

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*

DECLARATION OF DR. CHAD. M. KERKSICK, PH.D.

Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd., hereby respectfully submits the following Declaration of Dr. Chad M. Kerksick, Ph.D. to the Board in support of Patent Owner's Preliminary Response.

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TABLE OF EXHIBITS

EXHIBIT NUMBER	DESCRIPTION
2092	Curriculum Vitae of Dr. Chad M. Kerksick
2093	Bertorello, S. The Future Exploring of Gut Microbiome-Immunity Interactions: From In Vivo/Vitro Models to In Silico Innovations. <i>Microorganisms</i> 2024, 12(9), 1828.PMID: 39338502. (“Bertorello”)
2094	Bowe JE, et al. Metabolic Phenotyping Guidelines: Assessing glucose homeostasis in rodent models. <i>J Endocrinol.</i> 2014/222(3):G13-G25. PMID: 25056117. (“Bowe”)
2095	Nagpal R, et al. Comparative Microbiome Signatures and SCFA in Mouse, Rats, Non-Human Primate, and Human Feces. <i>Front Microbiol.</i> , 30 Nov 2018 Nov 30;9:2897. PMID: 30555441. (“Nagpal”)
2096	Nguyen TLA, et al. How informative is the mouse for human gut microbiota research? <i>Dis Model Mech.</i> 2015 Jan;8(1):1-16. PMID: 25561744. (“Nguyen”)
2097	DeSesso JM and Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. <i>Food Chem Toxicol.</i> March 2001;39(3):209-228. PMID: 11278053. (“DeSesso”)
2098	Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren P-O, Caicedo A. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. <i>Proc Natl Acad Sci USA.</i> 2006 Feb 14;103(7):2334-9. PMID: 16461897. (“Cabrera”)
2099	Small L, et al. Comparative analysis of oral and intraperitoneal glucose tolerance tests in mice. <i>Molecular Metabolism.</i> 2022 Mar;57:101440. PMID: 35026435. (“Small”)

2100	Martic-Kehl MI, et al. Can animals data predict human outcome? Problems and pitfalls of translational animal research. <i>Eur J Nucl Med Mol Imaging</i> . 2012 Sep;39(9):1492-6. PMID: 22790876. (“Martic-Kehl”).
2101	Shoyaib AAI, Archie SR, Karamyan VT. Intraperitoneal Route of Drug Administration: Should it Be Used in Experimental Animal Studies? <i>Pharm Res</i> . 2019 Dec 23;37(1):12. PMID: 31873819. (“Shoyaib”)
2102	Kowalski GM and Bruce CR. The regulation of glucose metabolism: implications and considerations for the assessment of glucose homeostasis in rodents. <i>Am J Physiol Endocrinol Metab</i> . 307:E859-E871, 2014. PMID: 25205823. (“Kowalski”)
2103	Ye J, Iglesias MA, Watson DG, Ellis B, Wood L, et al. PPAR α / γ ragaglitazar eliminates fatty liver and enhances insulin action in fat-fed rats in the absence of hepatomegaly. <i>Am J Physiol Endocrinol Metab</i> . 2003;284:E531-E540. PMID: 12556350. (“Ye”)
2104	Saha JK, Xia J, Grondin JM, Engle SK, Jakubowski JA. Acute hyperglycemia induced by ketamine/xylazine anesthesia in rats: mechanisms and implications for preclinical models. <i>Exp Biol Med (Maywood)</i> . 2005 Nov;230(10):777-84. PMID: 16246906. (“Saha”)
2105	Molero JC, Turner N, Thien CBF, Langdon WY, James DE, Cooney GJ. Genetic ablation of the c-Cbl ubiquitin ligase domain results in increased energy expenditure and improved insulin action. <i>Diabetes</i> . 2006 Dec;55(12):3411-7. PMID: 17130487

DECLARATION OF DR. CHAD M. KERKSICK, PH.D.

I, Chad M. Kerksick, declare as follows:

I. INTRODUCTION

1. This section contains a summary of my educational background, career history, publications, and other relevant qualifications. My full curriculum vitae is attached as Exhibit 2092 to this declaration.

2. I am currently a Professor of Exercise Science in the Exercise Science Department in the College of Science, Technology, and Health at Lindenwood University in St. Charles, Missouri. I currently serve as the Director of the Exercise and Performance Nutrition Laboratory (www.lindenwood.edu/epnl). I am also an Assistant Dean of Research & Innovation. My primary research interests examine the biochemical, cellular, and molecular adaptations relative to various forms of exercise and nutrition interventions, primarily those that promote muscle hypertrophy, prevent muscle atrophy, and promote health and recovery in healthy as well as clinical populations.

3. I earned my B.S. in Health & Exercise Science from Truman State University in Kirksville, Missouri in 1999, followed by a M.S. in Exercise and Sport Science from the University of Memphis in 2002. I completed my Ph.D. in Exercise, Nutrition and Preventative Health in 2006 at Baylor University in Waco, Texas.

4. As also set forth in my CV (Exhibit 2092), I have worked as university

research professor since 2006 (Univ. of Oklahoma 2006-2012; Univ. of New Mexico 2012 – 2014; Lindenwood University since 2015). I have published over 150 peer-reviewed articles focusing on research examining exercise and nutrition interventions in humans. I have published two books, 13 book chapters, and currently have an h-index of 60 with over 16,000 citations.

I. COMPENSATION

5. I am a member of the scientific advisory board for Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. (“Patent Owner” or “NNB”). For my efforts in connection with the preparation of this declaration, I have been compensated based on a non-hourly rate, but the amount translates to approximately \$500.00/hour. My compensation is not in any way contingent on my performance, the result of this proceeding, or any of the issues involved therein.

II. MATERIALS REVIEWED

6. In preparing this declaration, I have reviewed and/or considered at least the documents cited in the List of Patent Owner’s Exhibits above, and the documents referenced in this declaration, as well as the Shebuski Declaration and exhibits relied upon by Dr. Shebuski in connection with the petition for inter partes review.

7. I note that in several instances, I have looked at materials that post-dated April 19, 2016. I did this by and large if the materials presented a statement relating to the state of the prior art at an earlier date, or if the materials made a

statement that I do not believe would have been materially if at all different had it been made prior to April 19, 2016. However, in some instances, the later research would tend to show that the invention in the '961 Patent was not known nor obvious prior to April 19, 2016.

III. RELEVANT LEGAL STANDARDS

8. I am not a lawyer. I have been provided with an understanding of the legal principles that govern patent validity and claim construction. I have conducted my analysis in conformance with these principles. I set forth those understandings below.

A. Obviousness

9. Patent Owner's counsel has informed me that the issue to contend with in this matter is obviousness, which is governed by Title 35 United States Code ("U.S.C.") § 103. The statute provides that a "patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." I have also been informed that issued patents are presumed to be valid. 35 U.S.C § 282(a).

10. The patent owner's counsel informed me that in an inter partes review, the Petitioner has the burden of proving, by a preponderance of the evidence, that

the challenged patent claims would have been obvious based on “prior art” before the effective filing date of the claimed invention (i.e., before April 19, 2016).

