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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.

Cases IPR2015-00990
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 46–52 and 61–75 (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 19 ("Prelim. Resp.").

Based on these submissions, we instituted trial on the following grounds of unpatentability asserted by Petitioner:

Ground	References	Basis	Claim[s] challenged
1	Drucker '379,[1] Kornfelt,[2] Osterberg[3]	§ 103(a)	46–50, 52, 69–75
2	Drucker '600,[4] Kornfelt, Osterberg, and Holthuis[5]	§ 103(a)	61–67
3	Drucker '379, Kornfelt, Osterberg, and Munroe[6]	§ 103(a)	51, 75

[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] Thomas Osterberg & Tommy Wadsten, *Physical state of L-histidine after freeze-drying and long-term storage*, 8 EP. J. OF PHARM. SCI. 301–08 (1999) (Ex. 1030) ("Osterberg").
[4] Drucker et al., PCT Publication WO 98/52600, published November 26, 1988 (Ex. 1028) ("Drucker '600").
[5] Holthuis et al., U.S. Patent No. 5,496,801, issued March 5, 1996 (Ex. 1005) ("Holthuis").
[6] Donald G. Munroe et al., *Prototypic G-protein coupled receptor for the intestinotrophic factor glucagon-like peptide 2*, 96 PROC. NAT'L ACAD. SCI. USA 1569–73 (1999) (Ex. 1022) ("Munroe").

Ground	References	Basis	Claim[s] challenged
4	Drucker ’600, Kornfelt, Osterberg, Holthuis, and Munroe	§ 103(a)	68

Decision to Institute (Paper 28, “Dec.”).

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 33, “PO Resp.”), to which Petitioner filed a Reply (Paper 42, “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. 2040; 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 51. Petitioner filed an opposition (Paper 55), and Patent Owner filed a reply (Paper 59).

Oral argument was conducted on June 23, 2016. A transcript is entered as Paper 67 (“Tr.”).

This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). We conclude for the reasons that follow that Petitioner has shown by a preponderance of the evidence that claims 46–52 and 61–75 of the ’886 patent are unpatentable.

A. Related Proceedings

Petitioner also filed a different Petition requesting *inter partes* review

of claims 1–45 of the ’886 patent (IPR2015-01093). We also instituted *inter partes* review in IPR2015-01093, and issue a final decision therein concurrently with this Final Written Decision.

B. The ’886 Patent (Ex. 1003)

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 acitivity [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 claims 46, 52, 61, and 69 are representative of the challenged claims, and are reproduced below:

> 46. A GLP-2 formulation comprising:
>
> (a) about 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof;
>
> (b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level;

(c) about 0.5 to about 1% L-histidine; and
(d) about 2 to about 5% mannitol.

52. A GLP-2 formulation comprising:
(a) a medically useful amount of a naturally occurring GLP-2 peptide 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 in an amount sufficient to stabilize the formulation; and
(d) a bulking agent selected from the group consisting of mannitol and sucrose.

61. A kit comprising:
(a) a lyophilized GLP-2 formulation comprising:
(i) a GLP-2 peptide or an analog thereof;
(ii) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically acceptable level;
(iii) L-histidine; and
(iv) a bulking agent selected from the group consisting of mannitol and sucrose;
(b) a vial of sterile water for reconstitution; and
(c) instructions directing reconstitution.

69. A method for treating a human or animal having a gastrointestinal disorder, disease or condition for which treatment with GLP-2 is indicated, the method comprising the step of administering a therapeutically effective amount of a GLP-2 formulation comprising:
(a) a GLP-2 peptide or an analog thereof;
(b) a phosphate buffer in an amount sufficient to adjust the pH of the formulation to a pharmaceutically tolerable level;
(c) L-histidine; and
(d) a bulking agent selected from the group consisting of mannitol and sucrose,

thereby enhancing, maintaining, or promoting the growth or functioning of the gastrointestinal tract.

Claims 47–51 depend from claim 46, directly or indirectly. Claims 62–68 depend from claim 61, directly or indirectly. Claims 70–75 depend from claim 69, 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, 2142–46 (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, 903–4 (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 (Gly^2)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.* 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 "[f]reeze drying of L-histidine from solutions having a pH in the range 4–8 showed that L-histidine has a rather low tendency to crystallize 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, 1570–71, 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 '600 (Ex. 1028)

Drucker '600 discloses a package (or kit) containing GLP-2 or a GLP-2 analog in lyophilized form that is "suitable for reconstitution in a suitable carrier, such as phosphate-buffered saline." Ex. 1028, 21:26–30, 19:25–36, 21:26–30, 45:35–46:13. The package provides a label instructing use. *Id.* at 21:15–30.

