UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COALITION FOR AFFORDABLE DRUGS II LLC
Petitioner

v.

NPS PHARMACEUTICALS, INC.
Patent Owner

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Case IPR2015-01093
Patent 7,056,886

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PATENT OWNER’S RESPONSE
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The Patent Trial and Appeal Board (“PTAB”), on October 23, 2015, implemented this Inter Partes Review (“IPR”) of certain claims of U.S. Patent No. 7,056,886 (“the ’886 patent”). Pursuant to 35 U.S.C. §§ 314 and 316((a)(8) and 37 C.F.R. §42.120, Patent Owner NPS Pharmaceuticals, Inc. submits this Patent Owner’s Response and requests issuance of a final written decision under 35 U.S.C. § 318 (a) and issuance and publication of a certificate under 35 U.S.C. § 318 (b) confirming the patentability of the challenged claims.

I. Introduction

The ’886 patent inventor discovered GLP-2/GLP-2 analog formulations “exhibiting superior stability following storage and/or exposure to elevated temperatures.” Ex. 1003, Abstract. The challenged claims (1-45) are directed to formulations of GLP-2 or an analog that are stabilized, particularly when lyophilized (i.e., six months at ambient temperature, 18 months at 4°C with less than about 5% peptide degradation) at a pharmaceutically tolerable or acceptable pH (i.e., a pH that can be administered without patient reactions that preclude further administration) by a combination of L-histidine, phosphate buffer, and mannitol (18-24) or mannitol or sucrose (1-17 and 25-45). This invention resulted in a successfully marketed GLP-2 analog product and an approved drug treatment for short bowel syndrome - GATTEX®.
The PTAB instituted this IPR because:

[t]he information relied upon in the Petition tend[ed] to suggest that L-histidin e has a stabilizing effect on peptide drugs generally, indicating that properties of L-histidine peptides affecting peptide association (and, therefore, peptide stabilization) are relevant in a manner distinct from properties of L-histidine affecting biological activity of the peptides.

* * * * *

[the Petitioner showed] sufficiently that a person of ordinary skill in the art would have had a reasonable expectation of success in formulating GLP-2 in combination with L-histidine and sucrose or mannitol to create a lyophilized storage stable formulation in view of the guidance set forth in the prior art.

* * * * *

[t]he information set forth in the Petition [was] sufficient to establish that buffered pharmaceutical formulations of GLP-2 analogs were known and that Osterberg and Kornfelt suggests that the use of L-histidine in combination with an excipient such as mannitol or sucrose in protein formulations was a predictable variation within the technical grasp of a person of ordinary skill in the art done for the purposes of protein stabilization.

Paper 26, 19, 22-23. These conclusions are incorrect and arise from incomplete and unreliable expert testimony. The PTAB relied upon Petitioner’s alleged expert Dr. Anthony Palmieri, who provided an uninformed and less than expert explanation of the prior art, particularly Kornfelt et al., U.S. Patent No. 5,652,216 ("Kornfelt")
(Ex. 1027) and Osterberg et al., “Physical State of L-histidine after Freeze Drying and Long Term Storage.” E. J. Pharm. Sci. 8(1999) 301-308 (“Osterberg”) (Ex. 1030); misstated the level of ordinary skill in the art; incorrectly described and erroneously compared glucagon and GLP-2; misapplied and trivialized the difficulties and unpredictability of formulation science, particularly with regard to protein/peptide degradation and formulation; and found motivation to combine references to make a pH-acceptable stabilized peptide when there was not any and when any result was unpredictable. Furthermore, Petitioner’s and Dr. Palmieri’s obviousness analyses were plagued by hindsight. This was highlighted by cross-examination of Dr. Palmieri (see e.g., Ex. 2042, 194:9-21 (“Q. Did you consider the degradation pathway of a GLP-2 analog in forming your opinion of the obviousness of the claims of the ‘886 patent? […] A.] I did not think it was relevant to this – these opinions in my expert report. I knew I could make – I knew a person of skill in the art looking at the patent and scientific literature prior to the application date would know how to make it.”). Additionally, the PTAB discounted secondary considerations as the record was not fully developed. The PTAB’s initial obviousness impressions were based on hand-waiving and non-credible and simply incorrect information provided by Petitioner and Dr. Palmieri.

The record is corrected and completed by this Response and the concurrently submitted declarations of John F. Carpenter, Ph.D. and Gordon Rausser, Ph.D. Dr.
Carpenter is a Professor of Pharmaceutical Sciences, the Co-Director of the Center for Pharmaceutical Biotechnology at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, and a true expert formulation scientist with more than three decades of experience in studies including protein/peptide formulation development; protein/peptide degradation and stabilization during processing storage and administration to patients; rational development of stable lyophilized formulations; mechanisms by which excipients provide stabilization or fail to stabilize proteins/peptide during freezing, drying and storage in the dried solid; and development and testing of advanced analytical methods. He has published more that 250 peer-reviewed publications in the field, has consulted for dozens of pharmaceutical companies internationally, and has been an invited lecturer at conferences, pharmaceutical companies and universities around the world. Dr. Carpenter explains: the complexity and unpredictability of protein/peptide formulation science; what Kornfelt and Osterberg actually disclose (or more pertinently, fail to disclose) to one of ordinary skill in the art at the time of the invention; why Petitioner’s and Dr. Palmieri’s understanding of glucagon and GLP-2, their properties, and their structures is wrong; and why their application of formulation science, and in particular the formulation science of therapeutic proteins/peptides, and the prior art are incorrect, simplistic, and impermissibly retrospective. Formulation scientists working on therapeutic
protein/peptide products would not have followed Petitioner’s and Dr. Palmieri’s speculative path to obviousness and would not have proceeded from an evident lack of understanding of the science of stabilizing therapeutic peptides or proteins. They would not have reached Petitioner’s conclusory results, nor arrived at the ‘886 invention.

Unlike Dr. Palmieri, formulation scientists would have evaluated and compared the physical and chemical degradation pathways and solubilities of glucagon (formulated in the cited prior art) with those of GLP-2 (not yet formulated successfully) and found that they were entirely different. The artisan would have understood that what stabilized glucagon could not be expected to stabilize GLP-2 with any reasonable expectation of success. The PTAB’s basic understanding, coming as it did from Dr. Palmieri’s misguided assertions and lack of pertinent knowledge, is scientifically incorrect. There is no information suggesting to one skilled in the art that L-histidine has a stabilizing effect on peptide drugs generally. There was not a reasonable expectation of success in formulating GLP-2 with L-histidine and sucrose or mannitol to create a lyophilized storage stable formulation in view of the prior art. The prior art does not suggest that L-histidine in combination with mannitol or sucrose (and particularly mannitol) in protein formulations was a predictable variation within the technical grasp of a person of ordinary skill in the art done for protein stabilization.
Because the degradation pathways of glucagon and GLP-2 are so different, no conclusions could be drawn about GLP-2 stabilization from prior art glucagon stabilization. Those skilled in the art would have also known that there is a nearly infinite number of stabilizer, buffer, and bulking agent combinations that could be suggested by the prior art, but the prior art does not make any of them reasonably expected to be successful without undue and more than routine experimentation. Those skilled in the art would additionally have been aware of the many problems associated with histidine in peptide formulations, particularly when combined with additional buffers and mannitol or sucrose.

Dr. Palmieri never considered any of this; he did not need to because, according to him, it was all irrelevant. He simply looked at the present invention, then looked at the prior art, and made a retrospective reconstruction using the ‘886 patent as a blueprint. Those skilled in the art would have seen glaring deficiencies in Petitioner’s and Dr. Palmieri’s readings of Kornfelt and Osterberg. They would have rejected Dr. Palmieri’s unique misunderstandings of glucagon, GLP-2, histidine, mannitol, and sucrose and would have concluded that the ‘886 patent presents surprising and unexpected results when compared with combinations that include other amino acids and other sugars which the prior art alleged were equivalent. Those skilled in the art would never have entertained the notion that what is good for glucagon was also good for GLP-2. Nor would they have found
sufficient teaching, motivation, or suggestion to combine the prior art into a successfully stabilized GLP-2 formulation at acceptable pH.

Dr. Rausser is the Robert Gordon Sproul Distinguished Professor at the University of California, Berkeley. He has studied the evidence of long-felt need and commercial success of the present invention, including the required nexus. He found that the use of the traditional treatment for short bowel syndrome (“SBS”) (i.e., parenteral nutrition (“PN”)) is a significant burden for patients. He found that there was a strong need for better SBS treatments and that the commercial embodiment of the ‘886 patent invention (i.e., GATTEX) met this need by reducing dependence on PN, reducing treatment and other economic costs of SBS, increasing patient life expectancy, and enhancing patient quality of life. He also found GATTEX to be a commercial success by steadily capturing SBS patient share, commanding a reasonable price, having high sales with rapid sales growth, exceeding pre-launch sales expectations, quadrupling NPS’s share price before Shire’s acquisition of the company, and being a key value driver in that acquisition. Dr. Rausser shows that this commercial success is attributable to GATTEX’s therapeutic benefits and the long-felt need for a drug with its clinical properties, none of which would have been possible without the ability to stabilize the peptide in GATTEX – teduglutide – as provided by the ‘886 patent.
II. The Claimed Invention – Stable, Pharmaceutically Acceptable pH GLP-2 Formulations and Their Use to Treat Serious Diseases

The challenged claims encompass GLP-2/analog formulations stabilized at pharmaceutically/physiologically tolerable/acceptable pH by a combination of L-histidine, phosphate buffer, and mannitol or sucrose or just mannitol.

