

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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PFIZER INC.,  
Petitioner

v.

NOVO NORDISK A/S,  
Patent Owner.

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Case No.: IPR2020-01252  
United States Patent No. 8,114,833 B2  
Issued: February 14, 2012  
Filed: May 17, 2006

Title: Propylene Glycol-Containing Peptide Formulations Which Are Optimal for  
Productions and for Use in Injection devices

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**PETITION FOR *INTER PARTES* REVIEW**

Mail Stop **Patent Board**  
Patent Trial and Appeal Board  
U.S. Patent and Trademark Office  
P.O. Box 1450  
Alexandria, VA 22313-1450  
*Submitted Electronically via the Patent Review Processing System*

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1001	U.S. Patent No. 8,114,833, <i>Propylene Glycol-Containing Peptide Formulations which are Optimal for production and for Use in Injection Devices</i> (issued Feb. 14, 2012)
1002	Declaration of Laird Forrest, Ph.D. in Support of Petition for <i>Inter-Partes</i> Review
1003	Prosecution history excerpts for U.S. Patent No. 8,114,833
1004	International Publication NO. WO 03/002136, <i>Stable Formulation of Modified GLP-1</i> (published Jan. 9, 2003) (“Flink”)
1005	International Publication No. WO 2004/004781, <i>Liquid Formulations with High Concentration of Human Growth Hormone (hgh) Comprising 1,2-Propylene Glycol</i> (published Jan. 15, 2004) (“Betz”)
1006	U.S. Patent No. 6,268,343, <i>Derivatives of GLP-1 Analogs</i> (filed Feb. 26, 1999) (issued July 31, 2001)
1007	EP 0 923 950, <i>Liquid Agent for Contact Lens</i> (issued June 23, 1999)
1008	Powell et al., <i>Parenteral Peptide Formulations: Chemical and Physical Properties of Native Luteinizing Hormone-Releasing Hormone (LHRH) and Hydrophobic Analogues in Aqueous Solution</i> , 8(10) PHARMACEUTICAL RESEARCH 1258 (1991)
1009	E. Epperson, <i>Mannitol Crystallization in Plastic Containers</i> , 35 AM. J. HOSP. PHARM. 1337 (1978)
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1011	J. Jacobs, <i>Factors Influencing Drug Stability in Intravenous Infusions</i> , 27 J. HOSP. PHARM. 341 (1969)

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1027	Gaitlin, <i>Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products</i> in INJECTABLE DRUG DEVELOPMENT (1999)
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1041	International Publication No. WO 91/11457, <i>GLP-1 Analogs useful for Diabetes Treatment</i> (published Aug. 8, 1991)
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1072	C. Burke et al., <i>The Adsorption of Proteins to Pharmaceutical Container Surfaces</i> , 86 INT’L J. OF PHARMACEUTICS 89 (1992)
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## **I. INTRODUCTION**

Petitioner Pfizer Inc. (“Petitioner”) petitions for *Inter Partes* Review of claims 1-31 of U.S. Patent No. 8,114,833 (“the ’833 patent”) (Ex. 1001), which is assigned to Novo Nordisk A/S (“Patent Owner”), under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 and seeks a determination that all claims (1-31) of the ’833 patent be canceled as unpatentable.

## **II. MANDATORY NOTICES**

This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith is a power of attorney and exhibit list per § 42.10(b) and § 42.63(e). Pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(e) accompanies this Petition.

### **A. Real Parties-In-Interest**

In accordance with 37 C.F.R. § 42.8(b)(1), the real parties-in-interest are Pfizer Inc. and Hospira, Inc.

### **B. Related Matters**

In accordance with 37 C.F.R. § 42.8(b)(2), Petitioner is not aware of any reexamination certificates or pending prosecution concerning the ’833 patent.

The Board has instituted review of claims 1-31 of the ’833 patent in *Mylan Institutional LLC. v. Novo Nordisk A/S*, No. IPR2020-00324, and Petitioner has moved to join this Petition with that proceeding.

The ’833 patent has been asserted in: *Novo Nordisk Inc. et al. v. Teva Pharmaceuticals USA, Inc.*, No. 1:17-cv-00227 (D. Del.); *Novo Nordisk Inc. et al.*

*v. Mylan Institutional LLC*, No. 1:19-cv-01551 (D. Del.); *Novo Nordisk Inc. et al. v. Mylan Institutional LLC*, No. 1:19-cv-00164 (N.D. W.Va); *Novo Nordisk Inc. et al. v. Sandoz, Inc.*, No. 1:20-cv-00747 (D. Del.); and *Novo Nordisk Inc. et al. v. Sandoz, Inc.*, No. 1:20-cv-06842 (D.N.J.). The real parties-in-interest listed above are not parties to these litigations.

Petitioner is not aware of any other pending litigation, or any other pending proceedings in front of the Patent Trial and Appeal Board.

A patent application in the same patent family as the '833 patent is pending as U.S. Patent Application No. 16/260,204, filed January 29, 2019.

**C. Identification of Counsel (37 C.F.R. § 42.8(b)(3))**

Lead Counsel	Back-Up Counsel
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\* Back-up counsel to seek *pro hac vice* admission.

**D. Service Information**

Pursuant to 37 C.F.R. § 42.8(b)(5), Petitioner respectfully requests that all correspondence be directed to lead counsel and back-up counsel at the contact information provided below. Petitioner consents to electronic service by e-mail at the below listed email address:

- *Email address:* PfizerIPRs@winston.com
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1901 K Street, NW  
Washington, DC 20036
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**III. GROUNDS FOR STANDING**

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '833 patent is available for *inter partes* review and Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified herein.

**IV. IDENTIFICATION OF CHALLENGES AND STATEMENT OF PRECISE RELIEF REQUESTED**

Pursuant to 37 C.F.R. § 42.22(a) and 37 C.F.R. § 42.104(b), Petitioner requests *inter partes* review and cancellation of claims 1-31 on the following grounds:

Ground 1: Claims 1-15 of the '833 patent were anticipated by Flink (Ex. 1004).

Ground 2: Claims 1-15 of the '833 patent would have been obvious over Flink (Ex. 1004).

Ground 3: Claims 1-31 of the '833 patent would have been obvious over Flink (Ex. 1004) in view of Betz (Ex. 1005).

Petitioner's statement of the reasons for the relief is set forth below. In support of these grounds for unpatentability, Petitioner submits the declaration of Laird Forrest, Ph.D., and relies on the Exhibits identified in the concurrently-filed Listing of Exhibits.

## **V. THRESHOLD REQUIREMENTS FOR *INTER PARTES* REVIEW**

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). This Petition clears that threshold. There is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

## **VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED**

### **A. Summary of the Argument**

The challenged claims relate to a formulation containing a glucagon-like peptide 1 (“GLP-1”) agonist, a standard buffer to stabilize the pH of the formulation, and a common tonicity agent. This same formulation was, however, already

disclosed in the prior art, including in the Flink reference relied on here. The claims offer nothing new over the prior art, rendering them unpatentable.

### **B. Level of Ordinary Skill in the Art**

A person of ordinary skill in the art (“POSA”)<sup>1</sup> would have had (1) a Pharm. D., or a Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in the area of protein or peptide therapeutic development and/or manufacturing; and (3) experience with the development, design, manufacture, or formulation of therapeutic agents, and the literature concerning protein or peptide formulation and design. Ex. 1002, ¶¶26-27. In view of the relatively high level of skill and the clear teachings in the prior art, the level of skill of the POSA is not dispositive of any issue raised in this Petition.

### **C. The ’833 Patent and Its Prosecution**

#### **1. The ’833 Patent Disclosures**

The ’833 patent is titled “*Propylene Glycol-Containing Peptide Formulations Which Are Optimal for Production and For Use in Injection Devices.*” Ex. 1001. The ’833 patent is directed to pharmaceutical formulations containing a peptide and propylene glycol as a tonicity agent instead of one of the other tonicity agents known

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<sup>1</sup> All references herein to the knowledge or understanding of a POSA or a POSA’s interpretation or understanding of a prior art reference are as of the earliest possible priority date claimed on the face of the ’833 patent, November 20, 2003, unless specifically stated otherwise.

to be prone to crystallization. Ex. 1001, 1:18-22. According to the '833 patent, using propylene glycol as the tonicity agent, rather than an alternative like mannitol, reduces crystallization of the formulation, thereby reducing the formation of deposits on production equipment and the clogging of needles. Ex. 1001, 1:23-26, 53-57.

The patent teaches that formulations containing propylene glycol “may be formulated with *any peptide*” to achieve the same purported advantages. Ex. 1001, 1:57-58 (emphasis added). The specification discloses many peptides that may be used in the formulations (Ex. 1001, 3:49-4:2), and the claims as originally filed were directed to formulations that include GLP-1 agonists, insulin, human growth hormone (“hGH”), and analogues or derivatives of those peptides (Ex. 1003, 33-35). The specification describes a genus of GLP-1 agonists, GLP-1 analogues, and derivatives thereof, including Arg<sup>34</sup>, Lys<sup>26</sup>(N<sup>ε</sup>-(γ-Glu(N<sup>α</sup>-hexadecanoyl))) -GLP-1(7-37), known as liraglutide. Ex. 1001, 4:25-37, 4:53-7:64.

The patent includes six working examples disclosing studies comparing the effect of different tonicity agents on deposit formation and needle clogging. Based on results of the tests run in the first example, the patentee determined several tonicity agents were equally suitable candidates to replace mannitol in peptide formulations. *Id.* at 17:66-18:67. But the patentee chose only propylene glycol for further studies in formulations with a placebo, liraglutide, and insulin. *Id.* at 15:64-18:67.

## 2. The '833 Patent Priority Date

The '833 patent issued February 14, 2012, from U.S. Application No. 11/435,977 (“’977 application”), filed on May 17, 2006. Ex. 1001 ¶¶(21), (22). The '833 patent names Tina Bjeldskov Pedersen, Claude Bonde, and Dorthe Kot Engelund as inventors and Novo Nordisk A/S as assignee. *Id.* ¶(75).

The '977 application is a continuation of International Application No. PCT/DK2004/000792 (“’792 PCT”), filed November 18, 2004, and purports to claim priority to (i) U.S. Provisional Application No. 60/524,653 (“’653 provisional”) filed November 24, 2003, and (ii) Danish Patent Application No. DK 200301719 (“Danish priority application”) filed November 20, 2003. But the Examiner confirmed during prosecution of the '977 application (*see* Section VI.C.4) that the '792 PCT fails to include a priority claim to the '653 provisional, and can only claim priority to the Danish priority application. Ex. 1003, 163. And, the '833 patent cannot claim priority to the '653 provisional because the '977 application was filed more than twelve months after the provisional. Thus, for purposes of pre-AIA 35 U.S.C. § 102(b), the '833 patent’s priority date is November 18, 2004.<sup>2</sup>

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<sup>2</sup> The '833 patent cannot claim priority to the '653 provisional. Thus, the only proper priority claim for the '833 patent is to the Danish application filed on November 20, 2003. Under pre-AIA 35 U.S.C. § 102(b), the relevant date is the filing of a patent application “in this country,” which includes PCT applications, but not foreign priority documents. *See* 35 U.S.C. § 119(a) (pre-AIA); *see also* MPEP 706.02. Here, “the actual filing of the application in this country” is no earlier than November 18, 2004, PCT/DK2004/000792’s filing date. Therefore, references that pre-date

### 3. The '833 Patent Claims

The '833 patent's independent claims recite GLP-1 agonist formulations (claim 1), and methods of preparing GLP-1 agonist formulations (claim 16), reducing deposits during the production of such formulations (claims 23 and 26), and reducing clogging of injection devices by such formulations (claim 29). Ex. 1001, 22:49-54, 23:37-53, 24:7-13, 24:26-32, 24:45-50; Ex. 1002, ¶29. Independent claim 1 is representative of the formulation claims:

A pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.

