

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS II LLC,
Petitioner,

v.

NPS PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2015-01093
Patent 7,056,886 B2

Before LORA M. GREEN, JACQUELINE WRIGHT BONILLA, and
SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Coalition for Affordable Drugs II, LLC (“Petitioner”) filed a Petition to institute an *inter partes* review of claims 1–45 (Paper 1, “Pet.”) of U.S. Patent No. 7,056,886 B2 (Ex. 1003, “the ’886 patent”). NPS Pharmaceuticals, Inc., (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 18 (“Prelim. Resp.”).

Based on these submissions, we instituted trial as to claims 1–27, 31–40, and 44–45 of the ’886 patent on the following grounds of unpatentability asserted by Petitioner:

Ground	References	Basis	Claims challenged
1	Drucker ’379, ¹ Kornfelt, ² Osterberg ³	§ 103(a)	1–27, 33–35, 38, 45
2	Drucker ’379, Kornfelt, Osterberg, Munroe ⁴	§ 103(a)	31, 32, 44
3	Drucker ’379, Kornfelt, Osterberg, Holthuis ⁵	§ 103(a)	39–40

¹ Drucker et al., U.S. Patent No. 5,789,379, issued August 4, 1998. Ex. 1029 (“Drucker ’379”).

² Kornfelt et al., U.S. Patent No. 5,652,216, issued July 29, 1997. Ex. 1027 (“Kornfelt”).

³ Osterberg et al., *Physical state of L-histidine after freeze-drying and long-term storage*, 8 EP. J. OF PHARM. SCI. 301–308 (1999). Ex. 1030 (“Osterberg”).

⁴ Munroe et al., *Prototypic G-protein coupled receptor for the intestinotrophic factor glucagon-like peptide 2*, 96 PROC. NAT’L ACAD. SCI. 1569–1573 (1999). Ex. 1022 (“Munroe”).

⁵ Holthuis et al., U.S. Patent No. 5,496,801, issued March 5, 1996. Ex. 1005 (“Holthuis”).

Ground	References	Basis	Claims challenged
4	Drucker '547, ⁶ Kornfelt, Osterberg, Holthuis, Munroe	§ 103(a)	36–37

Decision to Institute (Paper 26, “Dec.”).

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 31, “PO Resp.”), to which Petitioner filed a Reply (Paper 40, “Pet. Reply”).

Petitioner relies on the Declarations of Anthony Palmieri III, Ph.D., R.Ph. (Exs. 1001, 1041) and Ivan T. Hoffmann (Ex. 1042) in support of the proposed grounds of unpatentability.

Patent Owner relies on the Declarations of John F. Carpenter, Ph.D. (Ex. 2051;⁷ redacted version Ex. 2148) and Gordon Rausser, Ph.D. (Ex. 2041; redacted version Ex. 2149).

Patent Owner filed a motion to exclude certain of Petitioner’s evidence. Paper 49. Petitioner filed an opposition (Paper 53), and Patent Owner filed a reply (Paper 57).

Oral argument was conducted on June 23, 2016. A transcript is entered as Paper 65 (“Tr.”).

This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a).

⁶ Drucker et al., PCT Publication WO 98/03547, published January 29, 1998. Ex. 1028 (“Drucker ’547”).

⁷ We note that throughout the Patent Owner Response, reference is made to Ex. 2040, the Exhibit number for Dr. Carpenter’s Declaration in related case IPR2015-00990 instead of Ex. 2051. We have interpreted those citations to Ex. 2040 to refer to Ex. 2051.

We conclude for the reasons that follow that Petitioner has shown by a preponderance of the evidence that claims 1–27, 31–40, and 44–45 of the '886 patent are unpatentable.

A. Related Proceedings

Petitioner also filed a different Petition requesting *inter partes* review of claims 46–52 and 61–75 of the '886 patent (IPR2015-00990). We also instituted *inter partes* review in IPR2015-00990, and issue a final decision therein concurrently with this Final Written Decision.

B. The '886 Patent (Ex. 1001)

The '886 patent discloses L-histidine stabilized drug formulations of glucagon-like peptide-2 (“GLP-2”) and GLP-2 analogs. Ex. 1003, Abstract. The '886 patent discloses that the GLP-2/GLP-2 analog formulations of the invention exhibit “superior stability following storage and/or exposure to elevated temperatures.” *Id.* The formulations comprise a phosphate buffer, L-histidine (as a stabilizing amino acid), and mannitol or sucrose (as a bulking agent). *Id.* at 2:7–27.

The GLP-2 analogs may be agonists or antagonists. *Id.* at 4:19–31. “[A]ntagonists of GLP-2 analogs include any mutation or variation of the naturally occurring GLP-2 peptide which results in the inhibition of intestinotrophic activity of naturally occurring GLP-2 or GLP-2 analogs which exhibit agonist activity [sic].” *Id.* at 4:61–67. The GLP-2 analog known as “h[Gly2]GLP-2” is specifically disclosed. *Id.* at 5:21–32.

C. Illustrative Claims

Independent claim 1 is illustrative of the challenged claims, and is

reproduced below:

1. A glucagon-like peptide 2 (GLP-2) formulation comprising:
 - (a) a medically useful amount of a naturally occurring GLP-2 or an analog thereof;
 - (b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a physiologically tolerable level;
 - (c) L-histidine; and
 - (d) a bulking agent selected from the group consisting of mannitol and sucrose.

Ex. 1003, 12:9–18. Claims 2–27, 31–40, and 44–45 depend from claim 1, directly or indirectly.

II. ANALYSIS

A. Claim Interpretation

We interpret claims using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131 (2016). Under the broadest reasonable construction standard, claim terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). “Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition.” *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). “Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir.

1994).

