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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELYSIUM HEALTH INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

Case No. IPR2017-01795
Patent 8,383,086 B2

Before SUSAN L.C. MITCHELL, CHRISTOPHER G. PAULRAJ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Elysium Health Inc. ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–5 of U.S. Patent No. 8,383,086 B2 ("the '086 patent"). Paper 1 ("Pet."). The Trustees of Dartmouth College ("Patent Owner") filed a Preliminary Response contending that the Petition should be denied as to all the challenged claims. Paper 8 ("Prelim. Resp."). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1 and 3–5 as unpatentable under 35 U.S.C. § 102(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on January 29, 2018, as to those claims. Paper 9 ("Institution Decision, "Dec.").

On April 24, 2018, the Supreme Court of the United States held that a final written decision under 35 U.S.C. § 318(a) must decide the patentability of all claims challenged in the petition. *SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1359–60 (2018). On April 26, 2018, the Office issued Guidance on the Impact of *SAS* on AIA Trial Proceedings,[1] which states that "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." The Guidance also states that, for pending trials, the panel may issue an order supplementing the institution decision to institute on all challenges raised in the petition. *Id.*

On April 27, 2018, pursuant to the Supreme Court's decision in *SAS* and the Guidance provided by the USPTO, we issued an Order Relating to

[1] *See* https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial ("Guidance").

the Conduct of the Proceedings modifying our institution decision to institute on all of the challenged claims and all of the grounds in the petition. Paper 22 ("Modified Institution Decision").

Patent Owner, Trustees of Dartmouth College, filed a Motion for Rehearing of our modified Decision to Institute *Inter Partes* Review as set forth in our April 27, 2018, Order Relating to the Conduct of the Proceeding. Paper 24. On September 5, 2018, we denied Patent Owner's Motion for Rehearing. Paper 36.

Patent Owner filed its Response to the Petition on June 4, 2018, Paper 28 ("Response"), and Petitioner filed its Reply to Patent Owner's response on August 22, 2018, Paper 33 ("Reply"). An oral hearing was held on October 2, 2018. The transcript of the hearing has been entered into the record. Paper 38 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden of persuasion 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 prove unpatentability 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 Petitioner has shown by a preponderance of the evidence that claims 1 and 3–5 of the '086 patent are unpatentable, but has not shown that claim 2 of the '086 patent is unpatentable. *See* 35 U.S.C. § 316(e).

B. Related Proceedings

Petitioner represents that the ’086 patent is at issue in *ChromaDex, Inc., v Elysium Health, Inc.*, Case No. 16-cv-02277-KES (C.D. Cal.). Pet. 30. Petitioner also represents that a petition for *inter partes* review has been filed challenging related patent U.S. Patent No. 8,197,807 in IPR2017-01796. *Id.* We denied institution of *inter partes* review of the petition in IPR2017-01796. *Elysium Health, Inc. v. Trustees of Dartmouth College*, Case IPR 2017-01795 (PTAB Jan. 18, 2018) (Paper 9).

C. The ’086 Patent

The ’086 patent issued on February 26, 2013, with Charles M. Brenner listed as the inventor. Ex. 1001, (45) (75). The ’086 Patent issued from an application filed on April 12, 2012, and claims priority to an application filed April 20, 2006. *Id.* (63). The parties have not disputed the claimed priority date for the ’086 Patent. Pet. 8 (addressing qualification as prior art according to the “earliest possible priority date” of the ’086 patent), 19 (same).

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 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. Ex. 1001, col. 4, ll. 14–16, col. 29, ll. 43–46.

D. Illustrative Claim

Petitioner challenges claims 1–5 of the ’086 Patent. Independent claim 1 is illustrative, and is reproduced below:

> 1. A pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration.

Ex. 1001, col. 53, ll. 38–40.

E. The Alleged Grounds of Unpatentability

Petitioner challenges the patentability of all of the claims of the '086 patent based on the following grounds:

References	Basis	Claims Challenged
Goldberger et al.[2]	35 U.S.C. § 102	1–5
Goldberger and Tanner[3]	35 U.S.C. § 102	1–5

Petitioner further relies on the declaration of Joseph A. Baur, Ph.D. Ex. 1002. Patent Owner relies on the declaration of Zhaohui Sunny Zhou, Ph.D. Ex 2002.

II. ANALYSIS

A. Claim Construction

For petitions filed prior to November 13, 2018,

> [a] claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R.

[2] 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. HEATH REPORTS 1385 (1928) ("Goldberger et al."). Ex. 1005.

[3] Goldberger and Tanner, *A Study of the Treatment and Prevention of Pellagra*, 39 PUB. HEALTH REPORTS 87 (1924) ("Goldberger and Tanner"). Ex. 1006.

§ 42.100(b).[4] When applying that standard, we interpret the claim language as it should be understood by one of ordinary skill in the art in light of the specification. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010). Under this standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Only terms that are in controversy need to be construed and only then to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

1. Pharmaceutical Composition

Claim 1 recites a "pharmaceutical composition comprising nicotinamide riboside . . . formulated for oral administration." Ex. 1001, col. 53, ll. 38–40. Claim 3 reads "[t]he pharmaceutical composition of claim 1, wherein the formulation comprises a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or food." Ex. 1001, col. 53, ll. 44–

[4] The Final Rule changing the claim construction standard to the federal court claim construction standard that is used to construe a claim in a civil action under 35 U.S.C. § 282(b) does not apply here as the Petitioner was filed before the effective date of the Final Rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340, 51,340, 51,344 (Oct. 11, 2018).

46.In our Institution Decision, we agreed with and adopted Petitioner's proposal that the term "pharmaceutical composition" should include food products, as that construction is supported by the language of claim 3 and disclosure in the Specification of the '086 patent. Dec. 5.

a. Food as a "Pharmaceutical Composition"

Patent Owner renews its argument that the term "pharmaceutical composition" should not be construed to include foods, and proposes its own construction of the term "pharmaceutical composition comprising nicotinamide riboside" as "a composition containing nicotinamide riboside as the active agent." Resp. 8–16.

As discussed in our Institution Decision, both the Specification and claims clearly teach that the claimed pharmaceutical composition can be a food. The Specification teaches:

> For oral therapeutic administration, the compound can be combined with one or more carriers and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, *foods* and the like.

