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Paper 63
Date: May 31, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THORNE RESEARCH, INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

IPR2021-00268
Patent 8,383,086 B2

Before SUSAN L.C. MITCHELL, ROBERT A. POLLOCK, and JOHN E. SCHNEIDER, *Administrative Patent Judges.*

SCHNEIDER, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining the Challenged Claim Unpatentable
35 U.S.C. § 318 (a)

Denying Petitioner's Motion to Exclude
Denying Patent Owner's Motion to Exclude
37C.F.R. § 42.64

I. INTRODUCTION

A. Background and Summary

Thorne Research, Inc. ("Petitioner") filed a Petition requesting *inter partes* review of claim 2 of U.S. Patent No. 8,383,086 B2 (Ex. 1001, "the '086 patent"). Paper 2 ("Pet."). The Trustees of Dartmouth College ("Patent Owner") filed a Preliminary Response contending that the Petition should be denied. Paper 10 ("Prelim. Resp."). During a telephone conference held on March 23, 2021, the panel authorized additional briefing on whether certain references were the works "by another" as the term is used in 35 U.S.C. § 102(a).[1] Ex. 1024, 23–24. In accordance with such authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response. Paper 15 ("Pet. Reply").We instituted *inter partes* review on June 10, 2021. Paper 21 ("Dec.")

Patent Owner then filed a response on September 21, 2021. Paper 27 ("PO Resp."). Petitioner then filed a Reply. Paper 34 ("Reply"). Patent Owner filed a sur-reply. Paper 36 ("Sur-Reply"). An oral hearing was conducted on March 15, 2022. A copy of the transcript has been made of record. Paper 62. ("Tr.")

We have jurisdiction under 35 U.S.C. § 6. This is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of the claim on which we instituted trail. Based on the complete record before us, we determine that Petitioner has shown, by a preponderance of the evidence, that claim 2 is unpatentable. In addition, for the reasons explained below, we

[1] 35 U.S.C. §§ 102 and 103 was amended by the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011). Because the '086 patent was filed before the effective date of the relevant amendment, the pre-AIA version of §§ 102 and 103 applies.

deny both Petitioner's Motion to Exclude Evidence and Patent Owner's Motion to Exclude Evidence.

B. Real Parties in Interest

Thorne Research, Inc. identifies itself as the real party-in-interest. Pet. 33. The Trustees of Dartmouth College identifies itself as the real parties-in-interest. Paper 5, 2.

C. Related Matters

Petitioner represents that a petition for *inter partes* review was filed challenging all claims (1–5) of the '086 patent in IPR2017-01795 ("the '1795 IPR"). Pet. 1, 33. We issued a final decision holding that all claims were unpatentable except claim 2. Ex. 1018. That decision was affirmed by the Federal Circuit on March 6, 2020. Ex. 1004 1–2.

Petitioner also represents that a petition for *inter partes* review was filed by a third party challenging related patent U.S. Patent No. 8,197,807 "the '807 patent") in IPR2017-01796. Pet. 34. We denied institution of *inter partes* review of the petition in IPR2017-01796. *Elysium Health, Inc. v. Trustees of Dartmouth College*, IPR2017-01796, Paper 9 (PTAB Jan. 18, 2018).

Petitioner represents that it filed a petition for *inter partes* review of the related '807 patent in IPR 2021-00491, filed February 1, 2021. Paper 18. We instituted trial in this proceeding on August 12, 2021 and the case is awaiting decision.

Patent Owner states that the '086 patent is the subject of an infringement action in the United States District Court for the District of Delaware in a case captioned *ChromaDex, Inc., et al. v. Elysium Health, Inc.,* Case No. 18-cv-01434 (D. Del.). Paper 5, 3. Patent Owner further states the '086 patent is also subject to a patent misuse counterclaim in

ChromaDex, Inc. v. Elysium Health, Inc., Case No. 16-cv-02277-CJC (C.D. Cal.). *Id.* Patent Owner has also indicated that it has filed an action against Petitioner for infringement of the ’086 patent and the ’807 patent in *ChromaDex, Inc., et al. v. Thorne Research, Inc.*, Case No. 1:21-cv-04241 (S.D.N.Y.). (Paper 19).

Petitioner represents that the district court in the Delaware action granted Elysium Health’s Motion for Summary Judgment of Invalidity of claim 2 of the ’086 patent and claims 1, 2, and 3 of the ’807 patent as invalid under 35 U.S.C. § 101 for claiming patent ineligible subject matter. Paper 32, 2. Patent Owner has appealed the district court’s decision. *Id.*

D. The ’086 Patent

The ’086 patent issued on February 26, 2013, with Charles M. Brenner listed as the inventor. Ex. 1001, codes (45), (75). The ’086 patent issued from an application filed on April 12, 2012, and on its face, claims priority to an application filed April 20, 2006. *Id.* at code (63). The Specification of the ’807 patent includes the following claim of priority:

> This application is a continuation of U.S. patent application Ser. No. 11/912,400 filed Nov. 20, 2007 now U.S. Pat. No. 8,197,807, which is the National Stage of International Application No. PCT/US2006/015495 filed Apr. 20, 2006, which claims benefit of priority to U.S. patent application Ser. No. 11/113,701 filed Apr. 25, 2005, the teachings of which are incorporated herein by reference in their entireties.

Ex. 1001 col. 1, ll. 7–13.

As discussed in Section II.D, below, the parties disagree as to whether the ’086 patent is entitled to an earlier priority date of April 25, 2005.

The ’086 Patent relates generally to the production of nicotinamide riboside (“NR”) and compositions containing NR. Ex. 1001, col. 4, ll. 1–16.

The ’086 patent also describes the use of compositions containing an effective amount of NR to treat various disorders stemming from a deficiency in NR. *Id.* at col. 4, ll. 17–29. The compositions can be in the form of a dietary supplement, such as ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, and food. *Id.* at col. 4, ll. 14–16, col. 29, ll. 43–46.

E. Illustrative Claims

Claim 2 is the only challenged claim before us. Claim 2 depends from claim 1 and therefore incorporates all of the limitations of claim 1. 35 U.S.C. § 112, fourth paragraph (2006). Claims 1 and 2 are reproduced below.

> 1. A pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration.
> 2. The pharmaceutical composition of claim 1, wherein the nicotinamide riboside is isolated from a natural or synthetic source.

Ex. 1001, col. 53, ll. 38–43.

F. Evidence

Petitioner relies on the following references:

Stamler et al., WO 02/055018 A2, published July 18, 2002. (“Stamler”) (Ex. 1006).

Brenner, et al., WO 2005/077091 A2, published August 25, 2005. (“Brenner”) (Ex. 1007).

Bieganowski et al., *Discoveries of Nicotinamide Riboside as a Nutrient and Conserved NRK Genes Establish a Preiss-Handler Independent Route to NAD$^+$ in Fungi and Humans*, 117 Cell 495 (May 14, 2004) (“Bieganowski”) (Ex. 1008).

Petitioner also relies on the Declarations of Dr. Samie Jaffrey, M.D., Ph.D. (Ex. 1002 and Ex. 1038). Patent Owner relies on the Declaration of Mansoor M. Amiji, Ph.D., R.PH. (Ex. 2014). Patent Owner also relies on the Declarations of Drs. Brenner and Bieganowski. (Exs. 2002, 2003, 2015, 2021, and 2022).

