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Paper 53
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
LUPIN LTD., and LUPIN PHARMACEUTICALS, INC.,

Petitioners,

v.

HORIZON THERAPEUTICS, LLC,[1]
Patent Owner.

Case IPR2015-01117[2]
Patent 8,642,012 B2

Before TONI R. SCHEINER, DEBORAH KATZ, and
GRACE KARAFFA OBERMANN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

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

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[1] Patent owner represents "that it has changed name and converted form and is now Horizon Therapeutics, LLC." Paper 51.

[2] Case IPR2016-00283, instituted on a petition filed by Lupin Ltd. and Lupin Pharmaceuticals, Inc., has been joined with Case IPR2015-01117. *See* Paper 32.

I. INTRODUCTION

Par Pharmaceutical, Inc. ("Par" or "Petitioner Par") filed a Petition (Paper 2, "Pet.") on April 29, 2015, requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 8,642,012 B2 (Ex. 1001, "the '012 patent"). Horizon Therapeutics, Inc. ("Horizon" or "Patent Owner") filed a Preliminary Response (Paper 8) on August 5, 2015. On November 4, 2015, we instituted trial as to all of the challenged claims, on the following grounds.[3]

References	**Basis**	**Claims Challenged**
Brusilow '91,[4] Sherwin '19,[5] Comte,[6] and Shiple[7]	§ 103	1, 3, 4, 7, 8, 10, 12

[3] Par supported its challenge with a Declaration, executed April 29, 2015, by Neal Sondheimer, M.D., Ph.D. ("Sondheimer Declaration") (Ex. 1002).

[4] Saul W. Brusilow, *Phenylacetylglutamine May Replace Urea as a Vehicle for Waste Nitrogen Excretion*, 29 PEDIATRIC RESEARCH 147–150 (1991) ("Brusilow '91") (Ex. 1012).

[5] Carl P. Sherwin at al., *The Maximum Production of Glutamine by the Human Body as Measured by the Output of Phenylacetylglutamine,* 37 J. BIOL. CHEM. 113–119 (1919) ("Sherwin '19") (Ex. 1016).

[6] Blandine Comte et al., *Identification of phenylbutyrylglutamine, a new metabolite of phenylbutyrate metabolism in humans*, 37 J. MASS SPECTROM. 581–590 (2002) ("Comte") (Ex. 1025).

[7] George J. Shiple & Carl P. Sherwin, *Synthesis of Amino Acids in Animal Organisms. I. Synthesis of Glycocoll and Glutamine in the Human Organism*, 44 J. AMER. CHEM. SOC. 618–624 (1922) ("Shiple") (Ex. 1017).

References	Basis	Claims Challenged
Brusilow '91 , Sherwin '19, Shiple, and Fernandes[8]	§ 103	5
Brusilow '91, Sherwin '19, Shiple, and the '647 patent[9]	§ 103	2, 9
Brusilow '91, Sherwin '19, Shiple, Kasumov,[10] and the '979 patent[11]	§ 103	6, 11

After institution, Lupin Ltd. and Lupin Pharmaceuticals, Inc. ("Lupin") filed a Petition based on the same grounds as the Par Petition, with arguments and evidence substantially identical to those put forth by Par. *See* IPR2016-00283, Paper 1. Lupin's Petition was accompanied by a Motion for Joinder. *See* IPR2016-00283, Paper 4. We instituted trial on the same challenges of Lupin's Petition that we instituted trial on in the current *inter partes* review and joined the two proceedings in this single review. No

[8] INBORN METABOLIC DISEASES: DIAGNOSIS AND TREATMENT 219–220 (John Fernandes et al. eds., Springer Verlag 3d ed. 2000) ("Fernandes") (Ex. 1011).

[9] U.S. Patent No. 4,284,647, issued August 18, 1981 to Brusilow et al. ("the '647 patent") (Ex. 1018).

[10] Takhar Kasumov et al., *New Secondary Metabolites of Phenylbutyrate in Humans and Rats*, 32 DRUG METABOLISM AND DISPOSITION 10–19 (2004) ("Kasumov") (Ex. 1015).

[11] U.S. Patent No. 5,968,979, issued October 19, 1999 to Brusilow ("the '979 patent") (Ex. 1026).

further submissions have been entered on Lupin's part. Paper 32; *see* IPR2016-00283, Paper 12.

Horizon filed a Patent Owner Response (Paper 25, "PO Resp."), and Par filed a Reply (Paper 30, "Reply"). With our authorization, Horizon filed a Corrected Patent Owner Response (Paper 41, "Corr. PO Resp.")—superseding Paper 25—in order to correct citations to Exhibit 2012. *See* Paper 40. Petitioner Par, with our authorization, filed a Supplemental Reply to the Corrected Patent Owner Response (Paper 45, "Supp. Reply"). Horizon did not move to amend any claim of the '012 Patent.

Horizon and Par each filed a Motion to Exclude (Papers 36, 38), and each filed an Opposition to the Motion of the other party (Papers 42, 44). In addition, Horizon filed a Reply to Par's Opposition (Papers 46).

We heard oral argument on July 26, 2016. A transcript of the argument has been entered into the record as Paper 52.

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. *See* 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Par has not proved by a preponderance of the evidence that claims 1–12 are unpatentable.

A. Related Proceedings

Patent Owner filed suit against Petitioner, alleging infringement of the ’012 patent and U.S. Patent No. 8,404,215 B1 (“the ’215 patent) in *Hyperion Therapeutics, Inc. v. Par Pharmaceutical, Inc.*, Case No. 2:14-CV-384-JRG-RSP (E.D. Tex.). Pet. 7; Paper 5, 3. In addition, concurrently with the Petition under consideration here, Petitioner Par filed a petition challenging the claims of the ’215 patent (IPR2015-01127), but represents that that patent is not related to the ’012 patent. Pet. 7.

In addition, Patent Owner filed suit against Lupin, alleging infringement of the ’012 patent, in *Horizon Therapeutics, Inc. v. Lupin Ltd.*, Case No. 1:15-cv-07624-RBK-JS (D.N.J. filed Oct. 19, 2015). *See* IPR2016-00283, Paper 1, 8.