Ex. 1001, col. 29, ll. 43–47 (emphasis added). Claim 3 recites "[t]he pharmaceutical composition of claim 1, wherein the *formulation comprises* a tablet, troche, capsule, elixir, suspension, syrup, wafer, chewing gum, or *food*." Ex. 1001, col. 53, ll. 44–46 (emphasis added.). Thus, as used in the '086 patent, we find that the term "pharmaceutical composition" encompasses foods.

b. Active Agent

Patent Owner asks the Board to construe not just the term 'pharmaceutical composition" but the term "pharmaceutical composition comprising nicotinamide riboside." Resp. 8. Patent Owner contends that

the term should be construed to mean a pharmaceutical composition where NR is the active agent. *Id.* Patent Owner contends that this construction is consistent with the Specification, citing to several portions of the Specification teaching that NR is used to treat or prevent various conditions. Resp. 9–10. Patent Owner argues that these teachings in the Specification would lead one skilled in the art to understand that the pharmaceutical composition would include NR as an active agent as opposed to an inactive excipient. *Id.* at 10.

Petitioner responds that Patent Owner's proposed construction is improper. Reply 2. Petitioner contends that the use of the term "comprising" in the claims means that the claim includes, but is not limited to, NR as an active agent. Reply 3. Petitioner also argues that it is improper to read an active agent limitation into the claims. Reply 8. Petitioner contends that the Specification does not support construing the term "pharmaceutical composition" to require the presence of an active agent, nor does the Specification otherwise support a requirement that NR be the active agent in the claimed composition. Reply 6–8.

We have considered the parties' arguments, and find that the term "pharmaceutical agent" as used in the present claims calls for the presence of at least one active agent. As taught by the Specification, pharmaceutical composition is a composition which can be used to treat or prevent a disease or disorder. *See, e.g.*, Ex. 1001, col. 4, ll. 19–24; col. 31, ll. 42–46. One skilled in the art would understand from these teachings in the Specification concerning treating or preventing a disease or disorder that a pharmaceutical composition is one where at least one component of the composition acts to treat or prevent the disease or disorder. Such a component can properly be

described as an active agent regardless of whether it is purposefully added to the composition.

Turning to the language of claim 1, the inclusion of "pharmaceutical" in the claim phrase "a pharmaceutical composition comprising nicotinamide riboside" supports Patent Owner's argument that the claim phrase refers to a composition where NR is an active agent. This interpretation is consistent with the Specification as well as the wording of the claim itself. For example, the Specification states

> [T]he present invention is a method for preventing or treating a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis. The method involves administering to a patient having a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis *an effective amount of a nicotinamide riboside composition so that the signs or symptoms of the disease or condition are prevented or reduced.*

Ex. 1001, col. 4, ll. 17–24 (emphasis added).

The Specification also teaches, however, that NR is not the *sole* active agent that may be administered as part of such a composition. The Specification teaches that NR can be administered with additional NAD+ precursors such as tryptophan, nicotinic acid, and nicotinamide. *See, e.g.,* Ex. 1001, col. 4, ll. 27–29; col. 24, ll. 40–48. As Petitioner points out, the claims use the open transitional term "comprising" that allows for components other than NR for a pharmaceutical composition encompassed by the claims. *See* Pet. 2–4. Thus, we conclude that, when read in light of the Specification, the claims do not call for NR to be the sole active agent present in the composition, but must be at least one active agent in the claimed pharmaceutical compositions.

Petitioner contends that Patent Owner's proposed construction would render the claims indefinite. Reply 12. Petitioner argues that the Specification is silent as to the amount of NR that is needed to effectively treat or prevent any disease or disorder and that it would require an undue amount of experimentation to determine if NR were acting as an active agent. Reply 13–15.

We find this argument unpersuasive. Although the Specification and claims do not recite any specific amount of NR that constitutes an effective amount, the Specification does teach

> A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required for prevention or treatment in an animal subject such as a human, agriculturally-important animal, pet or zoological animal.

Ex. 1001, col. 31, ll. 42–46. In addition, the Specification teaches that an effective amount of NR is an amount sufficient to treat or prevent a disease or condition. *See*, *e.g.*, Ex. 1001, col. 4, ll. 19–24, col. 27, l. 66 – col. 28, l. 3. We agree with Patent Owner that, based on these teachings of the Specification, one skilled in the art would have been able to identify an effective amount of NR for use in a composition. Tr. 62–63. Thus, based on the full trial record, we do not find that Patent Owner's proposed construction renders the claim indefinite or otherwise invalid under 35 U.S.C. § 112.

Based on the foregoing analysis, we construe the term "pharmaceutical composition" to be 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.

2. Is Isolated

Claim 2 recites the limitation that the NR "is isolated from a natural or synthetic source." Ex. 1001, col. 53, ll. 41–44. In our Institution Decision, we construed the term 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." Dec. 9. We determined that the term "isolated," as used in the Specification, embraces compositions containing NR where only some of the other components of the naturally occurring organism are removed. Dec. 8; Ex. 1001, col. 9, ll. 3–10. We also determined that the Specification provides guidance as to how pure a molecule needed to be to be deemed "isolated," and that one skilled in the art would have understood that in the context of the '086 patent, "isolated" refers to a molecule that is at least 25% pure (w/w). Dec. 8. Although the Specification discusses this level of purity with respect to proteins, we determined that one skilled in the art would have understood that this level of purity extends to other types of "isolated" molecules referenced in the Specification, including NR. *Id.*

In its Reply, Petitioner urges us to reconsider our construction of the term "is isolated." Reply 17. Petitioner contends our construction is based on a misreading of the Specification. *Id.* Petitioner argues that the teaching of 25% purity only applies to peptides and not to other molecules such as NR. Reply 17. Petitioner urges us to adopt its broader proposed construction–"separated or substantially free from at least some of the other components of the naturally occurring organism." Reply 18.

Patent Owner contends that Petitioner's proposed construction is unreasonably broad in that it would encompass milk when simply removed

from a cow. Resp. 18. Patent Owner agrees with the Board's analysis set forth in our Decision on Institution that Petitioner's proposed construction would encompass compositions where even an insignificant amount of additional components have been removed. *Id* (citing Dec. 8–9).

We have considered Petitioner's and Patent Owner's arguments and we see no need to alter our previous construction in light the full trial record. As we noted in our Institution Decision, construing the term "is isolated" as suggested by Petitioner would render the term unreasonably broad in that it would encompass separation of even an insignificant amount of other components. Dec. 8–9. The teachings in the Specification of the '086 patent counsel against such a broad construction when defining the term "isolated" with respect to 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 more than simply separating or rendering it substantially free from any amount of the other components of the naturally occurring organism. 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, the percentage of purity upon which we rely for the definition of "is isolated"—at least 25% (w/w) of the composition—in light of the complete disclosure of the Specification of the '086 patent we find in light of the complete disclosure of the Specification of the '086 patent 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.