A therapeutic protein/peptide product’s safety and efficacy can be compromised by even small levels of degradation. Ex. 2040, ¶ 55. For example, even a few percent of protein/peptide aggregation or precipitation (i.e., physical degradation) can render a product medically unacceptable. Id. at ¶ 58. A protein/peptide medicine is usually rendered pharmaceutically unacceptable upon visibility of particles in the solution. Id. at ¶ 59. The mass percent of the protein/peptide in these visible particles can be less than 1%. Id. It is challenging to develop a formulation for a given protein/peptide that provides sufficient stabilization to prevent this. Additionally, even traces of physical degradation (e.g., a few percent or less) of the protein/peptide to soluble aggregates or subvisible particles can cause adverse, unwanted immunogenicity in patients (resulting in loss of drug efficacy), as well as dangerous infusion reactions. Id. at ¶ 60. Thus, simply showing a relative decrease in degradation of a protein/peptide during processing and storage is not valuable. Id. at ¶ 61. There must be a quantitative reduction in degradation such that it is kept to an absolute minimum. Id.
Similar concerns apply to chemical degradation, such as oxidation or deamidation. *Id.* at ¶ 62. These alterations in the protein/peptide can contribute to adverse immunogenicity and can reduce the potency of the medicine. *Id.* Also, chemical degradation may foster greater sensitivity of the protein/peptide to physical degradation. *Id.* Accordingly, all key routes of degradation for a given protein/peptide, not just selected routes, should be characterized and inhibited to the greatest degree possible for a successful, commercial protein- or peptide-based formulation. *Id.* at ¶ 63. Failure to develop an adequately stabilized product can result directly in non-approval by regulatory agencies, halting of clinical trials, and development-halting adverse clinical events. The success of a therapeutic protein/peptide product depends on meeting the great challenge of developing a properly stable formulation.

Furthermore, each protein/peptide has unique physicochemical properties, degradation routes, sensitivities to processing stresses (e.g., freezing and drying steps of the lyophilization process), and responses to stabilizing excipients. *Id.* at ¶ 64. Even those with similar sequences may have vastly different degradation routes and different specific condition requirements for optimal stability and response to stabilizing excipients. *Id.* For example, typically during formulation development for a given protein/peptide, scientists must empirically determine the optimal pH to minimize physical/chemical degradation pathways. *Id.* Particularly here, GLP-2
precipitates to insoluble aggregates at acidic pHs, whereas glucagon is soluble and resistant to aggregation at very acid conditions of pH 2.8 and lower). *Id.*

Formulation science is unpredictable. Many excipients that may be used to stabilize proteins/peptides during processing (e.g., lyophilization) and storage may not provide sufficient stability to a given protein/peptide because of unique critical degradation pathways of each protein/peptide and their unique responses to a given excipient. *Id.* at ¶ 65. The effects of degradation products on safety and efficacy also differ for each protein/peptide. *Id.* For example, oxidation of a methionine residue in one peptide may render it biologically inactive, whereas in a different one, methionine oxidation may not alter activity. *Id.* There is no way reasonably to predict whether a particular excipient will provide a pharmaceutically necessary degree of stability in a given protein/peptide product, as does the ‘886 patent. *Id.*

Finally, proteins/peptides are subject to many different degradation pathways, stresses, and formulation issues than are small molecules. *Id.* at ¶ 56. Also, unlike small molecule drugs, which are often administered orally, therapeutic peptides and proteins are administered parenterally which raises additional product quality and safety requirements. See generally Ex. 2053. The challenges in formulating a protein/peptide are often more difficult than those in formulating a small molecule. *Id.*

The commercial embodiment of the ’886 patent invention, GATTEX, is a
formulation of the GLP-2 analog [Gly2]GLP-2 (i.e., teduglutide) that is stabilized at a pharmaceutically acceptable pH by a combination of L-histidine, phosphate buffer, and mannitol. Id. at ¶ 72-73. Each vial of GATTEX contains 5 mg of teduglutide, 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, and 3.434 mg dibasic sodium phosphate heptahydrate as a white lyophilized powder for solution for subcutaneous injection. Ex. 2027, 5. GATTEX is a drug product for treating adult patients with SBS who are dependent on parenteral support. Ex. 2041, ¶ 17. It was approved by the U.S. Food and Drug Administration (“FDA”) on December 21, 2012, as an orphan drug and has been sold by NPS (now a part of Shire PLC) since February 2013. The ’886 patent is listed in the FDA’s Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”) for GATTEX. Ex. 2058.

SBS is a highly disabling condition. It has life-threatening complications, can severely impair quality of life, and is associated with intestinal failure and the inability to absorb sufficient nutrients and fluids through the GI tract. Ex. 2041, ¶ 17. SBS typically arises after extensive bowel resection of the bowel due to Crohn’s disease, ischemia, or trauma. Id. at ¶ 19. SBS patients are highly prone to malnutrition, diarrhea, dehydration, and inability to maintain weight due to reduced intestinal capacity to absorb macronutrients, water, and electrolytes. Id. at ¶ 33.

Consequently, many SBS patients require chronic parenteral nutrition
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(“PN”) and intravenous (“IV”) fluids for nutritional supplementation and hydration. *Id.* at ¶¶ 19-20, 33. PN/IV fluids bypass the digestive tract and are delivered directly into the bloodstream through a central venous catheter. *Id.* at ¶ 22. However, PN/IV fluids do not improve the ability to absorb nutrients, and their long-term use can shorten life span and can cause life-threatening complications such as blood clots and liver damage. *Id.* at ¶ 23-24, 29, 34. Development of PN-associated liver disease predisposes patients to an increased incidence of sepsis, increased mortality rates, and potentially irreversible liver damage. *Id.* Patients on parenteral support often experience poor quality of life including difficulty sleeping, frequent urination and bowel movements, need for and problems with ostomy bags, and loss of independence. *Id.* at ¶ 35. There are an estimated 10,000 to 15,000 PN/IV fluids-dependent SBS patients in the U.S. *Id.* at ¶ 27.

GATTEX improves intestinal rehabilitation by promoting mucosal growth, inhibiting gastric acid secretion and emptying, increasing intestinal barrier function, and enhancing nutrient and fluid absorption. *Id.* at ¶ 31, 45-46. GATTEX treatment is associated with enhancement/restoration of the remaining intestine’s structural and functional integrity, thereby improving absorption and reducing PN needs. *Id.* GATTEX allows patients more independence and self esteem and the ability to lead rewarding personal, social, and working lives. *Id.*

III. The Petitioner’s Challenges - Obviousness

Petitioner argues obviousness by assembling disparate “facts” that are overstated, do not apply to GLP-2, or both.1

1 See Pet., 22, 23, 26, 27 (Drucker ’379 discloses GLP-2 peptide formulations); 22-25, 49-51, 53-55 (Osterberg and Kornfelt disclose L-histidine stabilization of glucagon); 46-47 (Drucker ’547 discloses GLP-2 antagonists); 27 (Munroe discloses a cell line and screening); 42-43 (Holthius discloses a parathyroid hormone formulation); 49-51 (motivation to combine because of FDA, structural
Petitioner then hedges its bet and submits that “[a]t the very least, the L-histidine stabilized formulation taught by Kornfelt would be obvious to try with GLP-2 or an analog thereof [because] Kornfelt and Osterberg teach that preparing stable formulations do not involve numerous parameters.” Id., 54. According to Petitioner, “Kornfelt provides specific guidance as to a small number of known options, such as L-histidine and sucrose or mannitol, for preparing a storage stable formulation of glucagon” and “provides a detailed methodology for preparing formulations of glucagon [not GLP-2 or GLP-2 analogs] with L-histidine as a stabilizing amino acid and an excipient like lactose or mannitol.” Id., 54-55.

Petitioner ignores what really matters to formulation scientists, in favor of exaggerated generalities and unfounded extrapolations. This is a mistake the artisan (lacking hindsight and Petitioner’s motives) would not have made. Petitioner ignores, as explained in more detail below, that Drucker ‘379 does not disclose a stabilized GLP-2/analog formulation at pharmaceutically tolerable pH containing L-histidine, phosphate buffer, and mannitol or sucrose.

Crucially, glucagon and GLP-2 degrade differently and do not have similar physico-chemical profiles, which means that a skilled artisan would not believe similarity between glucagon and GLP-2). 52-55 (expectation of success).
that what stabilizes glucagon would stabilize GLP-2. Glucagon is not the alpha helix Dr. Palmieri claims it is. (That glucagon is an alpha helix is essential to his obviousness opinions.) Further, the primary structures of glucagon and GLP-2 are different. Also, glucagon has a pI (i.e., isoelectric point) of around 7.0, where the pI of GLP-2 is about 4.0. These are vastly different physical characteristics and are vitally important in formulation science because the optimal pH for minimizing aggregation and precipitation of a peptide is one that is not near the peptide’s pI. Therefore, Petitioner’s and Dr. Palmieri’s theory - “what is good for glucagon is good for GLP-2” - is baseless and not all reflective of what has been learned in the decades of the challenging work of developing stable formulations for proteins/peptides. Rather, the opposite is true, and the dissimilarities between the two molecules teach away from Petitioner’s hindsight hypothesis.

Osterberg does not describe any protein/peptide formulations. It only describes tests of solutions of L-histidine and sucrose or mannitol and nothing else. No conclusions about protein/peptide stability, solubility, or solubility and proper pH can be inferred. Whether solutions or lyophilized forms of L-histidine and sucrose absent the particular protein/peptide to be studied are storage stable from pH 4-8 discloses nothing about their ability to stabilize GLP-2 or its analogs.

Kornfelt does not help. Kornfelt did not formulate glucagon with L-histidine at any pH other than 2.8. It does not disclose that storage stable glucagon
formulations have a pH range of 1-7; Kornfelt formulated glucagon at pH 2.8. Kornfelt discloses millions of millions of possible combinations of excipients for glucagon and nothing about GLP-2.

Of course the FDA requires all drugs to be stable. This identifies a problem, but does not motivate any particular solution generally, nor does it indicate any specific “how to” for GLP-2. Relying on that as motivation to combine references is like saying that wishing makes world peace a reality.

Neither Munroe, Drucker ‘547, nor Holthius discuss amino acid, buffer, bulking agent stabilization. Holthius is directed to parathyroid hormone, which is not even a member of the glucagon super family that uses to relate prior art glucagon to GLP-2

Furthermore, L-histidine is a problematic formulation component; the ‘886 patent demonstrates surprising and unexpected results of the combination of L-histidine, phosphate buffer and mannitol/sucrose; there was a long-felt need for the ‘886 patent invention; and the invention is a great commercial success.

Unaided by hindsight, the combinations relied upon by the Petitioner are no more than an invitation to experiment with no reasonable expectation of success.