B. The ’012 Patent (Ex. 1001)

The ’012 patent, titled “Methods of Treatment Using Ammonia-Scavenging Drugs,” is directed to “treatment of patients with nitrogen retention states, in particular urea cycle disorders (UCDs) . . . [by] administer[ing] compounds that assist in elimination of waste nitrogen from the body.” Ex. 1001, 1:18–25. These compounds—or “nitrogen scavenging drugs”[12]—include glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA)—both of which are prodrugs that are converted *in vivo* to phenylacetic acid (PAA). *Id.* at 3:61–66.

[12] The terms “ammonia scavenger” and “nitrogen scavenger” are used interchangeably in the ’012 patent. Ex. 1001, 4:6–7.

"For patients with nitrogen retention states such as UCD . . . the body's intrinsic capacity for waste nitrogen excretion is less than the body's waste nitrogen production based on a normal diet that contains significant amounts of protein." *Id.* at 2:22–25. "As a result, nitrogen builds up in the body . . . and usually results in excess ammonia in the blood . . . [which] has various toxic effects." *Id.* at 2:25–28.

HPN-100 and PBA "reduce excess waste nitrogen and ammonia by converting it to readily-excreted forms, such as phenylacetyl glutamine (PAGN)." *Id.* at 2:45–47. "The capacity to eliminate excess ammonia in treated patients can be considered the sum of the patient's endogenous capacity for nitrogen elimination (if any) plus the amount of additional nitrogen-elimination capacity that is provided by a nitrogen scavenging drug." *Id.* at 2:39–44.

According to the '012 patent, "[i]t has generally been assumed . . . that a prodrug would be converted with 100% efficiency into PAGN for elimination" (*id.* at 9:21–23), but "[i]t has now been found that HPN-100 and phenylbutyrate are both converted into urinary PAGN at an overall efficiency of about 60% to about 75% on average (about 60% conversion efficiency was seen in UCD patients and about 75% conversion was seen in cirrhotic patients, for example)" (*id.* at 9:27–32). "[C]onsequently, this efficiency factor can be used to more accurately calculate or determine initial dosing levels for these drugs, or dietary protein levels acceptable for patients who use these drugs." *Id.* at 9:32–35. Moreover, "urinary PAGN

provides a convenient method for monitoring ammonia elimination induced by the administered drug, which does not require drawing blood and directly relates to the actual nitrogen elimination provided by the . . . drug without being influenced by the many other factors that can affect plasma ammonia levels." *Id.* at 7:24–30.

> One embodiment of the invention is a method for determining and/or adjusting the dose of ammonia scavenging drugs in patients with UCDs, whereby [the] dose would be based on the amount of dietary protein the patient is consuming, the anticipated percentage conversion of the drug to PAGN, and the patient's residual urea synthetic capacity, if any. Dose adjustments, if necessary, would be based on the observed urinary excretion of PAGN and/or total urinary nitrogen (TUN), the difference between the two reflecting the patient's endogenous capacity for waste nitrogen excretion . . . referred to sometimes as their residual urea synthesis capacity.

Id. at 8:16–30.

C. Illustrative Claims

Par challenges claims 1–12 of the '012 patent. Claims 1 and 8 are independent claims. Claims 1 and 8, reproduced below (with formatting added), are illustrative.

> 1. A method of treating a patient having a urea cycle disorder comprising
>
> (a) determining a target urinary phenylacetyl glutamine (PAGN) output
>
> (b) calculating an effective initial dosage of phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA, wherein the effective

> dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and
>
> (c) administering the effective initial dosage of PAA prodrug to the patient.
>
> 8. A method of administering a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA to a patient having a urea cycle disorder comprising
>
> (a) administering a first dosage of the PAA prodrug;
>
> (b) determining urinary phenylacetyl glutamine (PAGN) excretion following administration of the first dosage of the PAA prodrug;
>
> (c) determining an effective dosage of the PAA prodrug based on the urinary PAGN excretion, wherein the effective dosage is based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and
>
> (d) administering the effective dosage to the patient.

Id. at 42:16–15, 41–52 (*see* Certificate of Correction for claim 8).

II. ANALYSIS

A. Level of Skill in the Art

Par, supported by Dr. Sondheimer's testimony, contends that a person of ordinary skill in the art "is a physician or scientist with a Ph.D or M.D. degree and specialized training in the diagnosis or treatment of inherited metabolic disorders, such as UCD and other nitrogen retention disorders." Pet. 8–9 (citing Ex. 1002 ¶ 24).

Horizon, on the other hand, contends that a person of ordinary skill in the art would have the following qualifications:

> (a) An M.D. or equivalent degree; (b) 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; and (c) At least five years of experience treating patients with nitrogen retention disorders, including UCDs.

Corr. PO Resp. 26.

Horizon contends that Par's definition "does not require . . . any experience treating patients with urea cycle disorders or other nitrogen retention disorders," but "simply requires 'specialized training in the diagnosis *or* treatment of inherited metabolic disorders, such as UCD and other nitrogen retention disorders.'" *Id.* Horizon contends because "the challenged claims specifically relate to methods of *treating* UCD patients," one of ordinary skill in the art should have experience treating UCD patients. *Id.*

Horizon's point is well taken—that is, we agree that one of ordinary skill in the art should have experience treating, as well as diagnosing, UCD patients. In any case, our ultimate disposition of this case would not change under either Par's or Horizon's definition.

B. Petitioner's Witness, Dr. Sondheimer

As discussed above, Par relies on the testimony of Neal Sondheimer, M.D., Ph.D. (Ex. 1002). Dr. Sondheimer testifies that he currently holds

several positions at the Children's Hospital of Philadelphia and the University of Pennsylvania, including Attending Physician in the Division of Biochemical Genetics, Training Director for the Clinical Biochemical Genetics Group, Program Director for Medical Genetics, and Assistant Professor of Pediatrics. Ex. 1002 ¶ 10. Dr. Sondheimer testifies that he has been involved in several research studies involving the treatment of urea cycle defects and has co-authored several publications about the use of ammonia-scavenging medications. *Id.* ¶ 12.

Horizon does not take issue with Dr. Sondheimer's qualifications, and we find Dr. Sondheimer qualified to provide opinions on the subject matter at issue.

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

"mean conversion . . . of about 60%"

The term "mean conversion of PAA prodrug to urinary PAGN of about 60%" appears in both independent claims 1 and 8.

