

IPR2025-01593
Patent 10,278,961

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BONERGE LIFESCIENCE (HUNAN) CO., LTD.,
Petitioner,

v.

NANJING NUTRABUILDING BIO-TECH CO., LTD.,
Patent Owner.

IPR2025-01593
Patent 10,278,961

Before KAREN I. SWEENEY, *Trial Paralegal*

**PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S
PRELIMINARY RESPONSE**

Pursuant to 37 C.F.R. § 42.107, Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. hereby respectfully submits its Patent Owner Preliminary Response setting forth reasons to deny Bonerge Lifescience (Hunan) Co., Ltd.'s Petition for inter partes review of claims 1, 2, 3, 5, 6, and 7 of U.S. Patent No. 10,278,961.

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2106	Declaration of Mark D. Nielsen in support of Patent Owner’s Preliminary Response
2107	Declaration of Dr. Thomas Hartung, M.D., Ph.D.
2108	Declaration of Chad M. Kerksick, Ph.D.
2109	Declaration of Qiang Tong, Ph.D.

PATENT OWNER’S PRELIMINARY RESPONSE

I. INTRODUCTION

Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. (“Patent Owner” or “NNB”) respectfully requests that the Board deny institution of Bonerge Lifescience (Hunan) Co., Ltd.’s (“Petitioner” or “Bonerge”) petition for inter partes review of claims 1, 2, 5, 6, and 7 of U.S. Patent No. 10,278,961 (the “’961 patent”). Petitioner fails to demonstrate a reasonable likelihood that at least one of the claims challenged in the petition is unpatentable as obvious. 35 U.S.C. §324(a). As such, institution should be denied. For reference, Patent Owner may refer herein to the petition as “Petition” and inter partes review as “IPR”.

II. BACKGROUND

A. Brief Background of U.S. Patent 10,278,961

NNB owns the ‘961 Patent by assignment. Independent claim 1 of the ‘961 Patent reads:

A method of managing glucose tolerance in an individual, the method comprising: administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.

Exh. 1001 (at p. 11).

The application process for the '961 Patent commenced with the filing of U.S. Provisional Patent Application number 62/324,794, filed on April 19, 2016. Exh. 1001 (at p. 1). Non-Provisional Patent Application number 15/491,933 was filed on April 19, 2017 with a priority claim to the provisional application. *Id.* Following a restriction requirement dated December 4, 2017 (Exh. 1002 at p. 158) and a response thereto (*Id.* at p. 149-153), the Examiner issued a § 102 rejection on May 24, 2018 (*Id.* at pp. 121-124), including to claim 1, which read:

A method of managing glucose tolerance in an individual,
the method comprising: administering to an individual, a
pharmaceutically effective amount of dihydroberberine.

Id. at p. 150.

In response to the § 102 rejection, on November 20, 2018, Applicant amended claim 1 to read

A method of managing glucose tolerance in an individual,
the method comprising: administering to an individual, a
pharmaceutically effective amount of dihydroberberine,
wherein the pharmaceutically effective amount of
dihydroberberine comprises approximately 25 mg to
approximately 800 mg of dihydroberberine.

Id. at p. 116 (underline in original).

On December 26, 2018, the Examiner issued a Notice of Allowance allowing claim 1 (and its dependents). *Id.* at pp. 94-100.

The '961 Patent issued on May 7, 2019. Exh. 1001 (at p. 1).

B. Background of the Parties' Dispute and the Parallel Litigation

The details regarding the background of the parties' dispute, and particularly the parallel litigation, are set forth in Patent Owner's Discretionary Denial Brief. Paper 6 at 2-5 (Dec. 2, 2025).

In short, NNB and Petitioner are in the business of supplying dihydroberberine (referred to herein in full or as "dhBBR") to re-sellers and compounders who then formulate products containing dhBBR to sell to consumers. On September 12, 2024, shortly after learning of Petitioner's infringing activities, NNB notified Petitioner of the alleged infringement. Exh. 2002. Petitioner admits to having received this letter on September 25, 2024. Exh. 2003 at p. 006¹ (Resp. to Req. for Adm. No. 1). NNB sent Petitioner another letter in late October of 2024. Exh. 2004. Petitioner admitted that it did not respond to either of these letters. *Cf.* Exh. 2001 (¶ 18) to Exh. 2005 (¶ 18).

On or about November 5, 2024, NNB sent a letter to Nature's Fusions, an entity also selling a dhBBR product for blood sugar control. Exh. 2006. Nature's

¹ Exhibit page references herein are to the "Bates" numbered pagination on the exhibits submitted herewith or otherwise in the record.

Fusions responded and directed NNB to its “manufacturer,” which happened to be Petitioner. Exh. 2007 at p. 004. Petitioner did not agree to cease selling dhBBR into the U.S. for purposes of managing glucose tolerance in individuals, and thus, NNB filed a lawsuit for patent infringement in the United States District Court for the Central District of California on January 31, 2025. Exh. 2001.

The case is proceeding along expeditiously, including claim construction and discovery. The parties are in the process of conferring on claim construction and will begin their claim construction submissions to the Court next month, with a Markman hearing scheduled for April 21, 2026. Exh. 2010 at p. 001. Following completion of fact and expert discovery, the Court will receive dispositive motions in early 2027 with a trial date scheduled for April 20, 2027. Exh. 2011 at p. 002 therein. The litigation is efficiently proceeding and no temporal benefit will be gained by instituting review.

C. Procedural Details Regarding this Proceeding

On September 26, 2025, *exactly a year and a day after receiving NNB’s first cease and desist letter* (Exhs. 2002, 2003), and 7.5 months after it was *served* with the Complaint in the parallel litigation, Petitioner filed its Petition for IPR. Paper No. 2.

On December 2, 2025, Patent Owner filed its Discretionary Denial Brief detailing numerous reasons why institution should be denied, including the fact that

the trial date will likely be about the same time as the deadline for a Final Written Decision. Paper No. 6.

Now, the Patent Owner submits numerous additional, merit-based reasons as to why institution should also be denied. For these reasons, as well as those set forth below, Petitioner's IPR Petition should not be instituted.

III. CLAIM CONSTRUCTION

A. Claim Construction

In an IPR, claim language is given its ordinary and customary meaning in light of the specification. 37 CFR §42.100(b). Further, claim language, to the extent it requires construction, is interpreted according to the well-known Federal Circuit case, *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

In terms of claim construction, while Petitioner seems to suggest that the phrase “**the administration of dihydroberberine reduces fasting glucose levels**” requires construction, Petitioner did not propose a specific construction. Paper 2 at 10-11. To the extent what Petitioner wrote in Paper 2 at 10-11 is deemed to be a proposed construction (which it should not be), all Petitioner has done is drag limitations from the specification into its discussion, which is not proper claim construction per *Phillips*. *Phillips*, 415 F.3d at 1320, 1323. This is so because Petitioner provided no basis for suggesting that a POSITA would import (or even need to import) limitations from the specification in order to understand the meaning

of any part of the phrase, “the administration of dihydroberberine reduces fasting glucose levels.”

Rather, a POSITA would understand this claim language based on the plain meaning of its plain language, which, in context, would be, giving dhBBR to a person will lower glucose levels when the person had fasted for a typical period of time when glucose levels would be at rest for purposes of determining glucose levels – not a protracted, multi-day fast. Simply, a POSITA would understand that when a person goes to a doctor for an annual physical, the standard bloodwork tests for blood glucose levels, and the person is typically instructed to fast overnight before a morning test or for approximately 6-8 hours if the test is later in the day. This is a standard understanding of the general population and a POSITA.

Accordingly, if this term requires construction at all, which Patent Owner does not believe it does, the Board should refrain from adopting Petitioner’s tortured, specification-laden guidelines, and simply interpret this language based on its plain, well-understood meaning as suggested immediately above.

In addition, the Board should also construe the preamble of claim 1 (“A method of managing glucose tolerance in an individual, the method comprising”) as limiting. It breathes life into the claim. *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34 (Fed. Cir. 2003) (preamble limiting where it is not merely a statement of effect that may or may not be desired or appreciated, but rather is a statement of

the intentional purpose for which the method must be performed).

The preamble language should also be limiting because it was relied upon by the Examiner in the prior art rejection (Exh. 1002 at p. 124), the response by Applicant (*Id.* at p. 112), and in the Reasons for Allowance (*Id.* at 102). *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-09 (Fed. Cir. 2002).

Furthermore, in the parallel litigation, the parties seem to be in agreement that the preamble of claim 1 should be read as limiting (although Petitioner's importation of limitations from the specification in its proposed construction is entirely unwarranted and unsupported. Declaration of Mark D. Nielsen (submitted herewith as Exh. 2106) at ¶¶ 3-6.

IV. PETITIONER'S CHALLENGES FAIL ON THE MERITS

The basis of all Petitioner's challenges in this proceeding is obviousness under 35 U.S.C. § 103. In an IPR, the Petitioner has the burden of proving by a preponderance of the evidence that the challenged claims were obvious before the effective filing date of the claimed invention. *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1375-76 (Fed. Cir. 2016).

A. Legal Standard for Obviousness

A claim is unpatentable as obvious under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious before the effective filing date to a person

having ordinary skill in the art to which the claimed invention pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *see also* 35 U.S.C. § 103 (amended by America Invents Act in 2011 to change “at the time the invention was made” to “before the effective filing date of the claimed invention”, CHISUM ON PATENTS § 5.03[2][a]). A determination of obviousness “requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so.” *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019) (quoting *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018)). The obviousness inquiry is performed from the viewpoint of the knowledge of a person having ordinary skill in the art at the time of the invention. *Graham v. John Deere Co.*, 383 U.S. 1, 3 (1966).