G. Prior Art and Asserted Grounds

Petitioner asserts that claim 2 would have been unpatentable on the following grounds:

Claim Challenged	35 U.S.C. §	Reference(s)/Basis
2	102(b)	Stamler
2	103(a)	Stamler
2	102(b)	Bieganowski
2	103(a)	Bieganowski
2	102(a) or (e)	Brenner

H. The Prior Proceeding

As noted above, the '086 patent was the subject of a prior IPR proceeding, the '1795 IPR, initiated by a third party, Elysium Health, Inc., on July 17, 2017. Elysium requested review of original claims 1–5 of the '086 patent on grounds that: (1) claims 1–5 were anticipated under 35 U.S.C. § 102(b) by Goldberger et al., *A Study of the Blacktongue-Preventive Action of 16 Foodstuffs, with Special Reference to the Identity of Blacktongue of Dogs and Pellagra of Man*, 43 Pub. Health Reports 1385 (1928) (Ex. 1011, "Goldberger"); and (2) claims 1–5 were anticipated under § 102(b) by Goldberger and Tanner*, A Study of the Treatment and Prevention of Pellagra*, 39 Pub. Health Reports 87 (1924) (Ex. 1012, "Goldberger/Tanner"). *See* Ex. 1018, 5. We granted Elysium's petition on January 29, 2018. *Id*. at 2.

In our Final Written Decision, we concluded that Elysium had demonstrated by a preponderance of the evidence that claims 1 and 3–5 were unpatentable as anticipated by both Goldberger and Goldberger/Tanner. *Id*. at 42. We also concluded that Elysium had not demonstrated that claim 2 was unpatentable. *Id*. Central to our holding with respect to claim 2 was our finding that Elysium had not demonstrated that the compositions disclosed in Goldberger and Goldberger/ Tanner comprised "isolated" NR, as we construed that claim term. *Id*. at 12–14, 26–27; *see also id.* at 12–15 (construing "isolated" NR to mean "that the nicotinamide riboside is separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition").

II. ANALYSIS

A. Collateral Estoppel

Before we proceed with our analysis of claim 2, we must address the issue of collateral estoppel. In our Decision to Institute, we concluded that collateral estoppel precluded the relitigation of the patentability of the independent claims, including independent claim 1 from which presently challenged claim 2 depends. Dec. 13. We found that the present proceeding is limited to the requirement in claim 2 that the NR be isolated. *Id.*

In its Response, Patent Owner contends that we erred in finding that it was estopped from relitigating the limitations of claim 1. PO Resp. 34–38. Patent Owner contends that collateral estoppel is not applicable to the present proceeding because Petitioner has not made the requisite showing for collateral estoppel to apply. *Id.* at 35–36. Patent Owner argues that because the present proceeding involves different prior art, the identical issue was not litigated in the prior proceeding. *Id.* at 37. Thus, Patent Owner

contends that collateral estoppel does not apply as claim 2 presents a materially different issue of patentability than that addressed with respect to claim 1. *Id.* at 37–38. Patent Owner contends that collateral estoppel does not preclude Patent Owner from litigating whether Stamler teaches all the elements of claim 2, including those incorporated from claim 1. *Id.* at 38; Sur-Reply 15.

Petitioner responds that while this proceeding does involve different art, collateral estoppel prevents Patent Owner from relitigating "issues, including issues of fact, that were previously before the board." Reply 15 (emphasis omitted).

We have considered the arguments presented by the parties and find the issue of collateral estoppel moot because we find Petitioner has established by a preponderance of the evidence that Stamler teaches all of the elements of claim 2 including the limitations of claim 1.

B. Legal Standards

1. Burden of Proof

At this stage of the proceeding, the burden rests on the petitioner to establish by a preponderance of the evidence that claim 2 is unpatentable. 35 U.S.C. § 316(e) (2008).

2. Anticipation[2]

"Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." *Gechter v. Davidson,* 116 F.3d 1454, 1457 (Fed. Cir. 1997). "[U]nless a reference discloses within the four corners of the document not only all of the

[2] As noted above, the pre-AIA provisions of 35 U.S.C. apply to the '086 patent.

limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc*., 545 F.3d 1359, 1371 (Fed. Cir. 2008).

3. Obviousness

The question of obviousness is resolved on the basis of 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) where in evidence,[3] so-called secondary considerations. *Graham v. John Deere Co.,* 383 U.S. 1, 17–18 (1966). If the differences between the claimed subject matter 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, the claim is unpatentable under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406 (2007).

A proper § 103 analysis requires "a searching comparison of the claimed invention—including all its limitations—with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995).

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.,* 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have

[3] Patent Owner does not present evidence of secondary considerations in this proceeding.

selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.*

C. Effective filing date of the '086 Patent

Petitioner contends that the '086 patent is not entitled to a priority date any earlier than April 20, 2006, the filing date of U.S. Application No. 11/912,400 ("the '400 application"), which is the national stage application of International Patent Application No. PCT/US2006/015495 ("the '495 PCT application"). Pet. 6. Petitioner contends that operation of both the Paris Convention and the Patent Cooperation Treaty ("PCT") precludes any claim of priority earlier than that date. Petitioner contend that under the Paris Convention and the PCT, Patent Owner may not claim priority back to US Application No. 11/113,701 ("the '701 application") as the '701 application does not meet the requirements of the PCT or the Paris convention. *Id.* at 7–14.

Patent Owner contends that the recited provisions of the Paris Convention and PCT are not applicable to the '086 patent, as all of the '086 patent's claim of priority, including the claim for priority to PCT applications, arise under 35 U.S.C. § 120 and not 35 U.S.C. § 119. Prelim. Resp. 17–20. Patent Owner contends the '086 patent meets all of the requirements of 35 U.S.C. § 120, and as such, Patent Owner contends the '086 patent is also entitled to claim priority to the April 25, 2005 filing date of U.S. Application No. 11/113,701 ("the '701 application"). *Id*. at 25.

In our Decision to Institute, we agreed with Patent Owner that the '086 patent was entitled to a filing date of April 25, 2005. Dec. 17. We based our decision of the fact that the '086 patent meets the requirements of 35 U.S.C. § 120. We found that the prior application supported the limitations recited in claims 2; Dr. Brenner was listed on all the prior

applications; there was co-pendency for the applications; and the specification of the ’086 patent specifically identified the earlier applications. Dec. 16–17.

In its Reply, Petitioner renews its contention that the ’086 patent is not entitled to a filing date earlier than April 20, 2006. Reply 1. In support of its contention, Petitioner points to the cover sheet of the ’086 patent, which does not state that the ’086 patent claims priority to the April 25, 2005 filing date of the ’701 application, but rather only recites a priority claim to the ’495 PCT application, which was filed on April 26, 2006, and which, in turn, claims priority back to the ’701 application. *Id.* at 1–2. Petitioner contends that Patent Owner requested a corrected filing receipt for the ’086 patent that recites a claim of priority back to the April 25, 2005 filing date of the ’701 application, but the request was denied. *Id.* at 2. Petitioner contends

> The priority grants by the USPTO for both the ’086 and ’807 patents are consistent with Article 4 of the Paris Convention. PO was put on notice through the corrected filing receipts issued by the USPTO and has failed to take any corrective action. IPR2015-00414, Paper 34, 15 (noting, in denying priority, PO could have sought certificate of correction or reissue, but failed to do so); *Braun v. Becton, Dickinson and Co.*, 1:16-cv-411-RGA, 7 (D. Del. June 9, 2017) (citing IPR2015-00414 for same proposition). PO’s arguments otherwise should be rejected.

Id.

In reply, Patent Owner contends that Petitioner is improperly raising a new argument. Sur-reply 1. Patent Owner contends the ’086 patent makes a proper claim of priority under 35 U.S.C. § 120, and the Board’s initial decision regarding the filing date of the ’086 patent was correct. *Id* at 2.