11. For purposes of this report, I understand that “prior art” consists of patents, patent applications, and printed publications that existed prior to April 19, 2016, if not prior to April 19, 2015.

12. I have been informed that when a single prior art reference does not contain every limitation or element of a single patent claim, the PTAB can only invalidate the claim if supplying the missing limitations through another prior art reference or modification of the existing prior art would have been obvious to a person of ordinary skill in the art, and doing so without applying hindsight bias (i.e., looking back to prior to April 19, 2015 or 2016 based on what is currently known so as to recreate the current invention in the prior art through what is now known because of the invention). I have been further informed that a claim is invalid for obviousness only if the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious to a person having ordinary skill in the art before the effective filing date of the claimed invention, again without the benefit of hindsight.

13. As part of the obviousness analysis, I have been informed that prior art references may be combined to show that a patent is invalid as obvious. I also understand that an obviousness evaluation may be based on a single reference or a

combination of multiple prior art references. For example, a single reference—when considered in light of the knowledge of a person of ordinary skill in the art—may render a claim obvious. Where a Petitioner attempts to prove obviousness by merely throw[ing] metaphorical darts at a board in hopes of arriving at a successful result where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, hindsight claims of obviousness may be rejected.

1. *Graham* Factors

14. Counsel for the Patent Owner has informed me that an obviousness analysis considers a number of factors that consider four factual inquiries underlying obviousness, otherwise known as the *Graham* Factors. I have been informed that the inquiries are as follows: 1) Scope and content of the prior art, 2) Differences between the claimed invention and the prior art, 3) Level of ordinary skill in the art (“POSA/POSITA”), and 4) Objective evidence of nonobviousness (otherwise known as the secondary considerations of non-obviousness).

a. Scope and Content of the Prior Art

15. I have been informed that for a reference to be proper for use in an obviousness rejection, the reference must be analogous art to the claimed invention in the patent. 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.

b. Differences Between the Claimed Invention and the Prior Art

16. I have been informed that an obviousness analysis requires that the differences between what is claimed in the patent under consideration and the prior art be ascertained. I have been informed that an invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent.

c. Level of Ordinary Skill in the Art

17. The Patent Owner's counsel has informed me that my analysis must be performed from the perspective of a hypothetical "person of ordinary skill in the art" ("POSITA") as of the priority date of the patent, which I understand to be April 19, 2015 or possibly 2016. I understand that a POSITA is a hypothetical person who is presumed to be aware of all pertinent prior art, has ordinary skill in the field of the invention, and is a person of ordinary creativity. I understand that my analysis should not be performed using a present-day perspective, and that I should not use hindsight or the perspective of the most knowledgeable experts in the field.

d. Secondary Considerations of Non-Obviousness

18. Patent owner's counsel informed me that evidence of nonobviousness—sometimes called "secondary considerations" or "objective

indicia”—must be considered when present. These factors include commercial success, long-felt but unmet need, failure of others, industry praise, unexpected results, copying, licensing or licensing interest, and skepticism of experts.

19. I have been informed that when a prior art reference suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant the prior art referenced may be said to “teach away” from the claimed invention.

2. Motivation to Combine with a Reasonable Likelihood of Success

20. I have been informed that after considering the scope and content of the prior art and identifying the differences between the prior art and the challenged claims, if any, the obviousness inquiry evaluates whether a person of ordinary skill in the art would have been motivated to combine or modify the existing prior art to bridge the differences between the prior art and the claimed invention; and if so, whether a person of ordinary skill in the art would have had a reasonable expectation of success in doing so.

21. I have been informed that, when assessing if there was motivation to combine the prior art references, important factors include (1) whether the claimed invention was merely the predictable result of using prior art elements according to their known functions; (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches

or suggests the desirability of combining elements in the invention; (4) whether the prior art teaches away from combining elements in the claimed inventions; and (5) whether it would have been obvious to try the combinations of elements.

i. Motivation to Combine

22. I have been informed that a motivation to combine may arise from the nature of the problem to be solved, design incentives, market pressure, common sense, or the teachings of prior art. I have further been informed that a motivation to combine must be based on articulated reasoning with some rational underpinning.

ii. Reasonable likelihood of Success

23. A reasonable likelihood of success in the combination of prior art references or modification of the prior art is also required to establish obviousness, and this requirement is independent of the motivation to combine.

24. I have been informed that the asserted expectation must be grounded in what the prior art actually teaches, and cannot be based on generalized disclosures, mere possibility, hope, or hindsight reconstruction. I have also been informed that where the art is unpredictable or the petition for inter partes review fails to tie the prior art to the claimed results, Petitioner has not met its burden to prove reasonable likelihood of success.

IV. SUMMARY OF OPINIONS

25. Based on my review of U.S. Patent No. 10,278,961 (Exh. 1001, the

“’961 patent”) and its prosecution history (Exh. 1002), the other materials I have considered as listed in the Exhibit List, and my knowledge and experience, my primary opinions are as follows:

26. Petitioner’s argument ignores the physiological differences between rodents and humans.

27. The ‘961 Patent is not obvious in light of the prior art.

28. A POSITA would not have had a reasonable likelihood of success in combining the prior art.

V. LEVEL OF ORDINARY SKILL IN THE ART FOR THE ’961 PATENT

29. I have been asked to offer my opinion and analysis regarding the level of ordinary skill in the art at the time of the invention or the effective filing date, which I understand to be April 19, 2016, for the ’961 Patent. I have considered the types of problems encountered in the art, the prior solutions to those problems found in prior art references, the rapidity with which innovations are made, the sophistication of the technology, the level of education of active workers in the field and my own experience working with those of skill in the art at the time of inventions. Because I have conducted research in a fairly similar area to that described in the ‘961 Patent, I believe I am very well qualified to opine on the level of ordinary skill in the art in this field.

30. Based on my education and experience, as described above and in my

CV, as well as consistent with the '961 Patent and the prior art described below, it is my opinion that a POSITA during the relevant period would be an individual with adequate expertise in physiology, not just chemistry, who is trained to understand and interpret the models used in the cited research studies. This would be someone with 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), or the like. In addition to the level of experience, I believe that a POSITA would not focus on statements by authors of research papers, but rather, on the data shown based on the methods utilized in such research papers. Furthermore, a POSITA would have a sufficient understanding of research design and basic statistics for the purpose of establishing whether data obtained from experiments is meaningful and trustworthy.

VI. OPINIONS

A. Petitioner's Argument Ignores the Physiological Differences Between Humans and Rodents

31. Petitioner relies on studies of the effects of dhBBR solely when administered to rodents. All other art provided by Petitioner recites studies done on the administration of BBR in animals or to diseased humans. Known differences between rodents and humans relative to glucose control, including varying microbiomes and islet structure and function, create widespread questions about the

translation of its results found in preliminary animal studies to humans. *See* Exh. 2098 at p. 001-002; Exh, 2096 at p. 009.

