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: IPR2017-01795
U.S. Patent No. 8,383,086 B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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1010	Laurent Mouchiroud et al., "NAD^+ Metabolism, a Therapeutic Target for Age-Related Metabolic Disease," *Crit. Rev. Biochem. Mol. Biol*., 48(4):397-408 (2013) ("Mouchiroud et al.")
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I. INTRODUCTION

The arguments in Patent Owner's Response largely rely on its proposal that the Board adopt a narrow construction of claim 1 by reading into it an "active agent" limitation.[1] As explained below, the Board should decline Patent Owner's invitation to ignore the well-established meaning of "comprising" and re-write the claims. If the Board rejects Patent Owner's proposed claim construction, virtually all of the arguments presented in its Response are moot. The few remaining arguments can be dismissed easily as conclusory and unsubstantiated.

[1] The terms of the '086 patent are given their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016). Petitioner's proposed claim constructions are also correct under the claim construction standard set forth in *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005) (en banc) and its progeny.

II. CLAIM CONSTRUCTION

A. The phrase "[a] pharmaceutical composition comprising nicotinamide riboside" should not be re-written to mean "a composition comprising nicotinamide riboside *as the active agent*."

1. "Comprising" means "including"

Claim 1 of the '086 patent is directed to "A pharmaceutical composition comprising nicotinamide riboside in admixture with a carrier, wherein said composition is formulated for oral administration." (Ex. 1001, '086 patent, at 53:38-40.) To avoid the invalidating prior art, Patent Owner now argues for the first time that the phrase "pharmaceutical composition comprising nicotinamide riboside" should be construed to require not only that the composition comprise nicotinamide riboside, but also that the nicotinamide riboside itself act "as the active agent" of the composition.[2] This construction contradicts well-established patent law, is not supported by the specification or the claims, and should be rejected.

[2] Patent Owner presented its proposed claim constructions in its Preliminary Response and never suggested that the claims contain an "active agent" limitation.

The transitional term "comprising" has a specific meaning in patent law. As the Federal Circuit has explained, the term "comprising" is "well understood in patent law to mean 'including but not limited to.'" *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1319 (Fed. Cir. 2009).[3] By reciting the phrase "comprising nicotinamide riboside," claim 1 therefore requires that the claimed composition include, but not be limited to, nicotinamide riboside. Patent Owner's assertion that the patentee expressed a "clear intent to identify nicotinamide riboside as the active agent of the claimed composition" cannot be squared with the plain language of the claims. (Patent Owner Response ("POR") at 10.)

If Patent Owner wanted to seek claims limited to pharmaceutical compositions in which nicotinamide riboside is the active agent, it could

[3] Consistent with this understanding, the specification explains that "the present invention is a dietary supplement composition ***containing*** nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." (Ex. 1001, '086 patent at 4:14-16 (emphasis added)).

easily have done so by expressly including an "active agent" limitation in the claims. Instead, it used the open-ended word "comprising" to seek and obtain broader claims.[4]

2. Patent Owner's proposed construction is not supported by the specification

The claims of the '086 patent do not recite an "active agent" limitation. And the specification of the '086 patent does not define any of

[4] As the Board noted in its Institution Decision, claim 3 of the '086 patent establishes that "as used in claim 1, the term 'pharmaceutical composition' includes food products." (Paper No. 9.) Patent Owner dismisses this conclusion as "absurd" because "any food would qualify." (POR at 14.) Patent Owner did not seek a construction of the phrase "pharmaceutical composition," and its proposed construction of "pharmaceutical composition comprising nicotinamide riboside" in incorrect for the reasons stated herein. Moreover, it is undisputed that Goldberger et al. discloses the administration of skim milk *to prevent disease*, and that Goldberger and Tanner discloses the administration of buttermilk *to prevent disease*. *See* Petition at 12, 22. Accordingly, to the extent the preamble of claim 1 is limiting, Goldberger et al. and Goldberger and Tanner disclose it.

the words that appear in the claims to impose an "active agent" requirement. Notably, Patent Owner does not argue otherwise.