We have considered the arguments presented by the parties and find that our initial decision on priority was correct. The ’086 patent claims

priority to domestic applications involving either US patent applications or a PCT application designating the United States. *See* Ex. 1001, col. 1, ll. 7–13.

> Under § 120, a patent is entitled to the priority date of an earlier filed application if (1) the written description of the earlier filed application discloses the invention claimed in the later filed application sufficient to satisfy the requirements of § 112; (2) the applications have at least one common inventor; (3) the later application is filed before the issuance or abandonment of the earlier filed application; and (4) the later application contains a reference to the earlier filed application.

In re NTP, Inc., 654 F.3d 1268, 1277 (Fed. Cir. 2011); *see also* 35 U.S.C. § 120 . As discussed above and in our Decision to Institute, the ’086 patent meets this criterion.

While we agree with Petitioner that the face of the ’086 patent does not include a citation of the ‘701 application, the specification does contain a clear claim of priority back to the ’701 application. Ex. 1001, col. 1. ll. 7–13; Ex. 1004 1.

Petitioner cites to *Apple Inc. v. e-Watch, Inc.,* IPR2015-00414, Paper 34 (PTAB June 22, 2016) to support its contention that Patent Owner’s failure to seek correction of the priority claim on the face of the ’086 patent is fatal to Patent Owner’s claim that the filing date should stretch back to April 25, 2005. *See* Reply. 2. The facts in *Apple* are different that the present case. In *Apple*, the priority claim in the specification misidentified the application as a divisional of a prior application when in fact it was not. *Apple*, Paper 35 7. The Board found this error in identifying the relationship of the applications was fatal to the patent owner’s priority claim. *Id.* at 17.

This is in contrast to the present case where the specification properly identifies each of the prior applications and states the proper relationship. Ex, 1001, col. 1, ll. 7–13. As the Board in *Apple* pointed out, pre-AIA

35 U.S.C. § 120 stated an application is entitled to the benefit of the filing date of the first application "if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application." *Apple*, Paper 34, 9 (quoting 35 U.S.C. § 120). In the present case, the specification contains a specific reference to the chain of applications extending back of the '701 application with appropriate co-pendency of the applications in the chain.

We are not persuaded by Petitioner's argument that the Office's refusal to grant Patent Owner's request for a corrected filing receipt confirms Petitioner's contention that the '086 patent is limited to an April 20, 2006 filing date. Reply 2. The Office did not unequivocally state that the '086 patent was not entitled to a priority date of April 26, 2005. Rather, in responding to Patent Owner's request for a corrected filing receipt the office indicated that it could not comply with the request because Patent Owner failed to submit a new application data sheet with the desired benefit claims. Ex. 1004 130.

Based on the foregoing, we confirm our earlier decision that the '086 patent is entitled to a filing date of April 25, 2005

D. Level of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.,* 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co*., 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc*., 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner contends that the definition of a person of ordinary skill in the art offered by Patent Owner in the '1795 IPR, which, as noted above, also involved the '086 patent, should apply to this proceeding, namely "someone with a Ph.D. in biochemistry or similar field in the pharmaceutical sciences, with familiarity and experience with pharmacokinetics." Pet. 33. Patent Owner does not dispute Petitioner's definition and, indeed, Patent Owner's expert, Dr. Amiji, used the same definition in his analysis. Ex. 2014 ¶ 21. For purposes of this Decision, therefore, we adopt Petitioner's description.

We also note that the applied prior art reflects the appropriate level of skill at the time of the claimed invention and supports Petitioner's definition. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

E. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.* Furthermore, we need only construe the claims to the extent necessary to determine the patentability of the challenged claims. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only 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))).

The parties have proposed constructions for three terms: "pharmaceutical composition comprising nicotinamide riboside"; "carrier"; and "isolated." We address each of these terms in turn.

1. Pharmaceutical Composition

Both Petitioner and Patent Owner argue that we should adopt the same construction for this term as we did in the '1795 IPR. Pet. 35–36; Prelim. Resp. 28. Absent any argument or evidence to the contrary, we apply the same construction in this proceeding that we applied in the '1795 IPR for the reasons set forth in that proceeding: "a composition, including a food composition, which contains NR as an active agent in an amount effective for the treatment or prevention of a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis." Ex. 1018, 10–11.

2. Carrier

Both Petitioner and Patent Owner argue that we should adopt the same construction for this term as we did in the '1795 IPR. Pet. 36; Prelim. Resp. 29. Absent any argument or evidence to the contrary, we apply the same construction in this proceeding that we applied in the '1795 IPR for the reasons set forth in that proceeding: "[A] liquid or solid filler, diluent, excipient, or solvent encapsulating material, [that] is involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient." Ex. 1018, 14–15.

3. Isolated

Initially, both Petitioner and Patent Owner argued that we should adopt the same construction for the term "isolated" NR as we did in the

'1795 IPR. Pet. 36–38; Prelim. Resp. 30–31. In our Decision to Institute, we adopted the construction we applied in the '1795 IPR proceeding "the nicotinamide riboside is separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition." Dec. 19.

In its Response, however, Patent Owner contends we need to construe the entire phrase "is isolated from a natural or synthetic source" and that the term should be given its plain and ordinary meaning. PO Resp. 32–33. Patent Owner contends that the ordinary meaning is that the NR is isolated from the source. *Id.* at 33. Patent Owner contends that this term requires an isolation or separation step that is distinct from an isolation step used as part of the manufacture of the synthetic product. *See* Sur-Reply 17–18; Ex. 1027 55.

Petitioner responds that the term does not require a separate isolation step after manufacture of the synthetic product and that the limitation is met if the NR is 25% pure. Reply 14–15.

We have considered the arguments presented by the parties, and find that our initial construction is proper for the reasons set forth in the '1795 proceeding. Ex. 1018 12–14. We decline to adopt Patent Owner's construction that calls for an isolation step separate from the process used to manufacture synthetic NR.

The Specification of the '086 patent teaches the following relating to the isolation of NR:

> Synthetic sources of nicotinamide riboside can include any library of chemicals commercially available from most large chemical companies including Merck, Glaxo, Bristol Meyers Squibb, Monsanto-Searle, Eli Lilly and Pharmacia. Natural sources which can be treated for the presence of a

> nicotinamide riboside include, but are not limited to, cow's milk, serum, meats, eggs, fruit and cereals. Isolated extracts of the natural sources can be prepared using standard methods. For example, the natural source can be ground or homogenized in a buffered solution, centrifuged to remove cellular debris, and fractionated to remove salts, carbohydrates, polypeptides, nucleic acids, fats and the like before being tested on the mutant[] strains of the invention. Any source of nicotinamide riboside that scores positively in the assay of the invention can be further fractionated and confirmed by standard methods of HPLC and mass spectrometry.

Ex. 1001, 26:64–27:12. This teaching suggests that isolating NR is nothing more than simply separating or rendering it substantially free from any amount of the other components of the naturally occurring source. Although we recognize that the Specification only expressly indicates the percentage of purity upon which we rely for the definition of "is isolated"—at least 25% (w/w) of the composition—as being applied to polypeptides, Ex. 100 col. 9, ll. 10–12, we find that the same minimum percentage is also appropriate for the measure of isolation of NR. In the context of the '086 patent, we find no reason why one skilled in the art would have viewed the term "isolated" differently for nucleic acids than for polypeptides.