1. *Graham* Factors

Obviousness is a question of law based on the following underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham*, 383 U.S. at 17-18. The obviousness inquiry requires examination of all four *Graham* factors. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1375 (Fed. Cir. 2012).

It is not sufficient that a challenger simply show that all elements of the

claimed invention are present in the prior art; *rather*, there are two additional elements required to be proven by a challenger: (1) motivation to combine or modify the prior art references and (2) a reasonable expectation of successfully achieving the claimed invention based on the combination or modification. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021); *see also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (“A party seeking to invalidate a patent based on obviousness must demonstrate ... that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007))).

“A finding by the Board that a patent challenger has demonstrated a motivation to combine references does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success in achieving a claimed method of treatment.” *Eli Lilly*, 8 F.4th at 1344 (citing *Novartis Pharmaceuticals Corp. v. West-Ward Pharmaceuticals International Ltd.*, 923 F.3d 1051, 1062 (Fed. Cir. 2019)).

a. Scope and Content of the Prior Art

In order for a patent or printed publication to be considered as prior art, it must qualify as prior art under 35 U.S.C. § 102. MPEP § 2141.01(I). In this proceeding,

it would appear that any reference used as prior art would have to be dated at least as early as April 18, 2016.

The scope and content of the prior art must be viewed from the time the invention was made to avoid impermissible hindsight. MPEP § 2141.01(III). And, “the prior art must be considered as a whole for what it teaches.” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166 (Fed. Cir. 2006).

For a reference to be proper for use in an obviousness rejection under 35 U.S.C. § 103, the reference must be analogous art to the claimed invention. *In re Bigio*, 381 F.3d 1320, 1325, (Fed. Cir. 2004). Prior art is considered non-analogous unless it is (1) from the same field of endeavor as the claimed invention, or (2) reasonably pertinent to the particular problem faced by the inventor. *Id.*

To determine whether a prior art meets same field of endeavor test for analogous art, the court looks to the “reality of the circumstances” which are weighed from the “vantage point of the common sense” likely exerted by the POSITA in assessing the scope. *Airbus S.A.S. v. Firepass Corp.*, 941 F.3d 1374, 1380 (Fed. Cir. 2019).

A reference outside the field of endeavor must be “reasonably pertinent” to the problem addressed by the inventor to be considered analogous. Art is “reasonably pertinent” when it “logically would have commended itself to an inventor’s attention in considering the problem.” *In re Clay*, 966 F.2d 656, 659 (Fed.

Cir. 1992). Conversely, when a reference is directed to a different purpose than the claimed invention, “an inventor would have less motivation or reason to consider it.” *Id.*

b. Differences Between the Claimed Invention and the Prior Art

This portion of the analysis requires that the differences between the prior art and the claimed invention be ascertained. *Graham*, 383 U.S. at 14. If needed, it is necessary to construe the challenged claims in order to be able to discern the differences between the prior art and claimed invention. *Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*, 452 F. 3d 1331, 1336 (Fed. Cir. 2006) (“Once the scope of the claims are determined, the actual obviousness determination under 35 U.S.C. § 103 begins.”).

c. Level of Ordinary Skill in the Art

Regarding this element of the obviousness inquiry, the Federal Circuit has described it as, “the characteristics and understanding of an individual of ordinary skill in the relevant field of art at the time of invention.” *Source Search Techs., LLC v. LendingTree, LLC*, 588 F.3d 1063, 1069 (Fed. Cir. 2009).

“Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *Mintz v. Dietz & Watson, Inc.*, 679 F. 3d 1372, 1376

(Fed. Cir. 2012) (*citing Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986)).

In determining the level of ordinary skill in the art, “The level of disclosure in the specification of the application under examination or in relevant references may also be informative of the knowledge and skills of a person of ordinary skill in the art.” MPEP 2141.03(I).

And, as it pertains to both the person of ordinary skill in the art and the entire inquiry, the obviousness analysis should *not* be performed using a present-day perspective, and should *not* use hindsight. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998).

d. Secondary Considerations of Non-Obviousness

Under *Graham v. John Deere*, objective evidence of nonobviousness—sometimes called “secondary considerations” or “objective indicia”—must be considered when present. *Apple, Inc. v. Samsung Electronics Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016). Objective indicia of nonobviousness includes: (1) commercial success, (2) copying, (3) industry praise, (4) skepticism, (5) long-felt but unsolved need, and (6) failure of others. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling U.S., Inc.*, 699 F.3d 1340, 1349-56 (Fed. Cir. 2012).. This evidence serves as a safeguard against hindsight and against reading into the prior art the teachings of the invention at issue. *Graham*, 383 U.S. at 36;

Apple v. Samsung, 839 F.3d at 1052-58.

e. Motivation to Combine or Modify the Prior Art

Assuming a challenger demonstrates that all elements of the claim are present in the prior art combination or modification proposed, the challenger must then also prove a reason to combine or modify the references to arrive at the claimed invention exists. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008). The question is whether a person of ordinary skill in the art would have combined elements from specific references in the way the claimed invention does (i.e., to arrive at the claims' actual limitations). *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950, 957-58 (Fed. Cir. 2023); *Active Video Networks, Inc. v. Verizon Communications, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012). A failure to establish this element can be fatal to an obviousness challenge. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F. 3d 1342, 1367, 1369-71 (Fed. Cir. 2012).

A patent “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l Co.*, 550 U.S. at 418.

A prior art reference may teach away from a given combination of prior art and thus negate a motivation to combine or modify the prior art to meet the claimed invention. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). “A reference may be said to teach away when a person of ordinary skill, upon

reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Kahn*, 441 F.3d at 977, 990 (Fed. Cir. 2006) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (internal quotation marks omitted).

f. Reasonable Expectation of Success

Reasonable likelihood of success is required to establish obviousness. MPEP § 2143.02; *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) (“An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.”). Even if a reason to combine or modify the prior art to overcome the differences between the existing art and the claimed invention, “the likelihood of success’ in combining or modifying prior art disclosures to meet the limitations of the claimed invention” is still required. MPEP § 2143.02 (quoting *Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1375, (Fed. Cir. 2023) and *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

A “finding by the Board that a patent challenger has demonstrated a motivation to combine references does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success in achieving a claimed method of treatment.” *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021).

V. PETITIONER'S PROPOSED PERSON OF ORDINARY SKILL IS INCORRECT AND INADEQUATE

Petitioner's proposed POSITA is incorrect and inadequate for the subject matter disclosed in the '961 Patent. As mentioned above, factors that are helpful in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *Mintz*, 679 F. 3d at 1376.

In considering these factors, Patent Owner proposes that a POSITA during the relevant time period would be an individual with significant knowledge of and skill in physiology, not just chemistry; one who is trained to understand and interpret the various models used in the cited research studies. Declaration of Dr. Chad M. Kerksick, Ph.D. (Exh. 2108) (hereafter "Kerksick Decl.") at ¶ 30. This characterization of the POSITA is relevant and important because the POSITA must be able to evaluate the quality and clinical relevance of studies in the field, which is not just a matter of medicinal chemistry. Patent owner contends that this POSITA would have approximately five to eight (5-8) years of experience in academic research and/or industry, and that five to eight (5-8) years may include a Master's degree or Ph.D., in the fields of diabetes research, glucose metabolism, exercise physiology (which necessarily requires an understanding of glucose metabolism), preclinical drug development, pharmaceutical sciences, translational medicine or

the like. Kerksick Decl. at ¶ 30; Declaration of Dr. Qiang Tong, Ph.D. (Exh. 2109) (hereafter “Tong Decl.”) at ¶ 29. This level of education is likely similar to that of other researchers and individuals publishing studies or applying for patents in the glucose metabolism field. This level of understanding is required to understand the technology, which is relatively sophisticated. This POSITA would not focus on statements and conclusions provided by authors of research papers, but rather, on the data actually shown based on the methods utilized in such research papers. *Id.* Furthermore, a POSITA would have a sufficient understanding of research design and basic statistics for the purpose of determining the statistical significance and relevance of data they observe. *Id.* This POSITA should be familiar with "prior art", such as the limitations of extrapolating efficacy, pharmacokinetics, and dosing from rodent models to humans. Tong Decl. ¶ 30. A POSITA with this relevant experience would be aware that the metabolism of berberine (used herein in full or as “BBR”) and its derivatives involves the digestive tract and gut microbiota, which differ between from species to species. *Id.*

VI. THE SCOPE AND CONTENT OF THE PRIOR ART DOES NOT TEACH THE CLAIM LIMITATIONS AS REQUIRED

The scope and content of the prior art cited by the Petitioner fails to teach each claim limitation. Petitioner argues that claims 1, 2, 5, 6, and 7 of the ‘961 Patent are obvious. Claim 1 is directed at a method of “managing glucose tolerance” in an individual by administration of dhBBR at “approximately 25 mg to approximately

800 mg.” Dependent claims 2, 5, 6, and 7 disclose additional limitations including “reduc[ing] fasting glucose levels,” “orally administered as a capsule or tablet,” “orally administered as at least one of a food product or beverage product,” and “administered at least once daily.”