For the reasons set forth above and in our Institution Decision, we construe the term "is isolated" as used in the '086 patent 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."

3. Carrier

In our Institution Decision we construed the term "carrier" to mean

> 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.

Dec. 6–7. The parties have not challenged this construction during trial. Response 6–19; Reply 2–18. We find no reason in view of the full trial record before us to revise this construction and apply it in our analysis in this final decision.

B. Anticipation

"Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). "A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014).

"Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Scaltech Inc. v. Retec/Tetra L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999) (citations omitted).

A product is inherently anticipated where it is the natural result of the prior art process, even though it would be possible to prevent the formation of the product through extraordinary measures. *See Allergan*, 754 F.3d at 961.

1. Goldberger et al.

Goldberger et al. discloses a study of foodstuffs for the prevention of blacktongue in dogs. Ex. 1005, 1385. Blacktongue is a canine condition similar to pellagra in humans. *Id*. at 1385–86. Like pellagra, blacktongue is caused by a deficiency of NAD+. Ex. 1010, 2. In the study, dogs were fed a blacktongue producing diet along with several candidates for preventing blacktongue. Ex. 1005, 1387–88. Among the candidates evaluated by

Goldberger et al. was milk, including skim milk. *Id*. at 1402–05. Goldberger et al. concluded that skim milk exercised a blacktongue preventative action. *Id*. at 1404.

Subsequent research has shown that one of the components in milk is nicotinamide riboside, a precursor of NAD+. Ex. 1007, 3 (Table 1), 5 (Table 3); Ex. 1008, 2 (milk a source of NR); Ex 1018, 838 (NR is found in milk); Ex. 1023, 22 (humans exposed to NR via dietary sources such as milk). Later studies also show that nicotinamide riboside increases the biosynthesis of NAD+. Ex. 1008, 6; Ex. 1018, 840.

Petitioner contends that all of the limitations of the claims of the ’086 patent are disclosed by Goldberger et al. Pet. 8–18. Patent Owner contends that Goldberger et al. does not anticipate any of the claims of the ‘086 patent. Resp. 20–30.

Based on the full trial record before us, we conclude that Petitioner has established by a preponderance of the evidence that claims 1 and 3–5 are anticipated by Goldberger et al. A preponderance of the evidence, however, does not support the conclusion that claim 2 is anticipated by Goldberger et al.

a. Claim 1

Claim 1 is directed to a pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier and formulated for oral administration. We consider each of these claim limitations in turn.

i. Pharmaceutical Composition comprising nicotinamide riboside

We have construed the term pharmaceutical composition comprising nicotinamide riboside to mean a composition, including food, which contains NR as an active agent. *See supra* Section II.A.1.

Petitioner contends that Goldberger et al. established that skim milk can be used to treat blacktongue, which is associated with a deficiency of NAD+. Pet. 11–12. Petitioner points to evidence in the record that NR is present in milk and is bioavailable. Pet. 12 (citing Ex. 1005, 1402–03; Ex. 1002 ¶ 31); Reply 19–23. Petitioner contends that the skim milk used by Goldberger et al. meets the claim limitations of a "pharmaceutical composition comprising [NR]." Pet. 12; Reply 20–23.

Patent Owner contends that Petitioner has not established that the skim milk used by Goldberger et al. constitutes a pharmaceutical composition containing NR as an active agent. Resp. 20. Patent Owner contends that Goldberger et al. is silent as to the presence of NR in the skim milk used and argues that Petitioner has not put forward any evidence that the milk used by Goldberger et al. contained NR. Resp. 23.

Patent Owner also argues that there is no evidence that the NR present in milk is active. Resp. 23. Patent Owner points to the teachings of Trammell I where it states that the NR in milk is bound to other molecules in milk to support its contention that the NR in milk is not active. Resp. 23; Ex. 1007, 2; *see* Ex 2002 ¶ 32. Patent Owner contends that Petitioner has not shown that the skim milk used by Goldberger et al. was not degraded by naturally occurring bacteria such that any NR present was eliminated or reduced to a level where it was ineffective. Resp. 23.

Patent Owner also contends that the skim milk used by Goldberger et al. is not a pharmaceutical composition. Resp. 21–22. Patent Owner contends that not all food qualifies as a pharmaceutical composition since a pharmaceutical composition must contain an active agent. Resp. 22. Patent Owner argues that since there is no evidence that the NR in milk is active, Petitioner has not shown that the skim milk of Goldberger et al. is a pharmaceutical composition under the proper claim construction. Resp. 22.

We have considered the parties' arguments as well as the evidence of record and conclude Petitioner has established by a preponderance of the evidence that the skim milk administered by Goldberger et al. is a "pharmaceutical composition" as we have construed that term.

Goldberger et al. report an experiment to determine if skim milk is effective in preventing blacktongue. Ex. 1005, 1404. Black tongue is caused by a deficiency of NAD+. Ex 1010, 2. Dr. Baur interprets the results of the experiment as establishing that milk alone improves the course of or prevents blacktongue. Ex. 1002 ¶ 21. Thus, the skim milk used by Goldberger et al. was administered to dogs "having a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis . . . such that the signs or symptoms of the disease are prevented or reduced" by the Goldberger's administration of the skim milk. Ex. 1001, col. 4, ll. 20–24.

As we previously addressed, Patent Owner's contention that foods are not pharmaceutical compositions is unpersuasive. Although we agree with Patent Owner that not all foods are necessarily pharmaceutical compositions, the Specification of the '086 patent expressly teaches that the pharmaceutical composition of the present invention can include food. Ex.

1001, col. 28, ll. 43–47, col. 53, ll. 44–46 (claim 3). In particular, where the food contains an active agent useful in treating or preventing a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis, we find it meets the definition of a pharmaceutical composition as that term is used in the challenged claims. *See* Tr.; 48; Ex. 1018, 1 (NR is found in milk constituting a dietary source or NAD^+ production) and Ex. 1008 2 (NR improves wellness and treats diseases).

Given that a food, such as the skim milk used by Goldberger et al. can be a pharmaceutical agent, there remains the questions of whether NR was necessarily present in Goldberger's skim milk and whether such NR was necessarily active in the manner required by our claim construction.

Patent Owner contends that while some of the references of record show that NR is present in milk, those references are all dated well after the Goldberger et al. study was published. Tr. 69. Patent Owner argues that there is nothing in the present record that shows that NR was present in the milk used by Goldberger et al or that it was active. Resp. 22–23.

We have considered Patent Owner's arguments and find that there is sufficient evidence in the present record to establish that NR was necessarily present in the skim milk used by Goldberger et al.