We do not discern any teaching in the '086 patent of an isolation step that is separate from the manufacture of synthetic NR as suggested by Patent Owner and its expert Dr. Amiji. *See* PO Resp. 43–44; Ex. 2014 ¶ 65. The '086 patent teaches that the NR can be chemically synthesized using established methods (Tanimori (2002) *Bioorg. Med. Chem. Lett.* 12:1135-1137; Franchetti (2004) *Bioorg. Med. Chem. Lett.* 14:4655-4658)." Ex. 1001 col. 28, ll. 18–21. These two references cited in the '086 patent both teach an isolation step to separate the synthetically manufactured NR from residual starting materials and reaction by products. Ex. 1010, 4656; Ex. 1014, 1136.

Patent Owner argues that the isolation step of Franchetti does not meet the requirement of claim 2 in that the synthetically manufactured NR is not isolated from a "source." *See* PO Resp. 43–45. We do not agree with Patent Owner's interpretation. The '086 patent states "[a]ny source of nicotinamide riboside that scores positively in the assay of the invention can be further fractionated and confirmed by standard methods of HPLC and mass spectrometry." Ex. 1001, col. 27, ll. 9–12. Thus, a "source" of NR is something that has detectable amounts of NR that can be further fractionated.

The reaction scheme taught by Franchetti produces a reaction mixture that produces NR, along with remaining starting materials and reaction by-products, components associated with the synthesis of NR. *See* Ex. 1010, 4656. We find the reaction mixture of Franchetti to be a source of NR as the term is used in claim 2. This is consistent with the position taken by Patent Owner in the *Elysium* litigation, where Patent Owner argued that "a compound produced by a synthetic reaction, from which NR can be isolated, is, by definition, a 'synthetic source' of NR. The NR that is subsequently isolated from the result of that synthetic reaction would be both 'chemically synthesized' and 'isolated from a natural or synthetic source.'" Ex. 2008, 45–46.

Patent Owner's contention that a separate isolation step is subsequently required post manufacture of synthetic NR appears inappropriately redundant and not in keeping with the plain and ordinary meaning of "is isolated from a natural or synthetic source." Such a subsequent isolation step would require one attempting to practice the invention recited in claim 2 to run NR though a purification step even if the NR were purchased from a manufacturer of NR who certified the NR to be

99% pure. *See* Tr. 60–61. This cannot be the result of the plain and ordinary meaning of "is isolated from a natural or synthetic source." *See Eon Corp. IP Holdings v. Silver Springs Networks,* 815 F.3d 1314, 1321 (Fed. Cir. 2016) (Court rejected construction "untethered to the contest of the invention.").

Based on the foregoing, we decline to adopt Patent Owner's construction and apply the construction recited in our Decision to Institute.

F. Ground 1 – Anticipation by Stamler

Petitioner contends that claim 2 is anticipated by Stamler. Pet. 38. Patent Owner disagrees. PO Resp. 39.

1. Stamler

Stamler discloses a method for modulating nitric oxide bioactivity in a patient by inhibiting the enzyme glutathione-dependent formaldehyde dehydrogenase. Ex. 1006, 1–2; Ex. 1002 ¶ 48. Stamler discloses that inhibiting glutathione-dependent formaldehyde dehydrogenase benefits patients with breathing disorders (e.g., asthma, cystic fibrosis, and ARDS), heart disease, hypertension, ischemic coronary syndromes, atherosclerosis, glaucoma, diseases characterized by angiogenesis (e.g., coronary artery disease), disorders where there is a risk of thrombosis or restenosis occurring, chronic inflammatory diseases (e.g., AIDS, dementia, and psoriasis), diseases where there is risk of apoptosis occurring (e.g., heart failure, atherosclerosis, degenerative neurologic disorders, arthritis and liver injury (ischemic or alcoholic)), impotence, obesity caused by eating in response to craving for food, stroke, reperfusion injury (e.g., traumatic muscle injury in heart or lung or crush injury), and disorders where preconditioning of heart or brain for nitric oxide ("NO") protection against subsequent ischemic events is beneficial. Ex. 1006, 13–14.

Stamler teaches that NR can act as an inhibitor of glutathione-dependent formaldehyde dehydrogenase and that NR and related nicotinamide-based inhibitors "are available commercially or their synthesis is described in or obvious from the literature." *Id.* at 3–4, 13; Ex. 1002 ¶¶ 52, 74. Stamler discloses that a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase ranges from 1 μg to 10 g/kg and often ranges from 10 μg to 1 g/kg, or 10 μg to 100 mg/kg body weight of the patient. Ex. 1006, 15; Ex. 1002 ¶ 50. Stamler discloses that oral administration of a glutathione-dependent formaldehyde dehydrogenase is preferred. Ex. 1006, 15; Ex. 1002 ¶ 51.

2. Analysis of Claim 2

Claim 2 depends from claim 1, and therefore includes each of the limitations recited in claim 1. 35 U.S.C. § 112, fourth paragraph.

a) A pharmaceutical composition comprising nicotinamide riboside

Petitioner contends that Stamler discloses this claim element. Pet. 38–39. Petitioner contends that Stamler discloses a method of treating a patient by administering an effective amount of a glutathione-dependent formaldehyde dehydrogenase inhibitor to treat certain disorders. *Id.* (citing Ex. 1006, 13–17; Ex. 1002 ¶ 70). Petitioner contends Stamler discloses that NR can be a glutathione-dependent formaldehyde dehydrogenase inhibitor, thus teaching a pharmaceutical composition comprising NR. *Id.* (citing Ex. 1006, 3–4; Ex. 1002 ¶¶ 70–71).

Patent Owner contends Petitioner has failed to show that Stamler discloses this limitation either expressly or inherently. PO Resp. 39. Patent Owner contends Stamler does not explicitly disclose a specific pharmaceutical composition comprising NR. *Id.* at 39–40. Patent Owner contends Stamler is directed to method of treating certain disorders with a

class of compounds. *Id.* at 40. Patent Owner contends Petitioner has not shown that the methods disclosed in Stamler constitute a pharmaceutical composition comprising NR. *Id.*

Petitioner responds by contending that Stamler's disclosure of methods of treatment with certain classes of compounds involves administering a composition containing a drug. Reply 15–16. Petitioner cites to Dr. Jaffrey's testimony that Stamler discloses a critical ingredient (NR) and its administration orally, which would lead one skilled in the art to understand as disclosing a pharmaceutical composition. *Id.* at 16 (citing Ex. 2016, 26–27).

In its Sur-Reply, Patent Owner reiterates its contention that Petitioner failed to establish that Stamler discloses a pharmaceutical composition comprising NR. Sur-Reply 16.

We have considered the arguments presented by the parties and the evidence of record, and find that Stamler discloses a pharmaceutical composition comprising NR.

As discussed above, we construe the term "pharmaceutical composition comprising NR" as meaning "a composition, including a food composition, which contains NR as an active agent in an amount effective for the treatment or prevention of a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis."

Stamler discloses a method for treating a "patient afflicted with a disorder ameliorated by NO donor therapy where the method comprises administering to the patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase." Ex. 1006 13. Stamler discloses "[o]ne class of compounds for use herein as the inhibitors of glutathione-dependent formaldehyde dehydrogenase is constituted of

competitors for NAD+ binding" and that one compound in that class is nicotinamide riboside (NR). *Id.* at 3–4. Thus, Stamler discloses a composition containing NR as an active agent for the treatment of a disorder associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis. Dr. Jaffrey's testimony is in accord with the conclusion and we credit Dr. Jaffrey's testimony. Ex. 1002 ¶¶ 70–71.