Based upon the facts presented, we determine that the explicit construction of any specific claim term is unnecessary to reach our decision in this case. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Principles of Law

To prevail in its challenges to the patentability of the claims, a petitioner must establish facts supporting its challenges by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

Obviousness is a question of law based on underlying determinations of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966); *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). The underlying factual determinations include: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham*, 383 U.S. at 17–18. Subsumed within the *Graham* factors are the requirements that all claim limitations be found in the prior art references and that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). “Obviousness does not require absolute predictability of success . . . all that is required is a reasonable

expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

In *KSR Int’l Co. v. Teleflex Inc.*, the Supreme Court stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. 398, 421 (2007). “KSR affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

The factual inquiries for an obviousness determination also include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). We acknowledge also that “there is a presumption of

nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘is the invention disclosed and claimed in the patent.’” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) (quoting *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed.Cir.1997)). That presumption may be rebutted, however, if there is evidence “that shows that the proffered objective evidence was ‘due to extraneous features other than the patented invention.’” *Id.* (quoting *Demaco Corp/ v. F. Von Langsdorff Licensing Ltd.*, 821 F.2d 1387, 1393 (Fed. Cir. 1988).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

C. Scope and Content of the Prior Art

1. Summary of Drucker ’379 (Ex. 1029)

Drucker ’379 discloses pharmaceutical compositions comprising a therapeutically effective amount of a GLP-2 analog. Ex. 1029, 3:23–27. The GLP-2 analogs have intestinotrophic activity. *Id.* at 2:20–23, 15:1–35. The analog (Gly²)hGLP-2 is disclosed. *Id.* at 6:52–55.

Drucker ’379 discloses GLP-2 formulations for injection buffered to physiologically tolerable pH. *Id.* at 9:35–56. Phosphate buffered saline is disclosed as a suitable buffer. *Id.* at 13:8–33. The GLP-2 formulations may be provided in lyophilized form. *Id.* at 10:25–33.

Drucker ’379 further discloses that the glucagon gene “yields a tissue-determined variety of peptide products that are processed from the 160 residue proglucagon product,” which include glucagon, glicentin, and the

two glucagon-like peptides, GLP-1 and GLP-2. *Id.* at 1:17–27.

2. *Summary of Osterberg (Ex. 1030)*

Osterberg discloses that “[p]rotein drugs are generally chemically and physically unstable in solution and freeze-drying is frequently used to obtain an acceptable shelf life.” Ex. 1030, 301. Osterberg further discloses that the “selection of buffer for a protein formulation is very important.” *Id.* at 303. In this context, Osterberg discloses that “[s]ugars and amino acids protect the protein by preferential exclusion during freezing and by glass formation and/ or by functioning as a water substitute in the dried state.” *Id.* at 301. Osterberg teaches that amino acids may act as both a stabilizer and buffer, and highlights L-histidine as one such “multifunctional protein stabili[z]er.” *Id.* at 301, 307.

Osterberg discloses that “Freeze drying of L-histidine from solutions having a pH in the range 4–8 showed that L-histidine has a rather low tendency to crystalli[z]e during freeze-drying.” *Id.* at 305.

Osterberg further discloses that:

Another important observation was that the addition of sucrose abolished the crystalli[z]ation of L-histidine. The reduced tendency for crystalli[z]ation of L-histidine is very important in the formulation design.

Id. at 304.

3. *Summary of Kornfelt (Ex. 1027)*

Kornfelt discloses stabilized pharmaceutical compositions comprising glucagon and a stabilizing amount of a pharmaceutically acceptable ampholyte, such as histidine. Ex. 1027, 2:21–44. The histidine may be

present in an amount from 0.01 to 50 micromoles per mg glucagon in order to obtain the desired stabilization. *Id.* at 2:20–53 and 2:65–67.

The pharmaceutical compositions may also include an “excipient, e.g. for facilitating the lyophilization and rapid and complete redissolution thereof when reconstituting the preparation before use.” *Id.* at 2:45–53. Such excipients include mannitol and sucrose. *Id.* The excipient may be present in an amount of from 10 to 600 micromoles per mg glucagon to give an optimum stabilization. *Id.* at 2:58–60.

4. *Summary of Munroe (Ex. 1022)*

Munroe discloses an assay for the screening and identification of GLP-2 analogs, wherein the assay uses a cell line that expresses the GLP-2 receptor. Ex. 1022, 1570–1571, 1573, Table 2. Munroe discloses that [Gly-2]Glp-2 binds to the GLP-2 receptor and has intestinotrophic activity. *Id.* at 1573 (Table 2); Ex. 1001 ¶ 36.

5. *Summary of Drucker '547 (Ex. 1028)*

Drucker '547 discloses GLP-2 antagonists that are structural analogs of the intestinotrophic GLP-2 peptides. Ex. 1028, Abstract, 3:29–4:4. The GLP-2 antagonists have been mutated so that at least one amino acid is substituted with an amino acid which does not naturally occur at that position in the reference GLP-2. *Id.* at 2:25–36. For example, amino acid positions of human GLP-2 at Asp¹⁵, Phe²², Thr²⁹, Thr³², and Asp³³ may be substituted with an amino acid which does not naturally occur at that position. *Id.* In another example, position Ala² is substituted with any one of Leu, Cys, Glu, Arg, Trp, and PO₃–Tyr. *Id.*

6. *Summary of Holthuis (Ex. 1005)*

Holthuis relates to freeze-dried “preparations containing parathyroid hormone that has been stabilized with an excipient and buffering agent.” Ex. 1005, Abstract, 6:6–58. “Preferred preparations incorporate human PTH(1–84), mannitol as excipient and citrate as buffering agent, and are incorporated in vials as a freeze-dried powder for reconstitution to treat osteoporosis.” *Id.* at Abstract. Holthuis discloses that the reconstituted PTH preparations according to its invention are stable. Specifically, Holthuis discloses as follows:

SDS-PAGE analysis of the reconstituted PTH preparations, performed in the conventional manner, similarly revealed no significant decrease of purity during storage at either pH, temperature and storage temperatures examined, as shown in FIG. 2. Some decrease in purity was revealed by RP-HPLC analysis of the reconstituted formulation, but only at the higher 37° C. storage temperature (0.7% decrease in purity per month of storage), with 4° C. storage showing no significant purity decrease by reversed phase-HPLC analysis. The stability of the intact PTH was also revealed by immunoassay (Allegro) to be constant throughout the storage period at all concentrations, pHs and temperatures evaluated.