Petitioner has read the cited prior art too broadly to attempt to meet the limitations disclosed in the ‘961 Patent. The prior art fails to teach administration of dhBBR to humans, exceeds the disclosed dosing range, and diverges in its administration methods including vessel for administration and timing.

A. Turner

1. Claim 1

a. A method of managing glucose tolerance in an individual

Turner (Exh. 1004) does not disclose a method for managing glucose tolerance to an individual. The preamble of claim 1 of the ‘961 Patent discloses a method for managing glucose tolerance in an individual. Given its plain and ordinary meaning, this teaches the management of glucose tolerance of a human. Turner conducted studies on the glucose metabolism in mice and rats fed a high-fat diet. Kerksick Decl. at ¶ 32. Turner provides no data related to managing a human’s glucose tolerance. *Id at* ¶ 65. In fact, Turner does not provide **any human data at all**. *Id*. Instead, Turner looks only at limited rat and mouse data and simply suggests that “during the discussion of their data (not from the data itself), that dhBBR **may**

be of interest for people with type 2 diabetes.” *Id.* at ¶ 69.

In addition to lacking disclosure of human data related to managing blood glucose, Turner is silent as to *how* its rodent data should be translated or applied to humans. Kerksick Decl. at ¶ 32. As detailed in the paragraphs below, rodent studies present significant hindrances to reliable translation to human application.

b. Administering, to an individual, a pharmaceutically effective amount of dihydroberberine

Claim 1 of the ‘961 Patent also discloses a limitation for the administration of a pharmaceutically effective amount of dhBBR. Petitioners rely solely on prior art demonstrating the administration of dhBBR to rodents in their chow. Kerksick Decl. at ¶100. As discussed above, and in the Expert Declarations of Dr. Kerksick, Dr. Tong, and Dr. Hartung, Turner does not teach the administration of any amount of dhBBR, let alone a pharmaceutically effective amount, **to humans**. Kerksick Decl. at ¶ 65; Tong Decl. at ¶ 31; Declaration of Dr. Thomas Hartung, M.D., Ph.D. (Exh. 2107) (hereafter “Hartung Decl.”) at ¶ 59. Petitioner overstates the scope of Turner, stating that it disclosed that dhBBR demonstrated improved “in vivo” efficacy for glucose tolerance over BBR due to lower dosing requirements and increased absorption and bioavailability. Paper No. 2 at 13. This assertion neglects the fact that these experimental conclusions were purely related to data derived from rodent models that does not provide “a scientifically reliable basis for predicting that [dhBBR] administration would have achieve the claimed human glucose-tolerance

outcomes” disclosed in the ‘961 Patent. Hartung Decl. at ¶ 30.

Because a POSITA would understand that “rodent metabolic efficacy, standing alone, does not reliably predict human therapeutic success,” the data disclosed in Turner provides “at most, a possible research hypothesis with several variables and inconsistencies, not a reasonable expectation that dhBBR would succeed in reducing glucose levels in humans, clinically or otherwise.” Tong Decl. ¶ 50. Petitioner’s characterization therefore exceeds the actual scope of Turner, which is confined to rodent studies and does not disclose improved in vivo pharmaceutical efficacy of dhBBR as asserted.

c. wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

Turner does not disclose a pharmaceutically effective amount of dhBBR within the dosing range of the ‘961 Patent. Turner teaches a dose of dhBBR that exceeds the disclosed range of 25 mg to 800 mg of dhBBR in Claim 1 of the ‘961 Patent. In Turner, both high-fat diet rats and mice were given 100 mg/kg of dhBBR per day. Exh. 1004, p. 2. Turner does not provide any dosing translation to humans, but if the average human weighs 60 kg, this dose translates to 6,000 mg of dhBBR per day, which far exceeds the range in claim 1 of the ‘961 Patent.

2. Claim 2: wherein the administration of dihydroberberine reduces fasting glucose levels

Turner does not disclose the administration of dhBBR reducing fasting

glucose levels of a human. The limitations of claim 2 are not met by Turner, both because claim 2 depends from claim 1 and because, as previously discussed, Turner does not disclose any human data relating to the administration of dhBBR, including any demonstration that dhBBR reduces fasting blood sugar levels.

3. Claim 5: wherein the dihydroberberine is orally administered as a capsule or tablet

Turner does not disclose the oral administration of dhBBR as a capsule or tablet. Not only is claim 5 nonobvious based on its dependent relationship to claim 1, but Turner (Exh. 1004) teaches that BBR and dhBBR were provided in the high-fat diet fed to the rodents (*Id.* at p. 4), not as a stand-alone capsule or tablet as stated in claim 5 of the '961 Patent. Tong Decl. at ¶ 56. When dhBBR “is incorporated into rodent feed, dosing is effectively continuous and dependent on both the frequency and quantity of food consumed by the animals.” *Id.* This means that the daily consumption of dhBBR may vary and rodents may consume some feed during the daytime, which is effectively nighttime for a human. *Id.* In contrast, “administration via a capsule represents a **discrete, one-time dosing event**, with drug delivery characteristics that differ substantially, including the fact that the compound would be provided in capsule or tablet form which can be taken close to a meals or between meals.” *Id.*

4. Claim 6: wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

Turner does not teach dhBBR or BBR delivery in a beverage product, or as a food product to humans, as claimed in the '961 patent. Not only does Turner fail to disclose all of the limitations of claim 5 based on its dependent relationship to claim 1, but Turner fails to teach the additional limitations disclosed in claim 6. Turner teaches the administration of dhBBR within the high-fat diet of rodents. Exh. 1004. Turner does not teach the administration of dhBBR as a beverage, or the administration of dhBBR to humans at all. *Id.*

5. Claim 7: wherein the dihydroberberine is administered at least once daily

Turner does not teach a once daily dose of dhBBR. As previously discussed, because Turner (Exh. 1004) added dhBBR in the high-fat diet, the dosing is continuous as rodents consume the diet. *Id.* Turner does not specify that the diet was consumed in one sitting or dose. *Id.*

B. Shaw

Petitioner extracts isolated guidance from Shaw (Exh. 1005) and removes it from its required context, thereby mischaracterizing the scope of what the reference actually teaches. Petitioner argues that Shaw discusses the use of the body surface Area (BSA) normalization method when “converting a dose for translation from animals to humans.” Paper No. 2 at 15. This is not incorrect; however, it is missing

important context which distinguishes the disclosure in Shaw from that of the '961 Patent.

Shaw does not discuss managing blood glucose, dhBBR, or even BBR; rather, it merely suggests that a BSA may be used to translate an animal dose to a **safe human starting dose**, without providing any specific application or instruction relevant to the claimed invention. Hartung Decl. at ¶ 68. On page 2, Shaw states that “BSA normalization of doses **must be used to determine safe starting doses** of new drugs because initial studies conducted in humans, by definition, lack formal allometric comparison of the pharmacokinetics of absorption, distribution, and elimination parameters.” *Id.* at 2. Exh. Additionally, as explained in Dr. Hartung’s Declaration, the FDA’s guidance, cited by petitioner (Exh. 1008) makes it clear that “such scaling is intended to estimate a safe first-in-human starting dose (typically from NOAELs [no observed adverse effect levels]) and explicitly cautions that human bioavailability, metabolism, and drug interactions may differ from animals.” Hartung Decl. at ¶ 64.

Because Shaw’s disclosure is inextricably tied to human toxicology and the calculation of safe starting doses—not pharmaceutical effectiveness as required by claim 1—it provides no guidance on do achieving therapeutic outcomes in humans. Shaw’s discussion of BSA scaling is limited to estimating conservative first-in-human doses based on animal toxicity data (e.g., NOAELs), and explicitly cautions

that such scaling does not account for differences in human bioavailability, metabolism, or drug interactions which would be relevant in establishing pharmaceutical effectiveness. As a result, Shaw cannot inform a person of ordinary skill in the art how to determine a pharmaceutically effective dose of dhBBR, nor does it teach or suggest any of the asserted claim limitations in the '961 Patent.

C. Feng

1. Claim 1:

a. A method of managing glucose tolerance in an individual

Feng (Exh. 1007) does not disclose a method for managing glucose tolerance to an individual. The Feng reference, entitled “Transforming berberine into its intestine-absorbable form by the gut microbiota” was focused on the “absorption mechanism” of BBR in rats. Exh. 1007 at p. 1. Like Turner, Feng does not disclose **any human data at all**. Kerksick Decl. at ¶ 77. Instead, Feng relies on cell and animal models that are fundamentally different than human individuals. *Id.* The animal models utilized in the study were rats, which face significant translation limitations as explained. Kerksick Decl. at ¶¶ 32, 42, 64, 76-84; Hartung Decl. at ¶ 63; Exh. 1007 at p. 3. A cell model used was a Caco-2 “which is an informative screening tool but not a direct measurement of in vivo human absorption.” Hartung Decl. at ¶ 64. While Feng briefly discusses the use of BBR to treat type 2 diabetes and other glucose related metabolic disorders, the glucose regulating effects of

dhBBR, which is the compound relevant to the '961 Patent, are never addressed. The conclusion of the study in Feng was that gut microbiota in rats oxidized dhBBR to BBR, which is irrelevant to glucose regulation properties of dhBBR disclosed in the '961 Patent because “[w]idespread compositional and functional differences exist between rodent and human microbiomes.” Kerksick Decl. at ¶ 77.