Trammell I reports a study on the concentration of NR in milk. Ex. 1007, 1. In the study, both conventional milk and organic milk were studied. *Id.* The researchers in Trammell I reported that both conventional milk and organic milk contained NR. *Id.* The researchers concluded that "NR is a major NAD+ precursor in cow milk." *Id.*

Trammell II reports a study of the bioavailability of NR taken orally. Ex. 1008, 1. In the background discussion, the researchers report that milk is a source of such NR. *Id.* at 2.

Canto reports a study using NR to enhance oxidative metabolism and protect against high fat induced obesity. Ex. 1018, 838. In the introduction, Canto states that "NR is found in milk . . . constituting a dietary source for NAD+ production." *Id.*

Bogan, a literature review of NAD+ precursors, teaches that "NR is a newly discovered salvageable precursor of NAD+ that occurs in cow's milk." Ex. 1025, 119. Bogan also teaches that milk is a source of NR in vertebrates. *Id.* at 120. Bogan goes on to teach that milk, a natural source of NR, was shown to be effective in treating pellagra-like symptoms in animals. *Id.* at 121–122 (citing Ex. 1005)

A filing with the Food and Drug Administration relating to the safety of an NR supplement Niagen teaches that "[h]umans are exposed to NR via dietary sources such as milk." Ex. 1023, 22.

Dr. Baur states in his declaration:

> As it is now known that blacktongue in dogs is a disease caused by NAD+ deficiency, it follows that the resolution or prevention of blacktongue by milk supplementation, as shown in Goldberger et al., is direct evidence that the milk stimulated greater NAD+ biosynthesis upon oral administration. (Ex. 1005, Goldberger et al., at 1404.) This conclusion is confirmed by later studies, discussed above in paragraphs 13-14, directly demonstrating that oral intake of NR increases NAD+ concentration in multiple tissues. Thus, Goldberger et al. teaches the oral administration of a composition containing NR that necessarily increases NAD+ biosynthesis upon oral administration

Ex. 1002, ¶ 36.

Each of these references clearly demonstrates that not only that NR is present in milk, but that it is a source or precursor for NAD+ production. Although the references do not qualify as prior art to the '086 patent, they may nonetheless be relied upon to show inherency. *See Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); *see also Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."). As such, we find that the references' teachings support the conclusion that not only is NR a constituent of milk, but that it is active in the production of NAD+. In other words, the NR in milk is an active agent as required under our claim construction. The evidence of record establishes that NR is also present in skim milk. NR is a water soluble component of milk. Ex. 1002, ¶ 12. Skim milk is milk from which practically all cream has been removed. [cite] It is rich in water soluble ((B complex) vitamins and in minerals." Ex. 101, 6. NR is a vitamin B3 derivative. E. 1017, 826. Thus, we further find that NR was present in the skim milk used by Goldberger et al.

Based on the evidence of record we find Patent Owner's contention that the NR in milk is not active because Trammell I teaches that NR in milk is bound to other components in milk to be unpersuasive in light of this clear demonstration in the record that NR is an active agent in milk. Resp. 23. In

support of this contention, Patent Owner relies on the Declaration of Dr. Zhou wherein he opines that since Trammell I states that the NR might be complexed to a protective factor in milk, it might not be freely available and may not act as an active agent. Ex. 2002 ¶ 35.

Patent Owner's argument is not persuasive. As demonstrated above, the references of record teach that milk is a source of NR for the production of NAD+ in vertebrates. While Trammell I suggests that the NR in milk might be bound to other components in milk, Trammell I also teaches that these substances improve the stability of NR. Ex. 1007, 2 and 5. Nothing in Trammell I or the other references of record suggest that the NR in milk is not available for NAD+ production; to the contrary, Trammel I teaches that the NR present in milk is active. *Id.*

Patent Owner also contends that Petitioner has not shown that the milk used in Goldberger et al. was not degraded by natural bacteria. Resp. 23. We are not persuaded. As Patent Owner points out, Goldberger et al. expressly states that the milk used was fresh skim milk that has been allowed to stand in an ice box for not more than 24 hours. Reply 22–23; Ex. 1005, 1403. The Inventor, Dr. Brenner, in his Declaration filed during prosecution of the '086 patent stated that NR is "stable for at least 24 hours at room temperature in milk." Ex. 1003, 132, *see also* Ex. 1023, 22 (NR levels do not change significantly when milk is stored at room temperature for 24 hours). Based on this admission, we find one of ordinary skill in the art would have expected the level of NR to remain substantially the same when the milk is stored in an ice box. While there may be unusual circumstances in which bacteria in the milk renders the NR inactive, nothing of record suggests that the skim milk of Goldberger at al. is unusual in any way. As

such, there is no basis for us to speculate that the NR in such skim milk was degraded or otherwise inactive. Inherency cannot be avoided by taking "extraordinary measures." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1350 (Fed. Cir. 1999).

Based on the foregoing analysis we find that that the skim milk used in Goldberger et al. was a pharmaceutical composition comprising 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.

ii. In admixture with a carrier.

Petitioner contends that the skim milk used in Goldberger et al. meets the limitation of the nicotinamide riboside "in admixture with a carrier" in that the NR is in a mixture with lactose and other components in milk that bind and stabilize the compound. Pet. 13. Petitioner relies on the Declaration of its expert Dr. Baur to support this contention. Ex. 1002 ¶ 32.

Patent Owner contends that the skim milk in Goldberger et al. does not comprise an admixture of NR with a carrier because the milk was not specifically prepared as an admixture of NR and a carrier. Resp. 25. Patent Owner contends that the term admixture calls for a purposeful combination of ingredients and not one that occurs naturally. *See* Prelim Resp. 24; Resp. 25.

As we noted in our Institution Decision, we find nothing in the record that supports Patent Owner's contention that the term "admixture" requires that the ingredients be purposefully mixed. Dec. 12. This observation remains true based on our consideration of the full trial record. Patent Owner has pointed us to disclosure in the Specification of the '086 patent

that states that compositions may be prepared by well-known methods and points to a compendium describing such methods, but such teaching does not support Patent Owner's proposition that the term "admixture" requires some affirmative purposeful act. *See* Resp. 25; Ex. 2002 ¶ 39; Ex. 1001, col. 28, ll. 49–60. The term "admixture" is not even mentioned in the referenced portion of the Specification of the '086 patent. Thus, we decline to interpret the term the claims to require a purposeful combination of ingredients.

The Specification teaches that materials that can be used as carriers "include sugars, such as lactose." Ex. 1001, col. 29, ll. 1–2. Trammell I teaches that milk contains a combination of NR and other components including lactose. Ex. 1007, 3 (Table 2). Dr. Baur testified that the NR present in skim milk is in an admixture with a carrier because the NR is in a mixture with other components of the milk, including components that bind and stabilize NR. Ex. 1002 ¶¶ 11, 31.