IV. Summary of Non-Obviousness of Each Challenged Claim

All of the terms of the challenged claims should be construed by their ordinary meanings unless otherwise discussed herein.
A. Ground 1 - Claims 1-27, 33-35, 38, and 45 Are Not Obvious over Drucker ’379 in view of Kornfelt and Osterberg

‘886 patent independent claim 1 claims a GLP-2 formulation of (a) a medically useful amount of GLP-2 or analog, (b) a phosphate buffer in an amount sufficient to adjust the formulation’s pH to a physiologically level, (c) L-histidine, and (d) mannitol or sucrose. Drucker ‘379 does not disclose any form of GLP-2 stabilization other than amino acid substitutions or using terminal blocking groups, which are intended to reduce in vivo degradation by proteases; does not disclose any in vitro stabilization other than simple lyophilization; and only exemplifies injectable GLP-2 analog formulations with either phosphate buffered saline or gelatin, sterile water, and sodium hydroxide to adjust the pH.

Osterberg does not disclose any protein/peptide formulations; the degradation pathways of glucagon or GLP-2; or any information about mannitol, let alone its superior effects in the ‘886 patent invention. The ‘886 patent formulations use a different buffer than histidine. Furthermore, histidine is a problematic excipient. It may not provide sufficient stabilization for a commercially successful human medicine containing a protein/peptide drug. Its usefulness in lyophilized formulations is largely dependent upon the solution conditions (e.g., pH) or lyophilization processing conditions (e.g., use of a post-freezing annealing step). Although histidine should remain amorphous during lyophilization, numerous factors affect the crystallization of histidine (and other
excipients that can crystallize) during freeze-drying including the initial solution pH, the presence and amounts of other excipients, the amount of protein/peptide in the formulation and the freeze-drying processing conditions. Accordingly, one cannot reasonably predict whether or the degree to which histidine will remain amorphous or if it will crystallize during freeze-drying or storage. Crystallization can compromise protein/peptide stability rendering histidine ineffective.

Histidine in a formulation is also susceptible to oxidation and can promote oxidation of proteins/peptides. It does not have a general pharmaceutically acceptable stabilizing effect on protein/peptide drugs in all formulations and uses.

Kornfelt does not disclose degradation pathways of glucagon or GLP-2 or their inhibition. Rather, it discloses a nearly limitless number of ampholytes and excipients combinations and formulates glucagon at a physiologically unacceptable pH 2.8 because this pH gives “a minimum for the rate of decomposition of glucagon.” Ex. 1027, 3:26-27. GLP-2 is insoluble at pH 2.8 and in fact, below pH 5.5, which would make the Kornfelt glucagon formulation and its required low pH stabilization contraindicated for formulated GLP-2. Furthermore, subsequent literature shows that Kornfelt’s formulation strategy did not work.

Kornfelt demonstrates that all amino acids tested with lactose (including histidine) were equally good glucagon stabilizers; that glycine, histidine, glycylglycine, aspartic acid, glutamic acid, leucine, alanine, asparagine, valine, and
mixtures are equivalent; that mannitol, sucrose, and lactose are equivalent; and that formulations with leucine, glycine or glycylglycine provided stability to glucagon equivalent to that observed in formulations containing histidine. However, the ‘886 patent shows different, surprising, and unexpected results from histidine with mannitol.

Furthermore, stabilization of glucagon is not predictive of GLP-2 stabilization. The pI, pH range for solubility, and chemical degradation pathways of glucagon and GLP-2 are different, as are their structures.

There is no teaching, motivation, or suggestion in the prior art to combine the references. Rather, there are teachings away. Protein/peptide stabilization is far from routine or predictable. Many factors can cause destabilization and degradation. Additionally, the number of components and combinations from which a formulation scientist can choose is voluminous, even if artificially constrained to the cited references. Formulation components and general approaches to formulation design do not provide definitive solutions; they just point to possible avenues for exploration, with essentially infinite possibilities of compositions to test and numerous avenues by which that testing may be done.

The FDA’s stability requirements are universal; there is no specific guidance for GLP-2 or its analogs. Glucagon’s and GLP-2’s physico-chemical properties differ greatly in important ways – structures, degradation pathways, pH optimum,
pI, solubility, etc. This teaches away from the present invention. One of ordinary skill would not conclude that what is good for glucagon is good for GLP-2.

There is no universal amino acid protein/peptide stabilizer, and processing issues and sensitivities to stress vary from molecule to molecule. L-histidine can create its own degradation pathways in protein/peptide formulations.

Furthermore, the commercial embodiment of this formulation, GATTEX, is a successful drug product for treating adult patients with SBS who are dependent on parenteral support.

The Petitioner’s combinations are, at most, no more than an invitation to experiment with no reasonable expectation of success. Absent the use impermissible use of hindsight, the artisan would not go from glucagon to GLP-2. She would not proceed routinely and would not predict a suitably stable GLP-2 composition as claimed.

Claims 2, 4, and 6 specify pH. The discussion above highlights the differences in pH properties of glucagon and GLP-2 and the meaning and effects of this difference. These limitations add to the non-obviousness of these claims.

Claim 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, and 45 provide that the GLP-2 is [Gly2]GLP-2. Claim 44 describes generally suitable GLP-2 analogs. The discussions of claim 1 and the claims from which these claims depend applies to these claimed formulations, as well.
Claims 8, 10, 12, and 14 provide concentrations ranges for the GLP-2 or GLP-2 analog. The discussions of claim 1 and the claims from which these claims depend apply to the claimed formulations with these concentrations, as well.

Claim 16 provides concentrations ranges for the L-histidine. The discussions of claim 1 and the claims from which claim 16 depends apply to the claimed formulations with these concentrations, as well.

Claim 18 provides that the bulking agent is mannitol, claims 20 and 22 provide concentrations for the mannitol. The ‘886 patent shows surprising and unexpected results here, making these claims further non-obvious.

Claims 24 and 26 specify the origin of the GLP-2. The discussion of claim 1 applies to these formulations, as well.

Claims 33-35 specify particular analogs. The discussion of claim 1 applies to these formulations, as well.

Claim 38 provides that the formulation is lyophilized. Lyophilization adds further complications to discovering a stable formulation, as discussed below. That the present invention overcomes these difficulties and the surprising results of the ‘886 patent invention adds to the non-obviousness of this claim.

B. Ground 2 - Claims 31, 32, and 44 Are Not Obvious over Drucker ’379 in view of Kornfelt, Osterberg, and Munroe

Munroe does not disclose glucagon, GLP-2, or analog stabilization. ‘886 patent claim 31 provides that the GLP-2 analog is identified by a screening
method, and claims 32 and 44 specify particular analogs. The discussion of claim 1 applies to these formulations, as well.

C. **Ground 3 - Claims 28-30 and 39-43 Are Not Obvious over Drucker ‘379 in view of Kornfelt, Osterberg, and Holthius**

Holthius does not disclose stabilization of glucagon, GLP-2, or GLP-2 analog formulations. Claims 28-30 and 41-43 provide stability criteria. The physico-chemical differences between glucagon and GLP-2 and the known disadvantages that histidine causes would have indicated to one of ordinary skill in the art that GLP-2 stabilization was not predictable. These claims are non-obvious.

Claims 39 and 40 provide limits on the amount of water in the lyophilized ‘886 patent formulations. The discussions of claim 1 and 38 apply to these claims, as well. Furthermore, water causes degradation problems in lyophilized formulations, as discussed below. That the ‘886 patent invention limits the amount of water in these formulations adds to the non-obviousness of these claims.

D. **Ground 4 – Claims 36 and 37 Are Not Obvious over Drucker ’379 in view of Kornfelt, Osterberg, and Drucker ‘574**
The only long-term stabilization technique disclosed in Drucker ‘547 is lyophilization. Claims 36 and 37 further specify the GLP-2 analog. These claims are non-obvious for the same reasons claim 1 is non-obvious.

V. State of the Art

A. The Field of the Invention and Level of Ordinary Skill in this Art

The field of the present invention is pharmaceutical protein/peptide formulation science – a field in which Petitioner’s Dr. Palmieri is neither an expert nor one of ordinary skill. Ex. 2040, ¶ 105-08. Dr. Carpenter certainly is, though. He is qualified to evaluate and explain what a person of ordinary skill in the art would have known and understood when the ‘886 invention was made. One of ordinary skill in the art would have been a pharmaceutical protein/peptide formulation scientist with a Ph.D. in pharmaceutical sciences or one of the biological sciences, including molecular biology, biochemistry, and protein chemistry, and would have had relevant post-doctorate experience in designing pharmaceutical formulations of proteins/peptides sufficient for a leadership role in a formulation design team. Id. at ¶ 106.

Petitioner’s description of one of ordinary skill in the art is incorrect. A Master’s degree is insufficient education for understanding this science and is insufficient training for leadership role in a formulation design team. Experience alone cannot substitute for being formally educated in the biological sciences
underlying protein/peptide formulation science. Ex. 2040, ¶ 107. Therefore, one of ordinary skill in the art at the time of the invention would have had a Ph.D. and (not or) the required experience. Id. at ¶ 106.