In addition, the “data” reported in rats is “highly suspect.” Kerksick Decl. at ¶ 79. Figure 3 of Feng reports the use of only 3 rats (n=3) for panels (b), (c), and (d), “which is inadequate and nothing more than a preliminary or exploratory test experiment as opposed to a rigorous study.” *Id.* Similarly, the error bars in panels (b), (c), and (d) of Figure 3 are “quite large to unacceptably large, which is further a function of an unsuitable sample size and further highlights that the ‘data’ presented is more of a moving target as opposed to a definitive finding.” *Id.* Of significant note, no statistical significance was shown for the data in panels (b), (c), and (d) of Figure 3. *Id.*

b. Administering, to an individual, a pharmaceutically effective amount of dihydroberberine

Feng also does not disclose the administration of a pharmaceutically effective amount of dhBBR. Feng administered dhBBR to compare its relative absorption to BBR. Relative absorption does not address therapeutic efficacy, dosing requirements, or clinical outcomes, and therefore falls entirely outside the scope of what is required to establish that Feng disclosed the administration of a

pharmaceutically effective amount under claim 1 of the '961 Patent.

c. Wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

Feng's dosing of BBR and dhBBR is inconsistent with what is taught in the '961 Patent. Kerksick Decl. at ¶ 77. Feng administered 200 mg dhBBR/kg/day in rats. Exh. 1007 at Fig. 3. If that amount was taken by a 60 Kg human, the dose would be 12,000 mg or 12 grams. Similarly, a conversion by the calculations from Shaw (Exh. 1005), teaches a human equivalent dose of 1945.9 mg (for a 60 kg person) of dhBBR. Kerksick Decl. at ¶ 77. The upper dosing limit highlighted in the '961 patent is ~800 mg dhBBR. *Id.* The dosage used in the Feng study is significantly higher than the upper limit highlighted in the patent when applied to an "average" 60 Kg adult. *Id.* Thus, its dosage makes it irrelevant as it does not teach the claims of the '961 Patent. *Id.*

2. Claim 2: wherein the administration of dihydroberberine reduces fasting glucose levels

Feng does not disclose the administration of dhBBR reducing fasting glucose levels of a human or a rat. The limitations of claim 2 are not met by Feng, both because claim 2 depends from claim 1 and because, as previously discussed, Feng discloses data on absorption of dhBBR and BBR, not efficacy, and does not disclose any human or animal data relating to reducing fasting glucose levels and the administration of dhBBR, including any demonstration that dhBBR reduces fasting

blood sugar levels.

3. Claim 5 and Claim 6:

Feng (1007) does not disclose the oral administration of dhBBR as a capsule, tablet, food product, or beverage. Not only are claim 5 and 6 nonobvious based on their dependent relationship to claim 1. Feng teaches that BBR and dhBBR were provided orally, however, the exact oral method is not disclosed. *Id.* at p. 10.

4. Claim 7: wherein the dihydroberberine is administered at least once daily

Feng does not disclose the administration of dhBBR to humans, or to rodents daily. (Exh. 1007). Instead, Feng discloses “[f]ive SD rats were fasted for 12 h and then orally administered 200 mg/ kg dhBBR. *Id.* at p. 12.

D. Zhang

1. Claim 1:

a. Administering, to an individual, a pharmaceutically effective amount of dihydroberberine

Zhang does not disclose the administration of a pharmaceutically effective amount of dhBBR because **only BBR** is administered in the study. (Exh. 1006).

b. wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

Again, Zhang does not disclose a pharmaceutically effective amount of dhBBR within the dosing range of the ‘961 Patent. Because Zhang only discusses the administration of BBR, no dose for dhBBR is disclosed at all. Kerksick Decl. ¶

71. Additionally, the dose disclosed for BBR, of 500 mg, twice a day, is outside of the upper limit, 800 mg/day of the dosing range of claim 1 of the '961 Patent. *Id.*

2. Claim 2: wherein the administration of dihydroberberine reduces fasting glucose levels

Zhang does not disclose the administration of dhBBR at all, let alone reducing fasting glucose levels of a human. The limitations of claim 2 are not met by Zhang, both because claim 2 depends from claim 1 and because, as previously discussed, Zhang does not disclose any data relating to the administration of dhBBR, including any demonstration that dhBBR reduces fasting blood sugar levels. Tong Decl. ¶ 71.

3. Claim 5: wherein the dihydroberberine is orally administered as a capsule or tablet

Zhang does not disclose the oral administration of dhBBR as a capsule or tablet. Not only is claim 5 nonobvious based on its dependent relationship to claim 1, but Zhang (Exh. 1006) does not teach the administration of dhBBR **at all**.

4. Claim 6: wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

Zhang (Exh. 1006) does not teach dhBBR or BBR delivery in a beverage product, or as a food product to humans, as claimed in the '961 patent. Zhang does not teach the administration of dhBBR at all. *Id.*

5. Claim 7: wherein the dihydroberberine is administered at least once daily

In Zhang (Exh. 1006), as previously stated, no dhBBR was administered, only

BBR. Tong Decl. ¶ 71. Additionally, Zhang did not disclose a one-daily dose. *Id.* The dosage delivered was **two doses per day** of 500 mg each dose (Total daily dose: 1000 mg, which is outside the range in claim 1.

VII. PETITIONER'S OBVIOUSNESS ANALYSIS IS DEFICIENT

Based on the legal standards set forth above for obviousness, none of the cited references alone or in combination disclose each limitation of the challenged claims.

A. Ground 1: Claims 1, 2, 5, 6, and 7 are Not Obvious in light of Turner in View of Shaw

In ground 1 of its obviousness claim, Petitioner relies on Turner in view of Shaw to argue that the '961 Patent would have been obvious to a POSITA at the time of filing. This combination is deficient because even combined, the prior art fails to meet the limitations of the asserted claims, and Petitioner has failed to provide a sufficient motivation to combine the prior art. Even if all the limitations were met and there was motivation for combining and modifying them, there is no reasonable expectation of success as set forth in Part VIII, *infra*.

1. Claim 1:

a. Turner fails to disclose that dhBBR is effective for managing glucose tolerance in individuals

Claim 1 of the '961 Patent discloses a method of managing glucose tolerance in an individual by administering a pharmaceutically effective amount of dhBBR, wherein the amount comprises approximately 25 mg to approximately 800 mg of dhBBR.

First, in addition to the Turner discussion in Part VII.A, *supra*, Turner does not disclose a method for managing glucose tolerance to a human individual. Turner conducted studies on the glucose metabolism **in mice and rats** fed a high-fat diet and does not explain how its data can or should be translated or applied to humans. Kerksick Decl. at ¶ 32. While Turner states that dhBBR may be of interest for people with type 2 diabetes, a POSITA would know that this is a mere hypothesis and no data is disclosed in Turner to support this suggestion. *Id.* at ¶ 69.

Along those lines, second, Turner also fails to disclose the administration of a pharmaceutically effective amount of dhBBR because it does not teach the administration of any amount of dhBBR, let alone a pharmaceutically effective amount, **to humans**. Kerksick Decl. at ¶ 65; Tong Decl. at ¶ 31.

Third, Turner does not disclose a pharmaceutically effective amount of dhBBR within the dosing range of the '961 Patent. Even if the rodent dose of dhBBR was found to teach a pharmaceutically effective dose in humans, Turner teaches a dose of 100 mg/Kg/day to rats and mice, or 6,000 mg dhBBR per day in humans, which exceeds the range in claim 1 of the '961 Patent.

In an attempt to stretch Turner to meet the limitations of the '961 Patent, Petitioner cites Shaw (Exh. 1005). Additionally, Shaw does not discuss managing blood glucose, dhBBR, or even BBR; rather, it merely suggests that a BSA calculation may be used to translate an animal dose to a **safe human starting dose**.

Petitioner oversimplifies Shaw, arguing that the use of the BSA normalization method can be used to convert a pharmaceutically effective dose from animals to humans. Petitioner's interpretation of Shaw is problematic as it ignores the purpose and stated goals of Shaw and of the '961 Patent. The FDA's guidance (Exh. 1008), which is consistent with Shaw, indicates that "such scaling is intended to estimate a safe first-in-human starting dose and cautions that human bioavailability, metabolism, and drug interactions may differ from animals." Hartung Decl. at ¶ 64. Because Shaw's scope is focused on safety considerations, not efficacy of effect, it does not inform a person of ordinary skill in the art how to establish a pharmaceutically effective dose, as opposed to merely a safe dose, of dhBBR, nor does it teach or suggest any of the asserted claim limitations in Claim 1.

When using the BSA method disclosed by Petitioner in Shaw (Exh. 1005), the human equivalent dose (HED) of dhBBR for rats is 972 mg/day while the HED of dhBBR for mice is 486 mg/day. Kerksick Decl. at ¶ 64. The range set forth in claim 1 of the '961 Patent is "approximately 25 mg to approximately 800 mg of dihydroberberine." 972 mg/day for rats is well outside the claimed range.

