

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

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

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IPR2025-01593  
Patent 10,278,961

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Before KAREN I. SWEENEY, *Trial Paralegal*

**DECLARATION OF DR. THOMAS HARTUNG, M.D., PH.D.**

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

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**TABLE OF EXHIBITS**

<b>EXHIBIT NUMBER</b>	<b>DESCRIPTION</b>
2021	Ali, Z., Chandrasekera, P.C. and Pippin, J.J. (2018) ‘Animal research for type 2 diabetes mellitus, its limited translation for clinical benefit, and the way forward’, Alternatives to Laboratory Animals, 46(1), pp. 13–22. <a href="https://doi.org/10.1177/026119291804600101">https://doi.org/10.1177/026119291804600101</a>
2022	Arrowsmith, J. and Miller, P. (2013) 'Trial watch: phase II and phase III attrition rates 2011-2012', Nature Reviews Drug Discovery, 12(8), p. 569. doi: 10.1038/nrd4090.
2023	Auricchio, S., Stellato, A., de Vizia, B (1981) ‘Development of Brush Border Peptidases in Human and Rat Small Intestine during Fetal and Neonatal Life’, Pediatric Research, 15:991-995.
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2025	Biotechnology Innovation Organization (BIO), Informa Pharma Intelligence and QLS Advisors (2021) Clinical Development Success Rates and Contributing Factors 2011-2020. Report (February 2021). Available at: <a href="https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf">https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf</a> (Accessed: 27 December 2025).
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2027	Dutta, S. and Sengupta, P. (2016) ‘Men and mice: Relating their ages’, Life Sciences, 152, pp. 244–248. doi:10.1016/j.lfs.2015.10.025.

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2029	Hartung, T. (2024a) 'The (misleading) role of animal models in drug development', <i>Frontiers in Drug Discovery</i> , 4, 1355044. doi: 10.3389/fddsv.2024.1355044.
2030	Hartung, T. (2008) 'Food for thought... on animal tests', <i>ALTEX</i> , 25(1), pp. 3-16. doi:10.14573/altex.2008.1.3.
2031	Hartung, T. (2024b) 'The validation of regulatory test methods - conceptual, ethical, and philosophical foundations', <i>ALTEX</i> , 41(4), pp. 525-544. doi:10.14573/altex.2409271.
2032	Hartung T. (2009) Toxicology for the twenty-first century. <i>Nature</i> , 460:208-212. doi:10.1038/460208a.
2033	Hartung, T., Hoffman, S., Whaley, P. (2025) 'Assessing risk of bias in toxicological studies in the era of artificial intelligence', <i>Arch. Toxicology</i> , 99:3065–3090.
2034	Hay, M., Thomas, D.W., Craighead, J.L., Economides, C. and Rosenthal, J. (2014) 'Clinical development success rates for investigational drugs', <i>Nature Biotechnology</i> , 32(1), pp. 40–51. doi: 10.1038/nbt.2786.
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2072	Wüerbel, H. (2000) ‘Behaviour and the standardization fallacy’, <i>Nature Genetics</i> , 26, p. 263. doi:10.1038/81541.
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2075	Curriculum Vitae of Dr. Thomas Hartung, M.D., Ph.D.

**DECLARATION OF DR. THOMAS HARTUNG, M.D., PH.D.**

I, Thomas Hartung, 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 submitted herewith as Exhibit 2075.

2. I currently serve as the Doerenkamp-Zbinden Chair for Evidence-Based Toxicology in the Department of Environmental Health and Engineering at the Johns Hopkins Bloomberg School of Public Health and the Whiting School of Engineering. I have joint appointments in the Department of Molecular Microbiology and Immunology as well as the School of Medicine in the Department of Cellular and Molecular Medicine. Additionally, I am an adjunct affiliate professor at Georgetown University and hold a joint appointment as Professor of Pharmacology and Toxicology at the University of Konstanz, Germany.