Drucker '600 discloses that lyophilized GLP-2 formulations can be administered by injection. *Id.* at 19:25–33. Drucker '600 also discloses the use of the h(Gly2)GLP-2 analog. *Id.* at 31:5–11.

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 and 3: Obviousness of Claims 46–52, and 69–75 over the Combination of Drucker '379, Kornfelt, Osterberg, and Munroe

In Ground 1, Petitioner contends that claims 46–50, 52, and 69–75

would have been obvious over the combination of Drucker '379, Kornfelt, and Osterberg. Pet. 22–37. In support of its assertion that those claims would have been obvious, Petitioner provides a detailed discussion and claim chart explaining how each claim limitation is disclosed by the combination of Drucker '379, Kornfelt, and Osterberg. Pet. 22–37.

With regard to independent claims 46 and 52, Petitioner contends that Drucker '379 discloses the recited GLP-2 peptide analogs. Pet. 22–23 (citing Ex. 1029, 3:23–27, 9:43–47, 13:8–33; Ex. 1001 ¶¶ 50, 52, 57–59, 78–88). In particular, Petitioner contends that Drucker '379 specifically discloses the h(Gly2)GLP-2 analog, as recited in dependent claims 47–50 and 72 (and dependent claims 64, discussed ahead in relation to Grounds 2 and 4). *Id.* at 25 (citing Ex. 1029, 6:52–55). Petitioner further contends that Drucker '379 discloses a pharmaceutical composition comprising a GLP-2 analog within the recited range of "about 0.1 to about 50 mg/ml of a GLP-2 peptide or an analog thereof," as required by element (a) of claim 46. *Id.* at 23–24 (citing Ex. 1029, 3:23–27, 11:22–26, 13:8–33; Ex. 1001 ¶¶ 49–51). Petitioner contends that Drucker '379 describes GLP-2 analogs in lyophilized form, as required in dependent claim 48 (and claim 61, discussed ahead in relation to Grounds 2 and 4). *Id.* at 25, 31 (citing Ex. 1029, 10:25–33; Ex. 1001 ¶ 146). Petitioner further relies on Drucker '379 as disclosing the use of phosphate buffered saline to generate from powder an injectable formulation at a physiologically tolerable pH, alleging that this disclosure meets element (b) of claims 46 and 52. *Id.* at 28–29 (citing Ex. 1029, 13:8–33).

With regard to independent claim 69, Petitioner contends that Drucker '379 discloses administering a GLP-2 formulation with a therapeutically effective amount of GLP-2 analog to treat gastrointestinal disease. *Id.* at 26 (citing Ex. 1029 at 3:33–39; Ex. 1001 ¶¶ 110–15). According to Petitioner, Drucker '379 further discloses GLP-2 formulations administered by injection or infusion, as required in dependent claims 73 and 74 (and claim 65, discussed ahead in relation to Grounds 2 and 4). *Id.* at 27 (citing Ex. 1029, 9:43–51, 13:8–33; Ex. 1001 ¶¶ 153–54).

Drucker '379 does not disclose a formulation including L-histidine, mannitol, or sucrose. For these claim elements, 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). *Id.* at 23 (citing Ex.1027, 3:9–11; Ex. 1001 ¶¶ 73, 101). Further, with regard to claims 49, 50, 70 and 71, Petitioner contends that Drucker '379 teaches the pH of the GLP-2 formulation as "slightly acidic or physiological pH." *Id.* at 31 (citing Ex. 1029 at 9:43–51).

Petitioner further contends that Kornfelt discloses an amount of L-histidine per mg of peptide (i.e., glucagon) that is within the range specified in element (c) of claim 46. *Id.* at 24–25 (citing Ex. 1027, 2:65–67; Ex. 1001 ¶¶ 62–64); *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. *Id.* at 23 (citing Ex.

1030, 305, 307; Ex. 1001 ¶¶ 73, 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. 17–18 (citing Ex. 1027, 2:43–57; Ex. 1030, 301; Ex. 1001 ¶¶ 37–38). Petitioner contends that Kornfelt discloses that "[t]he excipient is preferably present in an amount of from 10 to 600 micromoles per mg glucagon giving an optimum stabilization," which falls within the range of 2% to about 5% mannitol required by element (d) of claim 46. *Id.* at 25 (citing Ex. 1027, 2:58–60; Ex. 1001 ¶ 65). Osterberg discloses that sucrose abolishes the crystallization of L-histidine, which Osterberg notes is "very important in the formulation design." *Id.* at 33 (citing Ex. 1030, 304).