Ex. 1001, 22:49-54; Ex. 1002, ¶30. The method of preparing the formulations recited in independent claim 16 relates to a formulation like that of claim 1 with the addition of a preservative. Ex. 1002, ¶32.

Claims depending from claims 1 and 16 are directed to narrowing concentration ranges of propylene glycol (claims 2-4, and 17-19), narrowing pH ranges (claims 5-7 and 20-22), adding a preservative (claims 8-9), and specific GLP-

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November 18, 2003, are § 102(b) prior art. MPEP 2123(II); *In re Katz*, 687 F.2d 450, 454 (CCPA 1982).



1 agonists, analogues and derivatives (claims 10-15). Ex. 1002, ¶¶27, 31, 33. Liraglutide formulations are specifically claimed in claim 14.

Independent claims 23, 26, and 29 are directed to methods of replacing the isotonic agent of the formulation containing a disodium phosphate dihydrate buffer with propylene glycol. Claims 23 and 26 specify that the method is intended to reduce deposits on production equipment and in the final product, respectively, during production of the formulation. Ex. 1002, ¶¶34, 36. Claim 29 specifies that the method is intended to reduce clogging of injection devices. Ex. 1002, ¶38. Claims 24, 27, and 30 depend from claims 23, 26, and 29, respectively, each of which is directed to how the reduction of deposits or clogging is measured. Ex. 1002, ¶¶35, 37, 39. Claims 25, 28, and 31 also depend from claims 23, 26, and 29, respectively, and specify the isotonic agent that propylene glycol replaces. *Id.*

#### 4. Prosecution History of the '833 Patent

After a restriction requirement (Ex. 1003, 117-26), the Examiner issued only two substantive Office actions. In each, the Examiner raised issues of priority, novelty, obviousness, and double patenting.

As explained above, the Examiner first confirmed that, although apparently claiming priority to the '653 provisional, the '977 application is not entitled to that priority because (i) the '977 application was filed more than twelve months after the

'653 provisional was filed, and (ii) the PCT application to which the '977 application claims priority does not claim priority to the '653 provisional. *Id.*, 130.<sup>3</sup>

With respect to novelty, the Examiner rejected most of the claims under § 102(e) over US20060287221 (“Knudsen”). *Id.*, 131-33, 164-66. To overcome this rejection, the applicant amended the claims to require “a disodium phosphate dihydrate buffer.” *Id.*, 188, 191-92.

The Examiner also rejected the claims as obvious over Knudsen or US20060084605 (“Engelund”). *Id.*, 134-36. Those rejections were withdrawn in view the applicant’s response that the claimed subject matter was owned by the same entities as Knudsen and Engelund. *Id.*, 167.

The Examiner issued a Notice of Allowance on December 16, 2009, stating the rejections over Knudsen were overcome by applicant’s claim amendments requiring the claimed formulation to include a disodium phosphate dihydrate buffer because (i) the claims are not anticipated because Knudsen “teaches phosphate buffer which is generic to the species disodium phosphate dihydrate buffer now

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<sup>3</sup> The WIPO Patentscope bibliography data confirms that no priority claim was made to the '653 provisional. Ex. 1076 (identifying “priority data” as “PA 2003 01719 20.11.2003 DK”).

claimed” and (ii) Knudsen “is disqualified as prior art under 35 U.S.C. 103(c).” *Id.*, 204.

**D. Claim Construction (37 C.F.R. §§ 42.100(b), 42.104(b)(3))**

Under 37 C.F.R. § 42.100(b), patent claims “shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” Petitioner submits, for the purposes of this Petition only, that no claim terms currently require construction, and all terms have their plain meaning.<sup>4</sup>

Petitioner submits, however, that the preambles of claims 23, 26 and 29 should be construed as nonlimiting. Ex. 1002, ¶40. The preambles of claims 23, 26, and 29 recite statements of purpose and intended result. Claim 23 recites “[a] method for reducing deposits on production equipment during production of a GLP-1 agonist formulation....” Claim 26 recites “[a] method for reducing deposits in the final product during production of a GLP-1 agonist formulation....” Claim 29 recites “[a]

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<sup>4</sup> Petitioner may contend in district court that certain claim terms are indefinite. By filing this Petition, Petitioner does not relinquish its indefiniteness positions.

method for reducing the clogging of injection devices by a GLP-1 agonist formulation....”

These preambles state the inherent intended result of using a GLP-1 agonist formulation containing propylene glycol as an isotonic agent. None of the preambles result in a manipulative difference in the steps of the claim. Whether one wants to reduce deposits or reduce clogging, the method to achieve each purpose is identical. *See Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002) (“[P]reambles describing the use of an invention generally do not limit the claims....” (citation omitted)); *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1357 (Fed. Cir. 2014) (finding preambles nonlimiting where claim defines a structurally complete invention); *In re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018), (preambles nonlimiting when they did not alter the single manipulative step recited in the claims). Thus, the preambles are nonlimiting. And each claim is unpatentable as explained below. However, even if the Board finds the preambles limiting, these claims are still unpatentable as explained below.

**E. The POSA’s Knowledge of GLP-1 Agonists and Drug Formulation**

The ’833 patent relates to a formulation containing a GLP-1 agonist. By the priority date, GLP-1 agonists and their parenteral formulations were established in the art, having been disclosed and described in dozens of prior art references. The POSA looking to develop a GLP-1 agonist formulation would find no shortage of

successful examples of these types of formulations in the art, including formulations identical to those claimed in the '833 patent.

The POSA would have confronted the task of developing a parenteral formulation containing a GLP-1 with a wealth of background knowledge informing the desirable properties of a successful parenteral formulation, coupled with a deep understanding of the characteristics of conventional excipients and their established roles in such formulations (e.g., buffering the solution or adjusting the tonicity of the formulation). By the priority date, the POSA would have been well versed in designing formulations like those claimed in the '833 patent, as discussed herein and in the declaration of Laird Forrest, Ph.D. (Ex. 1002). *See, e.g.*, Ex. 1002 ¶¶99-147.

#### 1. GLP-1 Agonists Were Well Known in the Art

By the priority date, GLP-1 agonists<sup>5</sup> were well known in the art. Ex. 1002,

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<sup>5</sup> Human GLP-1 is a 37-amino acid peptide hormone (“GLP-1(1-37)”) originating from preproglucagon. Processing of preproglucagon yields two shorter forms of GLP-1: GLP-1(7-36)amide and GLP-1(7-37). Ex. 1006, 4:17-24. GLP-1(7-36) and GLP-1(7-37) have the following sequence:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-  
 Leu-Glu- Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-  
 Leu-Val-Lys-Gly-Arg-X

where X is hydrogen for GLP-1(7-36) and Gly for GLP-1(7-37). Ex. 1006, 4:50-60.

¶¶41-42. The '833 patent itself identifies numerous disclosures of prior art GLP-1 agonists. *Id.*, ¶42; *see also* Ex. 1001, 4:38-52 (citing WO93/19175, WO99/43705, WO 99/43706, WO99/43707, WO98/08871, WO02/46227, WO99/43708, WO99/43341, WO87/06941, WO90/11296, WO91/11457, WO98/43658, EP0708179, EP0699686, and WO01/98331) (Exs. 1031-1045, respectively); *see also* Ex. 1006, 268:15-16 (claiming liraglutide) and Ex. 1020, 199:66-67 (claiming liraglutide).

## 2. The POSA's Knowledge of Parenteral Dosage Forms

### a. Parenteral dosage forms are preferred for peptide-based drugs

Parenteral dosage forms are administered by injection (e.g., subcutaneous, intramuscular, intravenous, and intraarterial) and have certain advantages for treating patients. Ex. 1002 ¶¶43-45; Ex. 1013, 354-56. The POSA would have known that parenteral dosage forms need not pass through the digestive tract, unlike oral drugs that pass through the stomach and into the intestines before they are absorbed into the blood. Ex. 1002 ¶44; Ex. 1013, 157-60; Ex. 1012 at 29-39, 109-12, 247-50. POSAs also knew that parenteral dosage forms, especially subcutaneous and intramuscular, offer advantages for peptide-based drugs. Ex. 1002 ¶45. Peptide-based drugs generally are indistinguishable from other peptides and proteins that the intestines encounter in the digestion of food; so, if they were administered orally, they may be broken down into component amino acids and absorbed with other

nutrients, eliminating their therapeutic activity. Ex. 1002 ¶¶44-45; Ex. 1013, 157, 177-78, 200-01; 296-303; Ex. 1012, 41-44, 109-14, 126. POSAs knew that parenteral formulations maximize the amount of peptide-based drug that reaches the blood. Ex. 1002 ¶45; Ex. 1053, 8; Ex. 1013, 158-59; 296-303; Ex. 1052, 1, 3; Ex. 1055, 1. Injections for subcutaneous administration (unlike for intravenous formulations) allow a patient to self-administer the drug, in addition to offering other therapeutic advantages. Ex. 1002 ¶46; Ex. 1013, 153-64, 379-87; Ex. 1050, 1, 3-4; Ex. 1051, 1-2; *see also* Ex. 1030 (U.S. Patent 5,514,097); Ex. 1024, 53-54.

b. Stability of peptide formulations

Ensuring that protein and peptide formulations remain stable in aqueous solutions is an important, albeit conventional, aspect of formulation development. *See, e.g.*, Ex. 1024, 4-5; Ex. 1002, ¶63. Environmental factors *e.g.*, temperature or pH—may impact a protein or peptide’s conformational state and its stability. *See id.*, 3-8; Ex. 1002, ¶63. Stability of peptide formulations can also be impacted by chemical and physical issues. Ex. 1024, 8 (Table III); Ex. 1002, ¶63. Chemical instabilities affecting certain amino acids of the peptide are dependent on pH and exposure to oxygen, light, high temperature, metal ions, and free radicals. *See, e.g., id.*, 16-25; Ex. 1002, ¶63. Physical instabilities manifested by aggregation or precipitation can result from changes to the structure of the peptide caused by, for example, a change in pH or temperature, or exposure to certain chemicals. *See, e.g.,*

*id.*, 25-29; Ex. 1002, ¶¶63. To ensure that a protein or peptide drug remains safe and effective over its entire shelf life, POSAs consider how the drug is to be administered and design formulations to best stabilize the protein.

c. Formulation design for peptide-containing parenteral formulations

A POSA would have known that despite the numerous advantages of parenteral dosage, they also require unique considerations in developing a successful formulation. Ex. 1002, ¶¶47; Ex. 1013, 354-60, 376-77; 390-91; Ex. 1012, 187-188, 283-85. For example, if a dosage form is intended for multiple uses, a POSA would appreciate that anti-microbial excipients may be necessary. Ex. 1002, ¶¶48; Ex. 1013, 359; Ex. 1024, 36-40. And, for protein and peptide formulations, a POSA would have understood that stabilizers may be needed to ensure the drug's safety and efficacy over time. Ex. 1002, ¶¶122, 127; Ex. 1024, 16-21, 29-42; Ex. 1026, 22-29. Consequently, POSAs knew that parenteral formulations must be designed so that the physical and chemical stability of the formulation is maintained throughout its useful life. Ex. 1002, ¶¶48; Ex. 1013, 157-59, 354-60, 362-64. POSAs would also consider other factors that may impact the design of a parenteral formulation, including pH, buffering capacity, avoidance of particulates, biocompatibility of the vehicle, osmolarity, sterility, and choice of excipients. Ex. 1002, ¶¶49; Ex. 1013 at 54-55, 355-56; 358-59, 376-77; Ex. 1012 at 283-85; Ex. 1024 at 29-42.