Patent Owner argues Stamler is directed to a method of treating various disorders, but not with pharmaceutical compositions. PO Resp. 40; Ex. 2014 ¶ 46. Patent Owner additionally argues that Stamler does not disclose this limitation, as Stamler does not recite a specific composition containing NR. PO Resp. 39; Ex. 2014 ¶¶ 43–44.

We are not persuaded by Patent Owner's arguments or by the testimony of Dr. Amiji. While we agree with Patent Owner that Stamler does not disclose a specific example of an NR containing composition, that is not required for anticipation. "[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1382 (Fed. Cir. 2006) (quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001)). As demonstrated above, there is, within the four corners of Stamler, the disclosure of a composition containing an effective amount of NR as an active agent as required by claim 2.

Turning to whether Stamler is enabled, we begin by noting that in the context of enablement, a reference need not disclose, and preferably omits, that which is well known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Again, while we agree with Patent Owner and Dr. Amiji that Stamler does not include

specific instructions regarding how to prepare a pharmaceutical composition comprising NR, we find credible Dr. Jaffrey's testimony that one skilled in the art would understand how to prepare a pharmaceutical compound comprising an inhibitor of glutathione-dependent formaldehyde dehydrogenase such as NR. Ex. 2016, 26, 30–32. Moreover, as Petitioner points out, Stamler does disclose pharmaceutical compositions in its examples. Reply 16 (citing Ex. 1006, 29; Ex. 1027, 40–41).

b) In admixture with a carrier

Petitioner contends that Stamler discloses this limitation. Pet. 38–39. Petitioner contends the disclosure in Stamler that the NR can be administered orally in the amounts recited in Stamler would lead one skilled in the art to the understanding that the NR is mixed with a carrier. *Id.* at 39 (citing Ex. 1006, 15; Ex. 1002 ¶¶ 72–73).

Patent Owner contends that Stamler does not disclose this limitation. PO Resp. 41–42. Patent Owner contends that Stamler does not disclose any form of carrier either explicitly or inherently. *Id.* at 41. Patent Owner argues that Petitioner improperly relies on what one skilled in the art would have understood Stamler to disclose. *Id.* at 41–42.

We have considered the arguments presented by the parties and the evidence of record, and find Petitioner has established that Stamler discloses this limitation.

While we agree with Patent Owner that Stamler does not expressly disclose a specific composition comprising NR and a carrier, Stamler does disclose the use of a carrier with inhibitors of glutathione-dependent formaldehyde dehydrogenase. In Examples I, II, and XVII, Stamler discloses compositions comprising an inhibitor of glutathione-dependent

formaldehyde dehydrogenase combined with saline. Ex. 1006, 29, 32. The '086 patent teaches that saline is a carrier. Ex. 1001, col. 29, ll. 1–20.

In addition, Dr. Jaffrey testified that one skilled in the art would understand that Stamler's teaching of an oral composition to imply that the NR is combined with a carrier and would know how to prepare such a composition. Ex. 2016, 45–46; Ex 1002 ¶ 73. Dr. Amiji, one skilled in the art, testified "The inclusion of exicipent [sic] in pharmaceuticals is essential to allow for proper use." Ex. 2014 ¶ 52. Thus, while Stamler does not expressly disclose combining NR with a carrier, we agree with Dr. Jaffrey that one skilled in the art reading Stamler would know to add a carrier to NR to prepare an oral composition. Ex. 1002 ¶ 73. *See Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017) (The anticipation inquiry takes into account the prior art's literal teachings, and inferences the ordinarily skilled person would draw from it.)

c) Formulated for oral administration

Petitioner contends that Stamler discloses this limitation. Pet. 38–39. Petitioner contends that Stamler discloses that oral administration is preferred. *Id.* (citing Ex. 1006, 15; Ex. 1002 ¶ 72).

Patent Owner does not dispute that this limitation is taught by Stamler. *See* PO Resp. 39–47.

We agree with Petitioner that Stamler discloses "[t]he preferred route of administration is oral administration" limitation. Ex. 1006 15.

d) Is isolated from a natural or synthetic source

Petitioner contends that Stamler discloses this limitation. Pet. 40. Petitioner contends that Stamler discloses that the NR is commercially available or that its synthesis is described or obvious from the literature. *Id.*

(citing Ex. 1006, 13; Ex. 1002 ¶ 74). Petitioner contends that one skilled in the art would understand that synthetic and commercially available NR is isolated from a natural or synthetic source, thus meeting the limitation of claim 2. Pet. 40 (citing Ex. 1002 ¶¶ 75–76).

Patent Owner's arguments are based on its erroneous claim construction, which we decline to adopt. *See* Section II.E.3 above. Patent Owner contends Stamler's mention of commercially available NR or synthesized NR does not constitute disclosure of "a natural or synthetic source of NR" or NR that is isolated from such a source. *Id*. at 43. Patent Owner contends that NR obtained from a commercial source only meets the "natural or synthetic source" of the limitation, but does not meet the "is isolated" part of the limitation, therefore Stamler does not disclose isolating NR from the commercially available NR. *Id.*

With respect to Stamler's disclosure of synthesized NR, Patent Owner contends this disclosure is inadequate, in that it does not disclose isolating NR from the synthetically produced NR. *Id.* at 44.

Patent Owner contends that Petitioner's reliance on Franchetti is misplaced, as this reliance does not establish that Stamler discloses this limitation. *Id.* at 45. Patent Owner also contends that even if Petitioner could properly rely on Franchetti, Franchetti does not teach this limitation, as the isolation step in Franchetti is part of the synthesis of NR and is not a separate step after NR is synthesized. *Id.* at 45–46.

We have considered the arguments presented by the parties and the evidence of record, and find Stamler discloses this limitation.

Stamler discloses that the NR is "available commercially or [its] synthesis is described in or obvious from the literature." Ex. 1006, 13. We agree with Dr. Jaffrey that

> Those of ordinary skill in the art would have understood that such synthetic and commercially available NR would be substantially pure, and thus would be "isolated" as construed above. That is, synthetic and commercially obtained NR would be "separated or substantially free from at least some of the other components associate with the source of the molecule such that it constitutes at least 25% (w/w) of the composition."

Ex. 1002 ¶ 75. Dr. Jaffrey goes on to point out that Franchetti, a known method for synthesizing NR, discloses synthesis of NR followed by purification of the NR by Chromatography. *Id.* ¶ 76.

Patent Owner's arguments rely, in part, on its proposed interpretation of the term "is isolated from a natural or synthetic source." *See, e.g.,* PO Resp. 43–44. As discussed above, we decline to adopt Patent Owner's construction. Section II.E.3.

Turning to Petitioner's reliance on Franchetti, we do not read Dr. Jaffrey's anticipation analysis as attempting to incorporate Franchetti into Stamler. Instead, Dr. Jaffrey cites to Franchetti as an example of an NR synthesis technique that was known to those skilled in the art. *See* Ex. 1002 ¶¶ 75–76. Thus, Franchetti is evidence that supports Dr. Jaffrey's testimony about the inferences one skilled in the art would draw reading Stamler. *See Eli Lilly*, 849 F.3d at 1074–75.

3. Conclusion

Based on the foregoing, we conclude that Petitioner has shown by a preponderance of the evidence that claim 2 is anticipated by Stamler.