3. I also direct the Centers for Alternatives to Animal Testing (CAAT) at both Johns Hopkins for the U.S. and Konstanz for Europe, which host the Evidence-Based Toxicology Collaboration, and manage programs on Good Read-Across Practice, ToxAIcology, Good Cell Culture Practice, Green Toxicology, Developmental Neurotoxicity, Developmental Immunotoxicity, Microphysiological Systems, the Global Exposome Forum and Refinement. As Principal Investigator, I

led the NIH-funded Transformative Research for the Human Toxome Project and initiated the annual Microphysiological Systems World Summits, starting in 2022 with now more than 100 partner organizations.

4. My scientific work over more than three (3) decades has focused on the scientific question directly relevant to this proceeding: how reliably can preclinical evidence, especially animal studies, predict outcomes in humans? As Director of the CAATs at Johns Hopkins University and the University of Konstanz, I have led international programs on mechanistic toxicology, microphysiological systems (organ-on-chip), dose extrapolation, and evidence-based evaluation of preclinical research.

5. My 2013 analysis of clinical trial attrition demonstrated that approximately 95% of drug candidates that enter clinical development ultimately fail, and that these failures are overwhelmingly linked to the inability of animal studies to predict human efficacy and safety. *See* Exh. 2028.

6. In my 2024 review, I further documented that animal models - especially rodents - frequently generate false positives for efficacy, false negatives for safety, and mechanistic signals that do not translate into human physiology. *See* Exh. 2029. While this article was released in 2024, it cites numerous articles published prior to 2016, eighteen (18), I believe, to be specific.

7. I have summarized this earlier as “We are not 70kg rats.” *See* Exh.

2032 at p. 001. While this paper largely focuses on toxicological matters, the reason why animal models fail for drug toxicology studies is the same as why they would not be predictive of success for studies of drug efficacy studies – humans and rats are very different.

8. This background is directly relevant to evaluating whether a person of ordinary skill in the art (“POSITA”) (my understanding of which is defined in further detail below) would have had a reasonable expectation of success in predicting human glucose-tolerance outcomes from the rodent studies cited in the Petition. As described below, the scientific evidence available before 2016 (or in post-2016 literature that describes systems and the state of the prior art that existed as of April 2016) overwhelmingly demonstrated that no such expectation would have been reasonable.

9. As former Head of the European Commission’s Centre for the Validation of Alternative Methods (ECVAM), I oversaw international validation programs for preclinical assays and analyzed the causes of failed translation between laboratory findings and human outcomes. I have authored more than 760 scientific publications, including foundational work on read-across, mechanistic toxicology, microphysiological systems, artificial intelligence in toxicology, and the reproducibility crisis in preclinical research. My expertise includes quantitative translation across species, mechanistic modeling of toxicity pathways, and

systematic evaluation of evidence quality. Noteworthy, I have also carried out and published on animal experimentation.

10. I earned my Ph.D. in Biochemical Pharmacology from the University of Konstanz in 1991 and my M.D. with a focus on Toxicology from the University of Tübingen in 1992. I have a broad background in clinical and experimental pharmacology and toxicology documented in more than 760 publications, (h-index 127 with 55,000+ citations according to Google Scholar).

11. I have consulted 15 of the top 20 pharmaceutical companies on preclinical models for drug development. My work on preclinical models has been twice supported by the U.S. Food and Drug Administration (FDA) and we signed a Research Collaboration Agreement with the FDA in 2024 to train their staff on alternatives to animal testing and jointly build trust into these New Approach Methods.

## **II. COMPENSATION**

12. For my efforts in connection with the preparation of this declaration, I am being compensated at an hourly rate of \$500.00. My compensation is not in any way contingent on my performance, the result of this proceeding, or any of the issues involved therein. I am also being reimbursed for expenses incurred as a result of activities performed as an expert.

### **III. MATERIALS REVIEWED**

13. In preparing this declaration, I have reviewed and/or considered at least the documents cited in the List of Patent Owner's Exhibits, as well as the documents referenced in the Table of Exhibits herein. I have also relied on my own understanding and expertise.

### **IV. RELEVANT LEGAL STANDARDS**

14. I am not a lawyer. I am inventor on eight patent families, which allowed me to gain basic understanding of the legal principles of patent law. I have been provided by counsel with an understanding of applicable legal principles that govern patent validity and claim construction. As best as possible for a non-lawyer, I have conducted my analysis in conformance with these principles. I set forth those understandings below.