**B. The State of the Art Was Unpredictable and Complex**

The formulation of therapeutic proteins/peptides was, before December 30, 1999, and continues to be, a highly unpredictable, complicated, and specialized art. Ex. Id. at ¶ 54. The success of a protein/peptide drug often depends upon the delivery of the biologically active form of the protein/peptide to the site of action, as well as minimizing key degradation pathways (which are unique for each product). Ex. Id. at ¶ 63. A pair of prominent protein/peptide formulation scientists, Dr. Jeffery L. Cleland from Genentech, Inc. and Dr. Robert Langer from Massachusetts Institute of Technology, stated, in 1994 that “[e]ach molecule has its own unique physical and chemical properties which determine in vitro stability. The formulation scientist must also be concerned about the in vivo stability of the drug. Thus, the development of successful formulations is dependent upon the ability to study both the in vitro and in vivo characteristics of the drug as well as its intended application.” Ex. 1024, 2; Ex. 2040, ¶ 66; see also Ex. 1001, ¶¶ 37, 68, 102, 140, 194, (Cleland was relied upon by Petitioner and Dr. Palmieri.) This still holds true today. Ex. 2040, ¶ 66. This goal can only be achieved if the formulation scientist considers the clinical indication, pharmacokinetics, toxicity, and
physicochemical stability of the drug. *Id.* Degradation pathways of a protein/peptide must be individually analyzed and competing rates of different degradation pathways must be balanced to achieve the most stable formulation possible. *Id.* at ¶ 67. Formulation components besides the active protein/peptide must be considered and balanced in terms of, for example, protein/peptide stability and administration route, as well. *Id.* The analysis that guides a formulation scientist’s approach to development may be systematic rather than random, but it is not like a cookbook. *Id.* at ¶ 68. The solutions for successfully formulating a particular protein/peptide (even in light of known formulations for other or similar ones) are not formulaic. *Id.*

One example of a system for the formulation of therapeutic proteins/peptides is given in Cleland, Figure 2, which sets forth their process diagram for the development of a protein/peptide formulation. *Id.* at ¶ 69; Ex. 1024, 6. This is one, but not the only, system. Ex. 2040, ¶ 69. However, it, like most other protein/peptide formulation development systems, is really a list of first variables and a further list of variables for the first variables that should be addressed in order to narrow the possible substituents, based upon the individual formulation scientist’s artfulness, experience, and inventiveness. *Id.* at ¶¶ 69-70. These process diagrams are by no means simple recipes for success. *Id.* at ¶ 70.

The possible solutions are virtually endless based upon even Cleland’s
simple process diagram. *Id.* For example, Cleland lists at least three initial variables - the individual protein/peptide’s physicochemical properties, *in vivo* parameters, and degradation pathways. *Id.* Each of these have several non-exhaustive secondary variables – three or more for physicochemical properties, four for *in vivo* information, and five for degradation pathways. *Id.* This yields over 17,000 (3! x 3! x 4! x 5!) combinations of variables. *Id.* This is multiplied by thousands more when one addresses the number combinations of constituents that are available for each secondary variable and the necessity of testing different concentration of each excipient, even if some of these variables could be eliminated after proper analysis of a particular protein/peptide. *Id.* The experimentation is undue and more than routine. It is inventive to understand and implement this type of discovery process and to find the right combination of components that yield a successful formulation. *Id.* at ¶ 71; *c.f.* KSR Int’l. Co. v. Teleflex, Inc., 550 U.S. 398, 421 (2007) (“When there is a design need or market pressure to solve a problem and *there are a finite number of identified, predictable solutions*, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. … In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.”) (emphasis added). The ‘886 patent is a good example of such a non-obvious invention. There were NOT a finite number of solutions, nor did the prior art
C. Dr. Palmieri’s Testimony Is Unreliable; He Is Neither an Expert Nor One of Ordinary Skill in the Art

Fed. R. Evid. 702 requires an expert to be qualified. Dr. Palmieri admitted on cross-examination that he has never been part of a group that formulated proteins/peptides; he just talked, 15-20 years ago, to people who did. Ex. 2042, 30:12-32:11. He believes, mistakenly, that the science involved in formulating proteins/peptides is the same as with any other class of pharmaceutical agents, including small molecules. *Id.* at 32:4-33:21; 35:13-36:10; Ex. 2040, ¶ 55-56. He then equivocated and stated that the challenges of formulating different groups of APIs “are very different sometimes,” but still lumped all polypeptides together as a single group of APIs in which each one presents the same formulation challenges. *Id.* at 36:18-24. He has never worked with either glucagon or GLP-2. *Id.* at 33:23-34:9. He has never published a peer-reviewed paper on the stabilization of proteins/peptides in pharmaceutical formulations. *Id.* at 40:2-11. He does not understand the mechanisms of protein denaturation; he stated that proteins “just become inactive.” *Id.* at 310:10-15. He does not know about protein renaturation or molten globule states. *Id.* at 311:2-312:4. Dr. Palmieri lacks the experience or understanding of one of ordinary skill in the art, let alone of an expert, with respect to successfully discovering and developing pharmaceutical formulations of proteins/peptides.
His lack of expertise is further demonstrated by his lack of understanding of protein/peptide formulation science. He does not understand or appreciate how protein/peptides work in a formulation, including how they are stabilized, nor how formulation scientists actually work to develop a stable protein/peptide product. The way that he would formulate a protein/peptide is simply to go to the prior art “to determine where [his] best chance of success was.” *Id.* at 20:3-13. Here, his “best chance” came from hindsight knowledge of what to look for, which he got from the ‘886 patent. He would not bother to look at degradation pathways, even though Cleland (Ex. 1024), which he cited himself, says to do so, because Dr. Palmieri does not “think the specific degradation pathway is relevant.” *Id.* at 179:18-20; *see also id.* at 180:8-11 (“The exact degradation pathway of the peptide is not relevant.”). Perhaps that is because Dr. Palmieri does not know what even the most common protein degradation pathways are. When questioned about protein degradation pathways, he repeatedly insisted they were not relevant to his obviousness analysis and that if he wanted to learn about them, he would “look it up.” *See, e.g., id.* at 179:5-16, 181:4-182:3, 182:5-18, 183:6-14, 185:15-21, 189:7-13, 196:10-197, 197:8-25, 198:4-7, 222:17-223:2, 223:8-224:9, 19, 230:25-2317. (Dr. Palmieri did say, in one instance of his lack of knowledge, that he “could go to his colleagues.” Ex. 2042, 196:22-197:6. However, his colleagues are not providing “expert” opinions, here.)
He also lacks any expertise with respect to glucagon or GLP-2, which he also considers to be irrelevant to his “expert” opinions - again because of his belief that when it comes to formulation science, one size fits all. He admitted that he never studied the degradation pathways of glucagon or GLP-2 when he formed his opinion of obviousness, again because they were categorically irrelevant; he did not know them; and if he wanted to learn about them he “would have to look it up”. *Id.* at 190:7-13 and 23-24, 191:24-192:7, 192:9-193:10 and 15-22, 194:2-7 and 9-16, 195:11-18, 195:23-196:8, 200:16-20, 200:22-201:21, 209:12-20, 215:21-24, 216:2-21, 217:12-218:3, 218:5-12, 220:12-20, 220:25-221:10, 221:12-222:1, 222:4-15, 222:6-14, 288:20-25. But he never did. Even worse, he testified, contrary to what those skilled in the art knew, that aggregation and precipitation (the only degradation pathways he recognized) were not important degradation pathways from a formulation standpoint. *Id.* at 111:22-112:2. He also admitted that he did not know even the most basic properties of glucagon or GLP-2 (GLP-2 is soluble at pharmaceutically acceptable pH, *i.e.*, above pH 5.5) but, again, could “look it up” – even though he did not do so in forming his opinions in this IPR. *Id.* at 206:16-22. Dr. Palmieri was wrong even about the point he considered most critical: that GLP-2 would stabilize like glucagon because they share an “alpha helix” structure. Glucagon is not an alpha helix as he said it was. *See id.* at 160:18-22; *see also* Section VII.
He did not know how histidine acts as a stabilizer when it works at all or that histidine could cause problems as an excipient. Id. at 63:10-16, 75:20-76:9. He did not know the pH of phosphate buffers but would “have to look it up.” Id. at 106:5-10. Dr. Palmieri did not know much about lyophilization, either – but again he could look it up. See, e.g., id. at 83:11-84:8, 164:21-165:10, 236:16-22, 239:21-24. Dr. Palmieri was offered by Petitioner as an expert in the field of protein/peptide formulation science, not as a librarian. Furthermore, he did not even take the trouble to “look up” what he needed to know, in order to give his “expert” opinion in this proceeding.

Courts are expert witness gatekeepers who should exclude unreliable expert testimony. Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 589 (1993); see also Xilinx, Inc. v. Intellectual Ventures I LLC, IPR2013-00112, Paper 51, 44. Factors useful in evaluating whether a witness is an expert include: (1) whether the expert's technique or theory can be or has been tested—that is, whether the expert's theory can be challenged in some objective sense, or whether it is instead simply a subjective, conclusory approach that cannot reasonably be assessed for reliability; (2) whether the technique or theory has been subject to peer review and publication; (3) the known or potential rate of error of the technique or theory when applied; (4) the existence and maintenance of standards and controls; and (5) whether the technique or theory has been generally accepted in the scientific
community. *Id.* at 593-94. The answer to each of these is “no” with respect to Dr. Palmieri’s testimony. He has offered an unreliable, conclusory theory that “what is good for glucagon is good for GLP-2.” *See* section VII, below. He has conducted his analysis without regard for, and in disagreement with, industry practices and peer-reviewed publications. His theory has a large error potential since it is illogical and based on incorrect science such as a complete disregard of degradation pathways, disregard for L-histidine’s properties, and disregard for differences between GLP-2 and glucagon, including and an incorrect assumption that glucagon and GLP-2 are both alpha helices. *See* Section VII. His methodology and resulting theory has no standards or controls, and it is not accepted in the protein/peptide formulation science community.

Furthermore, Dr. Palmieri has not conducted research in protein/peptide formulation science; he has extrapolated from scientifically disproven and unaccepted premises to reach unfounded conclusions (*see* Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)), the intellectual rigor he has used in his opinion is questionable since he found basic formulation science “irrelevant” (*see* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999)); and his opinion is not grounded in scientific methodology (*see* Moore v. Ashland Chem., Inc., 151 F.3d 269, 275 (5th Cir. 1998) (en banc)). *See* Section V.

All of Dr. Palmieri’s testimony (declaration and deposition) should stricken;
he is not an expert. Alternatively, his testimony should be heavily discounted by the PTAB as lacking credibility.