1. Rodents' Microbiomes Vary Drastically from Humans'

32. Much of the evidence provided in the petition relies upon data generated in animals. This is problematic because notable differences have been documented between humans and rodent species, particularly when it pertains to glucose control and the species' microbiomes. *See* Exh, 2096 at p. 009. The areas of glucose regulation and microbiome are of particular importance because the Petitioner's stance has largely been based upon the work of Turner (Exh. 1004) and Feng (Exh. 1007). Turner used rodent models to briefly evaluate glucose changes in rodents administered dhBBR. However, Petitioner fails to provide any evidence or explanation showing that a person of ordinary skill in the art would have known if or how Turner's rodent glucose regulation data could be accurately applied and translated to humans. It is one thing to be able to run a calculation to ascertain a dosage for a human based on safety considerations. It is entirely another thing to know if such a calculated dosage would have any physiological effect, the same physiological effect, a toxic effect, or otherwise. This is so because, as noted in greater detail below, there are many design differences in the studies cited by Petitioner relative to how a study in humans would be (and would have to be) conducted, and there are a plethora of physical, physiological, and pharmacokinetic

differences between rodents and humans (also noted below), which would not permit a person of ordinary skill in the art to have any confidence that success would follow. There are just too many variables.

33. For example, Bertorello (Exh. 2093 at p. 002) and Nguyen (Exh. 2096 at p. 001-003, 005-006) explain that the diet, lifestyle, and social behaviors of rats and mice lead to physiological and metabolic differences that affect the relationship between the gut microbiota and the host, making it distinct from that in humans. Moreover, rodents have different metabolic rates, metabolism, heart rates, and macronutrient metabolism and turnover (*See e.g.* Kowalski, Exh. 2102 at p 002-003) that will further impact key outcomes central to the inventions indicated in the '961 patent. Additionally, housing conditions, diet, lifestyle, and social interactions all notably vary between animals and humans. Bertorello (Exh. 2093 at p. 002) and Nguyen (Exh. 2096 at p. 008-009). Collectively, all of these factors work to impact the composition and function of the microbiome.

34. These compositional differences are well known and addressed in Nagpal (Exh. 2095 at p. 001-002, 007-008). Nagpal explains first that *Bifidobacterium*, which have been clearly linked to human health are present in higher levels in humans and near non-existent levels in both rats and mice. Second, microbial diversity and composition varies significantly between rodents and humans. Human microbiota has a higher abundance of *Firmicutes* when compared

to *Bacteroidetes* with *Actinobacteria* being highest in humans and hardly detectable in mice or rats. Alternatively, rat microbiota is dominated by *Prevotella* and the S24-7 family (also called *Muribaculaceae*) and mouse microbiota is dominated by *Bacteroidetes* (mainly the S24-7 family) and *Clostridia*; the S24-7 family is humans was nearly non-detectable. See Exh. 2095 at p. 010. While Nagpal is from 2018, there is no reason to believe that the understanding in the art would have been different at the time of filing for the '961 Patent.

35. As referenced above from Nguyen, many parts of the gastrointestinal systems in the mouse and human are different. Box 2 on page 9 of Nguyen (Exh. 2096 at p. 009) highlighted advantages and limitations of mouse models in gut microbiota research. Many advantages relate to the ability to use control factors in a way you cannot when using humans. The author states that “[d]espite important similarities, mice are different from humans in anatomy, genetics and physiology, and thus mouse models cannot fully recapitulate human systems.” *Id.* Nguyen further explains that “[d]ifferent mouse models can give rise to diverged shifts in gut microbiota composition,” and “[c]ross-talk between gut microbiota and the host is host-specific so observations in mouse models might not be applicable in humans.” *Id.*

36. Mouse and rat models are typically extremely inbred to create genetic uniformity. *Id.* Nguyen explains that “[g]enetic homogeneity implies that the inbred

mouse strains cannot capture the inherent genetic variations in the human population.” *Id.* Additional factors, such as “genetic background, birth mode of delivery (caesarean or vaginal), mode of feeding (breast or bottle), diet, medical history, and social activities all contribute to shaping a ‘real-life’ gut microbiota in humans.” *Id.* Nguyen found that “[a]bsence of these factors in mice implies that gut microbiota in mouse models cannot reflect a ‘real-life’ gut microbiota.” *Id.*

37. Rodents and humans also have distinct differences in gastrointestinal anatomy and the resulting physiological function, particularly how these systems can absorb nutrients. DeSesso (Exh, 2097) at p. 001 (Abstract). Metabolic differences in the relationship between the gut microbiota and host differ between rats and humans as well.

38. The authors go on to state that, “Variations in these parameters among different organs of the GI tract and among species could affect the sites and rates of absorption, as well as the distribution and metabolism of the absorbed material.” *See* Exh. 2097 at p. 019.

39. They also state that, “Unfortunately, in many cases the data necessary to evaluate the importance of these parameters is not available, and experiments must be done to measure their effects on absorption. Only by doing so can we effectively understand and accurately model the kinetics of ingested compounds.” *Id.*

40. 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.

2. Difficulties in Applying Rodent Glucose Metabolism Research to Humans

41. Along with the microbiome differences described above, several additional, significant difficulties exist with respect to applying rodent glucose metabolism research to humans. For example, islet of Langerhans structure and function is different in rodents than in people. Islet cells are primarily responsible for glucose control. Cabrera (Exh. 2098 at p. 001). Cabrera highlighted that differences in the structure and function of pancreatic islets cells in rodents and humans. *See* Exh. 2098 generally. Pancreatic islet cells are key cells in the pancreas that coordinate changes in glucose.

42. In Cabrera, published in 2005, the authors stated that “contrary to descriptions of prototypical islets,” which are mouse islets, human islets had “striking species differences with regard to both cytoarchitecture and function.” (*Id.* at p. 001-002). First, the authors identified that while mouse islets “were mainly composed of insulin-expressing cells clustered in the core of the islet” with glucagon-immunoreactive cells localized to the periphery, humans lacked these “anatomical subdivisions,” and “glucagon containing cells were numerous and were

found scattered throughout the islet.” (*Id.* at p. 001). The data demonstrated that insulin-containing beta cells comprise approximately 77% of cells in mice, compared to only about 55% in humans, whereas glucagon-containing alpha cells account for roughly 18% in mice versus approximately 38% in humans. (*Id.* at p. 002). They also found that the alignment of cells in human islets suggested that in humans, “islet microcirculation likely does not determine the order of paracrine interactions,” (*Id.* at p. 001). The author investigated whether these morphological differences had functional implications and found that they did. When measuring Ca^{2+} levels in response to high glucose concentrations, “human islets did not show the typical oscillatory patterns described for rodent islets.” (*Id.* at p. 004). Additionally, data suggested that the increased proportion of alpha cells present in human islets led to a measurable Ca^{2+} response to low glucose concentrations which was absent in mice. (*Id.* at p. 005). Cabrera concluded that the way in which these structural and functional differences between human and mouse islets affect “cell-to-cell interactions that lead to regulated and concerted hormonal secretion remains to be determined.” (*Id.*). Because the structure and function of these key cells responsible for glucose control differ between rodents and humans, the idea that a POSITA would see blanket (or automatic) transferability of results between rodents and humans is far-fetched. A careful researcher would need to perform substantial additional experimentation to plausibly hypothesize such transferability of results.