In the Petition, Par argued that the term should be construed "as encompassing a range of mean conversion between 53–67%." Pet. 10–12. Horizon did not address this issue in its Preliminary Response, and we determined it was not necessary to construe the term for purposes of institution. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (Quoting *Vivid Techs., Inc. v. Am. Sci. Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

In its Corrected Patent Owner Response, Horizon contends that "the claim term 'about 60%' has its plain and ordinary meaning and would be understood by a [person of ordinary skill in the art] to encompass 67%" (Corr. PO Resp. 27), but nothing in the claims, specification or prosecution history of the '012 patent supports Par's "assertion that 'about 60%' should be construed to encompass 53%" (*id.*). Nevertheless, we again determine that it is not necessary to expressly construe the term for purposes of this decision. To the extent Par relies on the term as "encompassing a range of mean conversion between 53–67%," however, we reject its proposed construction.

The specification of the '012 patent states "in contrast to the assumptions inherent in current treatment guidelines that all administered

sodium PBA is converted to urinary PAGN, considerable inter-individual variability was observed in the percentage of administered PAA converted to PAGN, which averaged ~60% and similar [sic] both sodium PBA and HPN-100" in UCD patients. Ex. 1001, 32:3–9. The '012 patent further states that "HPN-100 is typically converted into urinary PAGN with an efficiency of about 60% to 75%," but clarifies that "typically about 60% conversion was found in UCD patients;" while "conversion in cirrhotic patients was about 75%." *Id.* at 40:33–36.

Nothing in the specification, then, explicitly supports Par's contention that the term "about 60%" encompasses a range of about 53–67%. That, in and of itself, does not settle the matter. We still must consider Par's contention that its construction is supported by the prosecution history of the '012 patent. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) ("In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence."); *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (stating that the PTO should consider prosecution history in *inter partes* review).

In support of its contention, Par directs us to "the November 20, 2012 Declaration of Bruce Scharschmidt [M.D.], [the] named inventor, submitted during prosecution of the '012 patent" (Pet. 11 (citing Ex. 1021 (prosecution history of the '012 patent), 682–683)); the Examiner's Amendment and

Reasons for Allowance (*id.* at 11–12 (citing Ex. 1021, 718–719)); and finally, Dr. Sondheimer's testimony regarding how a person of ordinary skill in the art would have construed the term "about 60%" given the Scharschmidt Declaration and Examiner's Amendment and Reasons for Allowance (*id.* at 6, 10 (citing Ex. 1002 ¶ 27)).

In his Declaration, Dr. Scharschmidt noted that "[t]he pending claims . . . have been amended to specify [treatment of] urea cycle disorder (rather than nitrogen retention disorders generally" and provided "detailed data for PAA prodrug conversion to urinary PAGN in approximately 65 UCD patients . . . during steady state dosing" with sodium PBA or HPN-100. Ex. 1021, 683. Dr. Scharschmidt reported that "the mean percent conversion of PAA prodrug to urinary PAGN in UCD patients was 67%, with a . . . 99% confidence range of 63–71%" (*id.*), which "falls squarely within the range [of 60% to 75%] recited in the present claims, and . . . well below 80%" (*id.*).

Following the submission of Dr. Scharschmidt's Declaration, the Examiner entered an Examiner's Amendment as follows, in relevant part: "wherein the effective dosage of PAA prodrug is calculated based on a mean conversion of PAA prodrug to urinary PAGN of <u>about</u> 60% ~~to 75%~~" (Ex. 1021, 718). In the Reasons for Allowance, the Examiner stated, in relevant part: "[Dr. Scharschmidt's] Declaration filed 11/21/2012 contains data drawn to an about 60% conversion rate of PAA to urinary PAGN as

disclosed in the specification, which supports applicants disclosed drug conversion in the as filed specification." *Id.* at 719.

Finally, Dr. Sondheimer "reviewed the correspondence between the patent office and the applicant" and testifies that "[t]he examiner would not grant a patent to the claimed methods until after applicant submitted test data showing a mean percent conversion of 67%, and the examiner narrowed the claims to a mean percent conversion of about 60%." Ex. 1002 ¶ 27. Based on this, Dr. Sondheimer concludes that "about 60% includes 67%," and further testifies that in his opinion, "a person of ordinary skill in the art would interpret the patent term 'mean conversion . . . of about 60%' as meaning at least 53–67%." *Id.*

Nevertheless, we are not persuaded that the Examiner's statement in the Reasons for Allowance that Dr. Scharschmidt's Declaration "contains data drawn to and about 60% conversion rate" unambiguously conveys to one of ordinary skill in the art that "about 60%" should be construed "as encompassing a range of mean conversion between 53–67%" (Pet. 10–12), inasmuch as the specification of the '012 patent discloses expressly that the conversion rate in UCD patients averages "about 60%," but a large portion of the range 53–67% does not even fall within the 99% confidence range of 63–71% reported in Dr. Scharschmidt's Declaration.

In any case, for the reasons discussed below, even if we credit Dr. Sondheimer's testimony in this regard and accept Par's proposed construction of the term "mean conversion . . . of about 60%" as

encompassing a range of mean conversion between 53–67%, it would not change our ultimate disposition of the case.

D. Claims 1, 3, 4, 7, 8, 10, 12—Asserted Obviousness over Brusilow '91, Sherwin '19, Comte, and Shiple

Par, relying on the testimony of Dr. Sondheimer, contends that Brusilow '91, Sherwin '19, Comte, and Shiple represent the state of the art with respect to treatment of urea cycle disorders with phenylbutyric acid, and that their combined teachings would have rendered the subject matter of claims 1, 3, 4, 7, 8, 10, and 12 obvious to one of ordinary skill in the art. Pet. 15–28.

Horizon argues, among other things, that the references relied on by Par represent an incomplete, and therefore misleading picture of the state of the art, and presents additional evidence in support of its arguments. Corr. PO Resp. 5–7, 41–47.

We begin our analysis of the state of the art with a discussion of the prior art cited by Par.