We conclude that Petitioner has shown sufficiently that the NR in the skim milk used by Goldberger et al. was in admixture with a carrier.

iii. Said composition formulated for oral consumption

Petitioner contends that the milk used by Goldberger et al. was administered orally and thus, was formulated for oral consumption. Pet. 12–14. In support of this contention, Petitioner points to the Declaration of Dr. Baur, who relies on the teachings of Goldberger et al. *Id.*; Ex. 1002 ¶ 32; Ex. 1005, 1403. Dr. Baur notes that the "skim milk in Goldberger et al. was administered orally," and concludes that Goldberger et al. teaches the claimed pharmaceutical composition that "is suitably formulated for oral administration." Ex. 1002 ¶ 32. Patent Owner does not dispute this fact.

We agree with and credit Dr. Baur's analysis of the teachings of the Goldberger et al. reference.

We find that Petitioner has shown that the milk in Goldberger et al. was formulated for oral consumption.

iv. Conclusion

We conclude that Petitioner has established by a preponderance of the evidence that claim 1 is anticipated by Goldberger et al.

b. Claim 2.

Claim 2 adds the additional limitation that the NR is isolated from a natural or synthetic source. Ex. 1001, col. 53, ll. 42–43. As discussed above, we have defined the term "isolated" to mean that the NR 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.

As discussed above, Petitioner contends that our construction of the term "is isolated" is improper and should not include the requirement that the NR comprise at least 25% (w/w) of the composition. Reply 15–18. Petitioner contends that the skim milk used by Goldberger et al. is isolated in that the skim milk is separated or substantially free of at least some of the components of the naturally occurring organism including the fat elements of milk. Reply 25.

Patent Owner contends that Petitioner has not met its burden in that there is no evidence of record to show that NR comprises 25% (w/w) of the skim milk used by Goldberger et al. Prelim. Resp. 13–14; Resp. 31.

As discussed above, we decline to adopt Petitioner's construction of the term "is isolated" and maintain the construction that calls for NR to constitute at least 25% (w/w) of the composition.

We have found no persuasive evidence in the record to show that NR constituted at least 25% (w/w) of the skim milk used by Goldberger et al. Therefore, we conclude that Petitioner has not established by a preponderance of the evidence that the NR in the skim milk was "isolated" as required by claim 2.

Our conclusion remains that same even if we were to agree with Petitioner's contention that it is improper to adopt the 25% purity level included in our construction of the term "is isolated." The Specification teaches that when NR is isolated from natural sources, such as cow's milk, it is separated from other components such as "salts, carbohydrates, polypeptides, nucleic acids, fats and the like." Ex. 1001 col. 27, ll. 6–7. The Specification makes it clear that not just one or some of these components should be removed, but that each of the components should be removed as part of the isolation process. *Id.*

While skim milk has had most, if not all, of the fat content removed, skim milk still retains other minerals, carbohydrates and proteins. *See*, Ex. 1007, 369 (protein fraction present in skim milk); Ex. 2003, 53–54 (lactose present in the skim milk used by Goldberger et al.); Ex. 1011, 6 (skim milk contains water soluble vitamins and minerals). Thus, regardless of whether the claims require a minimum percentage of NR, we find that the NR present in skim milk is not "isolated" because significant amounts of other components remain after the fat is removed.

We therefore conclude that claim 2 is not anticipated by Goldberger et al.

c. Claim 3.

Claim 3, which depends from claim 1, adds the additional limitation that the pharmaceutical composition comprises "a tablet, troche, capsule, elixir, suspension, syrup, wafer chewing gum or food." Ex. 1001, col. 53, ll. 44–46.

Petitioner contends that this element is satisfied by the skim milk of Goldberger et al. in that skim milk is a food. Pet. 15. Petitioner relies on the Declaration of Dr. Baur to support this contention. *Id.*; Ex. 1002 ¶ 34.

Patent Owner contends that claim 3 is not anticipated by Goldberger et al. for the same reasons that claim 1 is not anticipated. Resp. 26. Patent Owner argues that the skim milk of Goldberger et al. is not a pharmaceutical composition containing NR as an active ingredient. *Id.*

For the reasons stated above with respect to claim 1, we find Patent Owner's argument unpersuasive. The evidence of record demonstrates that skim milk, a food product, contains NR, and that the NR is an active agent in the skim milk. Ex. 1002 ¶ 34; Ex. 1007, 1; Ex. 1018, 838.

We conclude that Petitioner has established by a preponderance of the evidence that claim 3 is anticipated by Goldberger et al.

d. Claim 4.

Claim 4, which depends from claim 1, adds the additional limitation that the pharmaceutical composition comprises "one or more of tryptophan, nicotinic acid, or nicotinamide." Ex. 1001, col. 54, ll. 37–39.

Petitioner contends that this limitation is met in that the skim milk used in Goldberger at al. contains nicotinamide and tryptophan. Pet. 15–16. To support this contention, Petitioner cites to Trammell I where it states that "[i]t has long been known that NAD+ precursors in milk include nicotinamide and tryptophan." Ex. 1007, 1.

As with claim 3, Patent Owner contends that claim 4 is not anticipated for the same reasons that claim 1 is not anticipated. Resp. 27.

For the reasons stated above with respect to claim 1, we find Patent Owner's argument unpersuasive. The evidence of record also demonstrates

that skim milk, contains tryptophan and nicotinaminde as well as NR. Ex. 1007, 1, 3 Table 1; Ex. 1012, 293–294.

We conclude that Petitioner has established by a preponderance of the evidence that claim 4 is anticipated by Goldberger et al.

e. Claim 5.

Claim 5 depends from claim 1 and adds the limitation that the pharmaceutical composition "increases NAD+ biosynthesis upon oral administration." Ex. 1001, col. 54, ll. 41–42.

Petitioner contends that this limitation is inherently met by the skim milk used by Goldberger et al. Pet. 16–17. Petitioner relies on the teachings of Trammell I to show that milk contains nicotinamide riboside, a precursor of NAD+. Pet. 16; Ex. 1007, 6. Trammell II and Dr. Brenner's Declaration submitted during prosecution of the '086 patent are relied upon to show that administration of nicotinamide riboside, including oral administration, boosts production of NAD+. Ex. 1008, 6–7; Ex. 1003, 133–35.