Thus, I do not believe the prior art provides a motivation to combine or modify rodent studies to apply to humans. Additionally, I do not believe that the prior art would cause a POSITA to have a reasonable expectation of success in simply extending Turner, Feng, Shaw, or any of the other prior art to humans such that the claimed invention in the '961 Patent would be reached.

43. Cabrera also recites that “[t]he conclusion that human islet composition differs quantitatively from that of mouse islets thus seems inescapable.” *See* Exh. 2097 at p. 004). Bioavailability is different than physiologic action within the body. Simply because a compound might theoretically be absorbed into a rodent’s bloodstream does not mean that it will be absorbed at the same rate or in the same amount in a human, or have the same physiologic effect in a human as it did in a rodent because the species have distinct physiological differences in areas applicable to the present situation, as noted herein.

44. A unique consideration of Cabrera is that it was published not only prior to the patent, but also prior to any of the studies relied upon by Petitioner, thus highlighting that known differences in the species should have been considered and commented upon by authors of the prior art, but they do not appear to have been addressed.

45. Furthermore, as disclosed in Bowe (Exh. 2094), distinct differences exist in glucose metabolism between male and female animals. *Id.* at p. 003.

46. Additionally, as demonstrated in Bowe, some routes of administration are not reflective of human consumption. *Id.* at p. 004. Figures 3A and 3B from Bowe, showed statistically significant differences in glucose levels between oral and intraperitoneal administration. *Id.* The intraperitoneal administration of glucose at 2 g/kg caused a significantly greater increase in blood glucose levels at 15-, 30-, and 60-minutes post-injection when compared to the oral administration at the same dose. *Id.* Furthermore, the glucose AUC values over 2 hours were significantly higher in animals administered glucose via injection rather than by oral administration. *Id.*

47. Intraperitoneal administration of glucose is not physiological. It completely bypasses the gastrointestinal system. Outcomes using this approach should not be translated to how something would work with oral ingestion in humans. It simply makes no sense. This is particularly true inasmuch as Petitioner describes some of the working of BBR and dhBBR as occurring in the gut, particularly where the Petitioner relied heavily upon the findings of Feng, which extrapolated all of their outcomes from changes occurring at the gut level. Studies and outcomes generated using intraperitoneal injection avoid this part of our anatomical layout.

48. Intraperitoneal administration of glucose in mice was used in the Turner study (Exh. 1004), which is the same data relied extensively upon by the Petitioner

when making their invalidity argument. Based on this, in my opinion, Turner is entirely inapplicable, substantially different than at least claims 1 and 5 in the '961 Patent, which requires oral administration to humans, and ultimately does not support a finding of obviousness at all.

49. Another study, Small (Exh. 2099) aimed to directly compare the effect of two routes of glucose administration, oral or intraperitoneal injection, on glucose and insulin kinetics during a glucose tolerance test in mice. *See* Exh. 2099 generally. Even though Small post-dates the effective filing date of the '961 Patent, its results present an outcome that I believe would have been the same in 2016 had the experiments been done at that time.

50. Intraperitoneal administration resulted in significantly greater blood glucose levels when compared to oral administration. *Id.* at p. 001, 004. In other words, a non-physiological route of administering glucose (that cannot be done in humans) showed that glucose levels were different between this approach and oral administration. Glucose tolerance tests in humans are not performed with intraperitoneal administration of glucose, but oral consumption of a glucose or carbohydrate load. This is another substantial difference between Turner (Exh. 1004) and the '961 Patent, where the methods utilized in Turner bypass the physiological systems which are the subject of the '961 Patent. One should not forget that Bowe has previously taught that the method of intraperitoneal injection, when

directly compared to oral consumption, resulted in divergent and inconsistent patterns of glucose appearance, providing further evidence that the methods used by Turner should not be considered as evidence of prior art.

51. Intraperitoneal administration also resulted in a largely absent elevation in blood insulin and plasma incretin hormones when compared to oral administration and resulted in differences in exogenous glucose appearance between lean and obese animals, which wasn't observed in oral administration. *Id.* at p. 001. Thus, 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.

52. Small states “[a]s I.P. glucose administration is a non-physiological administration route of administration,...” *Id.* at p. 002. This quote emphasizes that caution with the findings in e.g., Turner (Exh. 1004) should be qualified to the extent beyond just the chemistry of the ingredients. Because the patent addresses the action of the claimed ingredient, then the physiology involved and how the physiology performs **have to** be a part of that discussion. Again, Turner, by virtue of using a non-physiological approach to assessing glucose metabolism, was fundamentally not evaluating how human physiology would perform with oral ingestion of dhBBR.

53. Additionally, animals consuming a high-fat diet are commonly used to

induce diabetes, similar to the methods used in Turner. Consuming this diet will lead to the development of glucose intolerance in rodents in weeks. In humans, the development of metabolic dysregulation and its co-morbidities takes years. Because it takes much longer for metabolic disorders to develop in humans, the wide disparity in time and course of pathology development is not fairly comparable to rodents developing metabolic disorders in mere weeks. Therefore, because the characteristics and pathology development varies significantly, it would not be obvious or anticipated that a metabolic disorder would behave in the same way in rodents and humans.

54. Many mice and rat strains are also completely inbred resulting in animals that are homozygous (genetically identical) (Martic-Kehl – *See* Exh. 2100 at p. 002). Animal researchers prefer this because it largely eliminates variability at the genetic level, but *how does this translate to whether something will work in humans?* When humans consume a dietary ingredient they have different genetics, different diets, different environments, etc. Animal researchers can conceivably eliminate disproportionate amounts of this variability, particularly when compared to research completed in free-living humans. Animals are kept in the same room, same cages, same light/dark cycles, same fluid to consume, same food, same time for exercise, and can be forced to consume things. *See Id.*, generally. This controlled, variable-free environment does not accurately translate to humans. This

is particularly true as it pertains to metabolism and glucose control, and, in fact, is a highly inaccurate model relative to how humans live.

55. Data provided by Kowalski (Exh. 2102) demonstrates differences in the research models involving humans, rats, and mice. *Id.* at p. 002-003. As can be seen, the regulatory mechanisms of rats and mice use to store carbohydrates across the body are different in and of themselves. *Id.* Specifically, notable differences are present in: circulating insulin, liver glycogen, muscle glycogen, and basal rates of endogenous glucose production. *Id.*

56. Table 1 from Kowalski (Exh. 2012) demonstrates these differences between mice and humans. *Id.* at p. 003. The outcomes highlighted are all outcomes directly related to how an animal processes glucose. *Id.*

57. A mouse has 7.5-fold greater basal metabolic rate than humans. As such, rodents (mice) are under much greater metabolic constraints than humans. This means that a rodent must expend greater amounts of energy to stay alive and generally maintain homeostatic balance with their surroundings. If rodents were a car their engine would be “redlined” all day long. *Id.* p. 002-003. This is meaningful because glucose control is central to this patent and glucose is a fuel animals use to power their physiology. If a rodent’s engine runs at a faster rate than humans, then the rates at which it uses glucose and how it controls glucose will be different. This is clearly observed in Kowalski (Exh. 2102 generally).