*i. pH and Buffering Capacity*

A buffering system contains a weak acid and its conjugate base or a weak base and its conjugate acid. Ex. 1028, 3-4. A buffer is “[a] solution that resists change in pH when an acid or alkali is added or when the solution is diluted.” *Id.*, 3; Ex. 1002, ¶50. Buffers thus establish and maintain the product pH. Ex. 1027, 20. POSAs would design parenteral formulations to have and to maintain a narrow pH range until the drug is administered. Ex. 1002, ¶¶51, 54-55; Ex. 1013, 54-55; Ex. 1012 at 146-51, 180, 262, 279. The POSA would understand that parenterally administered products should have a pH between about 5 and 9 for intravenous, intramuscular, and subcutaneous routes, and ideally close to 7.4 to minimize pain and tissue irritation. Ex. 1002, ¶¶47, 51-55; Ex. 1024, 4, 16-17; Ex. 1060, 1-2, 4-5; Ex. 1012 at 283-285; Ex. 1047, 1, 3-4; Ex. 1056, 1-3; Ex. 1058 at 26; Ex. 1054, 4-8. A pH of 7.4—often referred to as physiological pH—is desirable because that is the approximate pH of blood and other tissues. *Id.*; Ex. 1048, 2; Ex. 1013, 128; Ex. 1049, 1; Ex. 1057, 30; Ex. 1047, 1.

*ii. Vehicles and Diluents*

A POSA developing a parenteral formulation would have known that vehicles and/or diluents are necessary for most parenteral delivery routes. Ex. 1002, ¶57. The vehicle in parenteral formulations provides a liquid carrier for the drug. The vehicle may be composed of solvents, such as water; organic solvents (like

propylene glycol, glycerin, ethanol or sesame oil); or combinations of these. Ex. 1002, ¶57. Water-based vehicles are often preferred when possible due to the high solubility of many drugs in water and the safety of aqueous vehicles. Ex. 1002, ¶57; Ex. 1013, 234-38. However, POSAs knew that water alone is often insufficient, in which case an organic co-solvent may be used. Ex. 1002, ¶57. A POSA would appreciate that several organic solvents have been used in FDA-approved drug formulations to improve solubility, and common texts such as *Remington's* provide guidance on the use of organic solvents in parenteral formulations. Ex. 1002 ¶58; Ex. 1013, 234-51, 354-60.

### *iii. Tonicity and Osmolarity*

Tonicity of a formulation relates to its osmotic pressure (i.e., osmolarity and osmolality) as compared to that of a physiological fluid. Ex. 1013, 305; Ex. 1002, ¶60. A POSA would have appreciated that every ingredient that is not water contributes to the osmolarity (and thus tonicity) of a formulation. Ex. 1002 ¶59. Hypertonic or hypotonic formulations can cause pain and irritation at the site of administration and complications like hemolysis and tissue damage. Ex. 1026, 29; Ex. 1013, 308; Ex. 1027, 13; Ex. 1002 ¶¶47, 60. As such, a POSA would have appreciated that a formulation intended to be delivered parenterally should be “isotonic” with body fluids to minimize these risks. Ex. 1002, ¶¶60-62; *Id.*

*iv. Particulates*

The presence of particulates in formulations is generally undesirable because particulates may indicate the presence of foreign material that has compromised the sterility of the product or it may indicate that an excipient or drug has precipitated due to physical instabilities. Ex. 1002 ¶56. Unintended introduction of particulates into a parenteral formulation could lead to loss of drug activity, irritation at the patient's injection site, immunological sensitization to the medicant and/or the excipients, or even endanger the patient if the particulate enters the blood. Ex. 1002 ¶56; Ex. 1013, 376-77; Ex. 1067, 8. Proteins and peptides are particularly vulnerable to precipitating out of a formulation. Ex. 1002 ¶63.

*v. Excipient Selection*

Designing formulations for protein and peptide drugs further involves careful consideration of excipients, including buffers and isotonicity agents. *See, e.g.*, Ex. 1024, 16-42; Ex. 1002 ¶¶34-65. Regulatory agencies like the FDA require the role and amount of each excipient to be justified, require the developer to ensure there are no incompatibilities between the excipients and the active drug, and require ongoing quality control of each excipient during manufacturing. Ex. 1029, 15-36; Ex. 1002 ¶66. POSAs thus knew that it was desirable to keep protein/peptide formulations “as simple as possible...and, if possible, to use excipients that have previously been used in [FDA]-approved formulations.” Ex. 1002 ¶67; Ex. 1024, 7;

Ex. 1005, 4. Consequently, POSAs knew that it would be most preferable to minimize the number of excipients used. Ex. 1002 ¶67; Ex. 1005, 4, 7.

d. Propylene glycol offers several advantages in a peptide formulation

i. *Propylene glycol is a multi-functional excipient*

Propylene glycol was well known to function as an isotonicity agent in liquid formulations. Ex. 1002, ¶69; Ex. 1025, 28:24-27; Ex. 1017, 31 (21:66-22:4); Ex. 1007, ¶[0014]; Ex. 1013, 312; Ex. 1063 (U.S. Patent No. 4,425,346); Ex. 1064 (U.S. Patent No. 6,207,684); Ex. 1065 (U.S. Patent No. 6,440,460). In addition to its role as an isotonicity agent, propylene glycol was a well-known pharmaceutical excipient used in formulations for a wide variety of purposes. Ex. 1023, 17; *also see* Ex. 1024, 32; Ex. 1013, 312; Ex. 1002, ¶¶70-72. For example, propylene glycol—a polyhydric alcohol—was well known as a stabilizer used to prevent aggregation and precipitation in protein formulations. *See* Ex. 1023, 17; Ex. 1024, 32; Ex. 1026, 23-24 (Table 1); Ex. 1019, 10:10-18, 13:11-17, 23:10-22; Ex. 1008, 5; Ex. 1002, ¶70. Polyhydric alcohols were known to stabilize proteins in solution in concentrations from 1.0% to 10% (equivalent to 10mg/mL to 100mg/mL). Ex. 1026, 26; Ex. 1002, ¶70.

Propylene glycol was also known as an anti-microbial preservative and antiseptic similar in effectiveness to ethanol, which is advantageous for multi-use parenteral formulations vulnerable to microbial contamination. Ex. 1023, 17; Ex.

1013, 28. Other known functions of propylene glycol are as a disinfectant, humectant, plasticizer, solvent, and water-miscible co-solvent. Ex. 1023, 17; Ex. 1013, 312, 358; Ex. 1014, 10:1-8; 1018, ¶[0031]; Ex. 1002, ¶68.

*ii. Propylene glycol is safe*

POSAs knew that propylene glycol is a safe excipient. Ex. 1002, ¶73. Propylene glycol was included in the FDA Inactive Ingredients Guide for numerous routes of administration, including injection and was “generally regarded as a relatively nontoxic material.” Ex. 1023, 18; Ex. 1002, ¶73. Further, although some adverse reactions like pain, irritation, and hemolysis can occur in formulations containing high concentrations of propylene glycol, POSAs would have known that 2 vol.% propylene glycol (aqueous) is iso-osmotic with serum, obviating the need for high concentrations in a parenteral formulation. Ex. 1023, 18; Ex. 1002, ¶74.

*iii. Propylene glycol’s advantages over other isotonic agents*

POSAs knew propylene glycol had advantages over other isotonicity agents like glycerol, polyethylene glycols, mannitol, and other sugars. For example, propylene glycol would have been preferred over salts due to potential problems with protein stability. Ex. 1024, 40. Polyethylene glycols have the potential for forming peroxides that can damage a peptide. Glycerol was known to adversely increase viscosity. On the other hand, propylene glycol was known to be a better

general solvent than glycerol and was widely used as an alternative or replacement for glycerin. Ex. 1002, ¶75; Ex. 1013, 28; Ex. 1022, 17; Ex. 1023, 17.<sup>6</sup>

A POSA would have known that propylene glycol has several advantages over mannitol. For instance, propylene glycol's properties as a solvent would have been expected to reduce the propensity for precipitate formation in the formulation. POSAs knew that mannitol is naturally a solid under standard conditions. *See, e.g.*, Ex. 1023, 13; Ex. 1002, ¶76. Indeed, consistent with it being a solid at room temperature, mannitol was “widely used in pharmaceutical formulations,” primarily “as a diluent (10-90% w/w) in tablet formulations.” *Id.*, 12; Ex. 1002, ¶76. Each of its most common roles took advantage of mannitol's characteristics as a solid, including its frequent use in direct-compression tablets, chewable formulations, and lyophilized formulations, and as a plasticizer, solid diluent, carrier of dry powders, and bulking agent. *Id.*

POSAs knew that mannitol's solubility in aqueous solutions under standard conditions often required concentrations that risked mannitol precipitating out of solution. *See id.*, 5; Ex. 1009; Ex. 1002, ¶77; Ex. 1009; Ex. 1011, 4; Ex. 1010, 6. POSAs also knew that when a solution containing mannitol evaporates, it produces

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<sup>6</sup> The term “glycerin” used in the prior art is the same substance as “glycerol.” Ex. 1002, ¶136.

a stiff cake. Ex. 1022, 12; Ex. 1023, 12; Ex. 1002, ¶77. Moreover, in its dry state mannitol can be a crystalline powder that is cohesive. Ex. 1022, 12-13; Ex. 1023, 13; Ex. 1002, ¶78. Furthermore, POSAs would have expected that “reducing sugar impurities in mannitol” might destroy a peptide via oxidative mechanisms. Ex. 1022, 15; Ex. 1023, 14; Ex. 1062, 1, 3; Ex. 1002, ¶78. Reducing sugar impurities can lead to destructive Maillard reactions with the peptide, i.e., an irreversible chemical reaction occurs between reducing sugars and free amines in peptides and proteins. Ex. 1022, 15; Ex. 1067 at 11; Ex. 1002, ¶78. POSAs also knew that mannitol can “form complexes with some metals,” such as aluminum and iron. Ex. 1022, 15; Ex. 1023, 14; Ex. 1002, ¶78. Metals such as iron are often found in injection needles. Ex. 1002, ¶78.

In contrast to mannitol’s solid state, POSAs knew that propylene glycol is described as a “clear, colorless, viscous, practically odorless liquid,” that is freely miscible in water at all concentrations under standard conditions. *See, e.g.*, Ex. 1022, 17; Ex. 1023, 17; Ex. 1010, 6. Ex. 1002, ¶79. Thus, POSAs would have understood that propylene glycol was often used in dosage forms where its liquid characteristics were helpful, including in parenteral formulations. *Id.* Although some liquids readily evaporate at ambient conditions, leaving their non-volatile contents behind, the POSA would have known that propylene glycol, has a “lack of volatility” that is beneficial in certain formulations. *Id.*

**F. Scope and Content of the Prior Art Relied Upon in Grounds 1-3**

In addition to the prior art relied upon for Grounds 1-3 discussed below, Petitioner relies on the POSA's knowledge, experience and prior art contributing thereto (see Section VI.E). The Forrest declaration addresses additional prior art explaining and confirming the POSA's knowledge at the priority date.

1. International Publication No. WO003/002136 ("Flink") (Ex. 1004)

Flink disclosed formulations for GLP-1 compounds with improved physical and chemical stability with long-term storage potential suitable for parenteral administration. Ex. 1004, 4:17-30; Ex. 1002, ¶82.