To justify its proposed claim construction, Patent Owner largely relies on the specification. Patent Owner incorrectly asserts that "[t]he '086 patent consistently and repeatedly emphasizes nicotinamide riboside and its use as an active agent in the claimed pharmaceutical composition." (POR at 9.) Even if that were true—and it is not, as explained below—limitations from the specification cannot be read into the claims.

a. The specification's two references to a "pharmaceutical composition"

The phrase "pharmaceutical composition" is used only twice in the specification of the '086 patent, and neither usage refers to a pharmaceutical composition in which nicotinamide riboside is the active agent. Tellingly, neither usage is mentioned in Patent Owner's Response.

The first reference to a "pharmaceutical composition" does not even concern compositions containing nicotinamide riboside. Instead, it is directed to "[n]ucleic acids encoding Nrk, vectors containing the same, or Nrk polypeptides." (Ex. 1001, '086 patent, 23:14-26 (emphasis added).) In the second reference to a "pharmaceutical composition," the specification generally refers to the prescription of an effective amount *of a*

pharmaceutical composition, not an effective amount of any particular active ingredient, let alone nicotinamide riboside. (Ex. 1001, '086 patent, 31:42-46 (emphasis added).)

b. The portions of the specification cited by Patent Owner do not support its proposed claim construction

Patent Owner's Response relies on four bullet points with snippets from the specification of the '086 patent, but none supports Patent Owner's proposed claim construction. (*See* POR at 9-10.) In particular, none of the quoted passages refers to a "pharmaceutical composition comprising nicotinamide riboside" or to nicotinamide riboside as an active agent. For that reason alone, these portions of the specification cannot justify Patent Owner's proposed construction.

Two of the quoted excerpts (bullet points 1 and 3) refer to an "effective amount" of "a nicotinamide riboside composition" or "nicotinamide riboside." However, Patent Owner's own proposed claim construction does not refer an "effective amount." And for good reason: the claims say nothing about the presence of an "effective amount" of nicotinamide riboside. Indeed, Patent Owner's expert, Dr. Zhaohui Sunny Zhou, testified that the claims do ***not*** include an "effective amount" limitation:

> Q. . . . . Is that your understanding of Claim 1, that it requires that there be an amount that can be deemed an effective amount, meaning that it causes a certain effect with respect to a disease state?
>
> MR. ABRAMIC: Objection. Scope.
>
> A. When you ask me that question, ***I think that's not part of Claim 1 at all.*** Sorry, I said this very bluntly. I think maybe you confused the concept of the patent claim and the ultimate drug. That's maybe where the confusion comes from.

(Ex. 1026, Zhou Tr. at 28:15-29:3 (emphasis added).)

The other two cited excerpts (bullet points 2 and 4) refer to "a nicotinamide riboside composition" and "nicotinamide riboside treatments." Neither mentions the claim term "pharmaceutical composition comprising nicotinamide riboside" or an "active agent" requirement.

The only reference to an "active agent" in the specification that is cited in Patent Owner's Response simply states:

> Polypeptides, nucleic acids, vectors, dietary supplements (i.e. nicotinamide riboside), and nicotinamide riboside-related prodrugs produced or identified in accordance with the methods of the invention ***can be*** conveniently used or administered in a

composition containing the active agent in combination with a pharmaceutically acceptable carrier.

(Ex. 1001, '086 patent, at 28:49-54 (emphasis added).) This permissive language in one paragraph of the specification does not import limitations into the claims. *See i4i Ltd. P'ship v. Microsoft Corp.,* 598 F.3d 831, 844 (Fed. Cir. 2010) (claims not limited by specification's "permissive language").[5]

Moreover, the "composition" under discussion in this portion of the specification clearly does not require that nicotinamide riboside be the "active agent" of the composition. For example, the active agent of a composition containing "a nucleic acid[] . . . produced or identified in accordance with the methods of the invention" is *not* nicotinamide riboside. The only nucleic acids identified the '086 patent relate to the gene encoding the enzyme nicotinamide riboside kinese (NRk), not nicotinamide riboside.