#### **A. Obviousness**

15. The 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).

16. 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).

17. For purposes of this report, I understand that "prior art" consists patents, patent applications, and printed publications that existed prior to April 19, 2016, if not one year earlier, April 19, 2015.

18. 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 through modification of the existing prior art would have been obvious to a POSITA, and doing so without applying hindsight bias (i.e., looking back to April 19, 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.

**1. *Graham* Factors**

19. Counsel for the Patent Owner has informed me that an obviousness analysis considers four factual inquiries, otherwise known as the *Graham* Factors. I have been informed that the inquiries are as follows: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and, (4) objective evidence of nonobviousness.

**a. Scope and Content of the Prior Art**

20. I have been informed that for a reference to be considered prior art for this matter, it must be dated on or before April 18, 2016. I also understand that the prior art should be considered for all that it teaches, and not just be “cherry-picked.” I have further been informed that in order 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**

21. 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.

**c. Level of Ordinary Skill in the Art**

22. The Patent Owner's counsel has informed me that my analysis must be performed from the perspective of a hypothetical POSITA as of the effective filing date of the patent, which I understand to be April 19, 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 carried out using a present-day perspective, and that I should not use hindsight.

**d. Motivation to Combine with a Reasonable Expectation of Success**

23. 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 or likelihood of success in doing so.

**i. Motivation to Combine**

Assuming a challenger demonstrates that all elements of the invention are present in the prior art combination or modification proposed, the challenger must then also demonstrate that there would be a reason to combine or modify the

references to arrive at the claimed invention. I am informed that the question is whether a POSITA would have combined elements from specific references in the way the claimed invention does (i.e., to arrive at the claims' actual limitations). I am further informed that 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." Finally, I have further been informed that a motivation to combine must be based on articulated reasoning with some rational underpinning.

**ii. Reasonable Expectation of Success**

24. A reasonable expectation 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.

25. 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.

26. While I discuss factor (1) and touch on factor (2) in my report below, my primary focus is on the motivations of the POSITA in combining or modifying the prior art, and more particularly, whether a POSITA would have had a reasonable

expectation of success in combining or modifying the prior art to successfully reach the Patent Owner's claimed invention, even if the prior art taught all of the elements in Patent Owner's patent claims (1, 2, 5, 6, and 7, in particular), which I do not believe that it does because none of the prior art teaches a once a day administration of dihydroberberine (DHB) to humans in connection with managing glucose tolerance.

## V. SUMMARY OF OPINIONS

27. Based on my review of U.S. Patent No. 10,278,961 (Ex. 1001, the "'961 patent") and its prosecution history (Ex. 1002), the other materials I have considered, and my knowledge and experience, my opinions may be summarized as follows:

28. The Petitioner has not demonstrated that a POSITA would have possessed as of April 19, 2016 a reasonable expectation of success in predicting human glucose-tolerance outcomes from the rodent and other studies underlying the cited prior art.

29. Extensive empirical research shows that rodent metabolic, mitochondrial, and glycemic responses do not reliably translate to humans. Animal models routinely overestimate efficacy, underestimate toxicity, and produce mechanistic endpoints that fail to reproduce in clinical trials.

30. The cited references, Turner, Liu, Feng, Zhang, and others cited by Petitioner, contain rodent data, *in vitro* biochemical findings, or berberine-only

human data. None provide a scientifically reliable basis for predicting that DHB administration would achieve the claimed human glucose-tolerance outcomes.

31. Before 2016, as shown in the numerous references I have provided with my report and cited herein, it was well-established and widely recognized that glucose metabolism, mitochondrial complex-I responses, and intestinal transformation of xenobiotics differ profoundly between rodents and humans. A POSITA at that time (i.e., April of 2016) would not have expected rodent observations regarding DHB or berberine to predict human efficacy without direct human evidence or validated mechanistic support.

32. Accordingly, the Petition does not satisfy the requirement of showing obviousness with a reasonable likelihood of success.