Id. at 7:6–18.

D. *Patentability Analysis*

1. *Petitioner’s Asserted Grounds of Unpatentability*

- a. *Grounds 1, 2, and 4: Obviousness of Claims 1–27, 31–38, and 44–45 over the Combination of Drucker ’379, Kornfelt, Osterberg, Munroe, and Drucker ’547*

In Ground 1, Petitioner contends that claims 1–27, 33–35, 38, and 45 would have been obvious over the combination of Drucker ’379, Kornfelt,

and Osterberg. Pet. 22–42. In support of its assertion that the challenged claims would have been obvious, Petitioner summarizes the teachings of Drucker '379, Kornfelt, Osterberg, Munroe, and Drucker '574 and provides a detailed claim chart explaining how each claim limitation is disclosed in the combination of references. Pet. 22–42, 46–48. In particular, Petitioner contends that Drucker '379 discloses a pharmaceutical composition comprising a therapeutically effective amount of a GLP-2 analog meeting the requirement of claim 1 for “a medically useful amount of a naturally occurring GLP-2 or an analog thereof.” *Id.* at 28–29 (citing Ex. 1029, 3:23–27, 11:22–26, 13:8–33; Ex. 1001 ¶¶ 49–51). Drucker '379 specifically discloses the h(Gly2)GLP-2 analog. *Id.* at 25–26 (citing Ex. 1029, 6:52–55; Ex. 1001 ¶ 67).

Petitioner further relies on Drucker '379 for the use of phosphate buffered saline to buffer the formulation at a physiologically tolerable pH, thus meeting element (b) of claim 1. *Id.* at 29 (citing Ex. 1029, 13:8–33).

The formulation of Drucker '379 does not include L-histidine, as required by claim 1. For this claim element, Petitioner relies on the teachings of Kornfelt and Osterberg. Petitioner contends that Kornfelt teaches L-histidine as a stabilizing amino acid useful in the formulation of protein drugs across a broad range of pH levels (pH 1–7). Pet. 22 (citing Ex. 1027, 3:9–11; Ex. 1001 ¶ 101). Petitioner further contends that Kornfelt discloses an amount of L-histidine per mg of peptide (i.e., glucagon) that is within the range specified by the claims. *Id.* at 24 (citing Ex. 1027, 2:65–67; Ex. 1001 ¶ 63.); see Ex. 1003, claim 16 (“about 0.5 to about 1%” L-

histidine). Additionally, Petitioner contends that Osterberg further supports a finding that L-histidine was well known as a buffer and a stabilizing agent useful in lyophilized pharmaceutical formulations of peptides. Pet. 22 (citing Ex. 1030, 305, 307; Ex. 1001 ¶¶ 55–58, 101).

With regard to the use of mannitol or sucrose as a bulking agent, Petitioner contends that “sucrose and mannitol were both well known as conventional bulking agents or excipients in the art of pharmaceutical formulations prior to the effective filing date of the ’886 patent as described in Osterberg and Kornfelt.” Pet. 17 (citing Ex. 1027, 2:43–57; Ex. 1030, 301; Ex. 1001 ¶ 37). Petitioner also points to where the cited references disclose the limitations recited in dependent claims 2–27, 33–35, 38, and 45. *Id.* at 22–42, 46–48.

In Ground 2, Petitioner further relies on Munroe to meet the elements of dependent claims 31, 32, and 44. Pet. 27–28, 40–42. Petitioner contends that Munroe discloses an assay for the screening and identification GLP-2 analogs. *Id.* at 27, 40 (citing Ex. 1022, 1570–73 and Table 2; Ex. 1001 ¶¶ 76–77).

In Ground 4, Petitioner further relies on Drucker ’574 to meet the elements of dependent claims 36 and 37. Pet. 15, 46–48. Petitioner contends that Drucker ’574 discloses a GLP-2 formulation containing the specific GLP-2 antagonists specified in claim 36 and 37. *Id.* at 46–47 (citing Ex. 1028, 2:17–37; Ex. 1001 ¶ 88). Petitioner further contends that Holthuis provides a lyophilization process for use with a peptide hormone formulation containing mannitol. *Id.* at 51 (citing Ex. 1005 at 5:2–22).

Petitioner contends that one would have had a reason to combine the teachings of Drucker '379, Munroe, Holthuis, and Drucker '547, disclosing buffered GLP-2 analog formulations, with Osterburg and Kornfelt, because Osterburg and Kornfelt disclose the use of L-histidine in combination with an excipient such as mannitol or sucrose in protein formulations for the purposes of protein stabilization. *Id.* at 49–52. In particular, Petitioner contends that because all the elements of the invention are described in the combined references, and because the prior art provides guidance for preparing storage stable lyophilized formulations for peptide formulations, “[t]he claimed GLP-2 formulation is nothing more than a combination of known ingredients for a predictable result of stability as confirmed by routine testing.” *Id.* at 48–49 (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007); Ex. 1001 ¶ 91); *see also, id.* at 49 (“[O]ne of ordinary skill in the art would certainly recognize that the same storage stable formulation can be applied to molecules structurally similar to glucagon like GLP-2.”). Petitioner also argues that one 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 combination of references cited in this petition for IPR.” *Id.* at 52–55.