1. Brusilow '91 (Ex. 1012)

Brusilow '91 reports the results of an evaluation of PAG nitrogen (PAGN) as an alternate vehicle for waste nitrogen excretion in patients with inborn errors of urea synthesis (i.e., urea cycle disorders, or UCDs). Briefly, the daily protein intake of a 7½-year-old boy with a UCD was used to calculate his required waste nitrogen excretion, and the required nitrogen excretion was used to calculate a target amount of urinary PAGN to be

excreted. The target amount of PAGN to be excreted was used, in turn, to calculate initial doses of PAA and PBA, based on complete (i.e., 100%) conversion of the drugs to PAGN. Urinary excretion of PAGN was measured over three, three-day periods in which the patient was treated once with sodium phenylacetate (NaPAA) and twice with sodium phenylbutyrate (NaPBA). Ex. 1012, 147. Table 1 of Brusilow '91 is reproduced below:

Table 1. *Urinary excretion of PAG during three 3-d periods during which 7½-y-old boy with carbamyl phosphate synthetase deficiency was treated with sodium salts of phenylacetate and phenylbutyrate (g/3 d)*

	Period I Na phenylacetate	Period II Na phenylbutyrate	Period III Na phenylbutyrate
g/3 d	30	36	42
Predicted PAG excretion (mmol)	190	193	225
Measured PAG excretion (mmol)	157	174	181
$\frac{\text{Measured PAG}}{\text{Predicted PAG}} \times 100$	83%	90%	80%
$\frac{\text{PAG-N}}{\text{Dietary N}} \times 100^{*}$	38.1%	42%	44%

* Also shown is a calculation of the percentage of dietary nitrogen excreted as PAG nitrogen (PAG-N).

> Table 1 compares the stoichiometry between phenylacetate or phenylbutyrate administration and urinary excretion of PAG. The amount of PAG excreted was a function of phenylacetate or phenylbutyrate dose; between 80 and 90% of the predicted amount of PAG synthesized is excreted. That these may be minimum excretion values is suggested by the coefficient of variation of the creatinine excretion over the 9 d, which was 14%. . . . Phenylacetate, phenylbutyrate, or total glucuronide excretion in the urine did not exceed 1% of the administered drug in any period.

Ex. 1012, 148.

According to Brusilow '91, "Table 1 demonstrates both that phenylbutyrate appears to be completely oxidized to phenylacetate and that phenylacetate is completely, or nearly so, conjugated with glutamine." *Id.* at

149. "That complete conjugation of the drugs occurs may be further adduced by the insignificant amount of unchanged drugs or their esters in urine and by the lack of accumulation in overnight fasting plasma." *Id.*

2. Sherwin '19 (Ex. 1016)[13]

Sherwin '19 discusses the results of a study of the conversion of phenylacetic acid (PAA) into urinary PAGN in humans. Varying doses of PAA were administered to a normal man (i.e., a healthy subject). Ex. 1016, 114. The subject ingested doses of PAA ranging from 2.5–15.0 grams, and each dose was taken all at once over three to five minutes. *Id.* The subject's urine was collected during twenty-four hour periods beginning at the time of ingestion of the dose. *Id.* Urinary PAGN was measured and a percent conversion from PAA to PAGN was calculated. *Id*. at 114, 116, Table I. The conversion rate ranged from about 50–67% for all doses, and from about 51–52% for doses of 10 grams or more. *Id.* Moreover, Sherwin '19 suggests that "[i]t is probable that more of the [PAGN] would have appeared in the urine after each dose of the acid, had the acid been ingested at regular intervals covering a period of 10 or 12 hours." *Id*. at 118.

3. Comte (Ex. 1025)

Comte discloses that metabolism of phenylbutyrate in humans produces PAGN, as well as another metabolite, phenylbutyrlglutamine

[13] Horizon refers to Exhibit 1016 as "Sherwin '19" in the Corrected Patent Owner Response, and we do likewise throughout this opinion to avoid confusion with Exhibit 2027, "Sherwin '33."

(PBGN). Ex. 1025, 581. Comte observed that "[t]he total recovery of the ingested dose of phenylbutyrate as identified urinary compounds (PA+PB+PAGN+PBGN) was 53.4 ± 4.5% after 8 h." in seven normal subjects. *Id.* at 589. Comte postulates that "part of the ingested PB is converted to metabolite(s) which have not yet been identified." *Id.* at 590.

4. Shiple (Ex. 1017)

Shiple discloses that PAA suppresses urea production in normal subjects, and glutamine is synthesized at the expense of urea nitrogen in the presence of PAA. Ex. 1017, 619, 623. Shiple further discloses that about 95% of a 10 g dose of phenylacetic acid was excreted as phenylacetyl glutamine in a 24-hour urine sample, while only about 78% was recovered after smaller doses. *Id.* at 623.

5. Analysis

Claim 1

In its Petition, Par contends that Brusilow '91 discloses all the steps of the claimed method of treating a patient suffering from a UCD by administering a PAA prodrug, except that the dose of the PAA prodrug administered during period III (*see* Ex. 1012, Table 1) was calculated based on a mean conversion of PAA prodrug to urinary PAGN of about 90% during period II, rather than about 60%, as recited in claim 1. Pet. 20.

Nevertheless, Par, relying on the testimony of its witness, Dr. Sondheimer, contends that a person of ordinary skill in the art, recognizing that "*Brusilow '91* involved only a single subject and observed a

range of conversion rates (80–90%)" in that single subject, would have looked to other references, such as Sherwin '19 and Shiple, for more information on conversion rates, "because each discusses the conversion of PAA to PAGN" (Pet. 17 (citing Ex. 1002 ¶¶ 42–45)). Par contends that these additional references, in turn, would have led one of ordinary skill in the art to expect a lower conversion rate of PAA prodrugs to urinary PAGN—i.e., about 60%, or as construed by Par, between 53–67%. *Id.* at 19.

In this regard, Dr. Sondheimer testifies, "[a]s seen in Table I of *Sherwin ['19]*, the conversion of PAA into urinary PAGN in normal subjects ranged from about 50–67% for all doses" and "at clinically relevant doses (10 grams or higher), *Sherwin ['19]* teaches a 51–52% conversion of PAA into urinary PAGN in normal subjects." Ex. 1002 ¶ 52 (citing Ex. 1016, 114, 116, Table I). According to Dr. Sondheimer, "[a] person of ordinary skill reviewing *Sherwin ['19]* would understand that the 51–52% figures are low" because "*Sherwin ['19]* further states that '[i]t is probable that more of the [PAGN] would have appeared in the urine after each dose of the acid, had the acid been ingested at regular intervals covering a period of 10 or 12 hours.'" *Id.* (citing Ex. 1016, 118).