## **VI. OVERVIEW OF THE '961 PATENT**

33. The '961 Patent addresses longstanding barriers to the clinical utility of berberine-class compounds, including their extremely low oral bioavailability, extensive first-pass metabolism, and dependence on gut-microbiota transformation.

34. The patent discloses methods of administering dihydroberberine (DHB) to humans to achieve measurable improvements in glucose tolerance - outcomes that could not be predicted from preclinical evidence due to known species differences in metabolism, mitochondrial function, and intestinal pharmacokinetics.

35. In my scientific judgment, the invention identifies a specific human-

directed administration strategy for DHB that overcomes the barriers known and that existed in 2016, and yields clinically relevant outcomes that were not reasonably predictable based on rodent studies or prior berberine research.

## VII. OPINIONS

### A. The Petitioner has not demonstrated a Reasonable likelihood of Success

36. It has been well documented, both before and after 2016, that animal studies - particularly in rodents - do not reliably predict human metabolic outcomes. Published analyses show that 90–95% of drug candidates that appear promising in preclinical testing ultimately fail in human trials, largely due to poor translatability of efficacy and mechanistic readouts. *See Exhs. 2022 at p. 001; 2028 at p. 001; 2034 at p. 011; 2044, generally.*

#### 1. Difficulty in Translating Animal Data Generally

37. Animals, including rodents, differ from humans in fundamental features relevant to glucose metabolism, including mitochondrial regulation, glucoregulatory hormone dynamics, gut microbiota composition, intestinal enzyme expression, and hepatic metabolism. These differences routinely produce misleading efficacy signals in rodent diabetes models that do not reproduce in humans. Furthermore, two studies out of the pharmaceutical industry have clearly shown a general reproducibility problem of academic animal studies, which limits their reliability for drug development: Prinz et al. (2011) from Bayer HealthCare

stated in Nature Reviews in Drug Discovery, *“Believe it or not: how much can we rely on published data on potential drug targets? ... data from 67 projects, ... This analysis revealed that only in ~20-25% of the projects were the relevant published data completely in line with our in-house findings ... In almost two-thirds of the projects, there were inconsistencies between published data and in-house data that either considerably prolonged the duration of the target validation process or, in most cases, resulted in termination of the projects.”* See Exh. 2058 at p. 001-002.

38. Similarly, Begley and Ellis (2012) from Amgen in Nature *“Raise standards for preclinical cancer research ... Fifty-three papers were deemed ‘landmark’ studies ... scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result.”* See Exh. 2073 at p. 002. These studies showing the limited predictive value of single animal studies found a lot of attention in 2011/2012 and the following years.

39. In 2013, Seok et al. (see Exh. 2064) reported in another much-discussed article about dramatic differences in the molecular changes in mice and men in an inflammatory condition (see my comments in Leist and Hartung, 2013 – Exh. 2047, including at p. 003 therein), particularly relevant for diabetes, which has a strong inflammatory component. See Exh. 2074 at p. 001-002 and generally.

40. Translation of animal efficacy and safety findings into predictable human outcomes remains (and was in April of 2016) inherently uncertain and is

reflected in the persistent attrition of drug candidates in clinical development. Large industry and academic datasets estimate that only about 8-14% of programs that enter Phase I clinical trials ultimately reach regulatory approval (*see* Exhs. 2025 and 2070), implying that roughly 86-92% fail after first-in-human entry. In the BIO dataset (2011-2020), Phase II was the largest bottleneck (28.9% transition success) (*see* Exh. 2025 at p. 006), and analyses of late-stage terminations likewise show that lack of efficacy is the dominant stated cause of failure in both Phase II (59%) and Phase III and beyond (52%), with safety contributing substantially (22% in Phase II; 35% in Phase III and beyond) (*see* Exh. 2022). Such failure patterns are consistent with well-described limits of animal models: disease induction and controlled laboratory conditions can yield false-positive efficacy signals and incomplete anticipation of human adverse effects (summarized in Exh. 2028 at p. 001-002; Exh. 2029 at p. 002, 006-008).