Flink disclosed that the long-term stability of peptides was a known issue in the art. Ex. 1004, 3:12-28 (citing WO00/37098 (Ex. 1021)); Ex. 1021, 3-4; Ex. 1002, ¶83. Flink acknowledged that the usefulness of GLP-1 compounds were limited due to stability and solubility limitations and "thus there still is a need for improvements in this field." Ex. 1004, 3:21-24; Ex. 1002, ¶83. Flink taught formulations that addressed these concerns.

The formulations Flink disclosed included one having a GLP-1 compound at a concentration from 0.1 mg/mL to 100 mg/mL and a buffer with a pH from 7 to 10. *Id.*, 4:32-5:2. Ex. 1002, ¶84. Flink disclosed that the formulation may include one or more additional ingredients, such as a preservative, an isotonic agent, a chelating agent, a stabilizer, and a surfactant—specific, well-known examples of which were



disclosed as acceptable alternatives. *Id.*, 19:16-22:30; Ex. 1002, ¶85. Flink confirmed that the use of such preservatives, isotonic agents, chelating agents, stabilizers, and surfactants was both “well-known to the skilled person” and described in standard treatises. Ex. 1002, ¶85; *Id.*, 19:30-33, 20:17-19, 20:30-32, 21:24-26, 22:28-30.

With respect to the buffer, Flink disclosed and claimed GLP-1 formulations that included a “sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin [*sic*], sodium dihydrogen phosphate, *disodium hydrogen phosphate*, sodium phosphate, [or] tris(hydroxymethyl)-aminomethan” buffer. *Id.* at 18:27-30 (emphasis added); Ex. 1002, ¶84. Flink further disclosed that of these buffers, glycylglycine, sodium dihydrogen phosphate, *disodium hydrogen phosphate*, and sodium phosphate were particularly preferred. *Id.* at 18:30-33; Ex. 1002, ¶84.

Flink also disclosed use of isotonicity agents, stating that “[t]he use of an isotonic agent in pharmaceutical compositions is well-known to the skilled person,” citing the standard treatise, *Remington: The Science and Practice of Pharmacy*, in support thereof. Ex. 1004, 21:24-26. Flink identified several isotonicity agents that can be used in its disclosed and claimed formulations, including “a salt (e.g. sodium chloride), a polyhydric alcohol (e.g. *propyleneglycol*, xylitol, mannitol, sorbitol or glycerol), a monosaccharide (e.g. glucose or maltose), a disaccharide [*sic*] (e.g.

sucrose), an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine), polyethyleneglycol (e.g. PEG400).” *Id.*, 19:34-20:4 (emphasis added); Ex. 1002, ¶85. Flink also cautioned that neither sodium chloride nor mannitol should be used as the isotonicity agent when the formulation has a pH of 7.4. Ex. 1004, 10:9-22; Ex. 1002, ¶85.

Flink disclosed seven examples evaluating formulations containing an exemplary GLP-1 compound referred to as “Compound 1.” Ex. 1004, 37:27-28; Ex. 1002, ¶¶86-92. This compound was also known by the name liraglutide. Ex. 1046, 2; Ex. 1002, ¶151. Flink’s examples evaluated Compound 1 formulations for stability and turbidity. Flink’s examples demonstrated the disclosed and claimed GLP-1 formulations were stable for long periods of time.

Flink concluded with several claims, including claim 14, which claimed a GLP-1 formulation comprising an aqueous solution with a buffer, a tonicity agent, and a preservative, further describing the excipients’ concentrations and the solution’s pH.

Flink was filed on June 27, 2002, and published on January 9, 2003. Ex. 1002, ¶81. Because Flink was published more than one year before the ’833 patent’s earliest possible U.S. priority date, it qualifies as prior art to the patent at least under 35 U.S.C. § 102(b) (pre-AIA).

2. International Publication No. WO04/004781 (“Betz”) (Ex. 1005)

Betz disclosed aqueous pharmaceutical formulations of human growth hormone (hGH) that are stable—i.e., that exhibit minimal or no crystallization, aggregation, or degradation—when stored inside a refrigerator for at least several months or when stored outside of a refrigerator for at least several hours or longer. Ex. 1005, 5; Ex. 1002, ¶94.

Like Flink, Betz recognized that a “long appreciated problem with aqueous liquid formulations of pharmaceutical proteins, not just hGH, is that of instability during storage over a period of time.” *Id.*, 3; Ex. 1002, ¶95. Betz also noted that care must be taken to ensure that excipients used as stabilizers to address instability problems are clinically acceptable and “any unnecessary additives / excipients, particularly synthetic additives / excipients, must be avoided in order to reduce risks to patients.” *Id.*, 4; Ex. 1002, ¶95. To that end, Betz taught propylene glycol is a “favourable parameter regarding stability,” and by using propylene glycol “it [was] surprisingly established that a stable formulation can be composed of a smaller number of excipients than previously thought.” *Id.*, 5-6; Ex. 1002, ¶95.

As Betz further explained, propylene glycol not only acts as a stabilizer in the formulations, but “simultaneously, it contributes to the desired tonicity of the formulation.” *Id.* at 6; Ex. 1002, ¶96. Betz taught it would be preferred to avoid the well-known problem of crystallization of a peptide formulation; there, the peptide

was hGH and the excipient was mannitol (for formulations at pH 6.2). *See, e.g.*, Ex. 1005, 12-13, Ex. 1002, ¶¶96-98.

Betz was filed on July 8, 2003, and published on January 15, 2004. Ex. 1002, ¶93. Because Betz was filed before the '833 patent's earliest priority claim, it qualifies as prior art to the patent at least under 35 U.S.C. § 102(e) (pre-AIA).

### **G. Ground 1: Flink Anticipated Claims 1-15**

Flink both disclosed and claimed the exact formulation Patent Owner sought to patent in claims 1-15. Flink's disclosure renders these claims unpatentable as anticipated.

One way a patent claim is invalid as anticipated is if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b) (pre-AIA). That is the case here. Every element of claims 1-10 of the '833 patent was found in claim 14 of Flink. And every element of claims 11-15 of the '833 patent was found in claims 21-25 of Flink. Claims 1-15 of the '833 patent were therefore anticipated.

#### **1. Claim 1**

Claim 1 of the '833 patent recites "[a] pharmaceutical formulation" that includes

- i. "at least one GLP-1 agonist,"

- ii. “a disodium phosphate dihydrate buffer,” and
- iii. “propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.”

Claim 14<sup>7</sup> of Flink disclosed each element of claim 1 of the '833 patent. Ex. 1002, ¶¶148-150. Like claim 1, the formulation of Flink's claim 14 disclosed a formulation containing a GLP-1 compound at a dose from 1 mg/ml to 100 mg/ml, a buffer, and an isotonicity agent:

5. A pharmaceutical formulation comprising an aqueous solution of a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10; provided that if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent.
6. The formulation according to claim 5, wherein said GLP-1 compound is present in a concentration from 1 mg/ml to 100 mg/ml.
8. The formulation according to any one of claims 4 and 6, wherein said formulation has a pH from 7.5 to 10.
10. The formulation according to any one of claims 2, 4, 6, and 8, wherein the GLP-1 compound is present in a concentration from 1 mg/ml to 80 mg/ml, 1 mg/ml to 50 mg/ml, 1 mg/ml to 20 mg/ml, 1 mg/ml to 10 mg/ml, typically from 1-5 mg/ml.

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<sup>7</sup> Claim 14 depends from several claims, specifically independent claim 5 and dependent claims 6, 8, 10, 11, 12 and 13.

11. The formulation according to any one of claims 1-10, further comprising a preservative.
12. The formulation according to claim 11, wherein said preservative is present in a concentration from 0.1 mg/ml to 20 mg/ml.
13. The formulation according to any one of claims 1-12, further comprising an isotonic agent.
14. The formulation according to claim 13, wherein said isotonic agent is present in a concentration from 1 mg/ml to 50 mg/ml.

Ex. 1004, 47-48; Ex. 1002, ¶¶148-150.

Claim 14 of Flink disclosed a GLP-1 compound: Flink is directed to “formulations of GLP-1 compounds and methods for preparation thereof.” Ex. 1004, Abstract; *see also id.* at 2:4-5, 4:32-5:9. Claim 14 recited a “GLP-1 compound...wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer.” *Id.*, 47. One of the compounds Flink disclosed is liraglutide,<sup>8</sup> a prior art GLP-1 agonist. *Id.*, 5:13-14, 27:26-27; *see also* Ex. 1046, 2, 8; Ex. 1002, ¶151.

Claim 14 of Flink disclosed the claimed buffer. Claim 14 recited the use of a buffer in the GLP-1 formulation. Flink disclosed that disodium phosphate is one of

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<sup>8</sup> Arg<sup>34</sup>,Lys<sup>26</sup>(N<sup>ε</sup>-(γ-Glu(N<sup>α</sup>-hexadecanoyl))) -GLP-1 (7-37), which is the chemical name for liraglutide (also known as NN2211). Ex. 1046, 2. Liraglutide is referred to as “Compound 1” in Flink. Ex. 1004, 37:26–28, 38-46.

the small group of acceptable buffers captured by claim 14. *See, e.g.*, Ex. 1004, 18:27-33; Ex. 1002 at ¶¶152-153. Indeed, Flink specifically disclosed the use of a “disodium hydrogen phosphate” buffer, identifying that buffer as one that is particularly preferred. Ex. 1004, 18:31-33; Ex. 1002 at ¶¶153.<sup>9</sup> The POSA would understand that this disclosure included the various hydrated forms of the buffer, including the dihydrate form. Ex. 1002, ¶¶154-155. Indeed, the dihydrate form is specifically used in Flink’s Example 7 at a concentration of 1.42 mg/ml. Ex. 1004 at 45-46; Ex. 1002, ¶156.

Claim 14 disclosed the claimed isotonicity agent. Similarly, claim 14 expressly recited an isotonic agent. Propylene glycol is one of a small group of isotonic agents captured by claim 14. *Id.* at 19:34-20:9. Claim 14 required the isotonic agent to be in a concentration of 1 mg/ml to 50 mg/ml. *Id.*, 48:17-18. In accordance with that disclosure, propylene glycol would be present in a GLP-1 formulation according to claim 14 of Flink at a concentration that falls within the claimed range. Ex. 1002, ¶157.

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<sup>9</sup> The terms “disodium hydrogen phosphate, dihydrate,” “disodium hydrogenphosphate, dihydrate,” “disodium phosphate dihydrate” and disodiumphosphate, dihydrate” are synonymous and all mean disodium phosphate dihydrate. Ex. 1002, ¶154, n.3.

Claim 14 disclosed the claimed pH. Claim 14 also recited that the pH of the formulation is between 7 and 10, exactly the range recited in claim 1. Ex. 1004, 4:17-20, 4:32-5:2; 5:17-6:15; 9:20-10:22; Ex. 1002, ¶169. Flink also disclosed numerous examples of formulations having a pH between 7 and 10. *See, e.g.*, Ex. 1004, 27-35, 38-46; Ex. 1002, ¶169.

\* \* \*

Anticipation is not avoided here simply because claim 14 disclosed buffers and isotonic agents without expressly stating that disodium phosphate dihydrate was the buffer and propylene glycol was the isotonic agent. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (“[A] reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a [POSA], reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” (second alteration in original) (citations omitted)).