VI. Petitioner Misconstrued the Disclosures of the Prior Art

A. Drucker ‘379

Drucker ‘379 discloses GLP-2 analogs, and particularly those with a amino acid substitution at X2 or X3 to resist in vivo (as opposed to in vitro) cleavage by DPP-IV. Ex. 1029, 2:56-59, 6:22-26; Ex. 2040, ¶ 109. Drucker ‘379 calls the first two amino acid residues at the C-terminus and the last two at the N-terminus of GLP-2 the “GLP-2 background.” Ex. 1029, 4:7-18; Ex. 2040, ¶ 110. Suitable analogs may also include protecting groups at the C- and N-termini “to confer biochemical stability and resistance to digestion by exopeptidase,” an in vivo, not in vitro, event. Ex. 1029, 5:33-34; Ex. 2040, ¶ 111. Other preferred analogs “replace the oxidatively sensitive Met at position X10 with an amino acid which is oxidatively stable” or incorporate a Hys or Lys at position X20 to facilitate chemical synthesis of the peptide. Ex. 1029, 2:59-3:1; Ex. 2040, ¶ 111. Formulations can include a pharmaceutically acceptable carrier and a buffer and can be in lyophilized form. Ex. 1029, 3:23-27, 9:35-54, 10:31; Ex. 2040, ¶ 112. Drucker ‘379 does not suggest any in vitro protein/peptide stabilization other than simple lyophilization. Id. at ¶ 114. Drucker ‘379 exemplifies injectable GLP-2 analog formulations that include only phosphate buffered saline or gelatin, sterile
water, and sodium hydroxide. Ex. 1029, Example 4, 13:9-48; Ex. 2040, ¶ 115.

B. Drucker ‘547

Drucker ‘547 discloses GLP-2 antagonists having the amino acid sequence of mammalian GLP-2 in which 1-4 of the first four amino acid residues at the N-terminus have been deleted; the amino acid sequence of human GLP-2 in which Asp15, Phe22, Thr29 or 32, or Asp 33 is substituted with another amino acid residue; Ala2 is substituted with Leu, Cys, Glu, Arg, Trp, and PO3-Tyr2; or any combinations of any of the foregoing. Ex. 1029, 2:20-37; Ex. 2040, ¶ 116. N- or C-terminal blocking groups can also be used. Ex. 1028, 11:19-23; Ex. 2040, ¶ 117. Formulations can be lyophilized. Ex. 1028, 19:35-36. Drucker ‘547 does not disclose any other long-term stabilization. Ex. 2040, ¶ 118. Samples were tested for DDP-IV cleavage, which is an *in vivo* degradation issue. *Id.*

C. Osterberg

Osterberg discloses that: (1) dried, amorphous L-histidine crystallizes when exposed to moisture, even as low as 20-40% relative humidity (Ex. 1030, Abstract, 6; Ex. 2040, ¶ 119); (2) crystallization of L-histidine during freezing and thawing is dependent on the pH of the solution and is at a minimum at pH 6 (Ex. 1030, Abstract; Ex. 2040, ¶ 120); (3) sucrose inhibits the crystallization of L-histidine during thawing (Ex. 1030, Abstract; Ex. 2040, ¶ 121); (4) the physical state of L-histidine after freeze-drying is dependent on both the pH of the solution and the
freezing cycle (Ex. 1030, Abstract; Ex. 2040, ¶ 122); (5) the risk of crystallization of amorphous L-histidine is lower if the freeze-dried material is protected from moisture (Ex. 1030, Abstract; Ex. 2040, ¶ 123); (6) L-histidine acts as both a buffer and a stabilizer in freeze-dried formulations of recombinant factor IX (Ex. 1030, 1; Ex. 2040, ¶ 124); and (7) L-histidine “may be regarded as a multifunction protein stabilizer since it can function as a buffer and a metal ion scavenger.” Ex. 1030, 1, 7 (emphasis added); Ex. 2040, ¶ 125.

Notably, the ‘886 patent formulations use a different buffer, i.e., phosphate buffers, and GLP-2 and its analogs do not include any metal ions. Ex. 2040, ¶ 126-27. Dr. Palmieri admitted that freeze-dried formulations always have moisture, the enemy of amorphous L-histidine. Ex. 2042, 70:8-24. Accordingly, histidine’s possible stabilization properties remain subject to unpredictable conditions and would not appear to one of ordinary skill to be pertinent to the presently claimed formulations. Ex. 2040, ¶ 128.

Osterberg itself discloses to one skilled in the art that histidine crystallization during freezing, drying, and storage in the dried solid state is complex and becomes more complex if one considers the potential impact of each protein/peptide’s stability requirements, including those during processing and storage, and each protein/peptide’s pharmaceutical properties. Id. at ¶ 129. Far from presenting L-histidine as a universal stabilizer, Osterberg informs the artisan
that L-histidine is fraught with difficulties. Its successful use in any given formulation of any given protein/peptide, even Kornfelt’s glucagon, was unpredictable, and does not make it predictable in other formulations, including those with GLP-2.

Furthermore, Dr. Palmieri admitted that Osterberg does not disclose (1) any protein/peptide formulations (Ex. 2042, 81:21-25, 85:10-21); (2) the degradation pathways of glucagon or GLP-2 (id. at 74:17-75:9); and (3) any information about mannitol, let alone its superior effects in the ‘886 patent invention (id. at 85:23-86:2; see Section VI).

D. Kornfelt

Kornfelt discloses a pharmaceutical preparation of glucagon (not GLP-2 or a GLP-2 analog), an ampholyte, and optionally, an excipient. Ex. 1027, Abstract; 2:21-25; Ex. 2040, ¶ 130. Kornfelt alleges that this preparation is stable for extended periods of time in solution at room temperature. Ex. 1027, Abstract, 1:31-33; 2:25-27; Ex. 2040, ¶ 131. Kornfelt’s exemplary list of suitable ampholytes includes 23 different naturally occurring and non-naturally occurring amino acids (individually or in combination), a limitless number of sulfonic acids (i.e., all organic acid containing the group —SO$_2$OH) and their derivatives, creatine, and EDTA. Ex. 1027, 2:38; Ex. 2040, ¶ 132. Even if one were to include only three sulfonic acids (for the sake of argument only) and were to exclude sulfonic acid
derivatives (again, for the sake of argument only), the number of ampholyte combinations disclosed total 304,888,344,611,713,860,501,504,000,000 (i.e., 28!). Ex. 2040, ¶ 133. Kornfelt also provides excipients, including all disaccharides, sugar alcohols, polysaccharides, and polyvalent alcohols, to facilitate lyophilization. Ex. 1027, 2:45-57; Ex. 2040, ¶ 134. The number of combinations that can be made from Kornfelt’s lists of suitable ampholytes and excipients is astronomical. Ex. 2040, ¶ 135. Absent hindsight, the artisan does not come to L-histidine, phosphate buffers, mannitol or sucrose, and GLP-2 or analogs specifically, and even then would worry about it from Osterberg and from its known properties.

Kornfelt discloses that the pH of its compositions should be adjusted to range from 1-7, preferably 2-4 and most preferably 2.8. Ex. 1027, 3:9-13; Ex. 2040, ¶ 136. This is important to keep in mind when reading Kornfelt, because when Kornfelt describes their most preferred glucagon formulation which includes glucagon, lactose or mannitol, and glycine, histidine, glycylglycine, or a mixture of two or more of these, the preparation has a buffer effect at pH about 2.8 in order to “give a minimum for the rate of decomposition of glucagon.” Ex. 1027, 3:25-26, 4:22-26; Ex. 2040, ¶ 136. Kornfelt clearly teaches that low pH has a major and important role in stabilizing glucagon. Ex. 2040, ¶ 136. However, GLP-2 is insoluble at pH 2.8 and in fact, below pH 5.5, which would make the Kornfelt
formulation and its required low pH stabilization contraindicated for GLP-2 since GLP-2 is insoluble below pH 5.5 and it is injected as a solution when reconstituted. See Ex. 1003, 5:21-22; Ex. 1016, 16; Ex. 2040, ¶ 136. The ‘886 patent claims 
require “a phosphate buffer in an amount sufficient to adjust the pH of the 
formulation to a pharmaceutically acceptable level,” which, according to the ‘886 patent is from about above 5.5 and up to 7.9. Ex. 1003, independent claims 46, 61, 
and 69; dependent claims 49, 50, 62, 63, 70, and 71, 1:63-67, 2:9-11, 2:20-21, 
2:31-34, 5:45-56, 6:26-29; Ex. 2040, ¶ 137. Kornfelt clearly teaches away from 
using histidine and mannitol in a formulation at physiological pH. Ex. 2040, ¶ 138.

Furthermore, Kornfelt demonstrates that all amino acids tested with lactose were equally good stabilizers for glucagon. See Ex. 1027, 4:18-45, Figs. 1-9; Ex. 
2040, ¶ 139. Kornfelt teaches that glycine, histidine, glycyglycine, aspartic acid, 
glutamic acid, leucine, alanine, asparagine, valine, and mixtures are equivalent to 
one another and that mannitol, sucrose, and lactose are equivalent to one another. 
See, e.g., Ex. 1027, Table 1-3, 4:55-5:52; Ex. 2040, ¶ 140. The ‘886 patent presents surprising and unexpected results to the contrary. See section VI.

Of particular importance are observations from Kornfelt relating to the stabilization of glucagon and GLP-2. Kornberg shows that formulations containing leucine or glycine provided stability to glucagon equivalent to that observed in formulations containing histidine. Ex. 1027, Figs. 1, 2, 4,5,7, and 8, Table 2; Ex.
2040, ¶ 141. However, the ‘886 patent examples clearly show that formulations containing leucine or glycine did not protect the GLP-2 analog and that glycine promoted extensive aggregation of the peptide. Ex. 2040, ¶ 141. Therefore, even though amino acids in general, and histidine in particular, may under some conditions have the capacity to stabilize some other proteins/peptides (including glucagon) to some degree, there is no reasonable expectation that they would be protective for GLP-2 analogs. Id.