[5] Each of the specification's references to "active compound" cited in Patent Owner's Response also appears in the context of permissive language.

3. Patent Owner's proposed construction is not supported by the claims

Contrary to Patent Owner's argument, the "carrier" requirement in claim 1 does not transform the phrase "comprising nicotinamide riboside" into "comprising nicotinamide riboside as the active agent." Patent Owner relies on a portion of the specification which explains that a carrier is involved in carrying "the subject compound." (POR at 11.) That portion of the specification begins with permissive language which, as discussed above, cannot support reading an "active agent" requirement into the claims. The specification's reference to "the subject compound" later in the same paragraph also cannot support the addition of this "active agent" requirement. Indeed, the specification's reference to a "subject compound" instead of "active agent" establishes that "subject compound" and "active agent" are different, and that "subject compound" includes compounds that are not the active agent.[6]

[6] The specification uses the word "compound" to refer to "[p]olypeptides, nucleic acids, vectors, dietary supplements, and nicotinamide riboside-related prodrugs produced or identified in accordance with the methods of the invention." (Ex. 1001, '086 patent at 29:21-24.) There is no reason to

Patent Owner's one-paragraph argument that its proposed claim construction is consistent with the dependent claims is both conclusory and incorrect. None of the limitations added by the dependent claims suggests that the nicotinamide riboside recited in claim 1 must be the active agent. Indeed, claims 4 and 5 establish the opposite.

Claim 4 provides that the pharmaceutical composition of claim 1 further comprises "one or more of tryptophan, nicotinic acid, or nicotinamide." Patent Owner concedes that claim 4 does *not* require that the tryptophan, nicotinic acid, or nicotinamide in the pharmaceutical composition act as an active agent. However, Patent Owner provides no logical basis for construing "comprising nicotinamide riboside" in claim 1 to mean "comprising nicotinamide riboside as the active agent" while construing "comprising one or more of tryptophan, nicotinic acid, or nicotinamide" simply to mean including one or more of tryptophan, nicotinic acid, or nicotinamide. Claims 1 and 4 should be construed the same way;

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conclude that the word "compound" narrowly refers to nicotinamide riboside as an active agent.

both require the presence of certain ingredients, whether they function as an active ingredient or not.

When Dr. Zhou was asked at his deposition about his interpretation of claims to pharmaceutical compositions comprising two ingredients, like claim 4, he was unable to furnish any reasoning that would support the claim construction positions advanced by Patent Owner:

> Q. Okay. I'm going to give you a third hypothetical.
>
> A pharmaceutical composition comprising calcium sulfate and tryptophan. How would you interpret that claim?
>
> MR. ABRAMIC: Same objection.
>
> A. Without any limitation?
>
> Q. Those are all of the words of the claim, a pharmaceutical composition comprising calcium sulfate and tryptophan.
>
> A. First, I haven't thought about this with two components in the past. Also, all the cases I've been involved is only a single active ingredient. So I'm not sure I can exactly answer your question when I have two components.

(Ex. 1026, Zhou Tr. at 20:16-21:6.)

Finally, dependent claim 5 requires that the composition "increase NAD+ biosynthesis upon oral administration." If claim 1 requires that the

pharmaceutical composition contain nicotinamide riboside as an "active ingredient," claim 5 would be superfluous. That is, there is no evidence that nicotinamide riboside could be an active ingredient without increasing NAD+ biosynthesis because that is the biological effect that the administration of nicotinamide riboside causes.

Contrary to Patent Owner's assertions, Petitioner's expert, Dr. Baur, did not testify that the claims require that nicotinamide riboside act as an active ingredient. (POR at 15.) To the contrary, Dr. Baur testified that the claims do not require the nicotinamide riboside in the pharmaceutical composition to confer a therapeutic benefit. (*See* Ex. 2003 at, *e.g.*, 16:8-16 (explaining that claim 5 "doesn't require that the nicotinamide riboside be the reason for the increase [in NAD biosynthesis].") While counsel for Patent Owner slipped the phrase "active agent" into a few questions to develop misleading testimony about Dr. Baur's opinions, counsel never sought to directly challenge Dr. Baur's opinion that claim 1 merely requires the composition to contain nicotinamide riboside.