G. Ground 2 – Obviousness based on Stamler

Petitioner contends that, to the extent Stamler does not anticipate claim 2, the subject matter of claim 2 would have been obvious over Stamler to one of ordinary skill in the art at the time the invention was made. Pet. 40–42. Petitioner reiterates its contentions that Stamler teaches a

pharmaceutical composition containing NR that can be administered orally. Pet. 41–42. With respect to the limitation calling for the NR to be in admixture with a carrier, Petitioner contends that if Stamler is not viewed as teaching the use of a carrier, it would have been obvious to use a carrier to facilitate administration of NR to a patient. *Id.* Petitioner also contends that one skilled in the art reading Stamler's reference to obtaining NR commercially or by using standard methods would have been led to use NR that is isolated as the term has been construed. *Id.* at 42.

Patent Owner contends Stamler does not teach all of the limitations of claim 2. PO Resp. 47. Patent Owner also contends Petitioner's obviousness analysis fails because the analysis is conclusory. *Id.* at 47–48. Patent Owner also contends Petitioner failed to show a motivation to modify Stamler, or that one skilled in the art would have had a reasonable expectation of success. *Id.* at 48.

Petitioner responds by arguing that Dr. Jaffrey's analysis in not conclusory but is in fact detailed and thorough. Reply 20–21. Petitioner contends that such motivation to modify Stamler was discussed in the Petition and that the motivation is found in Stamler. *Id.* at 21. Petitioner also contends that the expectation of success in modifying Stamler arises from the teachings of Stamler. *Id.* at 21–23.

Patent Owner responds by arguing that Stamler give no guidance as to how to make a pharmaceutical composition comprising NR. Sur-Reply 18. Patent Owner also contends that this supports its contention that one skilled in the art would not have a reasonable expectation of success. *Id.* at 18–19. Patent Owner argues that Petitioner improperly cites to the teachings of the '086 patent in support of its argument regarding a reasonable expectation of

success. *Id.* at 20. Patent Owner reiterates its argument that Stamler does not teach NR that is isolated from a source. *Id.* at 21–22.

We have considered the arguments of the parties and the evidence of record and, as explained more fully below, we find Petitioner has demonstrated that the subject matter of claim 2 would have been obvious to one of ordinary skill in the art at the time the invention was made over Stamler.

1. Analysis of Claim 2

a) A pharmaceutical composition comprising NR

Petitioner contends Stamler teaches this limitation. Pet. 41. Petitioner cites to the teachings in Stamler regarding administration of "an inhibitor of glutathione-dependent formaldehyde dehydrogenase to a patient, where that inhibitor specifically may be NR." *Id.* (citing Ex. 1006 2–4); Ex. 1002 ¶ 80. Petitioner contends that while Stamler does not teach a specific formulation containing NR, it would have been obvious to prepare such a composition given the teachings of Stamler. Pet. 41. In support of this contention, Petitioner cites to the testimony of Dr. Jaffrey wherein he states

> Although Stamler does not specifically exemplify a pharmaceutical composition of nicotinamide riboside, a person of ordinary skill in the art would have found it obvious to provide such a composition given Stamler's express suggestion of orally administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase, such as nicotinamide riboside, to treat a disorder ameliorated by NO donor therapy or afflicted with pathologically proliferating cells, which includes a "degenerative neurologic disorder."

Ex. 1002 ¶ 81.

Citing *TQ Delta, LLC v. Cisco Systems, Inc.,* 942 F.3d 1352 (Fed. Cir. 2019), Patent Owner contends Petitioner's arguments are based on mere

conclusory statements, which are inadequate to support a finding of obviousness. PO Resp. 48–49. Patent Owner contends Dr. Jaffrey's conclusions are not supported by any factual evidence, other than the disclosure of the patent at issue. *Id.* at 49.

For the reasons stated in Section II.F.2(a) above, we agree with Dr. Jaffrey that Stamler teaches a pharmaceutical composition comprising NR. Ex. 1002 ¶ 80. Stamler teaches "a method for treating a patient afflicted with a disorder ameliorated by NO donor therapy where the method comprises administering to the patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase." Ex. 1006, 13. Stamler teaches "[o]ne class of compounds for use herein as the inhibitors of glutathione-dependent formaldehyde dehydrogenase is constituted of competitors for NAD+ binding" and that one compound in that class is nicotinamide riboside (NR). *Id.* at 3–4. Thus, Stamler discloses a composition containing NR as an active agent for the treatment of a disorder associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis.

We find Patent Owner's reliance on *TQ Delta* to be misplaced. While *TQ Delta* held that obviousness determinations based on conclusory and unsupported expert testimony should be rejected, *TQ Delta*, 942 F. 3d at 1361, we do not agree that Dr. Jaffrey's analysis falls into the category. Dr. Jaffrey cites to specific portions of Stamler which support his analysis. *See* ex. 1002 ¶¶ 80–83. In addition, Dr. Jaffrey provided an analysis of the term "pharmaceutical composition comprising NR" as part of his anticipation analysis. *Id.* ¶¶ 70–73.

With respect to Dr. Jaffrey's citation to the '086 patent, as Petitioner points out, "[a] patent's admissions of the POSA's knowledge are proper

evidence of the level of ordinary skill." Reply 21, *citing In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). Here, the portions of the '086 patent relied on by Dr. Jaffrey are statements of what was well known to one of ordinary skill in the art. *See, e.g.,* Ex. 1002 ¶¶ 70–86; Ex. 1001, col. 28, ll. 49–60.

b) In admixture with a carrier

Petitioner contends that Stamler teaches this limitation. Pet. 41. Petitioner contends that Stamler's teaching of oral administration of an inhibitor of glutathione-dependent formaldehyde dehydrogenase would lead one skilled in the art to understand that the use of a carrier would facilitate administration of NR to a patient. *Id.* (citing Ex. 1002 ¶ 82).

Patent Owner presents the same arguments with respect to this limitation as it does with respect to the limitation calling for a pharmaceutical composition. PO Resp. 48–50.

We have considered the arguments presented by the parties and the evidence of record, and we agree with Petitioner that Stamler teaches this limitation.

While we agree with Patent Owner that Stamler does not expressly recite a specific composition comprising NR and a carrier, Stamler does teach the use of a carrier with inhibitors of glutathione-dependent formaldehyde dehydrogenase. In Examples I, II, and XVII, Stamler teaches compositions comprising an inhibitor of glutathione-dependent formaldehyde dehydrogenase combined with saline. Ex. 1006, 29, 30–31. The '086 patent teaches that saline is a carrier. Ex. 1001, col. 29, ll. 1–20.

In addition, Dr. Jaffrey testified that one skilled in the art would understand that Stamler's teaching of an oral composition to imply that NR is combined with a carrier and would know how to prepare such a composition. Ex. 2016, 45–46; Ex 1002 ¶¶ 73, 82. Dr. Amiji, one skilled in

the art, testified "The inclusion of exicipent [sic] in pharmaceuticals is essential to allow for proper use." Ex. 2014 ¶ 52. Thus, while Stamler does not explicitly recite combining NR with a carrier, we agree with Dr. Jaffrey that one skilled in the art reading Stamler would have known to add a carrier to NR to prepare an oral composition. Ex. 1002 ¶¶ 73, 82.

One skilled in the art must be presumed to know something about the art apart from what the references disclose. *In re Jacoby*, 309 F.2d 513, 516 (CCPA 1962); *see also In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985) (Skill in the art is presumed.). As *DeLisle* explains, "[a]dmittedly the references are not as explicit as the claim language; however, the issue of obviousness is not determined by what the references expressly state but by what they would reasonably suggest to one of ordinary skill in the art." *In re DeLisle*, 406 F.2d 1386, 1389 (citing *In re Siebentritt*, 372 F.2d 566 (CCPA 1967)).