Dr. Palmieri admitted that: (1) Kornfelt does not disclose degradation pathways of glucagon or GLP-2 (Ex. 2042, 90:4-17); (2) Kornfelt discloses numerous ampholytes and excipients for facilitating lyophilization and dissolution of ampholytes (id. at 90:13-25, 100:19-101:18); (3) Kornfelt’s preferred pH is a physiologically unacceptable 2.8 (id. at 104:10-20); (4) pH 2.8 minimizes the decomposition of glucagon (id. at 109:15-24); (5) Kornfelt does not discuss inhibiting aggregation or precipitation (id. at 111:7-21); and (6) although he opines that it would have been obvious to use histidine to stabilize GLP-2 since it stabilized glucagon, another member of the “glucagon superfamily of peptides,” he has no idea whether histidine would stabilize other members of the glucagon superfamily of peptides such as, for example GLP-1(7-37) or GLP-1(7-36), which are more homologous or similar to glucagon than GLP-2 is. Id. at 294:6-296:18; see also Ex. 1018, 4.
Furthermore, subsequent literature shows that Kornfelt’s formulation strategy did not work. See Ex. 2045, 705-706 (As late as 2012, there was still a “definite need for a preparation of glucagon … that is sufficiently stable so that it can be indwelled in a portable pump for at least three days, the currently allowed maximum for portable pump use.”); Ex. 2040, ¶ 142. Cleary, the Kornfelt glucagon formulations are not sufficiently stable for a medical product. Ex. 2040, ¶ 142.

E. Holthius

Holthius discloses a lyophilized parathyroid hormone preparation. Ex. 1005, 5:28-35; Ex. 2040, ¶ 143. There is no disclosure of any glucagon or GLP-2 formulations, stable or not. Ex. 2040, ¶ 144.

F. Munroe

Munroe discloses in vitro/in vivo test results of GLP-2 and analogs, including [Gly2]GLP-2, which, according to Munroe, suggest that GLP-2R mediates the intestinotrophic actions of GLP-2. Ex. 1022, 1573, Table 2, col. 1; Ex. 2040, ¶ 145. Munroe reports that small bowel wet weight was 40-70% greater in [Gly2]GLP-2-treated animals than in PBS-treated animals. Ex. 1022, 1571, col. 1, Table 2; Ex. 2040, ¶ 146. Munroe does not disclose stabilization of glucagon, GLP-2, or GLP-2 analog formulations. Ex. 2040, ¶ 147.
VII. Surprising and Unexpected Results of the ‘886 Patent Invention

Petitioner alleges that “Patentee … cannot argue that the claimed subject matter provides unexpected results ….” Pet., 2. That is wrong.

The ‘886 patent presents surprising and unexpected results. ‘886 patent Figure 2 is a bar graph illustration of the results of heat stress stability studies of GLP-2 analog formulations containing histidine, phosphate buffer, or both. Ex. 2040, ¶ 148. It is surprising and unexpected in light of Kornfelt that histidine stabilized the GLP-2 analog at the physiological pH (i.e., above 5.5) maintained by the phosphate buffer despite Kornfelt’s express teaching that histidine stabilized glucagon at pH 2.8. Id. The combination of phosphate buffer and histidine rendered the formulation useful since it could be made at a pH at which GLP-2 is soluble (i.e., above pH 5.5) and which is pharmaceutically acceptable, as opposed to that of Kornfelt (i.e., pH 2.8) at which GLP-2 would be insoluble. Id. Furthermore, one skilled in the art would expect competitive interaction between the phosphate buffers and histidine, which could include inhibition of each other’s crystallization during freeze-drying and storage in the dried solid, and competing buffer effects. Id. For example, a particular damaging effect to GLP-2 that could have been expected would be the acidification of the formulation because of precipitation of dibasic sodium phosphate during freeze-drying. Id. This could lead to increased buffering by histidine at acidic pH due to one of the pKa’s of
histidine, which is very acidic. *Id.* This highlights the complexity and unpredictability of the behavior of a combination of phosphates and histidine.

‘886 patent Figure 3 is a bar graph illustration of the results of heat stress stability studies of six GLP-2 analog formulations containing histidine and four different bulking agents, mannitol, sucrose, trehalose, and maltose. *Id.* at ¶ 149. The mannitol- and sucrose-containing formulations within the scope of the ‘886 patent claims surprisingly and unexpectedly showed better stability than those containing trehalose, maltose, and lactose. *Id.* This shows, surprisingly and unexpectedly, that mannitol and sucrose are superior with GLP-2, as opposed to Kornfelt, which found mannitol and lactose equivalent in glucagon formulations. *Id.* Furthermore, sucrose and trehalose are similar disaccharides that often provide similar levels of stabilization to protein/peptides. It is surprising that in ‘866 studies that formulations containing sucrose were stabilizing but those with trehalose were not. *Id.* These are other examples of unpredictability. *Id.*

‘886 patent Figure 4 is another bar graph illustration of the results of stability studies of these six GLP-2 analog formulations containing histidine and four different bulking agents. *Id.* at ¶ 150. The ‘886 patent reports that:

> [t]he SE-HPLC analysis (FIG. 4) also showed that, except for maltose and lactose (Formulations 6 and 7), the GLP-2 analog in all of the formulations eluted as a single peak without aggregation. Formulations 6 and 7 gave an additional high molecular weight
(HMW) impurity peak that accounted for approximately 6%. However when these samples were heat stressed at 60° C, the high molecular weight impurity aggregates increased to approximately 20% in Formulations 6 and 7.

Ex. 1003, 9:7-15. This means that there was significant aggregation with lactose which is unacceptable in a GLP-2 or analog pharmaceutical formulation. *Id.* at 9:16-19; Ex. 2040, ¶ 150. This shows, surprisingly and unexpectedly, that mannitol is superior with GLP-2, as opposed to Kornfelt, which found mannitol and lactose equivalent with glucagon. Ex. 2040, ¶ 150.

‘886 patent Figures 5 and 6 are bar graph illustrations of the results of stability studies following exposure to elevated temperatures of lyophilized and then reconstituted histidine or lysine stabilized GLP-2 analog formulations. *Id.* at ¶ 151. The ‘886 patent reports that:

> formulation 1, comprising L-histidine and mannitol, did not show evidence of GLP-2 degradation. However, Formulations 2, 3, and 4, comprising histidine/sucrose, lysine/mannitol, and lysine/mannitol, respectively, showed evidence of GLP-2 degradation over time (see FIG. 6). These results suggest that the addition of sucrose and lysine destabilizes the GLP-2 peptide (see also FIG. 5), following exposure to elevated temperatures.

Ex. 1003, 9:49-56. This shows, surprisingly and unexpectedly, that mannitol is superior with GLP-2 as opposed to Kornfelt, which found mannitol and lactose
equivalent in glucagon formulations. Ex. 2040, ¶ 151. This is also surprising and unexpected in light of Kornfelt’s teaching that all natural amino acids stabilized lyophilized and reconstituted glucagon formulations. *Id.*

Dr. Palmieri could offer no reason why these results were not surprising and unexpected. He simply said they were not, so, therefore, they were not. *See, e.g.*, Ex. 2042, 263:2-21.

**VIII. Stabilization of Glucagon Is not Predictive of Stabilization of GLP-2**

The pI, optimal pH, and chemical degradation pathways of glucagon and GLP-2 are different. Ex. 2040, ¶ 152. GLP-2 is soluble at about pH 5.5 and above, while glucagon is soluble at about pH 2.8. Ex. 1003, 5:21-22; Ex. 2059, 1; Ex. 2046, 1274, col. 2; Ex. 2040, ¶ 153. The recommended pH range for glucagon solutions in 1999 was between 2.5 and 3.0. Ex. 2047; Ex. 2040, ¶ 154. Glucagon has a pI of about 7, and GLP-2 has a pI of about 4. Ex. 2040, ¶ 155. These are vastly different physical characteristics, and they are vitally important in formulation science, including stabilization. *Id.* The pI is the pH at which a peptide's net charge is neutral. *Id.* A peptide’s solubility is usually lowest at a pH equal to its pI, and aggregation rate (*e.g.*, irreversible precipitation, fibrils formation, formation of non-equilibrium oligomers) is usually slowest for a given peptide at pH far away from the pI. *Id.* This is due to charge-charge repulsion between the peptide molecules. *Id.* Accordingly, the optimal pH for minimizing
aggregation and precipitation of a peptide is one that is not near the peptide’s pI. *Id.* Kornfelt teaches formulating glucagon at a highly acid pH of 2.8. Because glucagon has a pI of about 7.0, at pH 2.8 it would have a high degree of positive charge and would be relatively resistant to aggregation. *Id.* at ¶ 157. However, the ‘886 patent shows that GLP-2 precipitates at pHs of 5.5 or lower, so it should not be formulated at pH 2.8. *Id.*

Glucagon chemically degrades by aspartic acid hydrolysis at Asp9, 15, and 21, deamidation at Gln3, 20, and 24, and oxidation at Met27. Ex. 2048, Figure 1; Ex. 2040, ¶ 157. GLP-2 does not have Asp9, Gln3, 20, or 24, or Met27. Ex. 2040, ¶ 157. GLP-2 degrades chemically by methionine oxidation at Met10 and asparagine deamidation at Asn11, 16, and 24. Ex. 1003, 1:45-48; Ex. 2040, ¶ 158. Glucagon does not have Met10 or Asn11, 16, or 24. Ex. 2040, ¶ 158. Furthermore, even if these amino acid residues are in some other position in glucagon v. GLP-2, their susceptibility to degradation is not necessarily the same from molecule to molecule because of the structure of the particular molecule. Ex. 2040, ¶ 159.

The degradation pathways and stresses that must be addressed in formulating glucagon and GLP-2 are different, and nothing should be inferred about GLP-2 stabilization from glucagon stabilization. *Id.* at ¶ 160. Therefore, even if the misconception that there is a universal stabilizer composition for each
degradation pathway were accepted, the hypothetical universal stabilizer composition for glucagon would not be appropriate for GLP-2 protection.

Petitioner and Dr. Palmieri argue repeatedly that “GLP-2 is structurally similar to glucagon of the prior art” because the secondary structures of the glucagon and GLP-2 are the same (i.e., alpha helices). See, e.g., Pet., 51, 53; Ex. 2042, 59:60-60:22. They maintain that protecting the common alpha helix is “critical”. Ex. 2042, 149:21-150:8, 153:3-11, 264:18-22. Therefore, one of ordinary skill would be motivated to stabilize GLP-2 with whatever stabilized glucagon.

This most essential underpinning of Petitioner’s obviousness case is just plain wrong. First, maintaining or stabilizing the secondary structure of glucagon is not a prerequisite to its stability in lyophilized formulations. Ex. 2049, Abstract; Ex. 2040, ¶ 161.