Accordingly, even when considered alongside Shaw, Turner fails to disclose or suggest the claimed method, leaving critical gaps in dosing calculations, administration, and therapeutic application that cannot be bridged by safety-based guidance alone.

b. A POSITA would not be motivated to administer dhBBR for managing glucose tolerance in humans

On initial impressions alone “[b]ased on reports that dihydroberberine (dhBBR) improved insulin resistance in rodent models (e.g., Turner, Exh. 1004), a POSITA might generally contemplate whether dhBBR merited further investigation.” Tong Decl. ¶ 31. However, when looking at the prior art as a whole, “the ’961 patent would have **materially disincentivized** a POSITA from advancing dhBBR into human clinical trials as disclosed in the ’961 Patent. *Id.* at ¶ 31. Thus, the cited prior art fails to provide any meaningful rationale or expectation of success that would motivate a person of ordinary skill in the art to pursue the claimed invention. *Id.*; *see also* Tong Decl. at ¶¶ 32-35, 51. Dr. Kerksick also noted significant issues in terms of a lack of a motivation to combine or modify Turner. Kerksick Decl. at ¶¶ 51, 75.

c. Experimental Design Deficiencies in the Turner study

Petitioner relies heavily on the Turner study in its obviousness arguments, citing that preliminary rodent studies. Tong Decl. ¶ 42. However, “Turner’s data suffers from multiple translational limitations, including exclusive use of young male rodents and the use of intraperitoneal injection of glucose into C57Bl/6J mice with a known mutation predisposing mice to glucoregulatory defect (Fergusson 2014, Exh. 2086).” *Id.* Fergusson disclosed that this defect is known to cause irregularities in insulin secretion of C57Bl/6J mice (like the ones used in Turner)

during non-physiological (intravenous/non-oral) glucose tests. *Id.*

A POSITA would consider the fact that Turner did not use an oral glucose tolerance test using dhBBR, and instead adopted a non-physiological, gut-bypassing glucose administration method on C57BI/6J male mice with a known insulin secretion mutation when weighing the value of the Turner study. The POSITA would likely “conclude that Turner’s results are of limited value, particularly with respect to translating such results to human physiology.” Tong Decl. ¶ 42. These are not the only known translational issues with Turner. As further explained in Dr. Kerksick’s Declaration.

[S]everal methodological factors must be considered when evaluating the translatability of the Turner (#1004) results to human efficacy including (a) the use of intraperitoneal administration of glucose, (b) the dose of glucose used, (c) the duration of fasting prior to the glucose tolerance test, and (d) the anesthetic used. The methodological decisions in Turner resulted in a glucose tolerance test of rodents administered dhBBR that cannot be translated to humans with a reasonable likelihood of success in view of the cited prior art.

Kerksick Decl. at ¶ 107.

Furthermore, combining or modifying Turner (and its experimental design) with other references such as Shaw, Feng, and/or Zhang would require a change in the principle of operation of Turner, which used intraperitoneal, gut-bypassing injections, which are different than the claimed invention and also physiologically irrelevant. MPEP § 2143.01(VI) instructs that “[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious.” This further demonstrates the absence of a reason to combine or modify Turner with any other references.

Taken together, these methodological flaws and translational limitations render Turner’s rodent data unreliable for predicting human efficacy, and therefore provide no motivation or reasonable basis for concluding that dhBBR would achieve the claimed therapeutic outcomes in humans.

d. Chen is Not Analogous Art and Would Not Motivate a POSITA

Petitioner misguidedly supplements its obviousness combination in ground 1 (Paper No. 2 at 30, 37) with Chen (Exh. 1009). As set forth in the legal standards above, to support an obviousness rejection under 35 U.S.C. § 103, a reference must qualify as analogous art. *In re Bigio*, 381 F.3d at 1325.

Petitioners rely on Chen to argue that “researchers in the berberine field already relied on rodent studies to launch clinical studies that yielded successes.”

Paper No. 2 at 21. Chen is entitled “A randomized clinical trial of berberine hydrochloride in patients with **diarrhea-predominant irritable bowel syndrome.**”

Exh. 1009. Petitioner argues that Chen’s success in applying animal data provides a POSITA a motivation to combine Turner and Shaw. Chen, however, has nothing to do with glucose metabolism, diabetes, or blood sugar should not be considered analogous art for two reasons. First – Irritable bowel syndrome and diarrhea are not in the same field of endeavor as the study of glucose metabolism. Second, IBS and stomach problems are not reasonably pertinent to the particular problem of the ‘961 patent, managing blood sugar.

e. Lack of Validation

A POSITA’s motivation is further informed by the degree of independent validation and clinical interest reflected in the scientific record. Here, the lack of existing human clinical investigation of dhBBR prior to and following the filing of the ‘961 patent is evidence that would likely limit enthusiasm for its translation to humans. Tong Decl. ¶ 32. Furthermore, “[t]he lack of independent clinical investigation prior to the filing of the ‘961 Patent underscores that development of the compound was neither routine nor predictable at that time and supports the conclusion that a person of ordinary skill in the art would not have had a reasonable expectation of success in pursuing the claimed invention.” Tong Decl. ¶ 33.

2. Claim 2: wherein the administration of dihydroberberine reduces fasting glucose levels

The limitations of claim 2 are not met by Turner, both because claim 2 depends from claim 1 and because, as previously discussed, Turner does not disclose any human data relating to the administration of dhBBR, including any demonstration that dhBBR reduces fasting blood sugar levels in humans. Shaw does not mention glucose metabolism or dhBBR and directly warns against assuming animal models and humans will have the same effect from administered medication. Therefore, Turner in view of Shaw fails to meet the limitations of claim 2. Adding Chen into the combination accomplishes nothing because Chen pertains to irritable bowel syndrome, not blood sugar levels.

3. Claim 5: wherein the dihydroberberine is orally administered as a capsule or tablet

The combined claims of Ground 1 fail to demonstrate the administration of dhBBR by capsule or tablet. Turner does not disclose the oral administration of dhBBR as a capsule or tablet (Exh. 1004) because it teaches that BBR and dhBBR were provided in the high-fat diet fed to the rodent by way of continuous feeding, not a discrete capsule or tablet. *Id.* at p. 4. Shaw does not disclose any information related to the administration of dhBBR or any medication as a capsule or tablet. Therefore, Turner in view of Shaw fails to meet the limitations of claim 5. Chen does not specify that BBR (not dhBBR) was administered by capsule or tablet.

4. Claim 6: wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

The combined claims of Ground 1 fail to demonstrate the administration of dhBBR orally by food or beverage product. Turner (Exh. 1004) does not teach dhBBR or BBR delivery in a beverage product at all, or as a food product to humans, as claimed in the '961 patent. Again, Shaw is silent on dosing and administration of dhBBR. Therefore, Turner in view of Shaw fails to meet the limitations of claim 6.

5. Claim 7: wherein the dihydroberberine is administered at least once daily

The combined claims fail to demonstrate the administration of dhBBR at least once daily. Turner does not teach a once daily dose of dhBBR. As previously discussed, because Turner (Exh. 1004) added dhBBR in the high-fat diet, the dosing is continuous as rodents consume the diet. *Id.* Turner does not specify that the diet was consumed in one sitting or dose. *Id.* Shaw does not provide any teaching related to extent of human dosing in this context.

B. Ground 2: Claim 5 is Not Obvious in light of Turner in View of Shaw and Further in View of Zhang

Petitioner argues that “[b]ecause Turner teaches that dhBBR is dry and solid, and Zhang teaches that BBR has already been administered orally in tablet form, a POSITA would find it obvious to try to administrate dhBBR (a derivative of BBR) as a substitute oral drug also in tablet form.” Paper No. 2 at 40. Contrary to

Petitioner's argument, which refers to the supplementary methods for preparing dhBBR on p. 6 of Exh. 1004, Turner did not disclose administering dhBBR as a dry solid, and instead administered it in the high-fat diet of the test rodents. Exh. 1004 at p. 2. Zhang, on the other hand, administered BBR, not dhBBR. Shaw is silent on the administration of dhBBR. A POSITA would therefore not have been motivated to administer dhBBR in tablet form, when the only prior art teaching the administration of dhBBR, is including it in the subject's food, which is different than a capsule or tablet.

C. Ground 3: Claim 1, 2, 5, and 7 Are Not Obvious over Zhang in View of Feng

1. Claim 1

Claim 1 is not obvious in light of Zhang in view of Feng. Again, simply piecing together isolated elements from multiple references does not render a claim obvious; the prior art must collectively teach all limitations in the same arrangement as the claim, and with a proper reason to combine or modify the references (and a reasonable expectation of success, addressed below in Part VIII, *infra*). Petitioner fails to do the requisite showing.

a. A method of managing glucose tolerance in an individual

Feng (Exh. 1007) does not disclose a method for managing glucose tolerance to an individual. The Feng reference, entitled "Transforming berberine into its intestine-absorbable form by the gut microbiota" is focused on the "absorption

mechanism” of BBR in rats. Exh. 1007 at p. 1. Like Turner, Feng does not disclose **any human data at all**. Kerksick Decl. at ¶ 77. Instead, Feng relies on cell and animal models that are fundamentally different than human individuals. *Id.* The animal models utilized in the study were rats, which face significant translation limitations as explained by Dr. Kerksick in ¶¶ 41-62 of his declaration, and Dr. Hartung in ¶¶ 47-67 of his declaration. *See also* Tong Decl. at ¶ 67.