41. Empirical comparisons between animal and human evidence further underscore variable predictiveness: systematic review evidence shows that direction and magnitude of treatment effects in animals can diverge from those observed in human trials across multiple interventions (*see* Exh. 2054 at p. 004), and two multi-company toxicity analyses reported that rodent studies alone predicted a minority of toxicities later observed in humans (*see* Exh. 2048 at p. 005; Exh. 2052 at p. 006, 009). Methodological issues also contribute to overconfidence: publication bias and

study design/reporting shortcomings in preclinical animal research can inflate apparent efficacy and obscure uncertainty (*see* Exh. 2063 generally; Exh. 2036 at p. 003-004, 008; Exh. 2018 at p. 001-002; Exh. 2039 at p. 001 and 002 (“Because of these caveats, it is nearly impossible to rely on most animal data to predict whether or not an intervention will have a favorable clinical benefit-risk ration in human subjects.”)). Taken together, these lines of evidence support the conclusion that animal data alone, while sometimes informative for hazard identification or mechanistic exploration, often does not provide a reliable basis for expecting quantitative clinical efficacy or safety outcomes in humans without corroborating human-relevant mechanistic and clinical evidence (*see generally* Exhs. 2028, 2029).

42. Animal experiments are often indispensable for understanding biological mechanisms and for aspects of regulatory safety assessment, but the biomedical literature demonstrates well-documented limitations in the ability of animal experiments to predict human efficacy and safety. Fundamental interspecies differences (genetics, immune systems, metabolism, and physiology), coupled with the fact that many models capture simplified or induced disease phenotypes under highly controlled conditions (e.g., young, healthy, inbred animals) rather than the heterogeneity, comorbidity and exposure histories typical of clinical populations, can lead to both false-positive and false-negative inferences about therapeutic benefit (*see* Exh. 2028 at p.004 and generally; Exh. 2030 at p. 003-004 and generally;

Exh. 2018 at p. 001-002; Exh. 2056 at p. 002, 004, 006; Exh. 2067 at p. 001-002, 004, 006).

43. Empirical analyses underscore the scale of translational attrition: an umbrella review of systematic reviews (covering 367 animal-tested interventions across 54 diseases) reported that ~50% progressed to any human study and ~40% to a randomized controlled trial, yet only ~5% ultimately obtained regulatory approval for human use. *See* Exh. 2038 at p. 001 (Abstract) and generally.

44. Earlier assessments of highly cited animal studies likewise found that only about one-third translated into human randomized trials and roughly one-tenth were eventually approved. *See* Exh. 2057 at p. 002; Exh. 2067 at p. 001. For safety, concordance between animal and human toxicities is incomplete - Olson et al. reported ~71% overall concordance when both rodent and non-rodent species were considered (with rodents alone substantially less predictive at 43%), and clinical experience continues to show that important toxicities may emerge despite apparently reassuring animal packages. *See* Exh. 2048 at p. 002; Exh. 2052 at p. 001, 010; Exh. 2068 at p. 001 (Summary) and 003; Exh. 2069 at p. 001 (Summary) and 007.

45. Translation is further impeded by remediable threats to internal validity (inadequate randomization/blinding, underpowered studies), selective reporting and publication bias, and inconsistent reporting of key design details - issues that have

motivated reporting guidelines, risk-of-bias tools and calls for more systematic evaluation and validation of preclinical evidence. *See* Exh. 2063 at p. 001-002; Exh. 2041 generally; Exh. 2046 at p. 001-002 and generally; Exh. 2036 at p. 003-004 and generally; Exh. 2029 at p. 008-012; Exh. 2031 at p. 005, 008-009, 011, 016 and generally re: validation; Exh. 2033 at p. 001-012, 016-017.

46. The uncertainty of preclinical animal models can be demonstrated in the case of safety testing as manifested by human side effects: human side effects were predicted by rodents in only 43% for 150 drug candidates as shown by Olson et al. (*see* Exh. 2052 at 001) and in only 48% for 192 drug candidates as shown by Monticello et al. (*see* Exh. 2048 at p. 001 (Abstract)).