58. The average glucose levels were measured over 24-hour period, with the animals measuring an average of 8.5 mM and humans measuring an average of 4.5-5.0 mM. *Id.* at p. 002-003. This means that mice had an average glucose level 70-89% higher than humans. *Id.*

59. Mice also had a basal glucose turnover rate of 20-30 mg/kg/min, which was 10-15 times greater than that of humans. *Id.*

60. When looking at liver glycogen stores (stored glucose), Kowalski found that mice deplete stores in a 16-24 hour fast while humans only experience a 10-20% reduction. *Id.*

61. All of these distinctions described above (e.g., in paragraphs 32-60) impact how human physiology works to control levels of glucose in the body and respond to various inputs that challenge glucose supply. This patent dispute is about an ingredient, dhBBR, that prior to the '961 Patent, to my knowledge, had not been administered to humans, which is further confirmed by the literature provided by the Petitioner's expert and that I reviewed. Most importantly, no prior art data has been provided to demonstrate how dhBBR functions upon oral ingestion in humans. The literature and my own knowledge and experience support the fact that there are substantial differences in how rats, mice, and humans regulate glucose.

62. Collectively, these results and studies demonstrate that animals and humans have drastically different patterns of glucose control and regulation across

their entire physiological system. Because of this, 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.

B. Petitioner Has Failed to Demonstrate That the ‘961 Patent is Obvious

1. The ‘961 Patent is Not Obvious in Light of the Cited Prior Art

63. The petitioner overstates the scope of the cited prior art and claims the result disclosed in the ‘961 patent was obvious and is not unexpected in light of what is disclosed in Turner (Exh. 1004), Feng (Exh. 1007), Chen (Exh. 1009), Liu (Exh. 1010), Shaw (Exh. 1005), and Zhang (Exh. 1006). The following addresses why the result of the ‘961 patent was unexpected and non-obvious in light of the scope of the prior art.

a. Turner

64. Turner used a dose of dihydroberberine (“dhBBR”) that exceeds the disclosed range in claim 1 (and its dependent claims) in the ‘961 Patent. The majority of the research in Turner centered around rodents, who were given 100 mg/kg of dhBBR per day. 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. 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. As noted in greater detail below under my discussion of Petitioner’s Feng reference, the dosage used in Feng was well above the upper limit of the range in the ‘961 Patent, so I do not believe Feng alone or in combination with Turner contributes to a finding of obviousness.

65. Additionally, no data provided by Turner was in humans. Petitioner did not provide any data or reference any data that involved administering dhBBR to humans in any administration method, let alone orally. These are significant and substantial differences between Turner and the invention claimed in claim 1 (and its dependent claims) of the ‘961 Patent.

66. The mice data in Turner were generated using a glucose administration method (intraperitoneal injection) that cannot be replicated in humans and in the simplest terms is not physiologically relevant to a human.

67. As discussed above, the known microbiome and physiological differences between rodents and humans relative to glucose control create numerous questions about the suitability of blanketly translating results in rodents to humans. For example, as previously described in Paragraphs 41-44 of this report, Cabrera (Exh. 2098) demonstrated key pancreatic cells involved with glucose control exhibit fundamental structural and functional differences between rodents and humans.

68. These differences indicate that significant caution should be observed

in attempting to extrapolate results from rodents to humans where, as here, there is no data to support such extrapolation.

69. All Turner has done is state, during the discussion of their data (not from the data itself), that dhBBR **may be of interest** for people with type 2 diabetes. As noted above, a person of ordinary skill in the art would not be motivated by Turner's statement because it was speculation and not based on data. And such speculation does not come anywhere close to providing a POSITA with a *reasonable expectation* of success in combining Turner with Feng, Shaw, or other references.

70. Notwithstanding Turner's statement, which I believe is ill-advised, widespread methodological decisions by Turner resulted in a glucose tolerance test that **should not** be translated to humans. The primary issues in this regard are: (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.

71. As discussed in Paragraphs 49-53 above, Small (Exh. 2099) demonstrates that there are major difficulties related to the translatability of intraperitoneal injections. These difficulties were echoed in another article Shoyaib (Exh. 2101), which stated that intraperitoneal injections have merit for some applications, but should not be used for clinical translation. *See* Exh. 2101 at p. 015. This is exactly what Turner (Exh. 1004) surmised and what Petitioner is doing in their arguments for obviousness.

72. Intraperitoneal injections are non-physiological. They completely bypass the gastrointestinal system, which is not how the overwhelming majority of nutrients in the human diet are consumed. Further, comparisons between metabolic responses to intraperitoneal injection and oral glucose consumption show substantial differences (Shoyaib (Exh. 2101) and Bowe (Exh, 2094))). This is a major deficiency in Petitioner's argument for obviousness in that Petitioner relies heavily on data from Turner, which utilized intraperitoneal injections bypassing the physiological system (i.e., the gut). Thus, Turner's study design is physiologically irrelevant and would not lead a POSITA to rely on its findings for potential dosages or effects in humans.

73. Another key factor highlighted in Small (Exh. 2099) relates to the large glucose dosing used in Turner, which further diminishes Turner's relevance. Larger doses (2 g/kg) of intraperitoneal injections create larger differences in outcomes. The dose used in Turner was 2 g/kg, which is nearly two (2) times greater (~120 g for 60 kg human) than what is commonly used in human oral glucose tolerance tests (75 g).

74. Another decision which calls into question the transferability of Turner's speculation was the duration of the fast selected. Turner used an overnight fast, as shown in Reference #10 in Turner, which is Molero (*See* Exh. 2105). As discussed in Paragraph 60, because of metabolic differences and the nocturnal nature

of rodents, overnight fasts result in near depletion of liver glycogen in rats, which invokes a stress response that goes on to impact regulation of different stress hormones and other body functions that do not appear to have been controlled for or taken into account by Turner. Kowalski (Exh. 2102 at p. 002-003); Bowe (Exh. 2094 at p. 003).

75. Notably, perhaps the most problematic methodology adopted by Turner was the use of anesthesia. The Ye paper (Exh. 2103) cited by Turner (Exh. 1004) as one of the methods papers explaining how they conducted their tests in the animals indicates they used ketamine-xylazine (90:10 mg/kg ip). This combination of anesthetic is documented to cause abrupt perturbations of glucose and insulin levels upon administration. The findings of Saha (Exh. 2014) discuss the dangers and concerns that should be considered when selecting an anesthetic for studies seeking to examine glucose and insulin changes. *See* Exh. 2104 at p. 001, 007. The Saha paper was published in 2005, prior to the Turner paper. Turner et al. would have had this information at their disposal and could have used a different anesthetic approach to conduct their study, but they used an approach that was known to distort glucose and insulin levels. This methodological consideration would have completely altered the regulation of glucose and insulin throughout the glucose tolerance tests completed by Turner. By using an incorrect anesthetic and not controlling for it in any way, the results in Turner are compromised and its gratuitous speculation about

possible human benefit is not based on any data, but rather unwarranted speculation. In my opinion, unprovoked speculation, particularly where the experiments were so poorly designed given the physiological system under investigation, does not make a researcher or clinician even curious, let alone motivated to investigate further. In my opinion, Turner is useless in the obviousness argument of Petitioner.

b. Feng

76. There are several inadequacies with Petitioner's use of Feng (Exh. 1007) to prove that the '961 Patent did not disclose unexpected results. First, Feng didn't show any data derived from humans at all.