In Feng, the glucose regulating effects of dhBBR, which is the compound relevant to the ‘961 Patent, are never addressed. Feng’s conclusion, that gut microbiota in rats oxidized dhBBR to BBR, is irrelevant to glucose regulation properties of dhBBR disclosed in the ‘961 Patent because “[w]idespread compositional and functional differences exist between rodent and human microbiomes.” Kerksick Decl. at ¶ 77; *see also* Kerksick Decl. at ¶ 32-40, 67, 81-83, 94, 110-111; Tong Decl. at ¶¶ 60-69; Hartung Decl. ¶¶ 37, 47, 54-56, 59, 63. Zhang only discloses the administration of BBR to humans.

b. Administering, to an individual, a pharmaceutically effective amount of dihydroberberine

Feng also does not disclose the administration of a pharmaceutically effective amount of dhBBR. The only situation in which Feng administered dhBBR was to compare its relative absorption to BBR. Relative absorption does not address therapeutic efficacy, dosing requirements, or clinical outcomes, especially with respect to managing glucose tolerance in an individual, and therefore falls outside

the scope of what is required by claim 1 of the '961 Patent.

Zhang only teaches the administration of BBR, not dhBBR. Petitioner claims that because “because BBR is converted to dhBBR by the gut microbiota after the oral administration of BBR, dhBBR had been effectively administered to humans for decades as BBR” and it is therefore safe. Paper No. 2 at 46-47. As explained in Dr. Tong’s declaration, the administration of BBR is not “effectively” the same as the administration of dhBBR and Petitioner has no provided sufficient support for such a claim in the prior art. Tong Decl. at ¶¶ 60-70.

c. Wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

Feng’s dosing of BBR and dhBBR is also inconsistent with what is taught in the '961 Patent. Kerksick Decl. at ¶ 77. Feng administered 200 mg dhBBR/kg/day in rats. Exh. 1007 at Fig. 3. If directly construed for a 60 kg human, the dose would be 12,000 mg. Similarly, a conversion by the calculations from Shaw (Exh. 1005), teaches a human equivalent dose of 1945.9 mg (for a 60 kg person) of dhBBR. Kerksick Decl. at ¶ 77. The upper dosing limit highlighted in the '961 patent is ~800 mg dhBBR per claim 1. The dosage used in Feng is significantly higher than the upper limit highlighted in the patent when applied to an “average” 60 Kg adult. *Id.* Because Zhang only discloses the administration of BBR, no dose for dhBBR is actually disclosed at all. Kerksick Decl. ¶ 71. Additionally, the dose disclosed for

BBR, of 500 mg, twice a day, is outside of the upper limit, 800 mg/day of the dosing range of claim 1 of the '961 Patent (if one were to use the Shaw dosing calculation).

Petitioner contends that Zhang in view of Feng teaches that administering dhBBR to humans at a dosage that is reduced from the pharmaceutically effective BBR dose of 1g/day would fall within the claimed dosage. Paper No. 2 at 51 (Table 2). This argument fails because Petitioner provides no evidence or rationale for how the dosing of dhBBR should be scaled relative to BBR. The prior art is silent on any correlation or conversion of pharmaceutically effective dose between BBR and dhBBR, leaving a critical gap that cannot be bridged by speculation. Moreover, Petitioner's reliance on dhBBR's higher absorption is rate for a pharmacologically effective dose is misplaced—improved absorption alone does not establish pharmaceutical effectiveness or therapeutic equivalence. Finally, because some of the dosing data is derived from rodent data, and given the significant differences in rodent and human gut microbiota and glucose metabolism (Kerksick Decl. at ¶¶ 32-44, 54-62; Hartung Decl. at ¶ 53-58; Tong Decl. at ¶¶ 61-69), attempting to calculate a human dhBBR dose would be sheer speculation.

d. Petitioner Fails to Articulate a Motivation to Combine

The Petitioner contends that because Zhang purports benefits of BBR for glucose tolerance in humans, BBR is known to have low bioavailability, and Feng shows dhBBR has improved absorption, a POSITA would have been motivated to

substitute dhBBR for BBR to manage human glucose levels. But its cited motivation to combine these references is lacking.

Zhang (Exh. 1006) discloses the administration of BBR to assist with glucose tolerance in humans, but does not at any point, disclose that those glucose managing properties are also shared by dhBBR. Petitioner contends that because “BBR is widely known to ‘exhibit[] poor water solubility’” according to Feng, and require a high dose according to Turner, that A POSITA would be motivated to find a more bioavailable derivative. Paper No. 2 at 43-44. Still, Petitioner notes that in Zhang, patients “receiving berberine had **a significant improvement in fasting plasma glucose.**” Exh. 1006 at p. 2. Zhang further discloses that the participants of the study experienced no serious adverse effects, with only mild to moderate side effects occurring in a handful of participants. Paper No. 2 at 43.

Petitioner asserts that multiple reports in the literature predict and demonstrate that dhBBR, as a derivative of BBR, has improved absorption characteristics. Paper No. 2 at 44. This assertion, however, lacks critical context. The cited prior art regarding dhBBR administration is limited to animal studies and in vitro cell models. No prior art cited in this proceeding discloses the administration of dhBBR to humans for managing glucose tolerance, and the reported absorption data was derived exclusively from non-human models. As also discussed below, there are significant differences between animals, cell models, and humans which make data

hard to translate. Hartung Decl. at ¶¶ 47-68; Tong Decl. at ¶¶ 43-45, 60-62; Kerksick Decl. ¶¶ 31-62.

Considering that BBR was known to provide improvement in fasting plasma glucose apparently without any serious adverse effects, it is unclear why a POSITA would have been motivated to search for an alternative. Moreover, the prior art provides no evidence that improved absorption alone would translate into improved therapeutic efficacy in humans. In fact, Dr. Tong noted that there are differences in the pharmacokinetics, absorption, and the like between BBR and dhBBR. Tong Decl. at ¶¶ 60-70. Without any human clinical data in connection with glucose tolerance that predates April 19, 2016, and given the substantial differences in metabolism, bioavailability, and gut microbiota between rodents and humans, as documented elsewhere herein, a POSITA would recognize that extrapolating rodent or cell-based absorption findings to human therapeutic outcomes involves significant uncertainty. Thus, the cited references fail to supply a compelling rationale to substitute dhBBR for BBR with respect to the elements of claim 1 in the '961 Patent.

2. Claim 2

Claim 2 is not rendered obvious by Zhang in View of Feng. Petitioner argues that Zhang teaches the administration of BBR reduces fasting glucose levels. Paper No. 2 at 55-56 (Table B); Exh. 1006 at p. 3. Petitioner argues that Zhang, in view

of Feng, “[f]urther teaches that administering dhBBR would be able to reduce fasting glucose levels because dhBBR is a transient form of BBR,” and that “orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro drug. *Id.* This assertion is baseless and without support from the prior art. The fact that once dhBBR is in the gut it oxidizes back to BBR, as disclosed in Feng, does not prove that administration of dhBBR and BBR would have substantially the same impacts on glucose tolerance. In fact, BBR and dhBBR are distinct (Tong Decl. at ¶¶ 60-70; Kersick Decl. at ¶ 85), and without any prior art demonstrating that the effects of BBR and dhBBR are substantially the same, particularly in humans, and particularly with respect to glucose tolerance, Petitioner’s assertions fail. Thus, claim 2 of the ‘961 Patent is not rendered obvious by Zhang in view of Feng.

3. Claim 5

Claim 5 is not obvious based on Feng in view of Zhang. Feng teaches the oral administration of dhBBR to rats, while Zhang teaches the oral administration of BBR to humans. Petitioner argues that (1) because it is “well known that BBR is to be administered orally in tablets to patients”, and (2) because an “orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro-drug,” a POSITA would have been motivated to administer dhBBR orally in tablets to improve intestinal absorption.

Both arguments improperly conflate BBR and dhBBR. First, the administration of BBR is not equivalent to the administration of dhBBR, as they are distinct compounds with different pharmacological profiles. Second, Petitioner has provided no evidence or rationale to support the assumption that dhBBR should be administered in the same manner or at the same doses as BBR. Dr. Tong highlighted significant differences between BBR and dhBBR. Tong Decl. at ¶¶ 60-70. Accordingly, because Petitioner's arguments rest on an unsupported equivalence or substantial equivalence, between BBR and dhBBR and fail to provide any evidence or rationale for dosing correlation, Claim 5 is not rendered obvious based on Zhang in view of Feng.

4. Claim 7

Claim 7 is not rendered obvious by Feng in view of Zhang. Petitioner argues the “[b]ecause BBR has already been administered orally at least once daily, and further because orally administered dhBBR would remain pharmacologically effective given BBR would enter the blood and remain as the active drug and dhBBR acts as a pro-drug, a POSITA would have been motivated to administrate dhBBR similarly - at least once daily.

In Zhang, only BBR is administered, and it is administered twice a day orally. However, no prior art is cited where dhBBR is administered once daily (which is within the scope of claim 7, which requires at least once daily administration). In

Feng, dhBBR appears to be administered to rats only once, following a fast. Petitioner again improperly conflates the pharmaceutical effect of BBR with that of dhBBR, despite the fact that they are distinct compounds with different pharmacological profiles as previously stated. Accordingly, because the prior art does not teach that dhBBR should be administered once daily or that its therapeutic effect mirrors BBR, claim 7 is not obvious based on Feng in view of Zhang.

D. Ground 4: Claim 6 is Not Obvious in light of Zhang in View of Feng and Further in View of Turner

Claim 6 is not obvious in light of Zhang in view of Feng and in further view of Turner. Petitioner argues that because Turner teaches administering dhBBR to rodents as a food product for managing glucose tolerance, a POSITA would find it obvious to try administering dhBBR as a food product to humans to manage glucose tolerance. This argument is fundamentally flawed. Turner's disclosure is confined to rodent studies and does not teach or suggest any administration of dhBBR to humans, nor does it provide guidance on human dosage, formulation, or clinical efficacy.