4. Patent Owner's proposed construction would render the claims invalid under 35 U.S.C. § 112

Patent Owner's Response does not articulate what "active agent" means in the context of its proposed claim construction. However, Dr.

Zhou, whose declaration Patent Owner relies upon to support its claim construction argument, testified that an "active ingredient" is one that "exhibits or confers certain therapeutic or preventative effects." (Ex. 1026, Zhou Tr. at 22:19-22.) There is nothing in the specification of the '086 patent to demonstrate that the inventor invented a composition in which the nicotinamide riboside "confers certain therapeutic or preventative effects." Nor does the specification disclose how to determine whether the nicotinamide riboside in a given composition elicits a therapeutic effect.

The specification of the '086 patent refers to a variety of diseases, but simply asserting that nicotinamide riboside can be used to treat diseases as diverse as hypercholesterolaemia, stroke, Alzheimer's disease, Multiple Sclerosis, *Candida glabrata* infection, and "the general health declines associated with aging," as the '086 patent does at col. 28, lines 3-15, does not mean the specification demonstrates that the inventor was actually in possession of treatments of all of these diseases. Dr. Zhou was unable to identify any specific therapeutic or preventative effect disclosed in the '086 patent. *Id*. at 23:8-14.

Indeed, Dr. Zhou testified that to determine whether the nicotinamide riboside in a hypothetical pill is the active agent, one would need to do rigorous but undefined testing:

> There are many, many complicated experiments one has to conduct to see, for example, whether NR, in the absence of NR, whether the same effect is observed or not. It's, you know, ***hundreds and thousands of experiments one has to conduct***, and there's always caveats how to interpret the data.
>
> But one experiment I think one must do is to remove NR from that pill, and they have everything else in that pill, and test it, and see whether the same activity is still being observed and whether it's the same degree of activity.
>
> That's, at least, I think scientifically that's a requirement to establish whether that pill has the activity of NR.

(Ex. 1026, Zhou Tr. at 34:16-35:7.) Nothing of the sort is disclosed in the '086 patent.

Moreover, the specification provides no guidance about which of "hundreds and thousands" of experiments one would need to perform to determine whether nicotinamide riboside acts as an "active

agent" in a composition. Dr. Zhou testified that one could never rule out the possibility that the nicotinamide riboside is an active agent. (Ex. 1026, Zhou Tr. at 36:11-37:5.) *See Teva Pharms, USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344-45 (Fed. Cir. 2015) (claim invalid for indefiniteness where specification did not disclose method for measuring "molecular weight").

Accordingly, Patent Owner's proposed construction should be rejected for the further reason that it would render the claims invalid for lack of written description and for indefiniteness.

B. The specification's express definition of "is isolated" should be applied

In its Petition, Petitioner stated that the phrase "is isolated" in claim 2 should be understood to mean "is separated or substantially free from at least some of the other components of the naturally occurring organism." In support of this proposed construction, Petitioner cited the express definition of "is isolated" in the specification of the '086 patent, which states:

> As used herein, an isolated molecule . . . means a molecule separated or substantially free from at least some of the other components of the naturally occurring organism, such as for

example, the cell structural components or other polypeptides or nucleic acids commonly found associated with the molecule.

(Ex. 1001, '086 patent at 9:3-9:10.) Contrary to Patent Owner's assertion (POR at 18), this definition not limited to nucleic acids. Rather, it applies to "an isolated *molecule*," and therefore includes isolated nicotinamide riboside.

In its Preliminary Response, Patent Owner argued that the phrase "is isolated from a natural or synthetic source" in claim 2 should be construed to mean "fractionated from other cellular components." (Preliminary Response at 11.)

In its Institution Decision, the Board disagreed with both parties' proposed constructions and ruled that the term "isolated" should be construed 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." (Paper No. 9 at 9.)

The Board correctly rejected the Patent Owner's proposed construction in its Institution Decision because it is not supported by the specification. In particular, as the Board pointed out, nothing in the

specification indicates that the nicotinamide riboside must be isolated by fractionation.