Dr. Sondheimer further testifies that one of ordinary skill in the art would also understand that "*Sherwin ['19's]* figures are lower than one would expect to see in a UCD patient" because "UCD patients are not dosed with a single large dose . . . and by dosing smaller doses over the course of a day, the percent conversion of PAA to PAGN would be higher." Ex. 1002

¶ 53. In addition, Dr. Sondheimer testifies that Shiple "demonstrates that urea synthesis in normal people is suppressed when treated with PAA" (*id.* ¶ 54 (citing Ex. 1017, 620, Table II, 623)), and "a person of ordinary skill in the art would have understood from reading *Shiple* and *Brusilow '91* that a normal subject treated with PAA excretes urea at about the same rate as a UCD patient" (*id.* ¶ 55). According to Dr. Sondheimer,

> A person of ordinary skill in the art would have understood that the conversion rates observed in *Sherwin ['19]* for the normal subject would also be applicable to the UCD patient. Therefore, a person of ordinary skill in the art reading *Sherwin ['19]* in view of *Shiple* would have understood that the percentage conversion of administered PAA to PAGN observed in the healthy volunteer of *Sherwin ['19]* would also have been observed in a UCD patient.

Ex. 1002 ¶ 55.

Consequently, Par, supported by the testimony of Dr. Sondheimer, contends that one of ordinary skill in the art "would have used *Sherwin ['19's]* conversion rates to obtain the effective dosage of NaPBA to be administered [to a UCD patient] according to the method described in *Brusilow '91*." Pet. 22–23 (citing Ex. 1002 ¶ 56).

In its Corrected Patent Owner Response, Horizon contends that "prior to August 2008, and as early as the 1980s," urinary PAGN "was understood to be a measure of the amount of nitrogen excreted by patients taking PAA prodrugs" (Corr. PO Resp. 17 (citing Ex. 1018, 4:35–50)), and contrary to Petitioner's contentions, "there was a consensus in the prior art that conjugation of PAA to [urinary PAGN] was close to 100% in UCD patients

and healthy subjects" (*id.* (citing Ex. 1018, 2:53–67, 4:35–50; Ex. 1012, 149; Ex. 2025; Ex. 2026; Ex. 2027)).

According to Horizon, Dr. Sondheimer's assertion that "Dr. Brusilow 'averaged the observed PAGN excretion in the first two phases to determine an effective dosage based on a mean conversion of PAA prodrug to urinary PAGN of about 86% . . . conflicts with and has no support in the text of Brusilow '91." *Id.* at 36–37 (citing Ex. 1002, 32).

In particular, Horizon contends that "the purpose of th[e] experiment in Brusilow '91 was not to make dosing recommendations for the patient based on the results of the experiment." Corr. PO Resp. 38. Rather,

> the purpose of the experiment [described in Brusilow '91] was to study the "stoichiometry between oral sodium phenylacetate or sodium phenylbutyrate administration and PAG[N] excretion." It follows that Brusilow predetermined the dosages of sodium phenylacetate or sodium phenylbutyrate (10 g, 12 g and 14 g, respectively) to administer to the patient, expressly predicted a 100% conversion of PAA to PAGN (190 mmol, 193 mmol, and 225 mmol, respectively) and then measured the resulting UPAGN excretion for each period I, II and III.

Id. (citing Ex. 1012, 147–148, Table 1) (internal citation omitted).

According to Horizon, Dr. Sondheimer

> acknowledged at his deposition that Table 1 of Brusilow '91 predicts a 100% conversion of PAAto PAGN (190, 193, and 225 mmol of PAGN) for each of the 10 g, 12 g, 14 g doses of PAA prodrug to be administered to the patient during Periods I–III of the study.

Corr. PO Resp., 39 (citing Ex. 1012, 148, Table 1; Ex. 2012, 116:20–117:7, 117:18–118:1, 118:13–17, 118:18–119:2 ("Q. . . . 225 millimoles assume[s]

100 percent conversion of the 14-gram dose of PBA to PAGN, correct? A. Yes.")). Consequently, Horizon contends there is no support for Dr. Sondheimer's "assertion that the increased dose in Period III was 'calculated to create an excretion of 193 mmol of PAGN with the new assumption that PAGN excretion after the administration of NaPBA was lower.'" *Id.* (citing Ex. 1002, 19).

Horizon further contends that "Dr. Brusilow does not state or even imply that he calculated the dosage for Period III based on the average of the observed PAGN excretion for Periods I and II" (*id.* at 40), and "Dr. Sondheimer's argument that Dr. Brusilow calculated the dosage for Period III to target 193 mmol PAGN excretion is belied by basic math." *Id.* at 39; *see id.* at 38–39 for Horizon's calculations.

Moreover, Horizon argues that Petitioner's contention that it would have been obvious to calculate an effective dosage of PAA prodrug based on a mean conversion of PAA prodrug to urinary PAGN of about 60% "hinges on Dr. Sondheimer's unsupported misreading of Brusilow '91." *Id.* at 36. Specifically, Horizon argues that "Dr. Sondheimer's claim that a [person of ordinary skill in the art] would have understood Brusilow '91 to teach or suggest incomplete conversion of PAA to PAGN . . . directly conflicts with the conclusions of Brusilow '91 and with the prior art." *Id.* (citing Ex. 1002, 30–31). According to Horizon,

> Brusilow '91 concludes that, with respect to conversion of PAA prodrug to UPAGN in the UCD patient studied, "Table 1 demonstrates both that phenylbutyrate appears to be completely

> oxidized to phenylacetate and that phenylacetate is completely, or nearly so, conjugated with glutamine." Dr. Brusilow explains that the 80–90% of PAGN recovered for the individual patient studied "may be minimum excretion values" because "the coefficient of variation of the creatinine excretion over the 9 d [of the study] was 14%." Brusilow further explains "[t]hat *complete conjugation* of the drugs occurs may be further adduced by the insignificant amount of unchanged drugs or their esters in urine and by the lack of accumulation in overnight fasting plasma."

Id. at 37 (citing Ex. 1012, 148, 149, Table 2) (internal citations omitted).

Additionally, Horizon contends

> because Comte only collected urine for 8 hours following administration of a single dose of PAA, a POSA would have recognized (and Dr. Sondheimer agrees) that Comte makes no conclusions concerning the total amount of PAGN that would have been excreted over 24 hours, which would have allowed for complete metabolism.

Id. at 47 (citing Ex. 1025 at 585; Ex. 1002 ¶ 23; Ex. 2012, 34:1–35:6, 124:14–21).