Petitioner further argues that “[a] design need for formulating a stable GLP-2 formulation for therapeutic use would be recognized by a person of ordinary skill in the art based on FDA requirements.” *Id.* at 49 (citing

Cleland,⁸ 8).

b. Ground 3: Obviousness of Claims 39–40 over the Combination of Drucker '379, Kornfelt, Osterberg, and Holthuis

Petitioner contends that dependent claims 39–40 would have been obvious over the combination of Drucker '379, Kornfelt, Osterberg, and Holthuis. Pet. 42–46. Petitioner relies on Osterberg and Holthuis for the elements of those dependent claims. *Id.*

Claims 39 and 40 are directed to lyophilized formulations comprising less than 5% or 2% water by weight. Ex. 1003, 14:10–13. With regard to claims 39 and 40, Petitioner contends that Holthuis discloses a lyophilized formulation of a peptide hormone that has 2% water or less. Pet. 43 (citing Ex. 1005, 7:19–23; Ex. 1001 ¶ 85). Specifically, Holthuis discloses that:

Residual moisture in the PTH preparation was determined by the standard Karl-Fischer technique and indicated that the water content of all freeze-dried preparations remained below 2% by weight, and typically at about 1% by weight, throughout the storage period.

Ex. 1005, 7:19–24.

Petitioner further relies on the on the declaration of Dr. Palmieri, who testifies that “[t]he level of moisture required by claims 38 and 39 were standard in the art the time of the invention.” Ex. 1001 ¶ 85 (citing Ex. 1031, 1545⁹ (“The [freeze-drying] process continues until the product is dry

⁸ Cleland *et al.*, Formulation and Delivery of Proteins and Peptides, American Chemical Society, Washington D.C., Chapter 1 (1994). Ex. 1024.

⁹ Remington: The Science and Practice of Pharmacy, Vol. II, 19th edition, Mack Publishing Co., Easton, PA. 1995 (Ex. 1031).

(usually 1% or less moisture).”)).

2. Discussion

Patent Owner does not argue that the combination of references fails to disclose each limitation of the challenged claims. Rather, Patent Owner provides a detailed discussion noting the deficiencies in each of the cited references as compared to the subject matter encompassed by the challenged claims. PO Resp. 17–23, 32–39. For example, Patent Owner argues that i) Drucker ‘379 does not suggest any “*in vitro* stabilization other than simple lyophilization;” ii) “Osterberg does not disclose any protein/peptide formulations;” iii) “Kornfelt does not disclose degradation pathways of glucagon or GLP-2 or their inhibition;” and iv) neither Holthius nor Munroe disclose stabilization of glucagon, GLP-2, or GLP-2 analog formulations. *Id.* at 17–18, 39 (citing Ex. 2051 ¶¶ 144, 147). Patent Owner’s arguments here essentially attack the merits of each of Drucker ‘379, Osterberg, Kornfelt, Holthius, and Munroe in isolation.

Such arguments, however, do not persuade us that the subject matter of the challenged claims is nonobvious in view of Petitioner’s proposed combination of references, because the asserted obviousness ground is predicated on a combination of the teachings of these references. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (“Non-obviousness cannot be established by attacking references individually where the [obviousness ground] is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.”).

We note that Petitioner relies on i) Drucker '379 and Drucker '547 for the disclosure of lyophilized GLP-2 and GLP-2 analog formulations (Pet. 15 (citing Ex. 1029, 4:6–7:20, 15:1–35; Ex. 1028, 4:3–10; Ex. 1001 ¶ 35)); ii) Osterberg for the disclosure that histidine and sugars (such as sucrose) may be used to stabilize lyophilized peptide formulations (*id.* at 16–17 (citing Ex. 1030, 301; Ex. 1001 ¶ 37)); iii) Kornfelt for the disclosure that histidine and conventional bulking agents or excipients (such as lactose and mannitol) are useful to stabilize glucagon formulations (*id.* (citing Ex. 1027, 2:28–38, 2:43–57; Ex. 1001 ¶ 37)); iv) Munroe for its disclosure of GLP-2 analogs and screening methods to identify analogs having the desired biological activity (*id.* at 27 (citing Ex. 1022, 1573, Table 2)); and v) Holthuis for its disclosure that lyophilized formulations of a peptide hormone have 2% water or less (*id.* at 43 (citing Ex. 1005, 7:19–23; Ex. 1001 at ¶ 85)). Patent Owner does not dispute persuasively that each of Drucker '379, Osterberg, Kornfelt, Holthuis, and Munroe presents the above-mentioned disclosures, as Petitioner contends.

Accordingly, we are persuaded that Petitioner has established that each limitation of claims 1–27, 31–40, and 44–45 was known in the art, as evidenced by the teachings of Drucker '379, Drucker '574, Kornfelt, Osterberg, Holthuis, and Munroe. *See e.g.*, Pet. 28–48 (providing detailed charts indicating where each limitation of the challenged claims is disclosed or discussed in each of the references relied upon by Petitioner).

A patent, however, “is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Petitioner must also show that there was a reason to

combine those elements to achieve the claimed invention with a reasonable expectation of success. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014). In this regard, as noted above, Petitioner argues that the cited prior art provides relevant guidance for preparing storage stable lyophilized formulations for peptide formulations, and that “[t]he claimed GLP-2 formulation is nothing more than a combination of known ingredients for a predictable result of stability as confirmed by routine testing.” Pet. 48–49. For the reasons presented in the Petition (*id.* at 49–55), Petitioner persuades us that an ordinary artisan would have had reason to combine teachings in the cited references to achieve the claimed invention with a reasonable expectation of success.