Second, glucagon has a great deal of conformational heterogenicity, particularly when formulated in solution or lyophilized in amorphous, non-crystalline form. See Ex. 2050, 37 (“In dilute aqueous solutions glucagon has little defined secondary structure and almost certainly exists as a population of conformers in equilibrium.”), 38 (“the flexibility of the glucagon conformation and especially its dependence on pH when in solution” and “even in the better ordered parts of the crystal structure there is considerable disorder.”), 46 (Glucagon has “a
predominantly flexible structure with little defined secondary structure in solution.”), 48 (glucagon forms a partly helical trimer, which is quartenary structure, not secondary structure), 50 (glucagon has been observed to form a more ordered alpha helix in chloroethanol, detergents, surfactant micelles, and sodium dodecyl sulfate); see also Ex. 2051, 209 ( “the conformational properties of glucagon manifested in the spectral parameters depend strongly on the solution conditions.” “[G]luca gon in freshly prepared dilute aqueous solution adopts predominantly a flexible 'random coil' form, while under different solution conditions or simply after prolonged standing of the solutions more highly structured aggregates were observed.”), 212 (“the NMR data indicate that monomeric glucagon in aqueous solution adopts primarily a flexible extended ‘random coil’ form.”), 213 (“…. it is also unlikely that the solution conformation of Fig.2A [random coil] occurs in an equilibrium with a sizably populated helical structure.”); Ex. 2040, ¶ 162. Accordingly, Petitioner’s and Dr. Palmieri’s “what’s good for glucagon is good for GLP-2 because they have the same secondary structure” argument is questionable, and the criticality of preserving glucagon’s secondary structure appears to be incorrect, as well.

Furthermore, even if one were to assume, for the sake of argument only, that Dr. Palmieri were correct about these molecules having the same secondary structure and that maintaining this was “critical” (although as explained above, he
is incorrect on both points), his obviousness analysis and finding of motivation to combine references are unsupportable. Certain secondary structures are common ones in the protein/peptide world, such as the alpha helix and the beta sheet. Ex. 2040, ¶ 163. However, the amino acids that form these secondary structures and their sequence often differ from one protein/peptide to another, and tertiary structure differs from one molecule to another. Id. This difference in primary, secondary, and tertiary structures makes different proteins/peptides subject to different degradation pathways, particularly since the differences in tertiary structure among molecules may change, from molecule to molecule, any protection or exposure of amino acid residues to degrading forces. Id. This also means that different alpha helices in different proteins/peptides are stabilized differently, even though the result – alpha helix secondary structure – may be the same. Id. Furthermore, simply stabilizing an alpha helix is not at all a sufficient condition for maintaining physical and chemical stability of a peptide during freezing, drying, and storage in the dried solid. Id.

The amino acid sequences of glucagon and GLP-2 are aligned in Ex. 1018, Figure 3 (relied upon by Petitioner and Dr. Palmieri). The substantial differences in sequence between the two molecules are self-evident. Id. at ¶ 162. Dr. Palmieri offers no basis by which the similarities cancel the differences. Actually, as shown in Fig. 3, the differences far outweigh a superficial alignment of a portion of the
amino acid sequence. What is stabilizing glucagon cannot reasonably be expected by one of ordinary skill in the art to stabilize GLP-2. Id. at ¶ 163.

It was merely serendipitous, not scientifically or reasonably expected, that L-histidinewith phosphate buffer and mannitol or sucrose results in a stable GLP-2 formulation, even if it were true (which is in serious doubt (see Ex. 2045, 705-706 (there was still a definite need for a stable glucagon preparation in 2012)) that L-histidine does stabilize glucagon.

IX. Histidine Is a Problematic Excipient

Amino acids, in general, have been tested as stabilizers for proteins in lyophilized formulations since as early as the mid 1930’s. Ex. 2040, ¶ 165. Although histidine, despite its problems, may, in some cases, provide some level of protection to proteins during freeze-drying and storage in the dried solid, in some published examples, the degree of stabilization provided by histidine would not be sufficient for a successful protein/peptide drug product. Id. at ¶ 166. Also, it has been demonstrated that the capacity of histidine, even to provide partial stabilization to a given protein/peptide, can be greatly influenced by solution conditions (e.g., pH) or lyophilization processing conditions (e.g., use of a post-freezing annealing step). Id. at ¶ 167. No one of ordinary skill in the art would have reasonably predicted the effect L-histidine would have in an untested formulation comprising an untried protein.
Overall, it is thought that histidine must remain amorphous during lyophilization in order to protect a protein/peptide during processing and storage in the dried solid. *Id.* at ¶ 168. But numerous factors can affect the crystallization of histidine (and other excipients that have the capacity to crystallize) during freeze-drying including the initial solution pH, the presence and amounts of other excipients, the amount of protein/peptide in the formulation and the freeze-drying processing conditions. *Id.* Therefore, for a given protein/peptide formulation, it is not possible accurately to predict whether or the degree to which histidine will stay amorphous during freeze-drying or the impact of such amount of amorphous histidine on the physical and chemical degradation pathways of the given protein/peptide. *Id.*

Furthermore, the presence of an amorphous fraction of an excipient which has a tendency to crystallize in a dried formulation increases the risk of unacceptable crystallization of the excipient during storage. *Id.* at ¶ 169. Crystallization of the excipient during storage can compromise the stability of the peptide or protein, as well as render the product pharmaceutically unacceptable because of phase alterations during the shelf life of the product. *Id.* Again, such behavior is not predictable and must be assessed for each formulation. *Id.* Simply because an excipient is amorphous sometimes does not predict whether the excipient will remain amorphous in a particular formulation during storage. *Id.* Nor
does an initially amorphous excipient assure that protein/peptide stabilization will be maintained during storage. *Id.*

Competitive interaction between histidine and other buffers can occur. Also, because of histidine’s one very acidic pKa, if (in a formulation with both histidine and sodium phosphate buffers) the formulation were acidified by crystallization of dibasic sodium phosphate, histidine may buffer the very acid pH. *Id.* at ¶ 170.

Histidine is also well known to cause instability problems with proteins/peptides in formulations. *Id.* at ¶ 171. Histidine in a formulation is susceptible to oxidation and can then promote oxidation of proteins/peptides. See, *e.g.*, Ex. 2052, 7 (“Histidine was used as a buffer system in an experimental formulation containing humanized IgG2 monoclonal antibody. Histidine underwent oxidation and the oxidation products caused a significant loss of potency of the monoclonal antibody.”) (citation omitted); Ex. 2040, ¶ 171. This means that with the use of histidine as an excipient there is a risk of oxidation of the excipient and resulting oxidation of the protein/peptide. *Id.* It is not known or predictable what the risks actually are in a given product or the potential impact on a given protein/peptide. *Id.* Nor is it known or predictable if a given potential mitigation strategy (*e.g.*, nitrogen overlay for a freeze-dried formulation) will work for a given protein/peptide product. *Id.*

Contrary to the Decision to Implement, L-histidine does not have a
stabilizing effect on protein/peptide drugs generally, especially to the degree needed for a successful medicine. See Decision to Implement 19; Ex. 2040, ¶ 172. Furthermore, neither Osterberg nor Kornfelt, alone or in combination, can be understood to disclose that L-histidine, which is fraught with problems, in combination with an excipient such as mannitol or sucrose in protein/peptide formulations was a predictable variation within the technical grasp of a skilled person done for the purposes of protein stabilization. Ex. 2040, ¶ 173.

X. There Is No Motivation to Combine the References to Arrive at the Claimed Invention with a Reasonable Expectation of Success; Rather, There Are Clear Teachings Away from Petitioner’s Combinations

To establish obviousness in view of a combination of references, Petitioner must set forth sufficiently articulated reasoning with rational underpinnings of why one skilled in the art would have been motivated to combine the teachings of those references to derive the claimed subject matter and would have had a reasonable expectation of success in doing so. Bumble Bee Foods, LLC v. Kowalski, IPR2014-00224, Paper 18, 25-26 (PTAB June 20, 2014). Furthermore, “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference or would be led in a direction divergent form the path taken by the applicant.” Ricoh Co. Ltd. v. Quanta Computer Inc., 550 F.3d 1325, 1332 (Fed.Cir. 2008).

Here, Petitioner ignores that protein/peptide stabilization is far from routine
or predictable. Minimally, there are many factors that can cause destabilization and degradation. See, generally Ex. 2039 (stabilization issues include, *inter alia*, hydrolysis, oxidation, disulfide bond scrambling, deamidation, Maldiard reaction, succinimide formation, diketopiperazine formation, deglycosylation and desialylation, and enzymatic proteolysis due to proteases, unfolding, dissociation, denaturation, aggregation, particle formation, fragmentation, adsorption to interfaces, fibril formation, gelation and precipitation); Ex. 2040, ¶ 174. Additionally, the number of components from which a formulation scientist can choose is voluminous. See generally 2054; 2062; Ex. 2040, ¶ 175. The development systems used by formulation scientists do not provide definitive solutions. Ex. 2040, ¶ 176. They just point to what the formulation scientist may consider on a protein/peptide to protein/peptide basis. *Id.* This is why there cannot be any reasonable expectation of success here.

The FDA’s requirements for stabilization apply universally to all medicines. Petitioner has not pointed to any requirements specific to GLP-2 or its analogs. This omnibus requirement is an insufficient motivation to combine Drucker ‘379, Drucker ‘600, Osterberg, and Kornfelt to render the challenged claims obvious.

The Petitioner’s arguments that structural similarity between glucagon and GLP-2 is motivation to combine these references fails because the two are not structurally similar, particularly in what Dr. Palmieri calls the most “critical”
aspect – an alpha helix. See Ex. 2042, 149:21-150:8, 153:3-11, 264:18-22. Glucagon has a heterogeneous secondary structure. Ex. 2040, ¶ 178. Furthermore, their degradation pathways are different, as are their primary structures and pI values. Id. at ¶ 179. The disparate degradation pathways and the dissimilarities of glucagon and GLP-2 teach away from the ‘886 patent invention. Id. One of ordinary skill in the art would not have concluded that what is good for glucagon is good for GLP-2. Id. There is simply no basis to do so.