For the reasons stated above in section II.G.1(b), we find Patent Owner's arguments unpersuasive.

c) Formulated for oral administration

Petitioner contends that Stamler teaches this limitation. Pet. 43. Petitioner contends that Stamler discloses that oral administration is preferred. *Id*. (citing Ex. 1006, 15; Ex. 1002 ¶ 80).

Patent Owner does not dispute that Stamler teaches this limitation. *See* PO Resp. 48–50.

We agree with Petitioner that Stamler discloses "[t]he preferred route of administration is oral administration" limitation. Ex. 1006, 15.

d) Is isolated from a natural or synthetic source

Petitioner contends Stamler teaches this limitation. Pet. 42. Petitioner contends that while Stamler does not specifically refer to NR that is isolated,

synthesis of isolated NR was known. *Id.* (citing Ex. 1002 ¶ 84); Ex. 1010, 4656.

Patent Owner contends Stamler does not teach this limitation. PO Resp. 56–61. Patent Owner contends that Petitioner has not shown that NR is obtained from a natural or synthetic source nor has Petitioner shown that the NR is isolated from such a source as Patent Owner construes the term. *Id.* at 56.

Petitioner responds by incorporating its arguments made in connection with its anticipation contentions discussed above. Reply 23–24.

We have considered the arguments presented by the parties as well as the evidence of record and find that Stamler teaches this limitation.

As Dr. Jaffrey points out, Stamler teaches that the inhibitors of glutathione-dependent formaldehyde dehydrogenase are available commercially can be prepared by well-known procedures. Ex. 1002 ¶ 74 (citing Ex. 1006, 13). We agree with Dr. Jaffrey that

> Those of ordinary skill in the art would have understood that such synthetic and commercially available NR would be substantially pure, and thus would be "isolated" as construed above. That is, synthetic and commercially obtained NR would be "separated or substantially free from at least some of the other components associate with the source of the molecule such that it constitutes at least 25% (w/w) of the composition."

Ex. 1002 ¶ 75. Dr. Jaffrey goes on to point out that Franchetti, a known method for synthesizing NR, discloses synthesis of NR followed by purification of the NR by chromatography. *Id.* ¶ 76.

When determining obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). In reaching his conclusion that one skilled in the art would consider

the NR used in Stamler to be isolated, Dr. Jaffrey persuasively explains how one skilled in the art would have reviewed the teachings of the prior art. *See* Ex. 1002 ¶¶ 75–77, 84–85.

Patent Owner's arguments are essentially the same as those made with in response to ground 1 above. *Compare* PO Resp. 42–47 *with id.* at 56–61. For the reasons stated in Section II.F.2(d) we find these arguments unpersuasive.

2. Motivation to Modify Stamler

In his declaration, Dr. Jaffrey stated that one skilled in the art would have been motivated to modify the teachings of Stamler to facilitate the administration of the active ingredient. Ex. 1002 ¶ 82.

Patent Owner contends Petitioner has failed to state a reason to modify Stamler and that Dr. Jaffrey's conclusory statement is insufficient. PO Resp. 50–51.

Petitioner responds

> the petition identified a sufficient rationale supported by the disclosure of Stamler itself. Pet., 41 (citing EX1002, ¶¶80-83). That is, as discussed above, Stamler discloses treating patients using NR and administering it orally, which would have suggested to a POSA to prepare a composition containing NR with a carrier for administration. *Supra*, sections IV.C.1-2. Indeed, Stamler evidences this point. EX1006, 29.

Reply 21.

We have considered the arguments presented by the parties and the evidence of record, and find one skilled in the art would have been motivated to apply the teachings of Stamler to arrive at the claimed invention.

Stamler teaches administration of an effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase to treat certain

disorders. Ex. 1006 2. The first mentioned inhibitor is NR. *Id.* at 4. We find this would have motivated one skilled in the art to use NR as the inhibitor of glutathione-dependent formaldehyde dehydrogenase.

Stamler also teaches the use of other glutathione-dependent formaldehyde dehydrogenase inhibitors in conjunction with saline, a known carrier. *Id.* at 29, 32. Dr. Jaffrey testified that one skilled in the art would recognize that Stamler's teaching of oral administration calls for the use of a carrier to facilitate administration. Ex. 1002 ¶ 83. Dr. Amiji also testified that the use of excipients is essential. Ex. 2014 ¶ 52. Based on this evidence, we agree with Dr. Jaffrey that one skilled in the art would have been motivated to include a carrier with NR to form a composition to use in the treatment method of Stamler. *See* Ex. 1002 ¶ 82.

3. Reasonable Expectation of Success

Patent Owner contends Petitioner has not established that one skilled in the art would have had a reasonable expectation of success in modifying the teachings of Stamler to produce a pharmaceutical composition containing NR in admixture with a carrier. PO Resp. 51. Patent Owner contends that one skilled in the art would not have a reasonable expectation of success because Stamler is devoid of any guidance as to how to make such a composition. *Id.* at 52. In support of this contention, Patent Owner points to the fact that Stamler does not teach how to use or select a carrier compatible with NR. *Id.* at 52–53. Patent Owner also contends that one skilled in the art would not have a reasonable expectation of success because the chemical arts are unpredictable, and Stamler lacks any guidance as to how to prepare a pharmaceutical composition. *Id.* at 54.

Petitioner responds that given the knowledge of one skilled in the art, there would have been a reasonable expectation of success. Reply 21–22.

Citing the testimony of Patent Owner's expert, Dr. Amiji, Petitioner contends one skilled in the art would have been aware of such references as Remington,[4] that would have provided guidance as to how to prepare a pharmaceutical composition containing NR. *Id.* at 22 (quoting Ex. 1027 20–21). Petitioner also cites to the testimony of Dr. Jaffrey, wherein he stated that once a person of ordinary skill in the art was aware of the structure of NR and the method of administration, the carriers that could be used and the preparation of a pharmaceutical composition would have been readily apparent. *Id.* (citing Ex. 2016, 46). Petitioner also contends that the formulation of NR into a pharmaceutical composition is not unpredictable. *Id.* at 22–23.

We have considered the arguments presented by the parties and the evidence of record, and find that one skilled in the art would have had a reasonable expectation of success in preparing a pharmaceutical composition containing NR.

"Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

We begin with the teachings of Stamler itself. While we agree with Patent Owner that Stamler does not include any specific guidance regarding preparation of a composition containing NR, the examples Stamler teach the preparation of composition comprises other inhibitors of glutathione-dependent formaldehyde dehydrogenase. In Examples I, II, and XVII, Stamler teaches compositions comprising an inhibitor of glutathione-

[4] Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro, ed. 20th ed. Lippingcott Williams & Wilkins: Philadelphia, Pa. 2000. ("Remington")

dependent formaldehyde dehydrogenase combined with saline and their effectiveness against various disorders. Ex. 1006, 29, 30–31.

When asked about what one would need to know to formulate a composition comprising NR, Dr. Jaffrey testified

> Well, the "other ingredients," I think, is largely referring to NR, right?
>
> So, a person would -- so, you know, a person of skill in this area would just look at the chemical structure of NR, and then they would know what the appropriate formulation would be.
>
> So, you look at the structure, you see does it have anything chemically reactive. With NR, the answer is no. And you look at SI change to see solubility, and you see very soluble, and you kind of know right from that all your options instantaneously, right?
>
> So, an average person could just look at the chemical structure and know how to prepare the formulations and what's compatible, because you're talking about compatibility.
>
> So, hopefully someone has taken a chemistry class, and they understand what makes molecules stable and what makes it unstable, right?
>
> And so, you just choose something that's compatible. And there's many, many, many, many options.

Ex. 2016, 46.