In response, Patent Owner presents several arguments as to why Petitioner’s proposed combination of references fails to render the challenged claims obvious. In particular, Patent Owner argues that i) the stabilization of glucagon is not predictive of stabilization of GLP-2; ii) that histidine is a “problematic excipient,” and thus its use in drug formulation unpredictable; and iii) that protein/peptide stabilization is far from routine or predictable. PO Resp. 43–56. Patent Owner further argues objective evidence of non-obviousness in the form of unexpected results, commercial success, and long-felt need. *Id.* at 40–43, 56–60. Because we are persuaded by Petitioner’s position (as discussed in more detail in the analysis section below), we summarize each of Patent Owner’s contentions just below.

a. Patent Owner’s Contentions

Patent Owner first argues that a person of ordinary skill in the art

would not have had a reasonable expectation of success in combining the references because the stabilization of glucagon, disclosed in Kornfelt, is not predictive of stabilization of GLP-2. PO Resp. 43–48. Patent Owner argues that, despite belonging to the same superfamily of proteins, glucagon and GLP-2 have vastly different physical characteristics affecting, for example, the aggregation rate and stability of the peptides. *Id.* To support its argument, Patent Owner cites evidence showing differences between glucagon and GLP-2, including the differences in pI (7 vs. 4, respectively), optimal pH (2.8 vs. 5.5, respectively), chemical degradation pathways, and primary and secondary structure. *Id.* (citing Ex. 1003, 5:21–22; Ex. 2051 ¶¶ 153–155, 157–163; Ex. 2047; Ex. 2059, 1; Ex. 2046, 1274). Because of these differences, Patent Owner contends that a person of ordinary skill in the art would have understood that the formulation science important to the stability of the two peptides would have resulted in distinct formulations. *See e.g., id.* at 45 (arguing that Petitioner’s contention that “one of ordinary skill would be motivated to stabilize GLP-2 with whatever stabilized glucagon . . . is just plain wrong”).

Patent Owner further argues that a person of ordinary skill in the art would not have had a reasonable expectation of success in combining the references because histidine is a “problematic excipient.” PO Resp. 48–51 (citing Ex. 2051 ¶ 165–167). Patent Owner’s arguments are summarized in the following excerpt from the Patent Owner’s Response:

Amino acids, in general, have been tested as stabilizers for proteins in lyophilized formulations since as early as the mid 1930’s. Ex. [2051] ¶ 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.

Id. at 48.

Next, Patent Owner argues that “protein/peptide stabilization is far from routine or predictable.” *Id.* at 51–52 (citing 2054; 2062; Ex. 2051 ¶¶ 174–175). Patent Owner lists the “many factors that can cause destabilization and degradation,” and also notes that “the number of components from which a formulation scientist can choose is voluminous.” *Id.* Patent Owner directs our attention to Cleland (Ex. 1024), and argues that Cleland discloses that

Each 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.

Id. at 24 (quoting Ex. 1024, 2).

Patent Owner further contends as follows:

The possible solutions are virtually endless based upon even Cleland’s simple process diagram. [Ex. 2051 ¶ 70]. For example,

Cleland lists at least three initial variables - the 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 [of] combinations of constituents that are available for each secondary variable and the necessity of testing different concentration[s] of each excipient, even if some of these variables could be eliminated after proper analysis of a particular protein/peptide. *Id.* The [necessary] experimentation is . . . more than routine. It is inventive to understand and implement this type of discovery process to find the combination of components that yield a successful formulation. *Id.* at ¶ 71.

PO Resp. 25–26.

b. Analysis

We are persuaded that Petitioner has sufficiently established that the prior art it relies upon render the challenged claim obvious, and Patent Owner's arguments do not persuade us otherwise. The question before us is whether a person of ordinary skill in the art would have been motivated to formulate GLP-2 analogs with histidine and the bulking agent/excipient mannitol with a reasonable expectation of success. We determine that Petitioner has established that a person of ordinary skill in the art would have been motivated and guided by the teachings of Osterberg and Kornfelt to modify the lyophilized GLP-2 analog formulation disclosed in either Drucker '379 or Drucker '574.

First, we note that Osterberg discloses that protein drugs are typically

freeze-dried (or lyophilized) “to obtain an acceptable shelf life.” Ex. 1030, 301. Osterberg discloses that sugars (such as mannitol) and amino acids (such as histidine), “are often included in the formulation to prevent inactivation during freeze-drying and to stabili[z]e the protein during long-term storage.” *Id.* The entirety of the disclosure of Osterberg is devoted to the study of the physical state of L-histidine after freeze-drying and long-term storage so as to better understand its use in protein formulation. *Id.* The results of the experiments disclosed in Osterberg suggest that the use of sugars, in particular sucrose, has the benefit of preventing the crystallization of L-histidine, where “[t]he reduced tendency for crystallization of L-histidine is very important in the formulation design.” *Id.* at 304.

The use of histidine in protein formulation disclosed in Osterberg is further supported by Kornfelt. Kornfelt discloses a freeze-dried formulation of the protein glucagon and an amino acid, where histidine is named as one of the three preferred amino acids. Ex. 1027, 2:39–44 (“An amino acid to be used in accordance with the present invention is preferably a naturally occurring alpha amino acid. . . . Preferably glycine, glycyglycine, histidine or a mixture of two or more of these is used.”). Kornfelt further suggests the addition of an excipient for “optimum stabilization,” where lactose and mannitol are preferred. *Id.* at 2:58–60, 3:22–25.

Although we acknowledge the numerous differences between a GLP-2 analog and glucagon highlighted by Patent Owner, we are not persuaded by Patent Owner’s arguments that a person of ordinary skill in the art would not have had a reasonable expectation of success in using histidine in GLP-2 formulations based on these differences. Osterberg discloses that the

addition of amino acids and sugars function to stabilize protein formulations generally, and Patent Owner has not directed us to sufficient evidence to support a conclusion that a person of ordinary skill in the art would have expected difficulty in formulating a GLP-2 analog by following the parameters disclosed in Osterberg. For example, both Kornfelt and Osterburg suggest that histidine would function for its intended purpose within a pH range acceptable for GLP-2 or analog thereof. Ex. 1027, 3:9–12, 6:33–34; Ex. 1041 ¶¶ 64–67.