The facts here bear a remarkable resemblance to the facts in *Wm. Wrigley Jr. Co. v. Cadbury Adams USA, LLC*, 683 F.3d 1356 (Fed. Cir. 2012). In *Wrigley*, the challenged claim recited a chewing gum having 0.1 to 10% of the flavoring agent known as WS-23 and menthol (a cooling agent). *Id.* at 1359. The prior art, a patent to Shahidi, disclosed compositions that identified categories of components to be included in a chewing gum composition. *Id.* at 1360. Shahidi identified flavoring



agents as one category, including WS-23 as one of three preferred flavoring agents. *Id.* Shahidi also disclosed menthol as one of 23 cooling agents that could be used in combination with a flavoring agent. *Id.* A patent incorporated by reference into Shahidi provided the amount of WS-23 to use. *Id.* The district court found this disclosure anticipated the challenged claim. On appeal, the Federal Circuit affirmed the decision, holding:

Shahidi envisions using WS-23 and menthol in a single product. While Shahidi discloses a number of different combinations of cooling and flavoring elements, one of them is the combination of menthol, which Shahidi identifies as one of the “most suitable” flavoring agents, with WS-23, which Shahidi identifies along with WS-3 as among a group of three “particularly preferred cooling agents.” Based on the disclosure of the combination of those components, we agree with the district court that Shahidi anticipates claim 34.

*Id.* at 1361; *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) (“This court rejects the notion that one of [14 listed] ingredients cannot anticipate because it appears without special emphasis in a longer list.”); *Ex parte A*, No. 89-2432, 1990 WL 354589 (BPAI June 5, 1990) (finding claims anticipated where the prior art disclosed 22 options); *In re Sivaramakrishnan*, 673 F.2d 1383 (CCPA 1982) (finding claims to a specific mixture of resin and cadmium salt anticipated by a disclosure of a lengthy list of specifically enumerated salts); *Illumina, Inc. v. Trustees of Columbia University*, IPR2013-00011, Paper 130 at 16-

17 (Final Written Decision) (PTAB Mar. 6, 2014) (finding claims anticipated where “each selection is made from a defined set of possible choices”).

Similarly, in *Kennametal*, the claim at issue was directed to a metal cutting tool made from a ruthenium binder and a physical vapor deposition (PVD) coating. *Kennametal*, 780 F.3d at 1379. The prior art reference (“Grab”) disclosed five binders—including ruthenium—and the specification “contemplated” the use of PVD coatings despite no specific example disclosing the coatings used. *Id.* at 1379-80. The Federal Circuit determined that the express “contemplat[ion]” of PVD was “sufficient evidence that a reasonable mind could find that a [POSA]...would immediately envisage applying a PVD coating.” *Id.* at 1383. In view of the five different binders, the court found that Grab “effectively teaches 15 combinations, of which one anticipates pending claim 1.” *Id.*

Here, like in *Wrigley*, Flink claimed a GLP-1 composition with four particularly preferred buffers and 18 preferred isotonicity agents.<sup>10</sup> Moreover, unlike in *Wrigley*, the POSA need not even go outside the four corners of the specification for any amount of a claimed ingredient; Flink disclosed the complete

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<sup>10</sup> Flink contemplates that if the claimed formulation is at the preferred physiological pH of 7.4, neither mannitol nor NaCl would be used as the isotonic agent. Ex. 1004, 10:9-22. This further winnows down the disclosed isotonic agents to just 16, far fewer than the number of flavoring agents in *Wrigley*.

roadmap to the claim. The POSA would have immediately and readily envisioned the combination recited in claim 1. *Kennametal*, 780 F.3d at 1383; *Famy Care Ltd. v. Allergan, Inc.*, No. IPR2017-00567, 2017 WL 2983375, at \*6 (P.T.A.B. July 10, 2017) (instituting review where POSA could at once envisage the challenged claim from the disclosed examples); Ex. 1002, ¶¶156-157. Flink’s claim 14 anticipated claim 1.

## 2. Claims 2-4

Claims 2-4 depend from claim 1 and further require that the propylene glycol concentration be:

“about 1 mg/ml to about 50 mg/ml” (claim 2),

“about 5 mg/ml to about 25 mg/ml” (claim 3), or

“about 8 mg/ml to about 16 mg/ml” (claim 4).

Flink’s claim 14 claimed the isotonic agent—e.g., propylene glycol—in a concentration “from 1 mg/ml to 50 mg/ml.” Claim 14 encompassed the concentrations of isotonic agents recited in each of claims 2-4. Ex. 1002, ¶¶170-171; *see also* Ex. 1004, 20:10-16 (disclosing an isotonic agent present in a concentration of “1 mg/ml to 7 mg/ml,” “8 mg/ml to 16 mg/ml,” and “17 mg/ml to 50mg/ml,”). The concentration ranges in claim 14 and in the exemplary embodiments thereof (see Examples 1-7) are provided with sufficient specificity to anticipate the claimed ranges. *See ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345

(Fed. Cir. 2012) (holding that prior art disclosure of less than 150 ppm anticipated claim to less than 50 ppm). Moreover, the '833 patent does not describe the ranges recited in claims 2-4 as being critical in any respect. *See id.* Accordingly, Flink's claim 14 anticipated claims 2-4.

3. Claims 5-7

Claims 5-7 depend from claim 1 and further require that the formulation have a pH of:

“about 7.0 to about 9.5” (claim 5),

“about 7.0 to about 8.3” (claim 6), or

“about 7.3 to about 8.3” (claim 7).

Flink's claim 14 claimed a formulation having a pH between 7.5 and 10. Ex. 1002, ¶¶172-173. Specific examples within that claimed range are provided in the examples embodying claim 14, including formulations having a pH of 7.0, 7.4, 7.7, 7.8, 7.9, 8.0, 8.1, 8.4, and 9.5. Ex. 1002, ¶173; Ex. 1004, 27-35, 38-46. The '833 patent nowhere suggests that any of these pH ranges is critical. *See generally* Ex. 1001. These ranges are therefore disclosed with sufficient particularity to anticipate claims 5-7. *See ClearValue*, 668 F.3d 1340 at 1345. Accordingly, Flink's claim 14 anticipated claims 5-7.

4. Claims 8-9

Claim 8 depends from claim 1 and requires that the formulation further include “a preservative.” Claim 9 depends from claim 8, and requires the preservative to be “present in a concentration from 0.1 mg/ml to 20 mg/ml.” Flink’s claim 14 expressly claimed a formulation having a preservative with this exact concentration range, thereby anticipating claims 8-9. Ex. 1002, ¶¶174-175; Ex. 1004, 27-38, 40-46.

5. Claim 10

Claim 10 depends from claim 1 and requires the GLP-1 agonist to be “selected from the group consisting of GLP-1(7-36)-amide, GLP-1(7-37), a GLP-1(7-36)-amide analogue, a GLP-1(7-37) analogue, or a derivative of any of these.”

Claim 14 of Flink expressly recited that the GLP-1 compound is GLP-1(7-37) or an analog thereof. Ex. 1002, ¶¶176-177; Ex. 1004, 47:18-24. Accordingly, claim 14 of Flink anticipated claim 10.

6. Claim 11

Claim 11 depends from claim 10 and requires the GLP-1 agonist to be “a derivative of GLP-1(7-36) or GLP-1(7-37) or a GLP-1(7-36)-amide analogue or a GLP-1(7-37) analogue, where said derivative has a lysine residue and a lipophilic substituent attached with or without a spacer to the epsilon amino group of said lysine.”

Claim 21<sup>11</sup> of Flink disclosed each element of claim 11. Ex. 1002, ¶178. Like claim 11, the formulation of Flink's claim 21 disclosed a GLP-1(7-37) analogue having a lipophilic substituent attached to the epsilon amino group of a lysine residue:

21. The formulation according to any one of claims 1-20, wherein said GLP-1 compound is selected from *a GLP-1 (7-36), GLP-1 (7-37), or GLP-1 (7-38) analogue having a lysine residue, such as one lysine, wherein a lipophilic substituent optionally via a spacer is attached to the epsilon amino group of said lysine.*

Accordingly, claim 21 of Flink anticipated claim 11. Ex. 1002, ¶¶178-179. *See also* Ex. 1004, 4:32-35, 5:17-20, 9:20-10:22, 26:7-16, 26:21-22.

#### 7. Claim 12

Claim 12 depends from claim 11 and requires the lipophilic substituent to have “from 8 to 40 carbon atoms.” Like claim 12, claim 23<sup>12</sup> of Flink disclosed that the lipophilic substituent has 8 to 40 carbon atoms:

23. The formulation according to any one of claims 1-22, wherein said lipophilic substituent *has from 8 to 40 carbon atoms*, preferably from 12 to 24, eg 14-18.

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<sup>11</sup> Claim 21 depends from several claims, including claim 14.

<sup>12</sup> Claim 23 depends from several claims, including claims 14 and 21.

Accordingly, claim 23 of Flink anticipated claim 12. Ex. 1002, ¶¶180-181.

*See also* Ex. 1004, 25:26-27.

#### 8. Claim 13

Claim 13 depends from claim 12 and requires the spacer to be an amino acid.

Like claim 13, claim 24<sup>13</sup> of Flink disclosed that the spacer, when present, is an amino acid:

24. The formulation according to any one of claims 1-23, wherein said *spacer is present and is selected from an amino acid*, eg. beta-Ala, L-Glu, aminobutyroyl.

Accordingly, claim 24 of Flink anticipated claim 13. Ex. 1002, ¶¶182-183.

*See also* Ex. 1004, 25:32-26:2.

#### 9. Claim 14

Claim 14 depends from claim 13 and requires the GLP-1 agonist to be Arg<sup>34</sup>, Lys<sup>26</sup>(N<sup>ε</sup>(γ-Glu(N<sup>α</sup>-hexadecanoyl))) -GLP-1 (7-37). Like claim 14, claim 25<sup>14</sup> of Flink disclosed liraglutide, which has the same chemical formula:

25. The formulation according to any one of claims 1-24, wherein said GLP-1 compound is *Arg<sup>34</sup>, Lys<sup>26</sup>(N-ε-(γ-Glu(N-α-hexadecanoyl))) -GLP-1 (7-37)*.

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<sup>13</sup> Claim 24 depends from several claims, including claims 14, 21, and 23.

<sup>14</sup> Claim 25 depends from several claims, including claims 14, 21, 23, and 24.

Accordingly, claim 25 of Flink anticipated claim 14. Ex. 1002, ¶¶184-185. *See also* Ex. 1004, 5:13-14, 27-35, 37:26-28, 38-46.

#### 10. Claim 15

Claim 15 depends from claim 1 and requires the GLP-1 agonist to be selected from the group consisting of Arg<sup>34</sup>GLP-1(7-37), Arg<sup>26</sup>GLP-1(7-37), and several others. Ex. 1001.

Like claim 15, claim 22<sup>15</sup> of Flink disclosed a GLP-1(7-37) analogue selected from a group including Arg<sup>34</sup>GLP-1 (7-37) and Arg<sup>26</sup>GLP-1 (7-37):

22. The formulation according to claim 21 , wherein said GLP-1(7-36), GLP-1(7-37), or GLP-1(7-38) analogue is selected from *Arg<sup>34</sup>GLP-1(7-37)*, *Arg<sup>26,34</sup>Lys<sup>36</sup>GLP-1(7-36)*, *Arg<sup>26</sup>GLP-1(7-37)*, or *Gly<sup>8</sup>,Arg<sup>26,34</sup>,Glu<sup>37</sup>,Lys<sup>38</sup>GLP-1(7-38)*.

Accordingly, claim 22 of Flink anticipated claim 15. Ex. 1002, ¶¶186-187. *See also* Ex. 1004, 23:9-12.

#### **H. Ground 2: Claims 1-15 Would Have Been Obvious Over Flink**

If claims 1-15 are not found to be anticipated, any gap between Flink's disclosure and these claims is one the POSA easily closes in view of Flink's teachings and the POSA's knowledge and experience.