Moreover, Dr. Amiji testified that one skilled in the art would be familiar with references such as Remington that provides guidance on the development of formulations and the use of excipients such as carriers. Ex. 1027 20:10–22:18.

Given that Stamler teaches that inhibitors of glutathione-dependent formaldehyde dehydrogenase can be successfully formulated into pharmaceutical compositions, and that the testimony of both experts that one would be able to readily ascertain how to formulate a composition

comprising NR, we find that one skilled in the art would have had a reasonable expectation of doing so.

We are not persuaded by Patent Owner's argument regarding the unpredictability of the art in preparing a composition comprising NR. While our reviewing court has stated that chemical arts are often unpredictable, *Eisai Co. Ltd. v. Dr. Reddy's Lab. Ltd.*, 553 F.3d 1353, 1359 (Fed. Cir. 2008), we discern no persuasive evidence, other than attorney argument, that the pharmaceutical formulation art is unpredictable. *See* PO Resp. 54. "Attorneys' argument is no substitute for evidence." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1581 (Fed. Cir. 1989). In fact, Dr. Jaffrey's testimony, which we credit, supports the opposite conclusion. Ex. 2016, 46.

4. Conclusion

Based on the foregoing, we conclude that Petitioner has demonstrated by a preponderance of the evidence that the subject matter of claim 2 would have been obvious to one skilled in the art at the time the invention was made over Stamler.

H. Grounds 3–5

Having found the Petitioner has demonstrated that claim 2 is either anticipated by or obvious over Stamler, we do not reach the issues of whether Brenner and Bieganowski are available as prior art, nor do we reach the issues of whether claim 2 is anticipated by Brenner or Bieganowski or obvious over Bieganowski.

I. Credibility of Dr. Jaffrey

Patent Owner argues that we should give little weight to the testimony of Dr. Jaffrey as compared to its expert Dr. Amiji. PO Resp. 54. Patent Owner contends that Dr. Jaffrey's declaration is conclusory in nature and he has little experience in formulating pharmaceutical compositions. *Id.* at 54–

55. Patent Owner also contends that Dr. Jaffrey is not one skilled in the art as his degrees are not in biochemistry or a similar field in the pharmaceutical sciences. *Id.* at 55.

Petitioner responds that while Dr. Jaffrey's degrees are in neuroscience, he is the "Greenberg-Star Professor in the Department of Pharmacology at the Weill Medical College at Cornell University" and has been a professor of pharmacology for over 20 years. Reply 24. Petitioner also points to Dr. Jaffrey's experience in formulating compositions containing NR. *Id.*

We have considered the arguments presented by the parties and find Dr. Jaffrey to be a credible witness who is qualified to present opinions related to the subject matter of the '086 patent. While Dr. Jaffrey's degrees are not in pharmacy or pharmacology, they are in a similar field and, coupled with over 20 years of experience in the field of pharmacy, render him qualified to opine about what one skilled in that field would understand from the teachings of Stamler. In Addition, Dr. Jaffrey's degree's in neuroscience are in a filed that is in a similar field of the pharmaceutical sciences and Dr. Jaffrey has experience in pharmokenetics.

III. PETITONER'S MOTION TO EXCLUDE EVIDENCE

Petitioner filed a Motion to Exclude the Declarations of Drs. Brenner and Bieganowski, Exs. 2002, 2003, 2015, 2021, and 2022, and the Declaration of Dr. Amiji, Ex. 2014. Pet. Mot. Ex. 2. (Paper 48). Patent Owner opposes the motion. PO Resp. Pet. Mot. Ex. (Paper 50)

A. The Declarations of Drs. Brenner and Bieganowski

Petitioner contends that Exhibits 2002, 2003, 2015, 2021, and 2022 should be excluded under Federal Rules of Evidence 701 and 702. Petitioner contends the declarations "provide insufficient evidence to show sufficient

basis for the matter to which the declarants testify, and they provide unqualified legal opinions that are not based on sufficient facts or data." Pet. Mot. Ex. 2.

The declarations of Dr. Brenner and Bieganowski relate to the issue of whether the Brenner and Bieganowski references are the work of another under 35 U.S.C. § 102(a) or 102(e). *See id.* at 3. As we stated above in Section II.H., we do not reach that issue in this decision. Therefore, we dismiss that portion of the Motion to Exclude as moot.

B. The Declaration of Dr. Amiji

Petitioner seeks to exclude the Declaration of Patent Owner's Expert, Dr. Amiji, under FRE 401-403 and 702. Pet. Mot Ex. 7. Petitioner contends Dr. Amiji's testimony "is not based on sufficient facts or data and is not the product of reliable principles and methods, thus making the testimony irrelevant to the proceeding and any probative value substantially outweighed by its undue prejudice and risk of confusing the issues." *Id.* Petitioner contends that in his analysis, Dr. Amiji ignored the constructions the Board gave for the terms "pharmaceutical composition" and "is isolated." *Id.* at 7–8.

In response, Patent Owner contends Dr. Amiji did not apply an incorrect claim construction. PO Resp. Pet. Mot Ex. 12. Patent Owner also contends that even if Dr. Amiji applied the wrong construction, that goes to the weight of the evidence, not the admissibility. *Id.* at 12–13.

We have considered the arguments presented by the parties and the testimony presented by Dr. Amiji, and we agree with Patent Owner that any inconsistencies in Dr. Amiji's testimony go the weight we should give his testimony. *See* Consolidated Trial Practice Guide (Nov. 2019), at 79; *Neptune Generics v. Eli Lilly & Co.*, IPR2016-00240, Paper 82 at 69–70

(PTAB Oct. 5, 2017) (statin that whether an expert "used incorrect legal standards" goes to "to the weight of the testimony, rather than its admissibility").

For this reason, we deny Petitioner's Motion to Exclude as it applies to Ex. 2104.

IV. PATENT OWNER'S MOTION TO EXLUDE EVIDENCE

Patent Owner filed a Motion to Exclude the Second Declaration of Dr. Samie Jaffrey, M.D., Ph.D. (Ex. 1038). PO Mot. Ex. (paper 59.) Petitioner opposes the motion. Pet. Resp. PO Mot. Ex. (paper 60).

Like the Declarations of Dr. Brenner and Bieganowski, the Second Declaration of Dr. Jaffrey relates to the issue of whether the Brenner and Bieganowski references are prior art, and more specifically, whether the work described in the Brenner and Bieganowski references is "work of another" under 35 U.S.C. §102(a) or 102(e). PO Mot Ex. 1–2. As we stated above, we do not reach that issue in this decision. Therefore, we dismiss the Motion to Exclude as moot.

V. CONCLUSION[5]

Based on the foregoing, we conclude that Petitioner has shown by a preponderance of the evidence that claim 2 of the '086 patent is unpatentable under either 35 U.S.C. § 102(b) or 35 U.S.C. § 103(a).

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[5] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we refer Patent Owner to the April 2019, *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claim 2 of the '086 patent is determined to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is dismissed in part as moot and denied in part;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot;

and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

In summary:

Claims	**35 U.S.C. §**	**Reference(s)/Basis**	**Claims Shown Unpatentable**	**Claims Not shown Unpatentable**
2	102(b)	Stamler	2	
2	103(a)	Stamler	2	
2	102(b)	Bieganowski[6]		
2	103(a)	Bieganowski[7]		
2	102(a) or (e)	Brenner[8]		
Overall Outcome			2	

[6] As discussed above, we do not reach this ground of unpatentability as the Petitioner has demonstrated the unpatentability of claim 2 over Stamler.
[7] *See* footnote 7.
[8] *See* footnote 7.

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