Similarly, Horizon contends that Shiple would not have prompted one of ordinary skill in the art to determine an effective dosage of PAA prodrug based on mean conversion of PAA prodrug to urinary PAGN of about 60%, because Shiple "found that conversion of PAA to UPAGN was as high as 95% after a dose of 10 g of PAA in a healthy subject" (*id.* at 19), and that "the amount of PAGN recovered in urine varied depending on the dosage of PAA ingested and the time allowed for excretion before measurement" (*id.* at 18 (citing Ex. 1017, 619–620, 623)).

More importantly, Horizon contends that Dr. Sondheimer provides no reason why a person of ordinary skill in the art "would have completely ignored the data in Brusilow '91, which at a minimum demonstrated 80-90% conversion, and instead rel[ied] solely on data dating from seventy years earlier [i.e., Sherwin '19] in determining the 'true rate of conversion'" (*id.* at 44), especially as Dr. Sondheimer "concedes that [one of ordinary skill in the art] would have considered later publications concerning PAA to PAGN conversion to be relevant" (*id.* at 5).

In any case, Horizon contends that Sherwin '19's "conclusions concerning incomplete conversion of PAA conversion to UPAGN were later expressly overturned by Sherwin 1933, a publication by the same group." *Id.* at 43 (citing Ex. 2027, "Sherwin '33").[14] According to Horizon, Sherwin '33 evaluated

> Sherwin's original findings in 1919 concerning percentage conversion of PAA to PAGN and determined that "the apparently incomplete conjugation of phenylacetic acid with glutamine when it is ingested by the human subject in moderate doses may best be ascribed to the hydrolysis of phenylacetylglutamine when the urine containing it is evaporated on the water bath."

Corr. PO Resp. 45 (citing Ex. 2027, 675). Horizon contends that Sherwin '33 "concluded that Sherwin's earlier low recovery of PAGN was most

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[14] Anthony M. Ambrose, Francis W. Power, and Carl P. Sherwin, *Further Studies on the Detoxication of Phenylacetic Acid*, 101 J. BIOL. CHEM. 669–75 (1933) (Ex. 2027, "Sherwin '33")—submitted with Horizon's Patent Owner Response (Paper 25).

likely due to difficulties in extraction of PAGN intact from urine and not because of incomplete conversion." *Id.* Further, Horizon contends that Sherwin '33 concluded, based on additional experiments, that "[a]bout 95 per cent of the phenylacetic acid ingested in moderate doses by the human subject is detoxicated with glutamine . . .'." *Id.* at 45–46.

In addition, according to Horizon, Dr. Sondheimer's conclusions "conflict with the 2003 FDA-approved prescribing information for Buphenyl (sodium phenylbutyrate), which provides (consistent with Brusilow '91) that conversion of PAA to PAGN is complete or nearly complete (about 80–100%) in UCD patients and teaches that the dosage of Buphenyl should be calculated based [on] patient weight." Corr. PO Resp. 41 (citing Ex. 2025, 2, 6).[15]

In response, Par contends "[w]ithout any expert testimony of its own, Patent Owner faults Dr. Sondheimer for both ignoring the conversion of PAA to UPAGN reported in *Brusilow '91*" and "determining that *Brusilow '91* adjusted dosages to account for incomplete conversion." Supp. Reply 2 (citing Ex. 2012, 49:10–14, 71:24–72:13, 120:7–25).

Par contends that Brusilow '91 calculated percent yield to assess the extent to which UPAGN was actually scavenging nitrogen in place of urea—a typical method for quantifying the extent to which a chemical reaction has

[15] "BUPHENYL® Prescribing Information (2003) (Ex. 2025)—submitted with Horizon's Patent Owner Response (Paper 25).

occurred. Reply 8. "Therefore, a POSA would not view *Brusilow '91's* use of the theoretical yield of UPAGN (which he called 'Predicted PAG') to imply that *Brusilow '91* literally anticipated obtaining 100% conversion in his study." *Id.* "In order to derive an experimental dose of NaPBA that would be expected to excrete the same amount of waste nitrogen as urea, *Brusilow '91* calculated the theoretical yield to use a comparator to the 'actual yield' that was observed in the laboratory. *Id.* (citing Ex. 1012, 147). "Although *Brusilow '91* calculated a theoretical 100% conversion value as a necessary step in performing his yield calculations, the *actual* experimental finding was 80–90% conversion—not 100%." *Id.* at 8–9.

Par further contends that a person of ordinary skill in the art would have recognized that Sherwin '19 "reported a conversion of PAA to UPAGN of about 50% to 67%." Reply 12 (citing Ex. 1016, 116, Table I, Ex. 1002 ¶ 38). Par contends that Sherwin '33 never mentions Sherwin '19, and Patent Owner provides no expert analysis of how Sherwin '33 supposedly discredits Sherwin '19, and has failed to show that Sherwin '19 and Sherwin '33 actually present conflicting information. *Id.* at 13.

Having considered the respective positions of the parties, together with the evidence submitted with the Petition and the Patent Owner Response, we conclude that Par has not met its burden of proving by a preponderance of the evidence that claims 1, 3, 4, 7, 8, 10, 12 are unpatentable over Brusilow '91, Sherwin '19, Comte, and Shiple. Our reasoning is as follows.

First, regardless of whether one of ordinary skill in the art would have understood Brusilow ’91 to teach 80% to 90% conversion, or something closer to 100% conversion, we credit Dr. Sondheimer’s testimony that one of ordinary skill in the art would have sought out prior art references “discuss[ing] the conversion of PAA to PAGN” (Ex. 1002 ¶ 42) if only “[b]ecause *Brusilow ’91* involved a single subject and observed a range of conversion rates” (*id.* at 43).

As for the parties’ diametrically opposed views on whether Dr. Brusilow preselected all three doses administered to the patient, or adjusted the dose in Period III to account for the 90% conversion observed in Period II (*see* Ex. 1012, Table 1), we find we need not resolve the controversy, because, even if we accept that the dose in Period III was adjusted based on the results in Period II, it would not change our ultimate disposition of the case.