In Ground 3, Petitioner further relies on Munroe to meet the elements of dependent claims 51 and 75. Pet. 27–28. Petitioner contends that Munroe discloses an assay for the screening and identification of GLP-2 analogs. *Id.* at 27 (citing Ex. 1022, 1570–73, Table 2; Ex.1001 ¶ 151).

Petitioner contends that one would have had a reason to combine the teachings of Drucker '379 and Munroe disclosing GLP-2 analogs and buffered pharmaceutical formulations, with Osterberg and Kornfelt, because Osterberg 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 49 (citing *Pfizer*, 480 F.3d 1348); *see also id.* at 50 ("[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[7] 8).

b. Grounds 2 and 4: Obviousness of Claims 61–68 over the Combination of Drucker '600, Kornfelt, Osterberg, Holthuis, and Munroe

In Ground 2, Petitioner contends that claims 61–67 would have been

[7] Jeffrey L. Cleland & Robert Langer, *Formulation and Delivery of Proteins and Peptides*, ACS Symposium Series; Am. Chem. Society, 1–19 (1994) (Chapter 1) (Washington, D.C.) (Ex. 1024) ("Cleland").

obvious over the combination of Drucker ’600, Kornfelt, Osterberg, and Holthuis. Pet. 37–49. In support of its assertion that claims 61–67 would have been obvious, Petitioner provides a detailed discussion and claim chart explaining how each claim limitation is disclosed by the combination of Drucker ’600, Kornfelt, Osterberg, and Holthuis. Pet. 40–49.

With regard to independent claims 61–67, Petitioner contends that Drucker ’600 discloses a package (or kit) containing GLP-2 or a GLP-2 analog in lyophilized form. *Id.* at 37 (citing Ex. 1028, 21:26–30; Ex. 1001 ¶¶ 161–62). Petitioner contends that Drucker ’600 also discloses a lyophilized GLP-2 formulation having the phosphate buffer according to the claims. *Id.* at 38 (citing Ex. 1028, 19:25–36, 21:26–30, 45:35–46:13; Ex. 1001 ¶¶ 164–67). Petitioner contends that the package of Drucker ’600 includes a label instructing use. *Id.* at 38–39 (citing Ex. 1028, 21:15–30; Ex. 1001 ¶ 182). Regarding dependent claims 62 and 63, Petitioner contends that Drucker ’600 teaches the pH of the GLP-2 formulation as “slightly acidic or physiological pH.” *Id.* at 45 (citing Ex. 1028 at 19:25–33). As with Grounds 1 and 3, discussed above, Petitioner relies on Osterberg and Kornfelt for the disclosure of L-histidine, sucrose, and mannitol in protein drug formulations to provide stability to the formulation, as required in dependent claims 66 and 67. *Id.* at 38–40, 46–47 (citing Ex. 1027, 2:20–50; Ex. 1030, 307; Ex. 1001 ¶ 169).

In Ground 4, Petitioner contends that claim 68 would have been obvious over the combination of Drucker ’600, Kornfelt, Osterberg, and Holthuis, and Munroe. Pet. 37–49. Petitioner contends that Drucker ’600

discloses a lyophilized GLP-2 formulation containing the GLP-2 analog required in claim 68. *Id.* at 40, 48–49 (citing Ex. 1028, 31:5–11, 30:30–31:1; Ex.1022, 1573, Table 2; Ex. 1001 ¶¶ 203–5). Petitioner further relies on Drucker '600 for its disclosure of "a kit including a lyophilized formulation of GLP-2 or GLP-2 analog and a desired carrier, as well as a label with instructions for use." *Id.* at 52 (citing Ex. 1028, 21:15–30; Ex. 1001 ¶¶166–173, 188–191). Petitioner relies on Munroe to establish that the [Gly-2]Glp-2 analog binds to the GLP-2 receptor and has the desired biological activity. *Id.* at 49 (citing Ex. 1022 at 1573, Table 2).