A patent claim is obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been

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<sup>15</sup> Claim 22 depends from claim 21, and from it, several others, including claim 14.



obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103(a). Obviousness is a question of law premised on underlying issues of fact, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations such as commercial success, long-felt need, and the failure of others. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1. Claim 1

Claim 1 is directed to a pharmaceutical formulation comprising a GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol at certain concentrations and a physiological pH. Flink renders this claim obvious.

a. Differences between the claimed invention and the prior art

As discussed above, Flink disclosed all elements of claims 1-15 and, in Example 7, disclosed specific GLP-1 agonist formulations having a pH between 7.0 and 10.0 and a disodium phosphate dihydrate buffer. With such remarkable similarity between Flink’s claims and the claims here, any differences between those claims falls into the category of legal technicality, not inventive contributions to the art. Indeed, the only minute differences, if they can even be characterized as differences, between the GLP-1 formulations disclosed by claim 14 of Flink and claims 1-15 of the ’833 patent are (i) express identification of the specific buffer

claimed and (ii) express identification of propylene glycol as the isotonic agent at a final concentration within the claimed range. But those elements are in fact both disclosed in, and indeed encouraged by, Flink. A POSA would have combined them, as Flink instructs, to produce the claimed formulation, and would have done so with a reasonable expectation of success. *See Purdue Pharma Prod. L.P. v. Par Pharm., Inc.*, 377 F. App'x 978, 982 (Fed. Cir. 2010) (finding patent obvious where prior art identified compound as one of fourteen compounds to use); *see also Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (holding prior art's disclosure of a multitude of combinations failed to render any particular formulation less obvious).

*i. Flink taught a POSA to use disodium phosphate dihydrate buffer*

Flink's claim 14 recites the use of a buffer in the claimed formulation. The specification suggested the use of the claimed disodium phosphate dihydrate buffer as one of several commonly used buffers. Ex. 1004, 18:27-33. Demonstrating Flink's preference for this buffer, Flink used disodium phosphate dihydrate buffer in the exemplary formulations. Ex. 1002, ¶¶152, 156; Ex. 1004, 27-35, 37-46. Moreover, POSAs knew that disodium hydrogen phosphate, including its salts, was a well-known buffer often used in pharmaceutical formulations. Ex. 1002, ¶¶153-154; Ex. 1022, 20; Ex. 1023, 20. So routine was the use of disodium hydrogen

phosphate as a buffer, *Remington's* characterized it as one of the “most frequently employed” along with citrates and acetates. Ex. 1013, 51, 359; Ex. 1002, ¶153.

The use of this buffer was nothing new to the POSA. A POSA would have known that a disodium hydrogen phosphate buffer can be readily prepared by dissolving the dihydrate form of disodium hydrogen phosphate in water, which is commonly done for buffers used in parenteral formulations. Ex. 1002, ¶155. POSAs knew how to prepare a disodium phosphate buffer using disodium hydrogen phosphate dihydrate, and would have every expectation that the buffer would work in a GLP-1 formulation. *Id.* But the POSA need not guess at this buffer's utility. Example 7 of Flink disclosed a formulation that included a disodium hydrogen phosphate dihydrate buffer. Ex. 1004, 45-46; Ex. 1002, ¶¶152, 156. Thus, it would have been obvious to use a disodium hydrogen phosphate dihydrate buffer in a GLP-1 formulation. Ex. 1002, ¶¶154-156.

*ii. Flink taught a POSA to use propylene glycol as an isotonic agent*

POSAs understood that parenteral formulations generally required the use of a tonicity agent. Ex. 1002, ¶¶60-62, 164. Flink confirmed this principle with its teaching that its GLP-1 formulations should include an isotonic agent (Ex. 1004, 19:33-20:9), and that “[t]he use of an isotonic agent in pharmaceutical compositions is well-known to the skilled person.” Ex. 1004, 20:17-19 (citing *Remington: The Science and Practice of Pharmacy*, 19th edition, 1995). The formulation of Flink's

claim 14 specifically required an isotonic agent. Flink identified eighteen appropriate options known in the art, including propylene glycol. Ex. 1004, 19:34-20:4; Ex. 1002, ¶157. From that short list, a POSA would have selected propylene glycol to adjust the tonicity of a parenteral formulation, with a reasonable expectation of success, for at least three reasons.

*First*, propylene glycol was known to be an efficient tonicity adjuster. *See* Section VI.E.2.d(i); Ex. 1002, ¶¶69, 158. The POSA knew propylene glycol could make a formulation isotonic. But propylene glycol, a well-known and widely-used excipient, brought with it a raft of other benefits encouraging its use. *See* Section VI.E.2.d(i); Ex. 1002, ¶¶70-72, 158-159. This would help the formulator achieve the art-recognized goal of minimizing the number of excipients used in a formulation. *See* Section VI.E.2.c(v); Ex. 1002, ¶65, 161.

*Second*, propylene glycol was known as an acceptable inactive ingredient in FDA-approved parenteral formulations and considered a non-toxic ingredient. *See* Section VI.E.2.dVI.E.2.b; Ex. 1002, ¶¶73-74, 160. The POSA knew that the use of an already-approved excipient would help clear the path to regulatory approval, again, encouraging its use. Ex. 1002, ¶160; *see, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007) (recognizing that a POSA “looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry”).

*Third*, propylene glycol had significant advantages over other tonicity agents, including mannitol, for the reasons explained above. *See* Section VI.E.2.d(iii); Ex. 1002, ¶¶75-80.

For at least these reasons, Flink taught POSAs that propylene glycol is a wise choice as the required isotonic agent in a GLP-1 formulation. Thus, it would have been obvious to include propylene glycol in a GLP-1 formulation. Ex. 1002, ¶¶158-162.

*iii. Determining concentrations of isotonicity agents is routine*

If the POSA had any concern about the concentration of propylene glycol to use in a GLP-1 formulation, basic calculations and the concentrations disclosed in Flink gave the POSA all that was needed to determine the concentration of propylene glycol to use to make an isotonic formulation.

The purpose of an isotonicity agent in a formulation is to adjust a solution's osmolarity—and thus its tonicity—relative to that of plasma to achieve an isotonic formulation. Ex. 1002, ¶¶59-60, 164. Calculating the concentration of an isotonicity agent needed to achieve a specific osmolarity is straightforward, and the POSA learns how to do it early in graduate school, if not before. *Id.* at ¶¶163, 166. Accordingly, once the isotonicity agent is selected, and the contribution to the total solution osmolarity has been determined, the POSA can readily calculate the concentration. Ex. 1002, ¶165-166.

Here, those determinations are further aided by Flink's examples which provide suitable formulations with specific concentrations of other isotonic agents, e.g., mannitol at 36.9 mg/ml and glycerol at 16.0 mg/ml. Ex. 1002, ¶166; Ex. 1004, 27-35, 37-46. With those concentrations in hand, a POSA could have performed a basic calculation to determine the amount of propylene glycol that would provide the same osmolarity as the specific formulations disclosed in Flink. Ex. 1002, ¶¶165-166. The formula to calculate that amount is:

$$\frac{\text{g/L}}{\text{mol wt}} \times 1000 = \text{mOsmol/L} \quad [\text{Formula 1}]$$

Ex. 1013, 307; Ex. 1002, ¶165. In Formula 1, [g/L] is the concentration of the isotonic agent, mol wt is the molecular weight of the isotonic agent, and the osmolarity (i.e., osmolar concentration) for the isotonic agent is expressed in mOsmol/L. *Id.* To determine the osmolar concentration of mannitol in the formulations disclosed in Flink, the concentration (36.9 mg/ml) and molecular weight (182.17 g/mol) of mannitol (Ex. 1022, 12; Ex. 1023, 12) is plugged into Formula 1 to solve for the osmolar concentration as shown in bold below:

$$\frac{36.9 \text{ g/L}}{182.17 \text{ g/mol}} \times 1000 = 202.56 \text{ mOsmol/L}$$

Ex. 1002, ¶166. To calculate an amount of propylene glycol that provides an equivalent osmolar concentration in the same formulations, a POSA would simply plug in the osmolar concentration for mannitol (202.56 mOsmol/L) and the molecular weight for propylene glycol (76.09 g/mol) (Ex. 1022, 17; Ex. 1023, 17)

into Formula 1 to solve for the concentration of propylene glycol as shown in bold below:

$$\frac{\text{propylene glycol g/L}}{76.09 \text{ g/mol}} \times 1000 = 202.56 \text{ mOsmol/L}$$

$$\text{Propylene glycol} = 15.41 \text{ mg/ml}$$

Ex. 1002, ¶¶167-168. The same calculation could also have been performed to determine the osmolar concentration of glycerol, which has a molecular weight of 92.09 g/mol (Ex. 1022, 9; Ex. 1023, 9) and a concentration of 16.0 mg/ml in the formulations disclosed in Flink:

$$\frac{16.0 \text{ g/L}}{92.09 \text{ g/mol}} \times 1000 = 173.74 \text{ mOsmol/L}$$

Ex. 1002, ¶166. The amount of propylene glycol that provides an equivalent osmolar concentration in the same formulations is calculated as follows:

$$\frac{\text{propylene glycol g/L}}{76.09 \text{ g/mol}} \times 1000 = 173.74 \text{ mOsmol/L}$$

$$\text{Propylene glycol} = 13.22 \text{ mg/ml}$$

Ex. 1002, ¶¶167-168. To POSAs, this math is a tool as readily accessible to them as a hammer is to a carpenter. These calculations allowed the POSA to understand that propylene glycol should be used at a concentration of 13.22 mg/ml or 15.41 mg/ml to produce formulations having an osmolarity equivalent to Flink's formulations containing glycerol or mannitol, respectively. *Id.* Accordingly, it

would have been obvious to use a concentration of propylene glycol that falls within the claimed range of “about 1 mg/ml to about 100 mg/ml.”

## 2. Claims 2-15

Claims 2-15 would have been obvious over Flink for the reasons set forth above in Sections VI.G.2-VI.G.10. *Also see* Ex. 1002, ¶¶170-187.

The concentration of propylene glycol suggested by Flink (see Sections VI.G.1, VI.H.1(iii)) falls squarely within the ranges recited in claims 2-4. Ex. 1002, ¶¶170-171.

Similarly, the pH ranges recited in Flink’s claim 14 and taught in Flink’s Example 7 (a pH of 7.4) again fall neatly within the ranges of claims 5-7. Moreover, the ranges recited in claims 5-7 each encompass pH 7.4, the preferred pH for an ordinary parenteral formulation. Ex. 1002, ¶¶172-173.

The use of a preservative at the claimed ranges as recited in claims 8-9 is, again, exactly as disclosed in claim 14 of Flink and as recited in Flink’s examples, including Example 7 (5 mg/ml of phenol). Ex. 1002, ¶¶174-175.

And the specific GLP-1 agonists recited in claims 10-15 are, again, expressly recited in the claims of Flink. Ex. 1002, ¶¶176-187.

## **I. Ground 3: Claims 1-31 Would Have Been Obvious Over Flink In View of Betz**

While Flink alone renders the ’833 patent’s claims unpatentable as discussed above, additional prior art provides yet more evidence of the obviousness of the



disputed claims. The first formulation listed in Flink's Example 7 differs from the '833 patent's claims only its use of mannitol as an isotonic agent. But art like Betz, particularly when coupled with other teachings in Flink, gave the POSA motivation to replace mannitol with propylene glycol as an isotonic. Accordingly, claims 1-31 would have been obvious over Flink in view of Betz.