Nevertheless, we are not persuaded that Par has established that the prior art it relies on presents a balanced picture of the state of the art at the time of the invention. Horizon, with its patent Owner Response, provided evidence that at least some references subsequent to Sherwin ’19 reported conversion rates of 80–100%. Horizon contends essentially that Sherwin ’33 reports a percent conversion more consistent with Brusilow ’91’s observations than Sherwin ’19’s. *See* Corr. PO Resp. 5. For example, Horizon points out that Sherwin ’33 explicitly discloses that “[a]bout 95 per cent of the phenylacetic acid ingested in moderate doses by the human

subject is detoxicated with glutamine, and about 5 percent with glucuronic acid." Corr. PO Resp. 19 (citing Ex. 2027, 675). Similarly, Horizon points out that Exhibit 2025, also provided by Horizon with its Patent Owner Response, and purporting to be "Prescribing Information as of August 2003" (Ex. 2025, 7) for Buphenyl (sodium phenylbutyrate) tablets and powder, states that, in normal adults, "[a] majority of the administered compound (approximately 80 – 100 %) [is] excreted by the kidneys within 24 hours as the conjugation product, phenylacetylglutamine." Corr. PO Resp. 22, 49 (citing Ex. 2025, 2). Additionally, Horizon notes that Exhibit 2025 teaches "that the dosage of Buphenyl should be calculated based on patient weight." Corr. PO Resp. 41 (citing Ex. 2025, 6 ("The usual total daily dose of BUPHENYL Tablets and Powder for patients with urea cycle disorders is 450 – 600 mg/kg/day in patients weighing less than 20 kg, or 9.9 – 13.0 g/m^2/day in larger patients.")).

Par criticizes Horizon's assertion that Sherwin '33 discredits Sherwin '19 as unsupported, and we agree. But that criticism does not address what the plain language of the reference states about the conversion of phenylacetic acid to urinary PAGN. Again, Horizon contends that Sherwin '33 concludes that "[a]bout 95 per cent of the phenylacetic acid ingested in moderate doses by the human subject is detoxicated with glutamine, and about 5 percent with glucuronic acid." Corr. PO Resp. 19 (citing Ex. 2027, 675).

Nor does Par address the substance of Exhibit 2025. As discussed above, Exhibit 2025 states that, in normal adults, "[a] majority of the administered compound (approximately 80 – 100 %) [is] excreted by the kidneys within 24 hours as the conjugation product, phenylacetylglutamine." Ex. 2025, 2. Again, this disclosure appears to be consistent with Brusilow '91's observations, rather than those reported in Sherwin '19.

In the absence of analysis of these subsequent references, we conclude that Par has not established that the prior art cited in its challenge adequately represents the state of the art at the time of the invention. Moreover, we note that Horizon points out that Shiple, relied on by Par for its teaching that normal subjects and UCD patients fed PAA experience suppressed urea production (Pet. 17 (citing Ex. 1017, 620, 623; Ex. 1002 ¶ 4), additionally discloses that about 95% of a 10 g dose of phenylacetic acid was excreted as phenylacetyl glutamine in a 24-hour urine sample. Corr. PO Resp. 32 (citing Ex. 1017, 623, Table II).

Consequently, we determine that Par has not established by a preponderance of the evidence that one of ordinary skill in the art would have had a reason to calculate the dose of PBA or HPN-100 for a UCD patient based on a mean conversion rate of about 60% (even if we accept that about 60% encompasses a mean conversion rate of 53–67%, as Par argues), given the apparent correspondence between Brusilow '91's observation of an 80% to 90% conversion rate, and the similar stated observations in Exhibits 2027 and 2025 (95% and 80–100 %,

respectively)—not to mention Shiple's disclosure of a 95% conversion rate for a 10 g dose of PAA.

Again, Petitioner bears the burden of proving unpatentability of the challenged claims in an *inter partes* review, and that burden never shifts to Patent Owner. Obviousness is resolved based on underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). It is not enough to address only those teachings that support the challenge, when there is evidence of record on its face at odds with the underlying premise of the challenge. *See e.g.*, Corr. PO Resp. 5, 15, 22, 32, 49 (discussing Exs. 2025, 2027, 1017).

We find that Par has failed to carry its burden of proving by a preponderance of the evidence that claim 1 would have been unpatentable over the prior art.

Claim 8

With respect to independent claim 8, Petitioner's contentions and cited evidence, discussed on pages 23 through 27 of the Petition, are essentially the same as for claim 1, and we find that Par has failed to carry its burden with respect to claim 8 for the same reason discussed in connection with claim 1.

Dependent Claims 3, 4, 7, 10, and 12

Claims 3 and 12 depend from claims 1 and 8, respectively, and require that administration of the effective initial dosage of PAA prodrug produces a normal plasma ammonia level in the patient. Par cites Brusilow '91's teaching that treatment with NaPBA produces a mean plasma ammonium level within the normal range as meeting this limitation (Pet. 27 (citing Ex. 1012, 148–149)).

Claim 4 depends from claim 1 and recites that calculation of the target PAGN output takes into account the patient's dietary protein intake. Par asserts that Brusilow '91 takes dietary protein intake into account in calculating the dosage for the PAA prodrug (Pet. 28 (citing Ex. 1012, 147)).

Claims 7 and 10 depend from claims 1 and 8, respectively, and require that the pharmaceutically acceptable salt of PBA is sodium PBA. Par cites Brusilow '91's disclosure of treating the patient with NaPBA as meeting this limitation (*id.* at 28 (citing Ex. 1012, 147–148, Table 1)).

Although we find that the record supports Par's contention that Brusilow '91 discloses the particular limitations recited by these dependent claims, we find that Par has failed to carry its burden with respect to claims 3, 4, 7, 10, and 12 for the same reasons discussed in connection with claim 1.

6. Conclusion

We conclude that Petitioner has not demonstrated by a preponderance of the evidence that claims 1, 3, 4, 7, 8, 10, and 12 are unpatentable over Brusilow '91, Sherwin '19, Comte, and Shiple.

E. Claim 5—Asserted Obviousness over Brusilow '91, Sherwin '19, Shiple, and Fernandes

Claim 5 depends from claim 1 and requires that the target PAGN output take into account the patient's dietary protein intake.

Fernandes discusses diagnosis and treatment of inborn metabolic diseases, including UCDs. Ex. 1011, 219–220. Fernandes discloses a guideline for the management of patients with UCDs, which includes the administration of nitrogen scavenging drugs such as phenylbutyrate. *Id.* at 219, Fig. 17.2. Fernandes teaches that nitrogen scavenging drugs reduce the load on the urea cycle in patients with UCDs. *Id.* at 219. Fernandes further discusses general aspects of therapy and, specifically, that the balance of diet and medicine is important (*id.* at 219), and that protein intake of patients varies considerably and that residual enzyme activity of the UCD patient must be taken into account during treatment (*id.* at 219–220).