Moreover, Zhang only teaches the administration of BBR, not dhBBR, and does so exclusively in tablet form—not as a food or beverage product. Feng likewise fails to disclose any administration of dhBBR as a food or beverage product to humans. Petitioner again improperly conflates the properties of BBR and dhBBR, despite their distinct pharmacological profiles, as previously discussed herein.

Further, Petitioner offers no sufficient evidence or rationale to support that such a modification would have been obvious or that a POSITA would have had a reasonable expectation of success. Petitioner's argument is a hindsight reconstruction. The prior art is entirely silent on any correlation between rodent feeding studies and human food-based administration, leaving a critical gap that cannot be bridged by speculation and can only be bridged by hindsight. Accordingly, because none of the cited references teach or suggest administering dhBBR as a food or beverage product to humans, and because Petitioner's reasoning relies on unsupported assumptions rather than disclosed teachings, Claim 6 cannot be rendered obvious based on Zhang in view of Feng and Turner.²

VIII. THERE IS NO REASONABLE EXPECTATION OF SUCCESS TO SUPPORT PETITIONER'S ASSERTION OF OBVIOUSNESS

Petitioner's assertion, through its expert, that there would be a reasonable expectation of success regarding administration of dhBBR to humans (Ex. 1003 at ¶ 70) is misguided and conclusory. A careful analysis of the prior art *as a whole* demonstrates the fallacy of Petitioner's assertion.

Here, because Petitioner and its expert did not take the prior art *as a whole* into account and missed key elements in the prior art that would not have provided

² Patent Owner believes evidence of secondary considerations of non-obviousness likely exist, and as such, Patent Owner reserves the right to introduce such evidence should review be instituted.

a POSITA with anything close to a reasonable expectation of success. Furthermore, because Petitioner and its expert divorced the portions of the prior art it cited from overall scientific and physiological context of the references it relied upon, Petitioner's assertions about a reasonable expectation of success are not based on the prior art as a whole and should be rejected.

A. Dr. Thomas Hartung Opines That There is no Reasonable Expectation of Success

For example, Petitioner's expert made a series of assumptions about the reliability of the high-fat diet mouse model of Type 2 Diabetes, the active moiety of dhBBR, the BSA/HED dose translation method as being "most appropriate," the glucose dynamics in that efficacy in a glucose tolerance test given to rodents translates to human glucose dynamics and outcomes, and the role of the gut microbiome in rodents versus humans. Hartung Decl. at ¶ 68 ("Petitioner's Assumption (Shebuski)" column of Table therein).

In response, Dr. Hartung opined on the substantial differences between rodents and humans that prevent viable translation of rodent results to humans. *Id.* ("Translational Reality (Scientific Context)" column of Table therein). These include the fact that rodents fundamentally differ from humans in mitochondrial control of glucose, hormone dynamics, and gut anatomy; species differences in liver glucose metabolism and processing of BBR and dhBBR exist; the BSA scaling calculation is for safety not efficacy; differences in how glucose is generated

between rodents and humans, and differences in rodent gut microbiota models that attempt to recreate human microbiota fall short of reproducing reality. *Id.*

After explaining the key issues with translatability of results between rodents and humans (*Id.* – “Specific Contention” column of Table therein), Dr. Hartung concluded in the “Success Probability” column of his Table in ¶ 68 of his declaration that because of the substantial differences in rodent and human physiology, including as to, among other things, glucose metabolism, the data shows that an extremely low number (~5%) of animal-tested interventions are ultimately approved for use in humans. *Id.*; *see also Id.* at ¶ 36. Five (5) percent does not translate to a reasonable expectation of success.

In support of the Table in ¶ 68 of his declaration, Dr. Hartung meticulously documented the bases for his conclusion that Petitioner failed to demonstrate a reasonable expectation of success, and in fact, that no such reasonable expectation exists. Dr. Hartung first summarized his opinions in ¶¶ 28-32 of his declaration:

- Rodent metabolic, mitochondrial, and glycemic responses do not reliably translate to humans, and animal models regularly overestimate efficacy, underestimate toxicity, and produce results that fail to reproduce in clinical trials.
- The references relied upon by Petitioner are based on rodent data, in vitro findings, or BBR-only human data, none of which reliably predict

how dhBBR would impact human glucose tolerance.

- There existed known, substantial differences between rodents and humans as to glucose metabolism, mitochondrial complex-I responses, and intestinal transformation of xenobiotics, and that as of April of 2016, a POSITA would not have expected rodent observations regarding BBR or dhBBR to predict human efficacy without direct human testing and/or validated mechanistic support for the results.

Hartung Decl. at ¶¶ 28-32.

Dr. Hartung then walks through in detail the reasons for his conclusion that there Petitioner failed to demonstrate a reasonable expectation or likelihood of success. First, Dr. Hartung discusses the difficulty in general of translating animal data to humans. *Id.* at ¶¶ 37-46.

Second, Dr. Hartung addresses the difficulty of translating rodent data to humans. *Id.* at ¶¶ 47-52.

Third, Dr. Hartung detailed the difficulty in translating animal data to humans in terms of metabolism and glucose regulation (*Id.* at ¶¶ 53-58), which is quite on point for the general background subject matter of the '961 Patent. Dr. Hartung noted that there are significant differences in human glucose homeostasis relative to rodents, and that rodent mitochondrial responses frequently fail to reproduce in human tissues. *Id.* at ¶ 53. Dr. Hartung's analysis further details differences in the

mitochondrial, hormonal, intestinal, and hepatic systems that lead to differences in whole-body glucose handling. *Id.* at ¶ 54-58.

Fourth, Dr. Hartung then addressed Petitioner’s cited prior art head on and explained not only the difficulty in translating the data in the cited prior art to humans (*Id.* at ¶¶ 59-67), but also why the prior art fails to establish all of the limitations of claim 1 of the ‘961 Patent (*Id.* at ¶ 59) (no human evidence for dhBBR administration). Dr. Hartung identifies the systems addressed by the prior art and how it falls short of not only meeting the challenged claims of the ‘961 Patent, but also that it uses methods such as intraperitoneal glucose tolerance testing in Hu (*Id.* at ¶ 61) and Turner (*Id.* at ¶ 62), as well as differences in gut microbiota between rodents and humans that lead to differences in metabolism of BBR and dhBBR (*Id.* at ¶¶ 63, 64), and finally, the general failure of animal-to-human drug effect translation (*Id.* at ¶¶ 65, 67), which leads to his conclusion that the prior art “does not bridge the well-known translation gap between rodent metabolic outcomes and human clinical efficacy.” *Id.* at ¶ 66.

B. Dr. Chad M. Kerksick Opines That There is no Reasonable Expectation of Success

In addition to Dr. Hartung, Patent Owner’s scientific advisory board member (Kerksick Decl. at ¶ 5), Dr. Kerksick, also provided statements and opinions addressing the lack of a reasonable expectation of success in Petitioner’s petition.

Consistent with Dr. Hartung, Dr. Kerksick also opined on the fact that rodent

microbiomes vary drastically from humans, and notes as much in the context of the prior art cited by Petitioner. *Id.* at ¶ 32. Dr. Kerksick supports his assertion in ¶¶ 33-40 of his declaration wherein he considers the prior art as a whole and points to substantial differences in rodent behavior that lead to differences from humans in terms of “metabolic rates, metabolism, heart rates, and macronutrient metabolism and turnover.” *Id.* at ¶ 33. Dr. Kerksick also notes the compositional differences between rodent and human microbiomes in terms of microbiota present, gut physiology, and anatomy, and how they limit transferability from rodent to human in terms of results. *Id.* at ¶¶ 34-39. Dr. Kerksick concludes:

These significant physiological and metabolic differences between rodents and humans, particularly in mechanisms of glucose regulation, make such extrapolation highly uncertain without supporting methodology or corroborating human data, which did not exist at the time of the ‘961 patent’s filing date.

Id. at ¶ 40.

Dr. Kerksick then discusses the significant difficulties that exist regarding applying data on glucose metabolism from rodents to humans. *Id.* at ¶ 41. Dr. Kerksick, in the context of whether data is transferable between rodents and humans in the context of the subject matter of the '961 Patent, then addresses in detail

additional physiological and anatomical differences between rodents and humans as it pertains to glucose metabolism. *Id.* at ¶¶ 42-44. Dr. Kerksick notes the teachings of the Cabrera article (Exh. 2097), which concluded that islet physiology between mice and humans is quantitatively different and anatomically different. Dr. Kerksick notes the Bowe article (Exh. 2094), which details issues with intraperitoneal administration of glucose compared to oral administration and further notes that intraperitoneal is “not physiological” (Dr. Kerksick’s words at ¶ 47). Kerksick Decl. at ¶¶ 45-47. Dr. Kerksick then shows that the Turner (Exh. 1004) reference heavily relied upon by Petitioner does not support a finding of obviousness at all because it utilized intraperitoneal glucose in its study. Kerksick Decl. at ¶ 48; *see also* Kerksick Decl. at ¶¶ 64-75, 107 (discussing the numerous ways in which Turner is deficient and irrelevant as a prior art reference including because of an inappropriate overnight fast (*Id.* at ¶ 74) and the use of anesthesia, among other things (*Id.* at ¶ 75), and that it would not motivate a POSITA to combine it with other references nor lead to a reasonable expectation of success (*Id.* at ¶ 75). The issue with the overnight fast is that rodents are nocturnal; and, the parallel to human testing is lost because humans typically fast while at rest (overnight) before glucose testing. And, the issue with anesthesia is that it can have effects on glucose metabolism, as noted by Dr. Kerksick. *Id.* at ¶¶ 75, 92. These problems with Turner defeat at least Grounds 1, 2, and 4 of Petitioner’s petition in that each substantially rely on Turner.