77. Feng's study and resulting conclusions highlighted that it was the gut microbiota that oxidized dhBBR to BBR. How is this helpful to Petitioner's obviousness analysis? It's not! Widespread compositional and functional differences exist between rodent and human microbiomes as discussed above in Paragraphs 32-40. Other authors have highlighted these differences and expressed hesitancy about directly translating the data from rodents to humans, but this is exactly what the Petitioner has done.

78. Feng's dosing of BBR and dhBBR is also inconsistent with what is taught in the '961 Patent. Feng administered 200 mg dhBBR/kg/day in rats (*See* Exh. 1007 at Fig. 3 and its description), not mice, which when converted by the calculations from Shaw (*See* Exh. 1005), teach a human equivalent dose of 1945.9

mg (for a 60 kg person) of dhBBR. The upper dosing limit highlighted in the patent is ~800 mg dhBBR. The dosage used in the Feng study is 2.43-fold higher than the upper limit highlighted in the patent. Thus, its dosage makes it irrelevant.

79. In addition, the “data” reported in rats is highly suspect. Figure 3 in Exh. 1007 reports that 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. Also, the error bars shown 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. It is not surprising, therefore, with an n value of 3 for these experiments, that no statistical significance was shown for the data in panels (b), (c), and (d) of Figure 3, even though statistical significance was claimed for data in Figures 2, 3(a), and 5. In other words, the data in panels (b), (c), and (d) of Figure 3, which seem to be of importance to Petitioner, is not something a POSITA would rely upon or be motivated by because it is suspect at best. Yet the Petitioner has decided to base its argument upon these questionable results.

80. Petitioner claims Feng is a key part of evidence of why the claims are invalid, but even Feng relied on research models where fundamental differences are known between humans and the research models they deployed (cell culture and

rodents). It would be difficult for a POSITA to transfer cell culture data to humans with a reasonable likelihood of success because a cell culture does not replicate human physiology; rather, it consists of a homogeneous population of cells maintained under optimized conditions and does not account for relevant systemic factors in absorption such as the gut microbiome. In my opinion, clinical translation should not be based on cell culture work. Similarly, the fundamental differences between rodent models and humans are explained in detail in Paragraphs 31-62. Knowing this divergence of research models, a POSITA would not have known whether or not dhBBR would work in humans. Put simply, there was no data available provided by the Petitioner or the published scientific literature prior to the data in the original '961 patent application that was filed that tells us how oral ingestion of dhBBR will impact glucose regulation in humans. This demonstrates the novelty and the unexpected results of the original patent.

81. Further to the point, Feng asserts that the microbiome is where dhBBR is reduced to BBR and the Petitioner cited comments from Turner that alluded to this as well. If the microbiome is where this conversion is happening as demonstrated by Feng, suggested by Turner, and acknowledged by the Petitioner, and key differences existing between the microbiome and in humans and rodents will impact how the microbiome functions (discussed in Paragraphs 32-40), then a POSITA would have major questions, if not substantial skepticism, as to whether

Turner (or Turner in view of Feng) would translate to humans.

82. Even further, the known differences in gut microbiomes between rodents and humans are not just compositional (rodents have different bacteria than humans), but the function of the microbiomes (the actions these bacteria have) are also different. If the microbiomes function differently, a POSITA would know this and not simply assume that because the rat microbiome was shown to do one thing that the human microbiome would indeed do the same. This simply does not provide a reason to combine Feng with Turner, nor *expect* success if such a combination were made.

83. There is no data that I observed in Petitioner's submission showing that the same dhBBR to BBR conversion happens in the human microbiome. Because of widespread compositional and functional differences, a POSITA could not know if the phenomena that Feng claims is happening in rats occurs in humans. A completely different mechanism could be used in humans and that is not discussed in the references. Again, there is no way a POSITA would *reasonably* expect success based on such divergent models and data, as well as dosage differences that are outside the patented range.

84. So, unless one can clearly demonstrate from the prior art that the microbiomes of rats will function in an equivalent fashion to humans in terms of their ability to reduce dhBBR to BBR, the obviousness argument of Petitioner should

be rejected.

c. Chen and Liu

85. Petitioner's reliance on Chen (Exh. 1009) and Liu (Exh. 1010) fails for similar reasons. Neither Chen nor Liu administered dhBBR and the word "dihydroberberine" isn't even mentioned **once** in either paper. This data, as it relates only to the administration of BBR, is irrelevant to the administration of dhBBR. It is known that BBR can impact glucose regulation, but BBR is chemically distinct from dhBBR, and neither article addresses the ability of dhBBR to impact glucose regulation.

86. In Chen, human participants were individuals with documented irritable bowel syndrome-diarrhea. Glucose was not evaluated throughout the entire study and the word 'glucose' does not appear in the entire manuscript. Irritable bowel syndrome-diarrhea and glucose metabolism were not shown to be related, and I am not aware that they are. As such, Chen has no relationship to the physiological system (glucose metabolism) addressed in the '961 Patent and is therefore not relevant.

87. Similarly, Liu was a study involving rats, not mice, with diabetes induced by streptozotocin (a research model that does not align with the pathogenesis of diabetes typically observed in humans). The rats once-daily doses of berberine ("BBR") in 100 mg/kg or 200 mg/kg doses are equivalent to either 972

mg/kg or 1945 mg/kg, respectively, for a 60 kg human. Both of these doses are well outside the dose range in claim 1 (and its dependent claims) in the '961 Patent. So, Liu is not relevant to the obviousness analysis. Furthermore, in the study, BBR reduced postprandial glucose, which is not surprising and not really meaningful to the '961 Patent or the argument brought forth by the Petitioner.

d. Shaw

88. As discussed above, while Shaw's (Exh. 1005) BSA method may generally be considered as acceptable, there are multiple instances where the extrapolated dosages from the Petitioner's alleged prior art fall well outside of the ~25- 800 mg range claimed in the '961 Patent, including the rat dosing in Turner. Thus, while Shaw may superficially be applicable, the references to which Petitioner applies Shaw are not.

e. Zhang

89. In Zhang (Exh. 1006), no dhBBR was administered, only BBR. All participants were diagnosed with Type 2 diabetes and the dosage delivered was two doses per day of 500 mg each dose (Daily dose: 1000 mg). Not only was the study not conducted using dhBBR, but the dosing was twice a day and the people in the study were not metabolically healthy as they were diagnosed with a metabolic disease.

90. Both Type 2 diabetes and dyslipidemia (which the participants in this

study were required to have) are known diseases that cause widespread metabolic dysregulation and impact how glucose is handled and signaled across nearly all tissues in the body. These metabolic underpinnings would undoubtedly impact how well (or poorly) these people would be able to process dhBBR as well as any resulting impact on glucose control. With all of the known areas where Type 2 diabetes and dyslipidemia alter how glucose and other cellular fuels are transferred throughout the cells and tissues of the body, it is not a foregone conclusion that BBR and dhBBR will behave the same way, and a POSITA would not have a reasonable likelihood of success based on these results.

f. Conclusion

91. In its obviousness argument, Petitioner overstates the scope of the cited prior art and has not provided any empirical support to rebut the claim that the '961 Patent was nonobvious and disclosed unexpected results. There are substantial differences between the scope of the cited prior art and the '961 Patent.

