was known that different patients could have different upper limits of normal plasma ammonia levels, for instance according to their age. *See* Ex. 1006, 273 (Table 11.5) (teaching that the upper limit of normal for neonates is 80 µmol/L and for 4-month olds is 50 µmol/L). Accordingly, we agree that claims 7, 8, and 9 would have been obvious. Patent Owner does not argue to the contrary in regard to claim 7, 8, or 9.

Claim 10 recites the method of claim 1 or claim 2 with additional steps to calculate the adjusted dosage of HPN-100 based on "based on a mean conversion of glyceryl tri-[4-phenylbutyrate] to urinary PAGN of 60 to 75%." Ex. 1001, 25:19–26:5. Claim 11 recites similar steps as additional limitations to claim 3 for a method of calculating the initial dosage of HPN-

100. Ex. 1001, 26:6–12. We agree with Petitioner that the '859 publication teaches that HPN-100 converts into urinary PAGN at a rate of 60–75% and that this rate may be used to determine an effective dose of HPN-100, thus rendering claim 10 obvious. *See* Pet. 34 (citing Ex. 1007 ¶¶ 43, 144–156. Patent Owner does not argue to the contrary in regard to claim 10.

Claims 12, 13, 14, and 15 depend on claims 1, 2, 3, and 6 respectively and require that the adjusted or initial dosage of HPN-100 is administered orally. Ex. 1001, 26:14–19. We agree with Petitioner that the '859 publication teaches oral administration of HPN-100, rendering these claims obvious. *See* Pet. 35 and 45–46 (citing Ex. 1007 ¶¶ 20–21). Patent Owner does not argue to the contrary in regard to claims 12–15.

III. Conclusion

Petitioner has demonstrated, by a preponderance of the evidence, that claims 1, 2, 4, 5, 7–10, 12, and 13 of the '559 patent are unpatentable over the '859 publication, Blau, and Simell under 35 U.S.C. § 103(a).

Petitioner has also demonstrated, by a preponderance of the evidence, that claims 3, 6, 11, 14, and 15 of the '559 patent are unpatentable over the '859 publication, Blau, Simell, and Brusilow '84 under 35 U.S.C. § 103(a).

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–15 of the '559 patent are unpatentable;

FURTHER ORDERED that Petitioner's motion to exclude is dismissed as moot, as discussed above.

This is a final decision. Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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