1. Claim 1

- a. The combination of Flink and Betz disclosed each element of claim 1

The first formulation listed in Flink's Example 7 is shown below:

Composition	pH	Temperature	Purity, Compound 1 (%) T = 12 weeks	Dimer formation, Compound 1 (%) T = 12 weeks
3 mg/ml Compound 1 1.42 mg/ml disodium hydrogenphosphate, dihydrate 5 mg/ml phenol 36.9 mg/ml mannitol	7.4	37°C	78.4	5.43

This formulation differs from claim 1 of the '833 patent only in that mannitol is used as an isotonic agent at a concentration of 36.9 mg/ml, instead of propylene glycol at a concentration between 1 and 100 mg/ml. Ex. 1002, ¶¶188-189. This formulation is otherwise identical to the '833 patent's claims: it includes a GLP-1 agonist ("3 mg/ml [liraglutide]") and a disodium phosphate dihydrate buffer ("1.42 mg/ml; disodium hydrogenphosphate, dihydrate") adjusted to pH 7.4. Ex. 1002, ¶188. Flink disclosed propylene glycol as an alternative isotonic agent to mannitol (*see* Section

VI.H.1.a(ii)), and one that is preferred when the formulation pH is 7.4 (*see* Sections VI.F.1, VI.G.3, VI.H.2).

Betz taught that propylene glycol was a well-known isotonic agent in parenteral peptide formulations with both formulation and manufacturing advantages over mannitol. Ex. 1005, 3-4, 5-8; Ex. 1002, ¶190. Indeed, much of Betz's contribution to the art is teaching the POSA the benefits that derive from the use of propylene glycol as a replacement for mannitol in peptide formulations. Ex. 1002, ¶¶190-192, 199. Betz taught POSAs that replacing mannitol with propylene glycol provided a more stable peptide formulation.<sup>16</sup> Ex. 1005, 5-8, 17-18; Ex. 1002, ¶¶190-192, 199. Betz demonstrated this with examples wherein mannitol is systematically replaced with propylene glycol, with a trend of increased stability (i.e., reduced crystallization) of the formulation with increased propylene glycol content. Ex. 1005, 17-18, and Table 2; Ex. 1002, ¶¶190-192, 199. Table 2 in Betz disclosed formulations wherein levels of mannitol are steadily reduced and

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<sup>16</sup> Patent Owner may argue that a POSA would not have looked to Betz because Betz is directed to improving stability of formulations containing hGH, not GLP-1 agonists. However, as discussed above, Section VI.E.2.d(i), polyhydric alcohols, including propylene glycol, were known in the prior art to successfully stabilize hGH and other peptides. A POSA looking to improve stability of GLP-1 agonists would have looked to other polyhydric alcohols as replacements for mannitol. Indeed, the '833 patent itself recognizes that the formulations disclosed therein improve not just GLP-1 agonist formulations, but other peptide formulations as well—including *hGH*. Ex. 1001, 1:57-63, 3:49-4:2.

propylene glycol are steadily increased, until mannitol was completely replaced by propylene glycol in Formulations 6 and 7. *Id.* As propylene glycol replaced mannitol, the stability of the peptide formulation increased. *Id.* Betz thus gave POSAs ample reason to replace mannitol with propylene glycol in peptide formulations to improve formulation stability.

- b. A POSA would have been motivated to modify Flink in view of Betz

There are several reasons why a POSA would have looked to Betz to modify the examples in Flink and would have done so with a reasonable expectation of success.

- i. Flink taught away from using mannitol in formulations having a pH of 7.4*

To start, Flink taught a POSA that mannitol should not be used in peptide formulations with a pH of 7.4, the desirable pH for many parenteral formulations. Ex. 1004, 5:22-23, 5:29-30, 47:23-24; Ex. 1024, 4; Ex. 1002 ¶¶197-198. A POSA looking at Flink's examples would thus be motivated and encouraged to replace mannitol in Flink's examples. Ex. 1004, 5:17-23; Ex. 1002, ¶¶197-198. Replacing the mannitol of the first Example 7 formulation with an equivalent amount of propylene glycol would have been obvious as a simple substitution of one known element for another to obtain predictable results, particularly when considered in view of Flink's teachings and the POSA's knowledge. *See* MPEP 2143(I)(B); *see*

*also Pfizer*, 480 F.3d at 1368; *Wrigley*, 683 F.3d at 1364-65; Ex. 1002, ¶197. As discussed above, Flink taught that propylene glycol was an appropriate isotonic agent for use in its disclosed GLP-1 formulations. Ex. 1004, 19:34-20:4; Ex. 1002, ¶157.

*ii. Betz and Flink both address the problem of peptide stability in formulation*

Betz provided further motivation to replace mannitol with propylene glycol. Protein instability is a well-known problem in the development of peptide drug formulations. Ex. 1002, ¶¶63, 194, 199; Ex. 1059, 1; Ex. 1024, 4-5; Ex. 1008 at 1; *also see* Section VI.E.2.b. Betz taught that replacing mannitol with propylene glycol improved the stability of peptide formulations. Betz's teachings were applicable to all aqueous liquid formulations of pharmaceutical proteins, not just hGH. Ex. 1005, 3; Ex. 1002, ¶¶195-196. A POSA would look to Betz for its teaching that propylene glycol reduces crystallization and improves long-term stability and storage. Ex. 1005 at 5-6; Ex. 1002, ¶196. When coupled with propylene glycol's known multi-purpose role as an excipient (Section VI.E.2.d(i)), Betz taught POSAs that a peptide formulation would be improved by the use of propylene glycol. *See Sanofi-Aventis Deutschland GMBH v. Mylan Pharm. Inc.*, No. 2019-1368, 2019 WL 6130471, at \*6-7 (Fed. Cir. Nov. 19, 2019) (finding claims obvious where the prior art taught that a particular excipient class—nonionic surfactants—were routinely used to address stability issues in peptide formulations).

\* \* \*

The considerations discussed above (Sections VI.E.2.d, VI.H.1.a(ii)) would have led a POSA to select propylene glycol as a desirable and predictable replacement for mannitol in the formulations disclosed in Flink. Ex. 1002, ¶¶193-204. While an express suggestion to substitute one equivalent for another is not required, Flink taught not to use mannitol in formulations adjusted to a pH of 7.4, motivating a POSA to replace mannitol in the Example 7 formulation. Ex. 1004, 5:17-23; Ex. 1002, ¶¶197-198; *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). Further, it would have been readily apparent to a POSA to use propylene glycol at a concentration of about 13.2 mg/ml and 15.4 mg/ml as explained above. Section VI.H.1.a(iii).

For the reasons set forth above, claim 1 would have been obvious over Flink in view of Betz.

## 2. Claims 2-15

Claims 2-15 are obvious in view Flink and Betz for the reasons set forth above in Sections VI.G.2-VI.G.10.

The concentration of propylene glycol suggested by Flink (*see* Sections VI.G.1, VI.G.2, VI.H.1.a(iii)) falls squarely within the ranges recited in claims 2-4. Ex. 1002, ¶¶170-171.

Similarly, the pH ranges recited in Flink's claim 14 and taught in Flink's Example 7 (pH of 7.4) again fall neatly within the ranges of claims 5-7. Ex. 1002, ¶¶172-173. Moreover, the ranges recited in claims 5-7 each encompass pH of 7.4, the preferred pH for an ordinary parenteral formulation. *Id.*

The use of a preservative at the claimed ranges as recited in claims 8-9 is, again, exactly as disclosed in Flink's claim 14 and as recited in Flink's examples, including Example 7 (5 mg/ml of phenol). Ex. 1002, ¶¶174-175.

And the specific GLP-1 agonists recited in claims 10-15 are, again, expressly recited in the claims of Flink. Ex. 1002, ¶¶176-187.

### 3. Claim 16

Claim 16 recites a method of preparing a formulation similar to that described in claims 1-15, which includes the steps of:

- a) preparing a first solution by dissolving preservative, propylene glycol and buffer in water;
- b) preparing a second solution by dissolving the GLP-1 agonist in water;
- c) mixing the first and second solutions; and
- d) adjusting the pH of the mixture in c) to a pH of from about 7.0 to about 10.0.

This claim makes no contribution to the art—it merely recites conventional mixing steps to arrive at the formulation recited in claim 1. The routine nature of these steps is confirmed by Betz. In Betz, the pharmaceutical formulations were

prepared by dilution of an excipient solution with the bulk peptide solution. Ex. 1005, 16-17. As shown in Table 1 of Betz, the excipient solution included propylene glycol. *Id.*, 17. After the excipient mixture is mixed with the peptide solution, the pH is adjusted to the desired value. Ex. 1005, 17. These are the same steps recited in claim 16. The POSA following conventional formulation techniques as demonstrated in Betz would have prepared the GLP-1 formulations here using the steps recited in claim 16. Ex. 1002, ¶¶205-209.

#### 4. Claims 17-22

Claims 17-22 are obvious in view of Flink and Betz for the reasons set forth above regarding claims 2-7. *See* Sections VI.G.2-VI.G.4. Considering the prior art, a POSA would not have found significant the minor differences between the pH values recited in claims 21 and 22, and those recited in claims 6 and 7. Ex. 1002 ¶¶210-211.

#### 5. Independent Claims 23, 26, and 29

- a. The effects recited in the preambles of claims 23, 26, and 29 are inherent to the claimed formulation

Claim 23 recites “[a] method for reducing deposits on production equipment during production of a GLP-1 agonist formulation. . .” Claim 26 recites “[a] method for reducing deposits in the final product during production of a GLP-1 agonist formulation. . .” Claim 29 recites “[a] method for reducing the clogging of injection devices by a GLP-1 agonist formulation. . .” Ex. 1001 (emphasis added).

The steps recited in the body of these claims are identical—the only difference between those claims is the preamble. But even to the extent that the preambles are limiting (*see* Section 0), the reduction of deposits and reduction of clogging of injection devices is inherent to the formulation and the obvious result of replacing an excipient known to cause crystallization with one known not to, as described in Betz. To be inherent in the context of obviousness, “the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Par*, 773 F.3d at 1196. Here, reducing deposits and clogging are the natural results of the peptide formulations containing propylene glycol instead of mannitol (*see* Section VI.E.2.d(iii); Ex. 1002, ¶¶76-79), and are thus an inherent property of prior art disclosures.

The formulation recited in these claims and those that depend therefrom is disclosed by Flink alone or in combination with Betz. Sections VI.G, VI.H, VI.I. POSAs would have found any limitation not expressly disclosed by Flink and Betz, including any effects that necessarily flow from the formulations disclosed, obvious over the same references. Ex. 1002, ¶212-213. The preamble recitations directed to reducing deposits and clogging would have been obvious over Flink and Betz because those effects are the natural result of using propylene glycol instead of mannitol in the formulations. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1072 (Fed. Cir. 2011). In *Kao*, the Federal Circuit affirmed the obviousness of a claim to using



a drug where “the only claim element not expressly disclosed in the prior art was the previously-unknown, yet inherent, food-effect property.” *Id.* The claims at issue related to a drug having a greater maximum blood serum concentration when administered with food. The Federal Circuit held that “the claimed ‘food effect’ is an inherent property of [the drug] itself.” *Id.* at 1070. The Federal Circuit explained that “[t]his is not a case where the Board relied on an unknown property of prior art for a teaching. Rather, [the prior art’s] express teachings render the claimed [drug] formulation obvious, and the claimed ‘food effect’ adds nothing of patentable consequence.” *Id.* (emphasis omitted). Other decisions are in accord. *See, e.g., Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (finding claim recitations directed to increasing bioavailability of a drug inherent in the administration the drug).