That the inventors of the '866 patent discovered that a particular GLP-2 analog performs best with a certain combination of amino acid and sugar, namely histidine and mannitol, does not persuade us by itself that the subject matter of the claims of the '866 patent is nonobvious. The preponderance of evidence of record shows that the identification of the optimal sugar and amino acid to add to a formulation for stability purposes was nothing more than routine experimentation. Here, in addition to the disclosures of Osterberg and Kornfelt, we credit the testimony of Dr. Palmieri and his analysis of publications authored by Dr. Carpenter that describe “rational” design choices for excipients in lyophilized protein formulations in order to optimize the formulation. Ex. 1041 ¶¶ 71–76 (citing Ex. 1049,¹⁰ 205–206,

¹⁰ John F. Carpenter, *LYOPHILIZATION OF PROTEIN PHARMACEUTICALS*, in *Biotechnology and Biopharmaceutical Manufacturing, Processing, and Preservation: Drug Manufacturing Tech. Series Vol. 2*, 199–264 (Kenneth E. Avis & Vincent L. Wu (eds.) (1999)) (Chapter 4) (Ex. 1049).

212, 214, 216, 250; Ex. 1050,¹¹ 969, 972, 974; Ex. 1043,¹² 212–215, 224, 227, 229, 240, 248–251, 266).

The choice of amino acid and sugar stabilizers disclosed in the art would have been finite. For example, Kornfelt provides the following list of amino acids for use in the disclosed protein formulations:

A pharmaceutically acceptable ampholyte to be used in accordance with the invention may be selected from the group consisting of amino acids or derivations thereof such as glycine, ethylglycine (sarcosine), trimethylglycine (betaine), alanine, β -alanine, valine, leucine, nor-leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, hydroxyglutamic acid, lysine, hydroxylysine, omithine, arginine, histidine, methionine, asparagine and glutamine.

Ex. 1027, 2:28–35. Kornfelt, however, names the following three as preferable amino acids for use in the disclosed formulations: glycine, glycyglycine, and histidine. *Id.* at 2:43–44. Kornfelt further suggests the addition of an excipient for “optimum stabilization.” *Id.* at 2:57–60. The list of excipients disclosed in Kornfelt is also finite:

An excipient may be selected from disaccharides such as lactose, trehalose, and sucrose, sugar alcohols such as sorbitol or mannitol, polysaccharides such as the polymers commercialized as Dextran® products such as Dextran® 40, Dextran® 70 or Dextran® 75, and Ficoll® and polyvalent alcohols such as

¹¹ Carpenter et al., 14(8) Pharmaceutical Research, 969–75 (1997) (Ex. 1050).

¹² Deposition Transcript of Dr. John Carpenter (Ex. 1043).

polyethylene glycol or polyvinyl alcohol or a combination of two or more of these.

Id. at 2:50–57. Again, however, Kornfelt guides to a preferred list of amino acids and excipient combinations: “A most preferred preparation according to the invention comprises glucagon, lactose or mannitol as excipient and glycine, histidine or glycyglycine or a mixture of two or more of these as a stabilizing agent.” *Id.* at 3:22–25. Thus, we are not persuaded that this is a case where there were “numerous parameters” to try so as to support a conclusion of nonobviousness. *Pfizer*, 480 F.3d at 1365 (“[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” (quoting *Medichem S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006))).

In view of the above, we conclude that the use of histidine and mannitol in protein formulation was disclosed in the prior art and the experimentation needed to confirm the successful application with GLP-2 analogs was “‘nothing more than [the] routine’ application of a well-known problem-solving strategy, . . . ‘the work of a skilled [artisan], not of an inventor.’” *Pfizer*, 480 F.3d at 1368 (quoting *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989)); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371 (Fed. Cir. 2006)). The motivation to optimize the lyophilized GLP-2 formulation disclosed in either Drucker ’370 or Drucker ’574 “flows from the ‘normal

desire of scientists or artisans to improve upon what is already generally known.” *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)). We, thus, determine that Petitioner has established that the claimed GLP-2 formulations, methods, and kits are a combination of known ingredients for a predictable result of stability achieved by routine testing. Furthermore, for the reasons presented in the Petition (Pet. 48–55), we are persuaded by Petitioner that an ordinary artisan would have had reason to combine teachings in the cited references to achieve the claimed invention with a reasonable expectation of success.

Lastly, we are not persuaded by Dr. Carpenter’s attempt to portray the use of L-histidine as unpredictable. As discussed above, the preponderance of the evidence establishes that histidine was a well-known component in protein/peptide formulations at the time of the invention with known advantageous properties. Ex. 1030; Ex. 1027; Ex. 1041 ¶ 90. A person of ordinary skill in the art thus would be motivated to use histidine in a GLP-2 formulation with a reasonable expectation of success. Ex. 1041 ¶¶ 96–100.

c. Secondary Considerations

Patent Owner argues that the nonobviousness of the challenged claims is supported by objective evidence of unexpected results, commercial success, and the satisfaction of a long-felt need. PO Resp. 56–60. As explained further below, we are not persuaded by Patent Owner’s argument and evidence of secondary considerations.