The Board should reconsider its rejection of Petitioner's proposed construction of claim 2, however, because the Board's construction is based on a misreading of the specification. The Board's construction relies on a statement concerning the purity of an isolated molecule *when the molecule is a polypeptide.* (*See* Ex. 1001, '086 patent at 9:10-13 ("When the isolated molecule is a polypeptide, said polypeptide is at least about 25% . . . or more pure (w/w)."). In claim 2, the isolated molecule is not a polypeptide, but rather is nicotinamide riboside. The portion of the specification cited by the Board not only is inapplicable to claim 2, it clearly implies that when the isolated molecule is not a polypeptide (*i.e.*, when it is nicotinamide riboside), the isolated molecule is not necessarily at least 25% pure. If the applicant intended to convey the meaning ascribed by the Board, the specification would have read: "An isolated molecule means a molecule that is at least 25% or more pure (w/w)."

The Board's construction also improperly construes "isolated" based on the relationship between the nicotinamide riboside in the composition and the other elements of the composition, rather than on the relationship

between the nicotinamide riboside and other molecules naturally associated with the nicotinamide riboside. Under the Board's construction, a tablet containing 1 mg of nicotinamide riboside that had been separated from a natural source would be "isolated" if the tablet contained only 2.9 mg of filler, but would not be "isolated" if the tablet contained 3.1 mg of filler. That interpretation of "isolated" is not supported by the specification, which expressly states that an isolated molecule is "separated or substantially free from at least some of the other components of the naturally occurring organism."

III. ANTICIPATION

A. Ground 1: Goldberger et al.

1. Claim 1

a. Because claim 1 does not require that the nicotinamide riboside is the "active agent," many of Patent Owner's arguments regarding claim 1 are moot

Patent Owner's arguments regarding claim 1 are aimed largely at showing that the milk used in Goldberger et al. to treat blacktongue does not anticipate *under Patent Owner's proposed construction*, because the nicotinamide riboside in that milk may not have been the "active agent" responsible for the therapeutic or preventative effects conferred by the milk

described in Goldberger et al. If the Board rejects Patent Owner's proposed construction of "pharmaceutical composition comprising nicotinamide riboside" these arguments are moot and must also be rejected.

For example, Patent Owner suggests that the nicotinamide riboside in Goldberger et al.'s milk might be "therapeutically inactive" because Trammell I indicates that nicotinamide riboside binds to some other molecule in milk. (POR at 23.) This argument is irrelevant because the claims of the '086 patent do not require that the nicotinamide riboside is "therapeutically active."

This argument also misreads the prior art. The authors of Trammell I (including Charles Brenner, the sole named inventor of the '086 patent) themselves concluded that the binding of nicotinamide riboside in milk made milk a *better* source of nicotinamide riboside. (Ex. 1007, Trammell I at 6 ("The ability of milk to bind and preserve the integrity of NR makes dairy products potentially good sources of supplemented NR.").) Dr. Zhou admitted that he was not aware of any data correlating NMR data, like the data in Trammell I, with the bioavailability of a nutrient. (Ex. 1026, Zhou Tr. at 63:18-24; see also Ex. 2003, Baur Tr. at 34:7-10.) Nor was he aware

of any publication stating that nicotinamide riboside in milk is not bioavailable. (Ex. 1026, Zhou Tr. at 64:6-14.)

In fact, named inventor Brenner submitted a declaration to the Patent Office during prosecution of the '086 patent's parent application in which he asserted that nicotinamide riboside added to milk *is* bioavailable. (Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132-135.) Similarly, the licensee of the '086 patent, ChromaDex, has relied on the presence of nicotinamide riboside in milk in FDA filings describing the history and use of nicotinamide riboside. (Ex. 1023, Generally Recognized as Safe (GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride), Prepared for ChromaDex, Inc. (Dec. 21. 2015) ("GRAS Filing"), at 22.) ChromaDex informed FDA, for example, that "[h]umans are exposed to NR via dietary sources such as milk" and that "the estimated amount of NR ingested by human from the equivalent of 710 ml/day (3 cups) of cow's milk is ~545 µg/day." (*Id*.) These statements would be irrelevant and misleading if nicotinamide riboside were not bioavailable in milk.