Petitioner also relies on the teaching in Goldberger et al. that dogs fed skim milk did not develop blacktongue. Pet. 17; Ex. 1005, 1403–04. Blacktongue is caused by a deficiency of NAD+. Ex. 1010, 2. Petitioner contends that the results in Goldberger et al. are evidence that NAD+ biosynthesis in the subject dogs was increased by administration of skim milk. Pet. 17.

Patent Owner contends that there is no evidence of record that the milk administered by Goldberger et al. actually increased NAD+ biosynthesis. Resp. 26. Patent Owner also contends that even if NAD+ biosynthesis was increased by the administration of skim milk by Goldberger at al., there is no evidence that the NR in the milk was the cause

of the increase in NAD+ biosynthesis as the milk contained other NDA+ precursors. *Id*. at 28. Patent Owner argues that the references cited by Petitioner do not demonstrate that any NR that is present in milk increases biosynthesis of NAD+. Resp. 29.

We have considered the parties' arguments and conclude that a preponderance of the evidence supports the conclusion that claim 5 is anticipated by Goldberger et al.

As Petitioner points out, claim 5 calls for the *composition* of claim 1 to increase the biosynthesis of NAD+ production. Reply 26–27. The claim does not call for the NR present in the composition to necessarily cause the increased biosynthesis. *Id.*

Goldberger et al. demonstrates that feeding skim milk to dogs prevents blacktongue. Ex. 1005, 1404. Blacktongue is caused by a deficiency of NAD+. Ex. 1010, 2. We agree with Petitioner that the evidence of record demonstrates that the consumption of milk increases NAD+ biosynthesis. *See also* Ex. 1026, 84:3–85:3 (Dr. Zhou agreeing that literature teaches that black tongue reflects a deficiency in NAD and NAD+ biosynthesis in dogs increased with oral administration of milk).

We also find that Petitioner has shown sufficiently based on the evidence presented at trial that the skim milk used by Goldberger et al. increases NAD+ biosynthesis.

As discussed above with respect to claim 1, the evidence of record demonstrates that NR is an active agent in milk. Ex. 1007, 1; Ex. 1008, 1; Ex. 1018, 838; Ex. 1025, 119–120. The evidence of record also demonstrates that the NR in milk is used to produce NAD+ *in vivo*. For example, Canto teaches that NR is found in milk, "constituting a dietary

source for NAD+ production." Ex. 1018, 1; *see also* ; Ex. 1002 ¶¶ 13–14 (discussing oral bioavailability of nicotinamide riboside), 43 (concluding "[a]s it is now known that pellagra is a disease caused by NAD+ deficiency, it follows that the prevention of pellegra by buttermilk supplementation demonstrated in Goldberger and Tanner is direct evidence that the buttermilk stimulated great NAD+ biosynthesis upon oral administration" and citing later studies demonstrating that oral NR increases NAD+ concentration in multiple tissues). Dr. Brenner in his declaration submitted during prosecution of the '086 patent stated that "NR unexpectedly is more orally available than nicotinamide to produce NAD and NADP in white blood cells in the 80 minute experiment." Ex. 1003, 135.

We, therefore, conclude that Petitioner has established by a preponderance of the evidence that claim 5 is anticipated by Goldberger et al.

2. *Goldberger and Tanner*

Goldberger and Tanner report a study of the treatment and prevention of pellagra in humans. Ex. 1006, 1. Pellagra is caused by a deficiency of NAD+. Ex. 1010, 2. In the study, 29 subjects were fed a diet that included 1,200 grams of buttermilk[5] a day for up to a year. Ex. 1006, 93. The subjects did not develop pellagra during the observation period despite the expectation that without the buttermilk, 40 to 50% of the subject would have developed the disease. *Id.* Goldberger and Tanner concluded that the results were "conclusive evidence of the preventive action of buttermilk." *Id.*

[5] "Buttermilk is the product that remains when butter is removed from milk or cream in the process of churning." Ex. 1011, 6.

As discussed above with respect to the anticipation grounds based on Goldberger et al., subsequent research has shown that one of the components in milk is nicotinamide riboside, a precursor of NAD+. Ex. 1007, 3 (Table 1), 5 (Table 3); Ex. 1008, 2 (milk a source of NR); Ex 1018, 838 (NR is found in milk); Ex. 1023, 22 (Humans are exposed to NR via dietary sources such as milk). Later studies also show that nicotinamide riboside increases the biosynthesis of NAD+. Ex. 1008, 6–7, Ex. 1018, 840.

Petitioner contends that all of the limitations of the claims of the ’086 patent are disclosed by Goldberger and Tanner. Pet. 18–29. Patent Owner contends that Goldberger and Tanner does not anticipate any of the claims of the ’086 patent. Resp. 32–34.

Based on the record before us, we conclude that Petitioner has established by a preponderance that claims 1 and 3–5 are anticipated by Goldberger and Tanner. However, Petitioner has failed to establish by a preponderance of the evidence claim 2 is anticipated by Goldberger and Tanner.

a. Claim 1.

Claim 1 is directed to a pharmaceutical composition comprising nicotinamide in admixture with a carrier and formulated for oral administration. We consider each of these claim limitations in turn.

i. Pharmaceutical Composition comprising nicotinamide riboside

We have construed the term pharmaceutical composition comprising nicotinamide riboside to mean a composition, including food, which contains NR as an active agent.

Petitioner contends that Goldberger and Tanner established that buttermilk milk can be used to treat pellagra which is associated with a

deficiency of NAD+. Pet. 22–23. Petitioner contends that the buttermilk is a pharmaceutical composition. *Id.* Petitioner points to evidence in the record that NR is present in milk and is bioavailable. Pet. 23; Reply 21–23 citing Exs. 1007, 3, 5; Ex. 1008, 2; Ex 1025, 119; Ex. 1023, 22. Petitioner contends that the buttermilk used by Goldberger and Tanner is a pharmaceutical composition that contains NR. Pet. 23–24; Reply 29.

Patent Owner makes similar arguments for why Goldberger and Tanner do not anticipate the challenged claims as it made for the anticipation grounds based on Goldberger et al. For instance, Patent Owner contends that Petitioner has not established that the milk used by Goldberger and Tanner constitutes a pharmaceutical composition containing NR as an active agent. Resp. 32–33. Patent Owner contends that Goldberger and Tanner is silent as to the presence of NR in the buttermilk used, and that Petitioner has not put forward any evidence that the buttermilk used by Goldberger and Tanner contained NR. *Id.*

Patent Owner goes on to argue that there is no evidence that the NR present in milk is active. Resp. 33. Patent Owner again points to the teachings of Trammell I where it states that the NR in milk is bound to other molecules in milk as supporting its contention that the NR in milk is not active. Resp. 33; Ex. 1007, 2; *See* Ex 2002 ¶ 34. Patent Owner contends that Petitioner has not shown that the buttermilk used by Goldberger and Tanner was not degraded by naturally occurring bacteria such that any NR present was eliminated or reduced to a level where it was ineffective. Resp. 33.