> 2. *Petitioner contends that one would have had a reason to combine the teachings of Drucker '600 and Munroe disclosing GLP-2 analog and buffered pharmaceutical formulations, with Osterberg and Kornfelt, because Osterberg 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 49 (citing Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007); see also id. at 50 ("[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.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, 32–40. For example, Patent Owner argues that i) Drucker '379 does not suggest any "*in vitro* protein/peptide 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) "Munroe does not disclose stabilization of glucagon, GLP-2, or GLP-2 analog formulations." *Id.* at 17–18, 33, 40 (citing Ex. 2040 ¶ 114). Patent Owner's arguments here essentially attack the merits of each of Drucker '379, Osterberg, Kornfelt, 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 '600 for the disclosure of lyophilized GLP-2 and GLP-2 analog formulations (Pet. 16 (citing Ex. 1029, 4:6–7:20, 15:1–35; Ex. 1028, 2:25–32; 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 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) is useful to stabilize glucagon formulations (*id.* (citing Ex. 1027, 1:23–30; 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 37 (citing Ex. 1022, 1573 (Table 2))); and v) Holthuis for its disclosure of kits including formulations of peptides prepared for injection, which include a vial of water and an injection device (*id.* at 18 (citing Ex. 1005, 5:28–36; Ex. 1001 ¶ 185)). 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 46–50, 52, and 69–75 was known in the art, as evidenced by the teachings of Drucker '379, Drucker '600, Kornfelt, Osterberg, Holthuis, and Munroe. *See e.g.*, Pet. 28–37, 40–49 (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. 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 cited 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. 2040 ¶ 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. 2040 ¶ 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. 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.

Id. at 48–49.

Next, Patent Owner argues that "protein/peptide stabilization is far from routine or predictable." *Id.* at 52 (citing Ex. 2054; Ex. 2062; Ex. 2040 ¶¶ 174–75). 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 24–25 (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. 2040 ¶ 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 many combinations of constituents available for each secondary variable and the necessity of testing different concentrations 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. 26–27.

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 '600.

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 suggests that the use of sugars, in particular sucrose, has the benefit of preventing the crystallization of L-histidine, where "[t]he reduced tendency for crystalli[z]ation 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, glycylglycine, 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 difficultly in formulating a GLP-2 analog by following the parameters disclosed in Osterberg. For example, both Kornfelt and Osterberg suggest that histidine would function for its intended purpose within a pH range acceptable for GLP-2 or analog thereof. Ex. 1027, 3:9–11, 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 (Ex. 1041 ¶¶ 71–76 (citing Ex.

1049,[8] 205–06, 212, 214, 216, 250; Ex. 1050,[9] 969, 972, 974; Ex. 1043,[10] 212–24, 240, 248–50, 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, glycylglycine, 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

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[8] 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).

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

[10] Deposition Transcript of Dr. John Carpenter (Ex. 1043).

> 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 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 glycylglycine or a mixture of two or more of these as a stabilizing agent." *Id.* at 3:22–29. 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 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. 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 '600 "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. For the reasons presented in the Petition (*id*. at 49–55), 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. 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. 53–60. 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. 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. 2040 ¶ 148. With reference to Figure 2, Patent Owner argues that “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.” 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 Osterberg teaches that histidine is suitable for use with protein drugs in the pH range 5–7. Ex. 1030, 310. 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 ¶¶ 107–9.

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, 3:29–33, 9:2–15; Ex. 2040 ¶ 149–50. 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, 3:40–44, 9:54–56; Ex. 2040 ¶ 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. 2040 ¶¶ 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 "the 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 ¶¶ 106–26). 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 Osterberg 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, such as the formulation disclosed in Drucker '379. 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. 57–60. 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 58–59 (citing Ex. 2041 ¶¶ 59–63). Patent Owner contends that "[Gly2]GLP-2 was known to be capable of treating [short bowel syndrome ("SBS")] at least as early as 1996, but there were no

marketable stable formulations." *Id.* at 59[11] (citing Ex. 1029; Ex. 2055 ¶ 14). As such, Patent Owner 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.* (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 & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *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

[11] Patent Owner cites to Exhibit 1029 and Exhibit 2055 paragraph 14, however, we find that the citations provided fail to support a conclusion that the reason that [Gly2]GLP-2 was not brought to market sooner was due to stability issues with the analog.

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 . . . 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 & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 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 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 Instr. 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.*, 392 F.3d at 1325 ("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 Piasecki*, 745 F.2d at 1475 (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 46–50, 52, and 69–75 are unpatentable as obvious over the combination of Drucker '379, Kornfelt, and Osterberg. We further conclude that Petitioner has shown by a preponderance of the evidence that each of the challenged claims 51 and 75 are unpatentable as obvious over the combination of Drucker '379, Kornfelt, Osterberg, and Munroe. We further conclude that Petitioner has shown by a preponderance of the evidence that each of the challenged claims 61–68 are unpatentable as obvious over the combination of Drucker '600, Kornfelt, Osterberg, Holthuis, and Munroe.

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 51. 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 Pharmaceutics 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 pharmaceutics, 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 ¶ 5.

Petitioner responds that Dr. Palmieri's training and experience qualify him to testify under Rule 702. Paper 55, 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., Inc.* 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 51, 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 46–52 and 61–75 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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