b. The evidence establishes that nicotinamide riboside is present in milk

Patent Owner obliquely argues that Petitioner failed to show that the milk in Goldberger et al. contained nicotinamide riboside at all because Goldberger et al. did not establish through testing that their milk, like all other milk, contained nicotinamide riboside. (POR at 22.) Patent Owner's argument is based on the assertion that one cannot say that nicotinamide riboside is present in a given sample of milk unless that very sample is tested and shown to contain nicotinamide riboside. (Ex. 1026, Zhou Tr. at 51:1-8.) However, there is no basis whatsoever to believe that the milk disclosed in Goldberger et al. lacked nicotinamide riboside, which may be why Patent Owner does not straightforwardly assert such a contention.

Dr. Zhou conceded that there has never been a report of a milk sample that completely lacks nicotinamide riboside. (*Id*. at 50:6-12; 52:1-8.) The '086 patent states, without qualification, that milk is a source of nicotinamide riboside. (Ex. 1001, '086 patent at 3:9:12.) The sole inventor named on the '086 patent, Charles Brenner, has stated in numerous scientific publications, again without qualification, that nicotinamide riboside is found in milk. (*See, e.g*., Ex. 1007, Trammell I, at 1; Ex. 1008, Trammell II, at 2; Ex. 1025, Katrina L. Bogan and Charles Brenner, "Nicotinic Acid, Nicotinamide, and Nicotinamide Riboside: A Molecular Evaluation of

NAD+ Precursor Vitamins in Human Nutrition," *Annu. Rev. Nutr.*, 28:115-30 (2008), at 11.) As noted above, the licensee of the '086 patent, ChromaDex, has relied on the presence of nicotinamide riboside in milk in FDA filings regarding the history and use of nicotinamide riboside. (Ex. 1023, GRAS Filing, at 22.)

Patent Owner has not pointed to any reason why nicotinamide riboside would be absent from the milk administered in Goldberger et al., unlike all other milk ever tested. In one sentence of its brief, Patent Owner states that Petitioner "has not shown that any alleged nicotinamide riboside in the milk was not degraded by naturally occurring bacteria." (POR at 23.) But Patent Owner does not even attempt to develop the argument that bacteria eliminated all the nicotinamide riboside in the prior art milk, likely because there is no evidence to support it.

It is undisputed that Trammel I, which Patent Owner relies upon for its bacteria degradation argument, reports that *every single* milk sample tested contained some nicotinamide riboside, regardless of the amount of bacteria that was also present in the sample. (Ex. 1007, Trammell I, at 3, 5; Ex. 1026, Zhou Tr. at 50:25-52:8; Ex. 2003, Baur Tr. at 54:15-18.) Furthermore, Goldberger et al. expressly states that the milk used in the

experiment was "fresh skim milk" that "was allowed to stand in an ice box for not more than 24 hours before being used." (Ex. 1005, Goldberger et al., at 1403.) There is no basis to conclude that, unlike all of the samples tested in Trammel I, bacteria destroyed all of the nicotinamide riboside in Goldberger et al.'s fresh skim milk. Indeed, Dr. Brenner informed the Patent Office in a Rule 132 Declaration that "nicotinamide riboside is stable for at least 24 hours at room temperature in milk." (Ex. 1003, Excerpts from Prosecution History of Serial No. 11/912,400, at 132.) Similarly, ChromaDex represented to FDA that "NR levels in milk do not change significantly when milk is stored at room temperature for 24 hrs." (Ex. 1023, GRAS Filing, at 22.)