## **2. Difficulty in Translating Rodent Data to Humans**

47. Rodent diabetes models typically rely on artificial induction (e.g., high-fat diet, streptozotocin), which does not reflect human type-2 diabetes physiology. Moreover, rodents metabolize berberine and DHB differently, exhibit higher intestinal absorption, and demonstrate microbiota-dependent transformations that do not correspond to human pathways. These factors prevent reliable extrapolation.

48. Rodent data can be particularly unreliable for direct extrapolation to humans because the standard laboratory mouse or rat differs from the intended clinical population along several interacting dimensions that are specific to the rodent research setting.

49. Rodents are short-lived and develop on a compressed timescale relative to humans, yet most biomedical studies use young “*adult*” animals - typically in the 6–20-week range - without prior disease history, multimorbidity, or concomitant medications, so chronic human conditions and lifetime exposure histories are necessarily simplified or experimentally induced (*see* Exh. 2028 at p. 004-005; Exh. 2040 at p. 001-002, 004, 006; Exh. 2027 generally).

50. Commonly used strains are inbred and genetically homogeneous and are housed under highly standardized, specific pathogen-free conditions with uniform housing and nutrition; moreover, “*standard chow*” or purified laboratory diets can differ substantially from human diets and may vary in non-nutrient content and contaminants, creating additional context-dependent effects on metabolism and the microbiome. *See* Exh. 2028 at p. 004; Exh. 2029 at p. 008, 010; Exh. 2072; Exh. 2060 generally; Exh. 2024 at p. 001-002; Exh. 2053 at p. 001-002 and generally; Exh. 2062 at p. 002-003, 005, 010.

51. In addition, rodents’ small body size and species-specific metabolism complicate translation of dose, route, and exposure–response relationships, even when using body-surface-area/allometric scaling approaches recommended for first-in-human starting doses. *See* Exh. 1008 generally.

52. Consistent with these biological and contextual gaps, rodent-based toxicology signals show limited concordance with human outcomes and can vary

substantially even between mice and rats, underscoring the context-dependence of “positive” and “negative” animal findings. *See* Exh. 2052 at 001; Exh. 2068 at p. 001 (Summary); Exh. 2018 at p. 003 and generally.

### **3. Difficulty in Translating Animal Data to Human Metabolism and Glucose Regulation**

53. The prior art describes mitochondrial complex-I inhibition and disaccharidase suppression in rodents. However, such findings have no established quantitative relationship to human glucose tolerance. Human glucose homeostasis is governed by multifactorial pathways not modeled in rodents, and rodent mitochondrial responses frequently fail to reproduce in human tissues.

54. Rodents differ from humans in several fundamental aspects of glucose regulation, including mitochondrial control of glucose handling, glucoregulatory hormone dynamics, gut microbiota composition, intestinal structure and enzyme expression, and hepatic glucose metabolism. Comparative physiology reviews and stable-isotope glucose tolerance studies show that rodents rely more heavily on gluconeogenesis and glucose effectiveness, exhibit smaller and more transient insulin responses, and show limited suppression of endogenous glucose production during a glucose challenge, in contrast to humans where prolonged glucose absorption provokes sustained insulin secretion and robust suppression of hepatic glucose output. *See* Exh. 2045 at p. 002-006; Exh. 2026 at p. 006-009; Exh. 2042 at p. 001-008, 010-011.

55. Cross-species microbiome analyses further demonstrate that the taxonomic composition and metabolite profiles of rodent gut microbiota differ markedly from those of humans, and that ‘humanized’ rodent microbiota only partially recapitulate the donor communities, implying host-specific microbiota–host metabolic interactions. *See* Exh. 2049 at p. 001-002, 007-008; Exh. 2071 at p. 002 (Abstract) and generally; Exh. 2051 at p. 001-004, 006, 008.

56. Differences in the anatomy and cellular architecture of the intestinal tract, together with species-specific developmental patterns of brush-border peptidase and disaccharidase activities, modify nutrient processing and postprandial glycaemia in ways that are not identical between rodents and humans; *See* Exh. 2023 generally; Exh. 2035 generally; Exh. 2051 at p. 001-004, 006, 008 and generally.