92. As highlighted throughout, the Petitioner's expert based much of his argument on the findings of Turner (#1004) and Feng (#1007). As discussed above, Turner relied upon a rodent model for its study of dhBBR, which creates problems due to the extensive physiological differences between rodents and humans. Further, Turner used methodological approaches (intraperitoneal injection of glucose vs. oral consumption, overnight fasting, a glucose load that is 2 times greater than what is

commonly used in human glucose tolerance studies, and an anesthetic approach shown to cause widespread glucose and insulin dysregulation independently of any investigated intervention), and the Turner findings should be calibrated against these considerations. There are several inadequacies with Petitioner's use of Feng to prove that the '961 Patent did not disclose unexpected results. First, Feng didn't show any data derived from humans at all.

93. Similarly, Feng's study and resulting conclusions highlighted that it was the gut microbiota that oxidized dhBBR to BBR. Like Turner, Feng relies on research models such as rodents and cell cultures where fundamental differences with humans' systems exist. Knowing this divergence, a POSITA would not have known whether or not dhBBR would work in humans.

94. Additionally, while Feng focuses on absorption and oxidation, differences existing between the microbiome and in humans and rodents will impact how the microbiome functions including absorption and oxidation (discussed in Paragraphs 32-40). Because the microbiomes in rodents function differently, a POSITA would not merely assume that because the rat microbiome was shown to do one thing that the human microbiome would indeed behave similarly.

95. Chen and Liu are not relevant to the teachings of the '961 Patent because neither Chen nor Liu administered dhBBR and dhBBR isn't even mentioned **once** in either paper. This data, as it relates only to the administration of BBR, and,

as such, is irrelevant to the administration of dhBBR. Neither article addresses the ability of dhBBR to impact glucose regulation. Moreover, in Chen, human participants were individuals with documented irritable bowel syndrome-diarrhea. Irritable bowel syndrome-diarrhea and glucose metabolism are not related, and Petitioner failed to explain the relevance of irritable bowel syndrome to managing glucose tolerance.

96. Liu was a study involving rats, not mice, with diabetes induced by streptozotocin. The rats once-daily doses of berberine (“BBR”) fall outside the dose range in claim 1 (and its dependent claims) in the ‘961 Patent. So, Liu is not relevant to the obviousness analysis.

97. Shaw’s BSA method may be considered as acceptable, however, the Petitioner's application of Shaw's teaching highlight multiple instances where the extrapolated dosages from the prior art fall well outside of the ~25-800 mg range claimed in the ‘961 Patent, including the rat dosing in Turner.

98. In Zhang, only BBR was administered, not dhBBR, and all participants were diagnosed with Type 2 diabetes, which likely impacted the results as well.

99. Because of these substantial differences between the prior art and the ‘961 Patent, not only does the prior art not teach what is claimed in the ‘961 Patent, but the prior art would not motivate a POSITA to invent what the Patent Owner has invented, nor would the prior art provide a POSITA with a reasonable expectation

that the results in rodents, cell culture, or otherwise from the experiments designed as they were in the prior art would produce the same or substantially similar effects at the claimed dosage range in humans. The evidence is just not there. Considering the scope of all the prior art disclosed by the Petitioner, the '961 Patent demonstrated unexpected results and was not obvious.

2. Petitioner Has Provided No Human Data to Support the Claimed Oral Dosage Range (25-800 Mg dhBBR)

100. Petitioner did not provide any data where dhBBR was orally administered *to humans*, because no human data exists from the time of filing where dhBBR was orally administered to humans. In support of Petitioner's argument that the dosing range was obvious, Petitioner references Turner (1004) that provides the only previous data relating to dhBBR administered to rodents in their chow.

101. The body surface normalization method outlined in Shaw is a commonly accepted standard, which may be more suitable than methods based upon body mass or other such approaches. However, several of the doses taught in the cited prior art fall outside of the dosing taught in the '961 patent, including the rat dosage of dhBBR in Turner as explained in Paragraph 64 and the dosage in Feng.

102. Several of the methodological approaches utilized in the Turner study should be critically evaluated for how successfully corresponding mechanisms in humans would respond to the interventions used on rodent models. As detailed above, glucose regulation is facilitated by distinct factors between rodents and

humans. As explained, the methods Turner used to evaluate glucose regulation in rodents rely on mechanisms and measurements that do not accurately reflect how these processes occur in humans.

103. Importantly, no other exhibits put forth by Petitioner provide any information to tell a POSITA how various oral doses of dhBBR would impact glucose and insulin amongst other outcomes in humans.

104. Petitioner's obviousness argument that the '961 Patent is obvious under Turner, in light of Shaw fails because it does not provide any additional teachings or logic that when combined with the mouse dose of dhBBR in Turner, would have made the '961 Patent's dosing obvious to a POSITA. As such, the nonobviousness put forth by the '961 Patent related to the oral administration of dhBBR to humans should be recognized.

3. The Prior Art Fails to Demonstrate Reduced Fasting Glucose in Humans Taking dhBBR

105. None of the studies provided by Petitioner tell us anything about how dhBBR impacts glucose regulation *in humans*. Instead, the Petitioner relied solely upon extrapolation from animal studies with dosages outside the patent's range and methodologies that are well-documented to instigate widespread and robust responses that have been reported in previous teachings to not align with human physiology.

106. None of the cited prior art teaches the administration of dhBBR to

humans.

107. Further, as mentioned in Paragraphs 64-75, several 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.

4. The Prior Art Fails to Demonstrate the Presence of Each Limitation in the Dependent Claims

108. The prior art fails to teach what is disclosed in the challenged dependent claims. Claim 5 claims dhBBR administered in a capsule or tablet form. No prior art cited by Petitioner exists to tell a POSITA anything about how any form of dhBBR will behave upon oral ingestion (e.g., via capsule or tablet) in humans. Turner had dhBBR in food, which does not meet the limitation of claim 5 at all, and dhBBR in a capsule or tablet may be processed by a human body in a much different way that the prior art Petitioner has heavily relied upon - Turner (Exh. 1004) and Feng (Exh. 1007) – which claim that dhBBR is oxidized back into BBR after orally consuming dhBBR in the chow (not in capsule or tablet form) of the rodent models they cited.

109. One must consider the fundamental differences that exist between rodent and human physiology as it specifically pertains to glucose metabolism and insulin control as outlined in Paragraphs 41-62. Additionally, one must also consider the fundamental differences that exist between the microbiomes of rodents and humans described in Paragraphs 32-40.