Accordingly, the evidence establishes that the milk administered in Goldberger et al. contained nicotinamide riboside.

c. Patent Owner's "admixture" argument relies on an incorrect, and previously rejected, claim construction

Patent Owner's argument that Goldberger et al. must disclose "purposefully mixing the carrier with the active agent (*i.e.*, nicotinamide riboside)" is incorrect. (POR at 24-25.) As the Board already found, the claim does not require "purposeful mixing." In its Institution Decision, the Board explained that "Patent Owner has not pointed to anything in the

record to support its contention regarding the meaning of the term 'admixture.'" (Paper 9 at 12.)

Patent Owner's Response likewise is devoid of any support in the record for its "admixture" argument. Instead, Patent Owner quotes a portion of the specification and makes the conclusory assertion that "purposefully mixing" is required. (POR at 24-25.) In fact, the specification never refers to "purposeful mixing." Instead, it simply indicates that a carrier may be present in the pharmaceutical composition. For example, the specification explains that "the present invention is a dietary supplement composition containing nicotinamide riboside identified in accordance with the methods of the present invention and a carrier." (Ex. 1001, '086 patent at 4:14-16.)

As the Board explained in its Institution Decision, the specification of the '086 patent states that "[e]xamples of materials which can serve as carriers include sugars, such as lactose." (Paper 9, at 12 (quoting Ex. 1001, '086 patent, at 29:1-2)) Patent Owner does not dispute that sugars can serve as carriers. Patent Owner also does not dispute the Board's observation that "milk contains a combination of nicotinamide riboside and other components including lactose." (*Id*.) Because milk contains a combination (or mixture) of nicotinamide riboside and other components including

lactose, it is a composition comprising nicotinamide riboside "in admixture with a carrier." (*See* Ex. 2003, Baur Tr. at 53:23-54:7.)

2. Claim 2

In arguing that claim 2 is not anticipated by Goldberger et al., Patent Owner relies on the Board's statement in its Institution Decision that "isolated" should be construed to mean "that the nicotinamide riboside is separated or substantially free from at least some of the of the other components associated with the source of the molecule such that it constitutes at least 25% (w/w) of the composition." (POR at 31; Paper 9 at 9.) Patent Owner does not attempt to show that Goldberger et al. does not anticipate under Petitioner's proposed construction of "isolated."

Because the nicotinamide riboside naturally present in the skim milk administered by Goldberger et al. unquestionably is separated or substantially free from at least some of the other components of the naturally occurring organism (first, the cow; and later from the fat elements of the milk), Goldberger et al. anticipates claim 2.

3. Claim 3

Patent Owner does not deny that the milk disclosed in the prior art meets the limitation added by dependent claim 3 (*i.e.*, the requirement that the formulation comprises a food or other specified form). Instead, Patent

Owner relies on its argument, discussed above, that milk is not "a pharmaceutical composition comprising nicotinamide riboside as the active agent as required by claim 1." (POR at 26.)

Patent Owner's assertion that "Petitioner's arguments would lead to the nonsensical conclusion that, any food, regardless of any other variable, would anticipate claim 3" is wrong. Petitioner never suggested that foods not containing nicotinamide riboside would anticipate claim 3. Only foods that also meet the limitations of claim 1, like the milk disclosed in Goldberger et al., anticipate claim 3.

4. Claim 4

As with claim 3, Patent Owner does not argue that the milk disclosed in Goldberger et al. lacks the limitation added by dependent claim 4 (*i.e.*, the requirement that the claimed composition further comprises one or more of tryptophan, nicotinic acid, or nicotinamide). Instead, Patent Owner relies on its argument, discussed above, that the prior art does not anticipate independent claim 1. Because that argument is incorrect, claim 4 is anticipated by Goldberger et al.

5. Claim 5

Patent Owner's argument with respect to claim 5 rests on a misinterpretation of that claim. Patent Owner argues that "there is no

evidence that the alleged nicotinamide riboside in the milk of Goldberger et al. actually increased NAD+ biosynthesis upon administration to dogs." (POR at 28.) This statement (setting aside its inaccuracy) does not address the actual requirement of claim 5, that ***"[t]he pharmaceutical composition of claim 1***"—not the nicotinamide riboside in the composition—"increase NAD+ biosynthesis upon oral administration." Patent Owner's argument is irrelevant.