57. On the hepatic side, human and rodent studies indicate that the liver contributes differently to fasting and postprandial glucose fluxes across species, with distinct regulation of hepatic gluconeogenesis, glycogen metabolism and responses to insulin and other hormones. *See* Exh. 2045 at p. 002-006; Exh. 2055 generally; Exh. 2061 at p. 001-010.

58. Because these mitochondrial, hormonal, intestinal, and hepatic differences shape whole-body glucose handling, interventions that appear to normalise glycaemia or insulin sensitivity in high-fat-fed or chemically induced

rodent diabetes models often fail to reproduce clinically meaningful benefits in human trials, a translational gap highlighted in systematic evaluations of rodent models and of type 2 diabetes therapeutics. *See* Exh. 2042 at p. 001-008, 010-011; Exh. 2020 at p. 001 (Abstract), 001-008; Exh. 2066 at p. 001 (Abstract), 001-002, 004, 011; Exh. 2021 at p. 001 (Summary), 002, 006.

#### **4. Difficulty in Translating Animal Data from the Alleged Prior Art**

59. None of the cited references provide human evidence for DHB administration. Turner reports rodent mitochondrial responses; Liu reports rodent intestinal enzyme changes; Feng demonstrates rodent microbiota transformation of berberine; Zhang provides human clinical data only for berberine, not DHB. A POSITA would have recognized that these findings do not establish a reasonable expectation that DHB would improve glucose tolerance in humans.

60. The alleged prior art relied upon by Petitioner for obviousness primarily provides short-term efficacy and pharmacokinetic observations in rodents and in vitro systems, and it therefore offers - at most - hypotheses rather than a reliable prediction of the claimed human glucose-tolerance outcomes and dose range.

61. For example, Hu (*see* Exh. 1012 at ¶¶ 217-219) reports that mice rendered obese by 10 weeks of high-fat feeding were treated for only two weeks with a DHB derivative (100 mg/kg/day) and then evaluated by an intraperitoneal glucose tolerance test (2 g/kg i.p.), with glucose measured over 0–120 minutes - an

endpoint and experimental context that differ materially from typical human oral glucose challenges and from the chronic, heterogeneous, comorbid nature of human metabolic disease. *See e.g.* Exh. 2042 at p. 011; Exh. 2020 at p. 001, 007-008.

62. Turner (*see* Exh. 1004 at p. 2, 4) similarly uses high-fat-fed rodents and intraperitoneal glucose challenge to report improved glucose tolerance at 100 mg/kg/day DHB over two weeks; however, Turner's pharmacokinetic data indicate that DHB is rapidly oxidized back to berberine after absorption and that berberine is likely the active moiety, meaning that any human extrapolation must contend with interspecies differences in metabolism and exposure rather than treating DHB as a "direct" human-active agent.

63. Feng (*see* Exh. 1007 at p. 1-7) likewise frames DHB as a transient, intestine-absorbable form generated by gut microbiota and shows that antibiotic treatment reduces DHB formation and attenuates glucose-lowering in mice, underscoring that efficacy depends on microbiome-mediated activation pathways that may not generalize across species or human populations, as discussed above in terms of the differences between rodent and human microbiota and other differences similarly noted above.

64. Proposed dose translation further rests on body-surface-area conversion and permeability surrogates (e.g., Caco-2), but the FDA's MRSD guidance makes clear that such scaling is intended to estimate a safe first-in-human starting dose

(typically from NOAELs) and explicitly cautions that human bioavailability, metabolism, and drug interactions may differ from animals; and Caco-2 is an informative screening tool but not a direct measurement of *in vivo* human absorption. *See* Exh. 1008 generally and at 12; Exh. 2037 generally; Exh. 2059 at p. 002.

65. More broadly, systematic evaluations of animal-to-human translation emphasize that animal models often overestimate efficacy and fail to reliably predict clinical outcomes, particularly when studies are performed in standardized, young, inbred animals under controlled conditions. *See* Exh. 2028 at p.004 and generally; Exh. 2029 at p. 008, 010; Exh. 2030 at p. 003-004 and generally; Exh. 2018 at p. 001-002; Exh. 2056 at p. 002, 004, 006; Exh. 2067 at p. 001-002, 004, 006.