110. The microbiomes of rodents and humans have differences in not only what types of bacteria are present (the composition of the microbiome), but also the functionality of the bacteria that are present. These differences are clearly highlighted throughout the teachings of Nguyen 2015 whereby certain bacterial species are abundant in human and not murine microbiomes (*Prevotella*, *Ruminococcus*, *Faecalibacterium*) while others are abundant in murine models and not human (*Lactobacillus*, *Turicibacter*, *Alistipes*). These conclusions were also seen by Nagpal (Exh. 2095) where they reported key differences between humans, rat, and mice models at the phylum, family, and genus levels (Nagpal Figures 2 - 4), describing details that likely were the same as of the effective filing date of the application for the '961 patent. Importantly, this compositional divergence will drive functional uniqueness as seen by how dietary components are digested, how cellular communication persists, and how host metabolism is regulated, ultimately leading to limits that should be placed on direct translational inference from one species to the next. This point is critical to evaluate against the points made by Feng (#1007)

because the Feng authors postulate that the microbiome of the rat is where dhBBR is rapidly oxidized to BBR, which then goes on to exert its functions. Petitioner's argument does not take into account these differences between rodent and human microbiomes.

111. Because the microbiomes of rodents and humans are different and behave differently, a POSITA cannot predict whether the action observed in the rodent microbiome will be the same as what might occur in humans. This is why clinical translation research in human models must be completed to validate the potential efficacy observed from pre-clinical models such as cell culture and animal models. Yet, Petitioner assumes they will be the same, without evidence to support that assumption.

112. Claim 7 teaches daily administration. Turner teaches dhBBR fed to rodents in a high-fat diet. Turner does not indicate whether the dhBBR-containing food was consumed all at once or throughout the day. Throughout the day would bear little or no physiological relevance to a person taking a dhBBR-containing capsule once per day. And, no prior art relied upon by Petitioner reads on the claim of once daily administration of dhBBR.

C. A POSITA Would Not Have Had a Reasonable Likelihood of Success

1. Petitioner's Definition of POSITA is Inadequate

113. As highlighted in Paragraphs 29-30, Petitioner's definition of a POSITA is inaccurate and short-sighted.

114. A POSITA with the qualifications and experience described above in Paragraphs 29-30 would have a substantial level of uncertainty towards the potential success of a human consuming dhBBR in the doses claimed in the '961 Patent (~25-800mg). Many fundamental and key aspects of understanding were still undetermined regarding the potential efficacy of orally ingesting dhBBR in humans prior to the filing date and even issuance of the '961 Patent. A POSITA would not have had a reasonable likelihood of success with respect to administering dhBBR to humans at the dosage range in the '961 Patent because of the known physiological differences between rodents and humans, but not knowing how those differences would play into the dosing requirements, efficacy, and transferability of data related to dhBBR. This uncertainty is magnified even further when one considers the shortcomings of the methodological approaches employed by Turner and Feng as previously highlighted in Paragraphs 64-84.

2. Bioavailability and Physiological Effects of dhBBR are Separate Questions

115. Petitioner's expert seems to argue that as long as someone can demonstrate that BBR is somehow being delivered that everything else is the same, or more specifically, that anything else that follows from there is not novel or nonobvious. Petitioner's expert based his perspective largely upon Turner (#1004)

and Feng (#1007) whereby both Turner and Feng used animal models and methods applied to those animal systems that have little or no practical translation to how things would occur in humans, as discussed above.

116. There are numerous published papers (a number of which I have cited in this declaration) that either in general, or in connection with glucose metabolism, discuss and document discordance in outcomes between animals and humans. A strong piece of evidence that speaks to lack of congruence between bioavailability and clinical outcomes may be observed in the Cabrera (Exh. 2098) and Kowalski (Exh. 2102) papers.

117. As detailed in Paragraphs 41-44, Cabrera demonstrated that pancreatic islet cells in animals versus those found in humans are arranged differently in terms of structure and have demonstrated differences in how they function. These findings speak directly to the importance of physiological function of the cells and tissues involved directly involved in glucose metabolism. Because if these islet cells (which are the primary drivers of glucose control) behave differently between rodents and humans, this provides immediate reason to question and doubt the notion of transferability of results from rodents to humans. In other words, these papers would cause a POSITA to believe that just because something may appear in the blood does not mean that it will have the same function as what was previously observed in animals. If dhBBR augments glucose control and the cells that are largely

responsible for executing glucose uptake are fundamentally different between rodents and humans, then one cannot automatically assume that the findings of Turner are translatable to humans. A substantial amount of additional research would be needed to come close to verifying such an assumption.

118. This point is reinforced by the stark differences observed between rodents and humans in terms of glucose metabolism and control disclosed in Kowalski (Exh. 2102) and discussed in Paragraphs 55-60 and Paragraph 74 of this declaration.

119. The reasonable expectation of success as outlined throughout Petitioner's expert's declaration is not present because a POSITA in microbiome research and animal physiology (not merely analytical chemistry and/or pharmaceutical development) would understand that the microbiomes of a rat and humans are significantly different and these differences lead to known differences in how the microbiomes function, notwithstanding those differences which have yet to be full realized. If the microbiome is identified as a key element in how dhBBR results in BBR being made available in the blood (which it is in Feng, as well as alluded to by Turner, and acknowledged by Petitioner's expert), then the invention claimed in the '961 Patent whereby the patent demonstrates dhBBR action in humans provides new information not provided before, not reasonably expected before, and not previously disclosed alone or in any combination or modification of

the prior art when a POSITA's knowledge and thought process about the prior art is properly and fully considered. Accordingly, I believe that claims 1, 2, 5, 6, and 7 of the '961 Patent are non-obvious.

VII. RIGHT TO SUPPLEMENT

120. I reserve the right to supplement my opinions in the future to respond to any arguments that Petitioner raises. This declaration represents only those opinions that I have formed to date. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information that becomes available to me and on my continuing analysis of the materials already provided. I may utilize the documents cited and/or listed herein, or portions of those documents, as exhibits at any hearing or trial in this proceeding. I may further prepare and use exhibits that summarize portions of my testimony or key terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this proceeding.

121. I reserve the right to supplement my testimony and this report in response to any judicial determinations, in response to the arguments expressed by Petitioner or the opinions of Petitioner's experts in this proceeding, and/or in light of additional evidence or testimony brought forth at trial or otherwise brought to my attention after the date of my signature below.

VIII. CONCLUSION

122. For the foregoing reasons, it is my opinion that Petitioner has failed to

prove that the challenged claims of the '961 Patent are obvious in light of the prior art they provided. A person of ordinary skill in the art at the time of filing the '961 Patent in 2016 would not have had a reasonable likelihood of success combining the cited prior art, nor a reasonable motivation to combine or modify the prior art to arrive at the invention claimed in the '961 Patent, and the Petitioner failed to rebut the claim that the '961 Patent disclosed unexpected results.

123. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on: January 3rd, 2026

Chad Kerksick

Dr. Chad M. Kerksick

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this DECLARATION OF DR. CHAD M. KERKSICK, PH.D. has been served on January 7, 2026 upon the following litigation counsel via electronic means:

- John Handy, RIMON PC (john.handy@rimonlaw.com)
- Jason Xu, RIMON PC (jason.xu@rimonlaw.com)
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Date: January 7, 2026

Respectfully submitted,

/s/ Mark D. Nielsen

Mark D. Nielsen

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Counsel for Patent Owner