(1) Unexpected Results

Patent Owner characterizes the data in Figures 2–6 of the ’886 patent

as unexpected results. *Id.* at 40–42. 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. 1003, 3:25–28, 8:45–48; Ex. 2148 ¶ 148. With reference to Figure 2, Patent Owner argues that “[i]t 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.” PO Resp. 40. We are not persuaded. Rather, we agree with Petitioner’s position that “[Patent Owner] incorrectly disregards Kornfelt’s disclosure of a pH of 1–7 and focuses on a pH 2.8 providing a minimum glucagon decomposition rate despite the claims at issue not including any such stability limitation.” Reply 21 (citing Ex. 1041 ¶ 107). We further note that Osterburg teaches that histidine is suitable for use with protein drugs in the pH range 5–7. Ex. 1030, 301. We therefore determine that the preponderance of evidence supports a conclusion that a person of ordinary skill in the art would have expected histidine to stabilize GLP-2 analogs at physiological pH, for example, pH 5.5. Ex. 1041 ¶¶ 106–109.

Figures 3 and 4 of the ’886 patent are bar graph illustrations 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. Ex. 1003, 3:29–38, 9:2–15; Ex. 2148 ¶ 149–150. The ’886 patent describes the results as follows:

As shown in FIGS. 3 and 4, the reverse phase HPLC data (FIG. 3) demonstrate that the mannitol samples (Formulations 1, 2, and 3) exhibited the least amount of GLP-2 degradation. In

addition, all three L-histidine concentrations (25 mM, 50 mM, and 75 mM) showed comparable stability. The 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.

Ex. 1003, 9:2–10.

Figures 5 and 6 of the '886 patent 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. Ex. 1003, 3:40–48, 9:54–56; Ex. 2051 ¶ 151. The '886 patent describes the results shown in Figures 5 and 6 as follows:

The stability of the formulations following lyophilization and exposure to elevated temperatures was then measured. 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, 9:47–56.

Patent Owner argues that each of Figures 3–6 “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.” PO Resp. 41, 42, 43 (citing Ex. 2051 ¶¶ 149, 150, 151).

Petitioner responds arguing that “Kornfelt does not show mannitol and lactose are equivalent” and cites to the statement of Dr. Palmieri

explaining that it is not possible to conclude that Kornfelt shows mannitol and lactose are equivalent because “[i]t is just a fact that there is no experimental data with mannitol” disclosed in Kornfelt. Reply 21 (citing Ex. 1041 ¶¶ 114, 119, 123); Ex. 1041¶ 119.

Petitioner further argues that “[t]he results in Figures 2–6 are not surprising or unexpected, and they are not commensurate in scope with the claims at issue.” Reply 20 (citing Ex. 1041 ¶¶ 106–126). Petitioner contends that the claims recite GLP-2 or an analog thereof, while the results shown in Figures 2–6 concern a single GLP-2 analog. Reply 9–10, 20–22 (“The results in [Figures 2–6] are also limited to the GLP-2 analog tested (h[Gly2]GLP-2), pH tested, time at which stability was measured, and percent peptide degradation; again, the claims are not so limited.”).

We are persuaded by Petitioner that a person of ordinary skill in the art would not have found the results shown in Figures 2–6 to be unexpected. Instead, we determine that a preponderance of the evidence demonstrates that an ordinary artisan would have expected the addition of histidine to improve the stability of a protein formulation, at least to some degree, based on the disclosures of Osterburg and Kornfelt. That histidine may or may not work better as compared to other amino acids is not relevant to our analysis. The question before us is whether a person of ordinary skill in the art would have expected histidine to improve the stability of a GLP-2 formulation as compared to a GLP-2 formulation without the addition of an amino acid stabilizer, as disclosed in Drucker ’379 and Drucker ’574. We conclude that the preponderance of evidence suggests that the addition of histidine to a protein formulation would have been expected to improve stability with a

reasonable expectation of success.

Moreover, even if an ordinary artisan considered the results shown in Figures 2–6 unexpected, we are not persuaded that the results are probative of nonobviousness. As the Federal Circuit has held, “[u]nexpected results that are probative of nonobviousness are those that are ‘different in kind and not merely in degree from the results of the prior art.’” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). Similarly, here, we determine that the difference in net stability improvement between histidine and mannitol and other amino acid and excipient combinations is a difference in degree, not kind.

(2) Commercial Success

Patent Owner offers evidence of commercial success of its marketed GLP-2 analog product, [Gly2]GLP-2 (“Gattex®”), to support the nonobviousness of the claims. PO Resp. 57–59. Patent Owner argues that commercial success of Gattex® is evidenced by its large market share, high price, sales and sales growth, and large economic returns for its shareholders. *Id.* at 57–59 (citing Ex. 2041 ¶¶ 49–63). Patent Owner contends that “[Gly2]GLP-2 was known to be capable of treating SBS at least as early as 1996, but there were no marketable stable formulations.” *Id.* at 59.¹³ (citing Ex. 1029; Ex. 2055 ¶ 14). As such, Patent Owner

¹³ Patent Owner cites to Ex. 1029 and Ex. 2055 ¶ 14, however, we find that the citations provided fail to support a conclusion that the reason that

contends that the commercial success of Gattex® is tied to its long shelf-life, which is long “enough for quality control testing and quality assurance release after manufacture and storage by wholesalers, pharmacists, doctors, and patients.” *Id.* at 60 (citing Ex. 2041 ¶ 67).

“When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention.” *J.T. Eaton*, 106 F.3d at 1571; *see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000) (stating the presumption that commercial success is due to the patented invention applies “if the marketed product embodies the claimed features, and is coextensive with them”).

A party asserting obviousness, however, may rebut the presumed nexus. *Brown & Williamson Tobacco*, 229 F.3d at 1130. To that end, Petitioner argues that Patent Owner and its expert, Dr. Rausser, do not consider the other patents listed in the Orange Book as covering Gattex®, which “includes the Drucker ’379 patent, which claims the active teduglutide compound ultimately providing the efficacy of Gattex®.” Reply 23 (citing Ex. 1042 ¶¶ 34–36). As such, Petitioner correctly notes that “[Patent Owner]’s commercial success analysis is flawed, in part, because [Patent Owner] cannot establish a nexus between the sales of Gattex® and

[Gly2]GLP-2 was not brought to market sooner was due to stability issues with the analog.