Dr. Kerksick, in ¶¶ 49-51 of his declaration, and the evidence cited in those paragraphs, notes the same issues with intraperitoneal injections of glucose based on another article (Small, Exh. 2099), and discusses how differences in intraperitoneal versus oral administration (as would be done in humans or in practical reality) and further states that:

intraperitoneal administration does not accurately reflect human physiology or metabolism. This would discourage a POSITA from considering Turner (Exh. 1004) as relevant or applicable prior art, combining it with other prior art, or reasonably expecting success in humans based on its teachings.

Kerksick Decl. at ¶ 51.

Dr. Kerksick again points out that Turner (Exh. 1004) does not support a finding of obviousness because intraperitoneal glucose is not a physiological means of administration, and that this would not only discourage a POSITA from combining Turner with other references, but it would not lead to a reasonable expectation of success. Kerksick Decl. at ¶¶ 51-52.

Dr. Kerksick further notes the prior art's explication of differences in rodents and humans in terms of carbohydrate storage, insulin, glycogen, and basal levels of glucose, pointing to the Kowalski article (Exh. 2102). Kerksick Decl. at ¶¶ 55-61.

These and other distinctions in rodent and human anatomy, physiology, behavior, and glucose metabolism led Dr. Kerksick to conclude that:

translatability of results between rodents and humans is highly suspect and I do not believe a person of ordinary skill in the art would believe or assume such translatability.

Kerksick Decl. at ¶ 62.

In other words, a person of ordinary skill in the art would not have a reasonable expectation of success in light of the prior art as a whole.

Dr. Kerksick has similar criticisms of the Feng reference (Exh. 1007) relied on by Petitioner. Feng's dosage was more than 2x higher than the upper limit of the range in claim 1 of the '961 Patent (Feng dosage, using the calculations from another reference Petitioner relied upon – Shaw (Exh. 1005) – translated the 200 mg dhBBR/kg/day in rats to ~1945 mg/day for a 60 kg human – upper limit in claim 1 - ~800 mg/day). Kerksick Decl. at ¶ 78.

Dr. Kerksick also took issue with the quality of the data in Feng Figs. 3b, 3c, and 3d, and noted that a POSITA would not rely on such suspect data. Kerksick Decl. at ¶ 79. The issue highlighted by Dr. Kerksick was that the “n” value for the experiments in Figs. 3b, 3c, and 3d was only 3, the error bars in the graphs were very large, and the data was not shown nor claimed to be statistically significant.

Kerksick Decl. at ¶ 79. Thus, a POSITA would not be motivated to rely on such junk data, nor would such junk data give a POSITA a reasonable expectation that the procedures and results of Feng would replicate in humans (particularly in light of all the other differences between rats and humans, as noted by each of Patent Owner's experts). Dr. Kerksick found that the prior art as a whole, including as discussed in ¶¶ 80-82 of his declaration, "simply does not provide a reason to combine Feng with Turner, nor expect success if such a combination were made." *Id.* at ¶ 82.

In short, because Feng is heavily relied on by Petitioner for at least Grounds 3 and 4 in its Petition, those grounds fail because Feng would not motivate a combination with other prior art, nor give a POSITA a reasonable expectation that such a combination would be effective in humans. *Id.* at ¶¶ 81-83; *see also* Kerksick Decl. at ¶¶ 93-94.

Dr. Kerksick also noted the *irrelevance* of the Chen reference (Exh. 1009), which looked reported an effect of BBR, not dhBBR, on irritable bowel syndrome, not glucose regulation. Kerksick Decl. at ¶¶ 85, 86; *see also* Kerksick Decl. at ¶ 95. Thus, it would not motivate any combination or provide a reasonable expectation of success on an entirely different physiological system.

Dr. Kerksick likewise noted the *irrelevance* of the Liu reference (Exh. 1010) because its dosages were outside the range of the '961 Patent once extrapolated to a

60 kg human using Petitioner's preferred method from Shaw. Kerksick Decl. at ¶87; *see also* Kerksick Decl. at ¶¶ 95-96. Thus, to the extent Petitioner relied upon Liu, it is not relevant to obviousness.

Dr. Kerksick noted that the Zhang reference (Exh. 1006) relied upon by Petitioner used BBR, not dhBBR in unhealthy individuals with significant metabolic issues that impact glucose metabolism such that its results would not give a POSITA a reasonable expectation of success in terms of an effect, if any, in terms of administering *dhBBR* to healthy humans. Kerksick Decl. at ¶¶ 89-90.

In addition to his “in-line” references to a lack of reasonable expectation of success in his analysis of the various prior art references, Dr. Kerksick summarizes and concludes that no reasonable expectation of success exists for the combination of references cited by Petitioner in its petition. Kerksick Decl. at ¶¶ 115-119.

C. Dr. Qiang Tong Opines That There is no Reasonable Expectation of Success

Dr. Tong opined in discussion of Turner (Exh. 1004) that there were a series of factors in the prior art that would have “materially disincentivized” a POSITA from advancing dhBBR into human clinical trials such that no motivation to combine or reasonable expectation of success existed. Tong Decl. at ¶ 31. Dr. Tong opined that a POSITA would look to whether any independent verification of Turner's results in clinical trials or otherwise existed. *Id.* at ¶ 32. Dr. Tong's searching found no such activities prior to the effective filing date of the application for the '961

Patent on April 19, 2016. *Id.* at ¶¶ 33-35.

Dr. Tong then noted that the metabolic disease literature did not provide any reasonable expectation of success here because such literature was “replete with examples where rodent efficacy failed to translate into clinical benefit in humans, including within the treatment of metabolic disorders” (*Id.* at ¶ 37), citing examples of such failure in various research settings (*Id.* at ¶¶ 37-40).

Dr. Tong also takes aim at Turner’s experimental design flaws including the intraperitoneal injection issue discussed above, and the use of C57Bl/6J mice, which have a known mutation impacting glucoregulation, which would skew results, particularly under the experimental design in Turner, such as intraperitoneal glucose administration. *Id.* at ¶¶ 42, 44-47 (and Exh. 2086). Dr. Tong also challenged the efficacy of the high-fat diet in rodents as a research model (Tong Decl. at ¶ 43 (and Exh. 2020 at p. 002)) and questioned Turner’s data in Supplementary Fig. 2C (Tong Decl. at ¶ 49). Ultimately, Dr. Tong concluded that a POSITA would not have a reasonable expectation of success at meeting the limitations of at least claims 1 and 2 based on at least Turner’s intraperitoneal glucose administration, questionable selection of mice strain, fasting rodents at night, and the lack of reliability of rodent data predicting human outcomes. Tong Decl. at ¶¶ 48, 50, 53-54.

Dr. Tong also notes that the FDA reference (Exh. 1008) does not assist in establishing obviousness because it is not directed to efficacy but safety and

“toxicology extrapolations.” Tong Decl. at ¶ 51.

In connection with Ground 3 of Petitioner’s obviousness challenge (Zhang plus Feng), Dr. Tong takes issue with Petitioner essentially equating BBR and dhBBR and simply cobbling together an assertion of obviousness from references that do not meet and limitations of any of the challenged claims. Zhang tested BBR on unhealthy human subjects and Feng testing BBR and dhBBR on rats. Reasons this combination of references fails include: (1) the gastric pH in rodents and humans differs significantly, which would cause differing pharmacokinetics and absorption based on BBR and dhBBR administration; (2) differences in drug absorption for BBR and dhBBR in different portions of the intestine; (3) differences in gut microbiota between rats and humans; (4) differences in effects between dhBBR and BBR. Tong Decl. at ¶¶ 60-69.

Dr. Tong also noted that the differences between BBR and dhBBR alone would not permit a reasonable or reliable expectation of success of dhBBR reducing fasting glucose levels in humans (claim 2). *Id.* at ¶ 70. And, he noted, the prior art did not teach capsules and tablets (claim 5), single dosing (claim 7), and would not motivate a POSITA to do so. *Id.* at ¶¶ 58, 71-73.

Based on the foregoing, Petitioner has failed to establish a reasonable expectation of success for any of the challenged claims (1, 2, 5, 6, 7). Because a reasonable expectation of success is a critical element of a prima facie case of

obviousness, and Petitioner has failed to establish this element, its Petition should be rejected and institution denied in its entirety. MPEP § 2143.02 (*quoting Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1375, (Fed. Cir. 2023) and *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) (“An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.”).

IX. CONCLUSION

For the aforementioned reasons, Petitioner’s petition should not be referred for institution.

Date: January 7, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this **PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S PRELIMINARY RESPONSE** has been served on January 7, 2026 upon the following litigation counsel via electronic means:

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**CERTIFICATE OF COMPLIANCE WITH WORD COUNT
REQUIREMENTS UNDER 37 C.F.R. § 42.24**

Under 37 C.F.R. § 42.24(d), the undersigned certifies that this **PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.’S PRELIMINARY RESPONSE** complies with the word count limitation in that it contains 13,938 words.

This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and the type style requirements of 37 C.F.R. § 42.6(a)(2)(iii) and (iv).

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