Patent Owner introduces one sentence of its brief with a phrase suggesting that Patent Owner doubts whether the milk administered in Goldberger et al. increased NAD+ biosynthesis. (*See* POR at 29 ("Not only is there no evidence in Goldberger et al. that NAD+ biosynthesis increased . . .")). However, Patent Owner does not even attempt to show that Goldberger et al. does not disclose increased NAD+ biosynthesis.

Patent Owner does not dispute that the blacktongue treated in Goldberger et al. is caused by NAD+ deficiencies, and Patent Owner's proffered expert admitted this fact at his deposition. (Ex. 1026, Zhou Tr. at 84:3-9.) Patent Owner also does not attempt to show that the results reported in Goldberger et al. fail to demonstrate that NAD+ biosynthesis in

the dogs increased upon oral administration of skim milk. Dr. Zhou admitted this fact as well. (*Id*. at Zhou Tr. 84:10-21.)

In short, Patent Owner does not attempt to rebut the Board's finding, in its Institution Decision "that the consumption of skim milk inherently increases the biosynthesis NAD+." (Paper 9 at 16.) Because this what claim 5 actually requires, the claim is anticipated by Goldberger et al.[7]

B. Ground II: Goldberger and Tanner

Patent Owner's arguments regarding Ground II repeat the arguments made for Ground I and should be rejected for the reasons discussed above.

Patent Owner asserts that "a person of ordinary skill in the art would not find any material difference between the disclosure of Goldberger et al. in Ground 1 and that of Goldberger and Tanner in Ground 2 for purposes of analyzing the patentability of the '086 patent claims." (POR at 32.) Thus, Patent Owner does not make any argument regarding Goldberger and

[7] Patent Owner's assertion that "Petitioner's expert expressly admits there is no proof that milk leads to such an increase" is incorrect and misleading. (POR at 2.) Dr. Baur clearly testified that the milk administered in Goldberger et al. "increases NAD biosynthesis after administration." (Ex. 2003, Baur Tr. at 16:10-14.)

Tanner that was not made with respect to Goldberger et al. Those arguments are incorrect, for the reasons stated above. In particular, whether the nicotinamide riboside in the buttermilk used in Goldberger and Tanner constitutes an "active agent" is irrelevant because the claims do not contain an "active agent" requirement.

Patent Owner's assertion that "[t]here is no disclosure of nicotinamide riboside in the buttermilk of Goldberger and Tanner" (POR at 33) rests on the argument that Goldberger and Tanner must have shown through testing that their buttermilk contained nicotinamide riboside. In fact, as explained above, the evidence shows that all milk contains nicotinamide riboside, and there is no reason to believe that it was absent from Goldberger and Tanner's buttermilk.

With respect to claim 5, Patent Owner's assertion that "Petitioner fails to present any evidence that NAD+ biosynthesis increased in Goldberger and Tanner" is erroneous. (POR at 33.) Petitioner explained that Goldberger and Tanner's results showing that buttermilk prevented pellagra—a disease caused by NAD+ deficiency—are direct evidence that NAD+ biosynthesis increased upon oral administration of buttermilk. At his deposition, Patent Owner's proffered expert agreed. (Ex. 1026, Zhou Tr., at

84:22-85:3.) Accordingly, there is no basis to conclude that claim 5 is not anticipated by Goldberger and Tanner.

IV. CONCLUSION

For the foregoing reasons and the reasons set forth in the Petition for *Inter Partes* Review, the Board should cancel claims 1-5 of the '086 patent because they are unpatentable under 35 U.S.C. § 102.

Dated: August 22, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Reply complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i) because, according to the "word count" function of Microsoft Word 2016, the Petition contains 5,485 words, excluding the parts of the Petition exempted from the word count by 37 C.F.R. §42.24(c)(1).

/Brendan T. Jones/
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(c), the undersigned hereby certifies that a copy of the foregoing document was served on August 22, 2018 by filing this document through the Patent Trial and Appeals Board End to End as well as by delivering a copy via the delivery method indicated to the attorneys of record for the Patent Owner as follows:

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