Patent Owner also contends that the buttermilk used by Goldberger and Tanner is not a pharmaceutical composition. Resp. 32–33. Patent

Owner contends that not all food qualifies as a pharmaceutical composition since a pharmaceutical composition must contain an active agent. Resp. 22. Patent Owner argues that since there is no evidence that the NR in milk is active, milk is not a pharmaceutical composition under the proper claim construction. Resp. 22.

We have considered the parties' arguments as well as the evidence of record and conclude Petitioner has shown that the buttermilk administered by Goldberger and Tanner is a "pharmaceutical composition" as we have construed that term.

Goldberger and Tanner report the results of an experiment testing whether buttermilk is effective in preventing pellagra. Ex. 1006, 93. Pellagra is caused by a deficiency of NAD+. Ex 1010, 2. Dr. Baur interprets the results of the experiment as establishing that milk alone improves the course of or prevents pellagra. Ex. 1002 ¶ 21. Thus, the buttermilk used by Goldberger and Tanner was administered to humans "having a disease or condition associated with the nicotinamide riboside kinase pathway of NAD+ biosynthesis . . . so that the signs of symptoms of the disease are prevented or reduced." Ex. 1001, col. 4, ll. 20–24.

As we previously addressed, Patent Owner's contention regarding foods not being pharmaceutical compositions is unpersuasive. However, given that a food, such as the buttermilk used by Goldberger and Tanner can be a pharmaceutical agent, there remains the questions of whether NR was necessarily present in the buttermilk and was the NR was necessarily active in the manner required by our claim construction.

Patent Owner contends that while some of the references of record show that NR is present in milk, those references are all dated well after the

Goldberger and Tanner study was published. Tr. 69. Patent Owner argues that there is nothing in the present record that shows that NR was present in the buttermilk used by Goldberger and Tanner or that it was active. Resp. 33.

We have considered Patent Owner's arguments and find that there is sufficient evidence in the present record to establish that NR was necessarily present as an active agent in the buttermilk used by Goldberger and Tanner. Our conclusion is based on the teachings of the same post-filing references (Trammell I, Tramell II, Cato, Bogan, and the Niagen FDA filing) discussed above with regard to the anticipation ground based on Goldberger et al. Ex. 1007; Ex. 1008, Ex. 1018, Ex. 1025; Ex. 1023. Furthermore, Dr. Baur states in his declaration:

> As it is now known that pellagra is a disease caused by NAD+ deficiency, it follows that the prevention of pellagra by buttermilk supplementation demonstrated in Goldberger and Tanner is direct evidence that the buttermilk stimulated greater NAD+ biosynthesis upon oral administration. (Ex. 1006, Goldberger and Tanner, at 93.) This conclusion is confirmed by later studies, discussed above in paragraphs 13-14, directly demonstrating that oral NR increases NAD+ concentration in multiple tissues. Thus, although the authors did not know it at the time, Goldberger and Tanner inherently discloses an NR-containing composition that can be orally administered and increases NAD+ biosynthesis upon oral administration.

Ex. 1002 ¶ 43. The evidence of record establishes that NR is also present in buttermilk. NR is a water soluble component of milk. Ex. 1002, ¶ 12. Buttermilk is what remains when butter is removed from milk. Ex. 1011, 6. Thus buttermilk contains the same water soluble components of milk as skim milk. Ex. 1002, ¶ 12. Moreover, Goldberger and Tanner teach that for

treating pellagra, fresh milk and buttermilk are interchangeable. Ex. 1006, 95. Thus, we find that NR was present in the buttermilk used by Goldberger and Tanner. Additionally, for the reasons already discussed above, we are unpersuaded by Patent Owner's arguments that the NR in milk is not active because Trammell I teaches that NR in milk is bound to other components in milk. Resp. 33. Goldberger and Tanner expressly states that the buttermilk used was "fresh, locally produced, and of fair quality." Ex. 1006, 93. As such, there is no basis for us to speculate that the NR in such buttermilk Based on the foregoing analysis, we conclude Petitioner has established that the buttermilk used in Goldberger and Tanner was a pharmaceutical composition comprising 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.

ii. In admixture with a carrier.

Petitioner contends that the buttermilk used in Goldberger and Tanner meets this limitation in that the NR is in a mixture with lactose and other components in milk that bind and stabilize the compound. Pet. 24. Petitioner relies on the Declaration of its expert Dr. Baur to support this contention. Ex. 1002 ¶ 32.

For the same reasons provided with regard to the skim milk used in Goldberger et al., Patent Owner contends that the buttermilk in Goldberger and Tanner does not comprise an admixture of NR with a carrier, i.e., because the milk was not specifically prepared as an admixture of NR and a

carrier. Resp. 25.[6] For the reasons that we have provided in relation to the skim milk used in Goldberger et al., we also find that the Petitioner has established that the NR in the buttermilk used by Goldberger and Tanner was in admixture with a carrier.

iii. Said composition formulated for oral consumption

Petitioner contends that the buttermilk used by Goldberger and Tanner was administered orally and thus, was formulated for oral consumption. Pet. 24–25. In support of this contention, Petitioner points to the Declaration of Dr. Baur who relies on the teachings of Goldberger and Tanner. *Id.*; Ex. 1002 ¶ 37; Ex. 1006, 1403. Dr. Baur notes that the "buttermilk in Goldberger and Tanner was administered orally," and concludes that Goldberger and Tanner teaches the claimed pharmaceutical composition that "is suitably formulated for oral administration." Ex. 1002 ¶ 37. We agree with and credit Dr. Baur's analysis of the teachings of the Goldberger and Tanner reference.

We find that Petitioner has shown that the buttermilk in Goldberger and Tanner was formulated for oral consumption.

iv. Conclusion

We conclude that Petitioner has established by a preponderance of the evidence that claim 1 is anticipated by Goldberger and Tanner.

a. Claim 2.

Claim 2 adds the additional limitation that the NR is isolated from a natural or synthetic source. Ex. 1001, col. 53, ll. 42–43. As discussed

[6] Patent Owner does not specifically address this limitation in its discussion of Goldberger and Tanner but refers to the reasons presented with respect to Goldberger et al. Resp. 34.

above, we have defined the term "isolated" in claim 2 to mean that the NR 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.