66. Taken together, the alleged prior art does not overcome the well-known translational gap between rodent metabolic outcomes and human clinical efficacy.

67. Finally, my opinions above are supported by the extremely high attrition rate of drugs entering clinical trials above 90% clearly demonstrates the high uncertainty even after up to \$1bn in preclinical research on average before entering clinical trials. This best shows the difficulty in applying animal study data to humans. Below, major drawbacks and inaccuracies of those studies are detailed. A POSITA will consider these drawbacks to take decision to enter clinical trials, to abandon them, or when predicting success in future trials based on animal study data.

68. My thoughts on portions of Dr. Shebuski's statements are as follows:

Feature	Petitioner's Assumption (Shebuski)	Translational Reality (Scientific Context)	Specific Contention
<b>Model Reliability</b>	The High-Fat-Diet (HFD) mouse is a common and reliable model for human Type 2 Diabetes.	Rodents differ fundamentally from humans in mitochondrial control of glucose, hormone dynamics, and gut anatomy.	Whether an induced rodent phenotype can reliably predict chronic, heterogeneous human metabolic disease.
<b>Active Moiety</b>	Once absorbed, dhBBR rapidly converts to BBR, making BBR the active moiety to be translated.	Interspecies differences in hepatic glucose metabolism and enzyme expression modify how BBR/dhBBR are processed.	Direct extrapolation fails to account for species-specific metabolism and "host-specific" interactions.
<b>Dose Translation</b>	Body Surface Area (BSA/HED) conversion is the "most appropriate" method to predict human effective doses.	BSA scaling is intended for estimating safe <i>starting</i> doses (MRSD), not for predicting clinical efficacy or bioavailability.	The HED provides a safety starting point but does not provide a reliable basis for quantitative therapeutic outcomes.
<b>Glucose Dynamics</b>	Efficacy in a rodent glucose challenge test (IPGTT) translates to human glucose tolerance outcomes.	Rodents rely more on gluconeogenesis and show limited suppression of hepatic glucose output compared to humans.	Rodents exhibit transient insulin responses, whereas humans require sustained secretion to suppress glucose production.
<b>Microbiome Role</b>	dhBBR is a transient intestinal form; human gut bacteria convert BBR to dhBBR similarly to rodent bacteria.	"Humanized" rodent microbiota only partially recapitulate human donor communities, implying unique metabolic interactions.	Taxonomic composition and metabolite profiles differ markedly between species, affecting the activation of dhBBR.

Feature	Petitioner's Assumption (Shebuski)	Translational Reality (Scientific Context)	Specific Contention
<b>Success Probability</b>	There is a "reasonable expectation of success" for human clinical trials based on positive rodent data.	Only ~5% of animal-tested interventions ultimately obtain regulatory approval for human use.	Large datasets show that 90-95% of drug candidates fail after first-in-human entry due to lack of efficacy.

### VIII. RIGHT TO SUPPLEMENT

69. 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.

70. 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

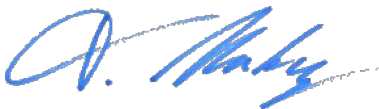
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## IX. CONCLUSION

71. For the foregoing reasons, including the well-established failure of rodent metabolic and mitochondrial studies to predict human glucose-tolerance outcomes, the mechanistic and pharmacokinetic differences between species, and the absence of any human DHB efficacy evidence in the cited prior art, it is my opinion that a POSITA would not have had a reasonable expectation of success in achieving the claimed human outcomes based on the prior art. Therefore, the petition does not demonstrate a colorable case of obviousness under 35 U.S.C. §103.

72. 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 4<sup>th</sup>, 2026



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Dr. Thomas Hartung, M.D., Ph.D.

**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this DECLARATION OF DR. THOMAS HARTUNG, M.D., 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)
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Date: January 7, 2026

Respectfully submitted,

/s/ Mark D. Nielsen

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