Osterberg discloses nothing about glucagon or GLP-2 stabilization, and there is no universal amino acid protein/peptide stabilizer. Id. at ¶¶ 180-81. Osterberg did not formulate a single protein/peptide, let alone GLP-2 or an analog. Id. at ¶ 181. Osterberg’s disclosure that the physical state of L-histidine after freeze-drying is dependent on both the pH of the solution and the freezing cycle and that water, a common component of drug formulations and a contaminant in most drug packaging, causes amorphous L-histidine to crystallize would cut against any expectation of success and would deter one skilled in the art from formulating GLP-2 and its analogs with it. Id. at ¶ 182. Furthermore, since L-histidine acts as a buffer at a different pHs than do phosphates, one skilled in the art would expect that L-histidine would compete with phosphate buffers and, therefore, one skilled in the art would not be inclined to use L-histidine in formulations that were buffered by phosphates. Id. at ¶ 183. Finally, L-histidine
creates a new degradation pathway in formulations – L-histidine oxidation - which can lead to protein/peptide oxidation and can unpredictably counter any hoped-for success. *Id.* at ¶ 184.

Kornfelt does not formulate glucagon with L-histidine at the ‘886 patent’s pharmaceutically acceptable pH. *Id.* at ¶ 185. Rather, Kornfelt’s glucagon/histidine formulation is very acidic, *i.e.*, pH 2.8. *Id.* This is obviously because glucagon is insoluble at higher pH. *Id.* This is clear evidence that the difference in solubilities and optimal pH’s of glucagon and GLP-2 impact the reasonable expectation of success in obtaining a storage stable formulation of GLP-2. *Id.*; *cf.* Pet., 54.

Unaided by hindsight, the combinations relied upon by the Petitioner are no more than an invitation to experiment with no reasonable expectation of success. The record shows no motivation, teaching, or suggestion to one of ordinary skill in the art to combine references as Petitioner has. The record shows that there could not be any reasonable expectation of success, either. Finally, the record shows that the prior art clearly teaches away from the ‘886 patent invention.

**XI. Petitioner’s Obviousness Analysis Was Plagued by Hindsight**

Petitioner’s and Dr. Palmieri’s obviousness analysis is improperly distorted by hindsight bias or arguments reliant on *ex post* reasoning. *See KSR*, 550 U.S. at 421. Dr. Palmieri admitted so. *See Ex* 2042, 194:9-21 (“Q. Did you consider the degradation pathway of a GLP-2 analog in forming your opinion of the
obviousness of the claims of the ‘886 patent? […] A.] I did not think it was relevant to this – these opinions in my expert report. I knew I could make – **I knew a person of skill in the art looking at the patent** and scientific literature prior to the application date would know how to make it.”) (emphasis added), 79:12-80:3 (Q. Sure. Based upon the pKa's of histidine -- A. pKa's of histidine. Q. -- and the optimal pH for stability of GLP-2, which you said is close to 7, would histidine be a good choice as a buffer for GLP-2 formulations? A. When we look at histidine, histidine is an ampholyte. It's a zwitterion. So it could be useful as a buffer. But we also look at the claims in the patent, and we see that phosphate buffers are used. The phosphate buffer is an excellent buffer. Whether or not histidine alone would function as a buffer in this formulation, I have not offered an opinion on that.”). Dr. Palmieri’s repeated reliance at deposition that a GLP-2 formulation with histidine and mannitol, as in the ‘886 patent claims, actually worked to produce a stable GLP-2 formulation demonstrates his impermissible reliance on hindsight, not a reasonable expectation of success at the time of the invention. **See Amgen Inc. v. F. Hoffmann-La Roche, Ltd.,** 580 F.3d 1340, 1363 (Fed. Cir. 2009). He improperly retraced the path of the ‘886 patent inventor with hindsight, discounted or did not even consider the number and complexity of the problems and alternatives, misstated the science, and arrived at a predetermined conclusion based upon the success of the present invention. He also ignored the subject matter as a
whole by focusing on L-histidine rather than the combination of L-histidine, phosphate buffer, and mannitol or sucrose as claimed. Neither is allowed. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed.Cir. 2008). The ‘886 patent inventor’s insights, willingness to go against the conventional wisdom at the time, and willingness to overcome obstacles cannot be discounted. See id..

That Dr. Palmieri has no relevant experience in formulating proteins/peptides is further evidence that he used impermissible hindsight of the claimed invention to reverse engineer the prior art. See Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 996-97 (Fed. Cir. 2009).

XII. Secondary Considerations Support a Finding of Non-Obviousness

GATTEX provided a solution to the long felt need for a drug product to treat SBS; it is a tremendous commercial success. Objective indicia are often the most probative evidence of non-obviousness and should not be relegated to mere afterthoughts. Apple Inc. v. ITC, 725 F.3d 1356, 1366 (Fed. Cir. 2013); Leo Pharm. Prods., Ltd. v. Rea, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Indeed, commercial success alone can be sufficient to establish non-obviousness. See Intrì-Plex, Inc. v. Saint-Gobain Performance Plastics Rencol Ltd., IPR2014-00309, Paper 83, 45-47.
A. The ‘886 Patent Solved a Long-Felt Need

SBS is a rare, socially-incapacitating, and often fatal condition. Ex. 2041, ¶ 17-19, 33-44; see also Section II, above. SBS patients, on average, require PN at least five days a week, each treatment taking up to nine hours. Id. at ¶ 21-22, Figures 2-3. PN also comes at high economic direct and indirect costs (i.e., $50-243,000+/patient/year). Id. at ¶ 37-39.

Zorbtive (human growth hormone) was the only drug prior GATTEX developed to reduce dependence on PN by improving intestinal absorptive capacity. Id. at ¶ 43-44. However, it failed. Id.

GATTEX provided a solution to this long-felt need. It obtained FDA orphan drug status as an approved GLP-2 analog product for SBS. Id. at ¶ 16-17. Physicians and medical publications have confirmed that GATTEX provides effective SBS treatment. Id. at ¶ 45-47.

B. GATTEX - The Commercial Embodiment of the ‘886 Patent Is a Significant Commercial Success

GATTEX has a large market share. By December 2015, approximately 564 patients (of the estimated possible 4,000 candidates) were using GATTEX, with a steady annual growth since its February 2013 launch. Id. at ¶ 49-52, Figure 4.

GATTEX commands a high price. The wholesale acquisition cost (“WAC”) for GATTEX in January of 2014 was $312-360,000/patient/year and in January 2015 was $376-433,000/patient/year. Id. at ¶ 53, Figure 5). The gross-to-net price
deductions for GATTEX (which are common in the pharmaceutical industry) are far lower than the industry average. *Id.* at ¶ 74. Third party payors would not reimburse at this price level unless the benefits from the drug product were impossible with alternative products. *Id.* at ¶ 54.

**GATTEX sales and sales growth are high.** GATTEX sales reached almost $40 million by 3Q2015, less than three years after launch. *Id.* at ¶ 55, Figure 6. This is remarkable for a highly specialized orphan drug targeted to a very small population. *Id.*

**GATTEX sales exceeded expectations.** GATTEX exceeded sales projections each year since launch, and sales are projected to increase. *Id.* at ¶ 56.

**GATTEX resulted in stock price increases.** When GATTEX launched, NPS’s share price was $7.54 and had been relatively flat (below $11.00) for over six years. *Id.* at ¶ 58, Figure 7. However, in the eight months following GATTEX’s launch, share price quickly rose to $34.98 per share (i.e., 364%). *Id.* at ¶ 58-59. Share price continued to rise for another 16 months to $45.97 per share on the last trading day prior to Shire’s acquisition of NPS – a more than 600% increase in less than two years. *Id.* During this time, GATTEX was the only product marketed by NPS. *Id.* at ¶ 59-60. The timing of this increase suggests it was largely linked to the launch and success of GATTEX. *Id.* at ¶ 60-62
**GATTEX was a key driver in Shire’s acquisition of NPS.** Shire acquired NPS for approximately $5.2 billion. *Id.* at ¶ 63. At the time GATTEX was valued at about $4.7 billion, but even considering all assumed liabilities, Gattex was valued at least $2.8 billion (i.e., 54% of the entire acquisition price). *Id.* GATTEX produced large economic returns for NPS and its shareholders. All of these factors are clear evidence of the commercial success of the ‘886 patent invention.

**C. The Nexus Between the Secondary Considerations and the Invention**

Although there must be a nexus between the claimed invention and the secondary considerations (*Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985)), a “strict” connection is not necessary. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013). Rather, the secondary considerations “need only be ‘reasonably commensurate with the scope of the claims.’” *Id.*

GATTEX is the commercial embodiment of the invention claimed in the ‘886 patent. Dr. Carpenter provides a chart showing this. Ex, 2040, ¶ 73. [Gly2]GLP-2 was known to be capable of treating SBS at least as early as 1996, but there were no marketable stable formulations. *See generally* Ex. 1029; Ex. 2055, ¶ 14. Absent such a formulation, as claimed in the ‘886 patent, no solution to the long-felt need discussed above would have existed. Ex. 2041, ¶ 65-67.
GATTEX’s commercial success is also linked to the claimed ‘886 patent formulations. Commercial drug products must have a shelf life long enough for quality control testing and quality assurance release after manufacture and storage by wholesalers, pharmacists, doctors, and patients. *Id.* at ¶ 67. This is typically at least 2-3 years. *Id.*

Peptides, such as [Gly2]GLP-2, can be particularly difficult to formulate, as discussed above. *See also* Ex. 2055, ¶¶ 14-16. GATTEX meets the necessary stability requirements, without which it could not be such a significant commercial success. Ex. 2041, ¶ 68-71. GATTEX’s commercial success cannot be attributed to other factors such as low prices, marketing, heavy rebates and discounts, and patient support programs. *Id.* at ¶ 72-77. This is all evidence of the strong nexus between the ‘886 patent claimed invention and secondary considerations of non-obvious.

**XIII. Conclusion**

Patent Owner submits that the challenged claims are non-obvious for the foregoing reasons.

Respectfully submitted,

Dated: January 20, 2016

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Patent Owner’s Response, Patent Owner’s Exhibit List, and associated exhibits were served via electronic mail on January 20, 2016 on attorney for Petitioner:

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