Here, the only step required to get the claimed effects of reducing deposits or clogging is to “replace the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.” The prior art encouraged the POSA to make this substitution. *See* Section VI.I.5.b. Accordingly, because the claimed formulation was disclosed by Flink alone or in combination with Betz, the resultant reduction in deposits and clogging followed directly from that formulation and are inherent aspects of the prior art. Ex. 1002, ¶¶212-213.

- b. Betz motivated the POSA to use propylene glycol in place of mannitol

Mannitol has known precipitation problems in solution and is likely to leave deposits on equipment and in the final product due to it being a solid. Sections VI.E.2.d(iii), VI.I.1.a, VI.I.1.b(ii); Ex. 1002, ¶¶199-204. Thus, a POSA would have been encouraged to replace mannitol with propylene glycol just as Betz taught. Section VI.I.1.a. Ex. 1002, ¶212.

6. Claims 24, 27, and 30

Claims 24, 27, and 30 depend from claims 23, 26, and 29, respectively, and recite different ways to measure whether clogging and depositing was reduced.

Claim 24 requires “the reduction in deposits on the production equipment during production by the propylene glycol-containing formulation relative to that observed for the formulation containing the previously utilized isotonicity agent [to be] measured by a simulated filling experiment.”

Claim 27 requires “the reduction in deposits in the final product [to be] measured by a reduction in the number of vials and/or cartridges of the propylene glycol-containing formulation that must be discarded due to deposits relative to number of vials and/or cartridges of the formulation containing the previously utilized isotonicity agent that must be discarded due to deposits.”

Claim 30 requires “the reduction in clogging of the injection device by the propylene glycol-containing formulation relative to that observed for the

formulation containing the previously utilized isotonicity agent [to be] measured in a simulated in use study.”

Claims 24, 27, and 30 do not include any patentable features, because the claimed methods for measuring the reduction in deposits or clogging amount to no more than routine testing that POSAs would have performed to test a final pharmaceutical product to ensure quality and stability. Ex. 1002, ¶214; Ex. 1024, 62-70, 98-99, 119-25; Ex. 1068, 3-158.

Regarding claim 24, a POSA would have known to test for deposits on production equipment to determine whether any adsorption or surface precipitation of the formulation would have taken place while in contact with the equipment. Ex. 1002, ¶¶214, 216; Ex. 1024, 120-25. After all, it was well known that precipitation “can occur in membrane filters, filtration equipment, pumps, and tubing” and that taking steps like adding known stabilizing ingredients to the formulation can reduce or avoid precipitation. Ex. 1026, 17-18. The POSA would have tested whether a formulation has the propensity to precipitate or become adsorbed onto the production equipment by exposing a small quantity of the formulation to a scaled-down version of the production equipment to detect whether such occurred. Ex. 1002, ¶216; Ex. 1024, 120-21; Ex. 1072, 1; Ex. 1075, 15-17.

Regarding claim 27, a POSA would have known to discard vials and/or cartridges having deposits as well as to keep track of the number of discarded vials.

For example, a POSA would have understood that all final product lots should be visually inspected and any products with particles or defects should be removed and kept track of for quality control. Ex. 1002, ¶214; Ex. 1024, 98-99; Ex. 1069, 4-8.

Regarding claim 30, POSAs knew to test for clogging of an injection device. For example, POSAs understood that delivery devices like cartridges and pens have many issues related to compatibility of the drug product it contains. They would have tested the final product for stability by (i) evaluating the visual appearance of the formulation for particulates under storage conditions in product samples maintained in inverted or horizontal positions and (ii) generated data that shows that multiple-dose applications are capable of withstanding repeated insertions and withdrawals. Ex. 1002, ¶¶214-215; Ex. 1024, 65 (Table XVI); Ex. 1070, 17, 18; Ex. 1071, 1-3; Ex. 1073, 1; Ex. 1074, 1, 4-5; Ex. 1075, 17, 19.

For the reasons set forth above, claims 24, 27, and 29 were obvious. Ex. 1002, ¶214-217.

#### 7. Claims 25, 28, and 31

Claims 25, 28, and 31 depend from claims 23, 26, and 29, respectively, and require “the isotonicity agent to be replaced by propylene glycol is selected from the group consisting of sorbitol, sucrose, glycine, mannitol, lactose monohydrate, arginin, myo-inositol and dimethylsulfon.” As discussed above regarding claims 23, 26, and 29 (*see* Section VI.I.5.b, VI.I.1.a, VI.I.1.b(ii)), Betz disclosed formulations

in which propylene glycol partially or fully replaced mannitol. Thus, claims 25, 28, and 31 would have been obvious over Flink and Betz for the same reasons set forth in claims 23, 26, and 29, respectively. Ex. 1002, 218. *See* Section VI.I.5.b, VI.I.1.a, VI.I.1.b(ii), VI.I.5.

#### **J. No Secondary Considerations Overcome *Prima Facie* Obviousness**

Patent Owner may argue secondary considerations of nonobviousness overcome the evidence of obviousness presented in this Petition.<sup>17</sup> While any such evidence would be “insufficient” to “overcome the strong [case] of obviousness” here, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007), Petitioner addresses some of the potentially alleged secondary considerations below, and reserves the right to respond to any arguments Patent Owner may assert. Ex. 1002, ¶229.

##### **1. The Methods Recited in the ’833 Patent Produce No Unexpected Results**

The subject matter of the claims of the ’833 patent recite formulations and methods disclosed, contemplated, and/or claimed in the prior art. Sections VI.G, VI.H, VI.I. The ’833 patent presents no unexpected results from these formulations or methods. Ex. 1002, ¶¶219-221.

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<sup>17</sup> Secondary indicia are not relevant to Ground 1, which is based on anticipation.

2. Long-Felt But Unmet Need

Any long-felt but unmet need Patent Owner may allege was satisfied by the formulations disclosed in the prior art. Ex. 1002 ¶222.

3. There Was No Commercial Success

Neither the patent nor its prosecution history presents any evidence of commercial success.

Patent Owner may allege that commercial success supports the non-obviousness of the challenged claims. Here, though, U.S. Patent No. 6,268,343 claimed liraglutide. Ex. 1006, claim 23. That prior art patent would have discouraged, if not outright blocked, others from developing formulations like those recited in the '833 patent, rendering any evidence of commercial success of minimum probative value. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018), cert. denied, 140 S. Ct. 111 (2019); *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013); *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005); see Ex. 1002, ¶¶225-228.

4. There Was No Industry Skepticism

The claimed formulation and methods were disclosed in the prior art. The patent presents no evidence of any skepticism in the art. Ex. 1002, ¶223.

### 5. Copying by Generic Drug Makers Is Irrelevant

Patent Owner may argue that Petitioner and other generic drug companies seek to copy the invention. But “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (citation omitted). *Also see* Ex. 1002, ¶224.

## **VII. THIS PETITION SHOULD NOT BE DENIED INSTITUTION UNDER 35 U.S.C. § 325(D)**

Under 35 U.S.C. § 325(d), the Board considers several factors to evaluate whether a petitioner relies on the same or substantially similar prior art or arguments as those previously presented to the Office. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017) (informative). Here, these factors favor institution.

### **A. Factor 1: Similarities and Material Differences Between the Asserted Art and the Prior Art Involved During Examination**

Flink is materially different from the prior art involved during examination in at least two significant ways. First, the Examiner allowed the claims of the ’833 patent, in part, because the prior art taught a formulation including “phosphate buffer,” which is generic to the claimed species “disodium phosphate dihydrate buffer,” thereby purportedly overcoming the anticipation rejection. Ex. 1003, 204. In contrast, Flink claimed and disclosed formulations containing the disodium

phosphate dihydrate buffer species. Second, unlike the prior art involved during examination, Flink qualifies as prior art under § 102(b) and thus cannot be disqualified under § 103(c).

Betz is also materially different from the prior art involved during examination in at least two ways. First, Betz disclosed using propylene glycol as an isotonic agent in liquid formulations to produce a stable protein formulation that exhibits reduced or no crystallization during storage. Ex. 1005, 2. None of the prior art involved during examination contained this disclosure. Second, Betz cannot be disqualified as prior art under § 103(c).

Factor 1 favors institution.

**B. Factor 2: Cumulative Nature of the Asserted Art to the Prior Art Evaluated During Examination**

Flink and Betz are not cumulative of the prior art evaluated during examination. Flink and Betz cannot be disqualified as prior art under § 103(c), distinguishing Flink and Betz from Knudsen and Engelund, the prior art evaluated during examination. Further, neither Knudsen nor Engelund taught a “disodium phosphate dihydrate buffer” or explicitly disclosed the use of propylene glycol to minimize or eliminate crystallization of protein formulations. Flink and Betz disclosed those features, distinguishing the references from Knudsen and Engelund.

Factor 2 favors institution.



**C. Factor 3: Extent to Which the Asserted Art Was Evaluated During Examination, Including Whether the Prior Art Was the Basis for Rejection**

Betz was never before the Examiner. Although Flink was cited as one of several references disclosed in one of the many IDSs filed during prosecution (Ex. 1003, 246), it was neither cited as a basis for rejecting the claims nor substantively discussed during prosecution. Thus, Factor 3 favors institution. *Unified Patents Inc. v. Pen-One Acquisition Grp., LLC*, IPR2017-02167, Paper 12, at 27 (PTAB Apr. 4, 2018) (instituting review based on two references cited in an IDS during prosecution but not substantively addressed by the Examiner); *Collective Minds Gaming Co. v. Ironburg Inventions Ltd.*, IPR2018-00356, Paper 11, at 8 (PTAB June 7, 2018) (similar).

**D. Factor 4: Extent of the Overlap Between the Arguments Made During Examination and the Manner in Which Petitioner Relies on the Prior Art or Patent Owner Distinguishes the Prior Art**

There is no overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or the manner in which Patent Owner may distinguish the prior art. Factor 4 favors institution.

**E. Factor 5: Whether Petitioner Pointed Out Sufficiently How the Examiner Erred in Its Evaluation of the Asserted Prior Art**

As noted for Factor 3, the Examiner did not address the asserted art during prosecution, nor is there any evidence that the asserted art was substantively evaluated. Factor 5 favors institution.

**F. Factor 6: Extent to Which Additional Evidence and Facts Presented in the Petition Warrant Reconsideration of the Prior Art or Arguments**

As discussed regarding Factor 3, the Examiner did not address the asserted art during prosecution, nor is there any evidence that the asserted art was substantively evaluated. Factor 6 favors institution.

**VIII. CONCLUSION**

Petitioner respectfully requests that the Board institute trial and find all claims of the '833 patent unpatentable.

Dated: July 22, 2020

Respectfully submitted,

/Jovial Wong/  
Jovial Wong  
Reg. No. 60,115

**CERTIFICATION UNDER 37 C.F.R. §42.24(d)**

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for *Inter Partes* Review totals 13,917, which is less than the 14,000 allowed under 37 C.F.R. 42.24(a)(i). In accordance with 37 C.F.R. 42.24(a), this word count does not include table of contents, table of authorities, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: July 22, 2020

Respectfully submitted,

/Jovial Wong/  
Jovial Wong  
Reg. No. 60,115

**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,114,833 and Exhibits 1001-1076** by Federal Express Next Business Day Delivery on the Patent Owner's correspondence address of record for the subject patent as follows:

Novo Nordisk Inc.  
Intellectual Property Department  
800 Scudders Mill Road  
Plainsboro NJ 08536

and by email to the service addresses for Patent Owner listed in Paper No. 16 in IPR2020-00324:

joelke@fenwick.com  
ryan.johnson@fenwick.com  
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Novo833IPR@fenwick.com

Dated: July 22, 2020

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