. . . the claims of the '886 patent,” as compared to the features of Gattex® covered by the Drucker '379 patent. *Id.* at 22. Specifically, as noted above, it is unclear if the sales are due to the stability of the product, or to the active agent, which is disclosed by the Drucker '379 patent. Consequently, we cannot conclude from the evidence before us whether the sales are due to the merits of the invention of the '886 patent and not, for example, the Drucker '379 patent. *J.T. Eaton*, 106 F.3d at 1571 (Fed. Cir. 1997) (“[T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art.”). Thus, we determine that Petitioner has presented sufficient evidence to rebut the presumption of nexus between the commercial success of Gattex® and the claimed invention.

Accordingly, we are not persuaded that Patent Owner’s evidence of commercial success supports the nonobviousness of the challenged claims.

(3) Long-Felt Need

Patent Owner also offers evidence of long-felt need for its marketed product Gattex® to support the nonobviousness of the challenged claims. PO Resp. 57. Patent Owner contends that Gattex® obtained FDA orphan drug status as the first approved GLP-2 analog product for short bowel syndrome (“SBS”) and that “[p]hysicians and medical publications have confirmed that GATTEx provides effective SBS treatment.” *Id.* (citing Ex. 2041 ¶¶ 16–17, 45–47).

Petitioner contends that a nexus between Gattex® and the claimed invention does not exist because “[t]he value of Gattex® to SBS patients is

the efficacy of the active teduglutide compound – not the use of L-histidine and mannitol or sucrose in the formulation of Gattex®.” Reply 24 (citing Ex. 1042 ¶ 22).

We conclude that Petitioner has the better position. Patent Owner does not provide evidence sufficient to permit a determination as to whether the long-felt need was met by the discovery of GLP-2 analogs having the necessary activity (disclosed in the prior art), or the use of L-histidine and mannitol or sucrose in a stabilized GLP-2 analog formulation. As such, the record before us does not sufficiently indicate that the claimed subject matter itself satisfied a long-felt need. *See Texas Instruments Inc. v. U.S. Int’l Trade Comm’n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993) (“[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.”); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) (“Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.”); *accord In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977); *see also In re Piasecki*, 745 F.2d 1468, 1475 (Fed. Cir. 1984) (finding patent owner must present affidavits or other factual evidence of “a failure of others to provide a feasible solution to [a] long-standing problem” and evidence “that experts did not foresee” the solution claimed).

As discussed above, the prior art teaches a lyophilized GLP-2 analog formulation. Patent Owner does not present sufficient evidence of long-felt need related to the need for a more stable formulation over what was already disclosed in the prior art—that is, a lyophilized GLP-2 analog formulation.

Ex. 1029. As such, we are not persuaded that Patent Owner's evidence of long-felt need supports the nonobviousness of the challenged claims.

3. Conclusion as to Obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding a patent invalid). In doing so, we conclude that Petitioner has shown by a preponderance of the evidence that each of the challenged claims 1–27, 31–40, and 44–45 are unpatentable as obvious with regard to each of Grounds 1–4 for the reasons set forth above.

III. PATENT OWNER'S MOTION TO EXCLUDE

A. Dr. Palmieri's Reply Declaration, Ex. 1041

Patent Owner contends that Dr. Palmieri is not an expert in the pertinent technical field and that he lacks personal knowledge on which to base his testimony. Paper 49. Patent Owner contends that Dr. Palmieri is unqualified to provide expert testimony under Fed. R. Evid. 702 and seeks to exclude the entirety of Dr. Palmieri's Reply Declaration, Exhibit 1041.

Dr. Palmieri's qualifications are summarized in his curriculum vitae. Ex. 1002. He holds a Ph.D. in Pharmaceuticals from the University of Georgia and M.S. and B.S. in Pharmacy from the University of Rhode Island. He has authored over 80 publications and presentations on pharmaceuticals, intellectual property, dosage forms, dissolutions, pharmacy

education and the history of pharmacy and has taught or worked in the field of pharmacy for over 35 years. *Id.*; Ex. 1001 ¶ 4.

Petitioner responds that Dr. Palmieri's training and experience qualify him to testify under Rule 702. Paper 53, 5. Petitioner points to Dr. Palmieri's experience in the pharmaceutical industry. *Id.* at 6–7.

We agree with Petitioner that Dr. Palmieri's testimony should not be excluded. Dr. Palmieri's qualifications and experience are sufficient to qualify him as an expert in the pertinent field under Rule 702. In any case, there is no requirement of a perfect match between the expert's experience and the field of the patent. *See SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010). We conclude, therefore, that Dr. Palmieri is sufficiently qualified to provide testimony that can assist the Board in determining the issues in this proceeding.

Furthermore, we conclude that Patent Owner's list of alleged insufficiencies in Dr. Palmieri's personal knowledge are an insufficient basis to exclude his testimony. At best, these go to the weight of his testimony, and not its admissibility.

B. Paragraphs 10–19 of Dr. Palmieri's Reply Declaration, Ex. 1041

Patent Owner seeks to exclude paragraphs 10–19 of Palmieri Declaration, Exhibit 1041, because the testimony allegedly is based on inadmissible hearsay and irrelevant testimony. Paper 49, 11–14. Because we do not rely on any of paragraphs 10–19 of Exhibit 1041 to reach the final decision, we dismiss Patent Owner's motion in this regard as moot.

IV. ORDER

For the reasons given, it is

ORDERED that claims 1–27, 31–40, and 44–45 of the '886 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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