We have found no persuasive evidence in the record to show that NR constituted at least 25% (w/w) of the buttermilk used by Goldberger and Tanner. Therefore, we conclude that Petitioner has not established that the NR in the skim milk was isolated as required for claim 2 under our claim construction.

Furthermore, as also discussed above, our conclusion remains the same even if we were to agree with Petitioner's contention that it is improper adopt the 25% purity level requirement. While buttermilk has had most, if not all of the butter content removed, it nonetheless retains other minerals, carbohydrates and proteins. *See, e.g.*, Ex. 1006, 93 (protein fraction present in buttermilk); Ex. 1012, 1602, 1604, 1608–09 (tryptophan and tyrosine present in buttermilk solids). Thus, regardless of whether the claims require a minimum percentage of NR, we find that the NR present in milk is not "isolated" because significant amounts of other components remain after the fat is removed.

We therefore conclude that Petitioner has not shown by a preponderance of the evidence that claim 2 is anticipated by Goldberger and Tanner.

b. Claim 3.

Claim 3, which depends from claim 1, adds the additional limitation that the pharmaceutical composition comprises "a tablet, troche, capsule,

elixir, suspension, syrup, wafer, chewing gum, or food." Ex. 1001, col. 53, ll. 44–46.

Petitioner contends that this element is satisfied by the buttermilk of Goldberger and Tanner in that buttermilk is a food. Pet. 26. Petitioner relies on the Declaration of Dr. Baur to support this contention. *Id.*; Ex. 1002 ¶ 39.

Patent Owner contends that claim 3 is not anticipated by Goldberger and Tanner for the same reasons that claim 1 is not anticipated. Resp. 26.

For the reasons stated above with respect to claim 1, we find Patent Owner's argument unpersuasive. The evidence of record demonstrates that buttermilk, a food product, contains NR and that the NR is an active agent in the buttermilk. Ex. 1002 ¶ 37; Ex. 1007, 1; Ex. 1018, 838.

We, therefore, conclude that Petitioner has established by a preponderance of the evidence that claim 3 is anticipated by Goldberger and Tanner.

c. Claim 4.

Claim 4, which depends from claim 1, adds the additional limitation that the pharmaceutical composition comprises "one or more of tryptophan, nicotinic acid, or nicotinamide." Ex. 1001, col. 54, ll. 37–39.

Petitioner contends that this limitation is met in that the buttermilk used in Goldberger and Tanner contains nicotinamide and tryptophan. Pet. 26–27. To support this contention, Petitioner cites to Trammell I where it states that "[i]t has long been known that NAD+ precursors in milk include nicotinamide and tryptophan." Ex. 1007, 1.

As with claim 3, Patent Owner contends that claim 4 is not anticipated for the same reasons that claim 1 is not anticipated. Resp. 27.

For the reasons stated above with respect to claim 1, we find Patent Owner's argument unpersuasive. The evidence of record also demonstrates that buttermilk contains tryptophan and nicotinaminde as well as NR. Ex. 1007, 1, 3 Table 1; Ex. 1012, 293–294.

We, therefore, conclude that Petitioner has established by a preponderance of the evidence that claim 4 is anticipated by Goldberger and Tanner.

d. Claim 5.

Claim 5 depends from claim 1 and adds the limitation that the pharmaceutical composition "increase[s] NAD+ biosynthesis upon oral administration." Ex. 1001, col. 54, ll. 41–42.

Petitioner contends that this limitation is inherently met by the buttermilk used by Goldberger and Tanner. Pet. 28–29. Petitioner relies on the teachings of Trammell I to show that buttermilk contains nicotinamide riboside, a precursor of NAD+. Pet. 28; Ex. 1007, 6. Trammell II and the Brenner Declaration are relied upon to show that administration of nicotinamide riboside, including oral administration, boosts production of NAD+. Ex. 1008, 6–7; Ex. 1003, 133–35.

Petitioner also relies on the teaching in Goldberger and Tanner that administration of buttermilk prevented the development of pellagra in humans. Pet. 28–29; Ex. 1006, 93. Pellagra is caused by a deficiency of NAD+. Ex. 1010, 2. Petitioner contends that the results in Goldberger and Tanner are evidence that NAD+ biosynthesis in the subjects was increased by administration of skim milk. Pet. 17.

Patent Owner contends that there is no evidence of record that the milk administer by Goldberger and Tanner actually increased NAD+

biosynthesis. Resp. 33. Patent Owner also contends that even if NAD+ biosynthesis was increased by the administration of buttermilk by Goldberger and Tanner, there is no evidence that the NR in the milk was the cause of the increase in NAD+ biosynthesis as the milk contained other NDA+ precursors. *Id.* at 34. Patent Owner argues that the references cited by Petitioner do not demonstrate that any NR occurring in milk increases biosynthesis of NAD+. Resp. 34.

We have considered the parties' arguments and conclude that a preponderance of the evidence supports the conclusion that claim 5 is anticipated by Goldberger and Tanner.

As Petitioner points out, claim 5 calls for the composition of claim 1 to increase the biosynthesis of NAD+ production. Reply 26–27. The claim does not call for the NR present in the composition to cause the increased biosynthesis. *Id.*

Goldberger and Tanner demonstrates that feeding buttermilk to humans prevented pellagra. Ex. 1006, 8. Pellagra is caused by a deficiency of NAD+. Ex. 1010, 2. The evidence of record demonstrates that the consumption of milk increases NAD+ biosynthesis.

Moreover, even if we accept Patent Owner's argument that claim 5 calls for the NR present in the composition to increase NR biosynthesis, we find that a preponderance of the evidence supports the conclusion that the skim milk used by Goldberger and Tanner increases NAD+ biosynthesis.

As discussed above with respect to claim 1, the evidence of record demonstrates that NR is an active agent in milk. Ex. 1007, 1; Ex. 1008, 1; Ex. 1018, 838; Ex. 1025, 119–120. The evidence of record also demonstrates that the NR in milk is used to create NAD+ in vivo. For

example, Canto teaches that NR is found in milk, "constituting a dietary source for NAD+ production." Ex. 1018, 1.

We, therefore, conclude that Petitioner has established by a preponderance of the evidence that claim 5 is anticipated by Goldberger and Tanner.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has shown by a preponderance of the evidence that: 1) claims 1 and 3–5 are unpatentable as anticipated by Goldberger et al.; and 2) claims 1 and 3–5 are unpatentable as anticipated by Goldberger and Tanner.

We also determine that Petitioner has not shown by a preponderance of the evidence that claim 2 is anticipated by either Goldberger et al. or Goldberger and Tanner.

IV. ORDER

Accordingly it is ORDERED that claims 1 and 3–5 have been shown by a preponderance of the evidence to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written 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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