Par contends that the subject matter of claim 5 would have been obvious because a person of ordinary skill in the art "reading *Brusilow '91* and *Fernandes* would have considered the residual enzyme activity of the

patient, and therefore his or her residual urea synthesis capacity." Pet. 30 (citing Ex. 1002 ¶ 76).

Although we agree with Par that one of ordinary skill in the art would have considered a patient's residual enzyme activity in determining an effective dosage of phenylbutyrate, we determine that Par has not demonstrated by a preponderance of the evidence that claim 5 would have been obvious over Brusilow '91, Sherwin '19, Shiple, and Fernandes, for the same reasons discussed in connection with claim 1.

F. Claims 2 and 9—Asserted Obviousness over Brusilow '91, Sherwin '19, Shiple, and the '647 Patent

Claims 2 and 9 depend from claims 1 and 8, respectively, and recite that target urinary PAGN output is determined as a ratio of the concentration of urinary PAGN to urinary creatinine.

Par notes that "*Brusilow '91* teaches measuring creatinine levels in the UCD patients treated with phenylacetate or NaPBA (Ex. 1012 at 148) but does not expressly mention determining target urinary PAGN output as a ratio of urinary PAGN to urinary creatinine." Pet. 33.

However, Par cites the '647 patent as disclosing measuring urinary creatinine, urinary PAGN, and total urinary nitrogen in a UCD patient after PAA administration, and as disclosing using the ratio of urinary PAGN to creatinine as a convenient measure for an increase in urinary excretion of nitrogen that does not require collection of total daily urine. Pet. 33 (citing Ex. 1018, 3:53–4:6, 4:35–50).

Par contends that one of ordinary skill in the art would have recognized that target urinary PAGN could conveniently be determined as a ratio of urinary PAGN to urinary creatinine. Pet. 33.

We agree with Par that one of ordinary skill in the art would have recognized that target urinary PAGN could conveniently be determined as a ratio of urinary PAGN to urinary creatinine, but again, we determine that Par has not demonstrated by a preponderance of the evidence that claims 2 and 9 would have been obvious over Brusilow '91, Sherwin '19, Shiple, and the '647 patent for the same reasons discussed in connection with claim 1.

G. Claims 6 and 11—Asserted Obviousness over Brusilow '91, Sherwin '19, Shiple, Kasumov, and the '979 Patent

Claims 6 and 11 depend from claims 1 and 8, respectively, and recite that the PAA prodrug is HPN-100.

Par acknowledges that none of Brusilow '91, Sherwin '19, or Shiple discloses HPN-100 as the nitrogen scavenging drug.

However, Par argues that it would have been obvious to substitute HPN-100 for NaPBA in Brusilow '91's method because Kasumov discloses that NaPBA may be toxic at high doses (Pet. 34 (citing Ex. 1015, 10, 13)), and because the '979 patent also discloses HPN-100, and teaches that such drugs are useful to treat patients with diseases of nitrogen accumulation.

For the reasons discussed above in connection with claim 1, we determine that Par has not demonstrated by a preponderance of the evidence

that claims 6 and 11 would have been obvious over Brusilow ’91, Sherwin ’19, Shiple, Kasumov, and the ’979 patent.

H. The Motions to Exclude

Both Horizon and Par filed motions to exclude evidence of the other party. Papers 36, 38.

Specifically, Horizon seeks to exclude certain portions of Dr. Sondheimer’s cross-examination testimony and Exhibits 1031–1033. Paper 36, 1–2. Horizon acknowledges that “[i]n its Reply (Paper No. 0030), Petitioner has not attempted to rely upon the portions of Dr. Sondheimer’s deposition transcript or the documents Patent Owner seeks to exclude.” Paper 36, 2–3. In addition, Horizon acknowledges that Exhibits 1031–1033 have not been made of record in this proceeding. *See* Paper 36, 12–13.

Because Horizon cannot point to where Par relies on the testimonial evidence, Par having apparently not relied on it, we have no basis on which to determine whether the evidence is inadmissible and no basis on which to exclude it. Furthermore, because Exhibits 1031–1033 have not been made of record in this proceeding, they cannot be excluded. Accordingly, we dismiss Horizon’s motion as moot.

Par argues that Horizon’s Exhibit 2027 (Sherwin ’33) “should be excluded as lacking relevance” under Federal Rules of Evidence 401 and 402, and under 403 “to prevent confusion of the issues.” Paper 38, 1–2. Par argues essentially that Horizon offers Sherwin ’33 for the purpose of discrediting Sherwin ’19 (Ex. 1016), but Sherwin ’33 never mentions

Sherwin ’19, and there is no evidence of record that Sherwin ’33 replicated the studies in Sherwin ’19. Nevertheless, we note that Horizon also cites Sherwin ’33 as “conclude[ing] that ‘[a]bout 95 per cent of the phenylacetic acid ingested in moderate doses by the human subject is detoxicated with glutamine [to PAGN] and about 5 per cent with glucuronic acid.’” Corr. PO Resp. 19 (citing Ex. 2027, 675). This latter disclosure is directly relevant to the issues raised by this *inter partes* review. Accordingly, Par’s motion is denied with respect to Exhibit 2027.

Par also argues that Exhibit 2028 (the joint claim construction chart submitted in the pending district court litigation with respect to the claim term “about 60%”) also should be excluded as lacking relevance under Federal Rules of Evidence 401 and 402, and under 403 to prevent confusion of the issues. Paper 38, 3.

As we did not rely on the district court claim construction, Par’s motion is dismissed as moot with respect to Exhibit 2028.

Finally, Par argues that Horizon relies on attorney argument to rebut Petitioners’ challenges, effectively providing impermissible expert evidence, which Petitioners seek to exclude. Paper 38, 3–12. We dismiss Par’s motion with respect to this issue because attorney argument is not evidence. *See Meitzner v. Mindick*, 549 F.2d 775, 782 (CCPA 1977) (“Argument of counsel cannot take the place of evidence lacking in the record.”). Therefore, Petitioners’ argument is improperly presented in a motion to exclude evidence.

III. CONCLUSION

We find that Par has failed to carry its burden of proving by a preponderance of the evidence that claims 1–12 would have been unpatentable over the prior art.

Horizon's Motion to Exclude is dismissed as moot.

Par's Motion to Exclude is denied-in-part and dismissed-in-part.

IV. ORDER

For the reasons given, it is

ORDERED that claims 1–12 have not been shown to be unpatentable by a preponderance of the evidence;

FURTHER ORDERED that, because 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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