Filed: March 27, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Patent Owner.

Case IPR2017-01526
Patent Number: 7,476,652

PATENT OWNER'S RESPONSE TO PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,476,652

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF EXHIBITS

Exhibit No.	Description
Ex. 2001	Excerpts from the 2001 Physicians' Desk Reference 1 ("PDR 1")
Ex. 2002	Yalkowsky, S.H.; Krzyzaniak, J.F.; and Ward, G.H. "Formulation-Related Problems Associated with Intravenous Drug Delivery," *J. Pharm. Sci.*, 87, 787-796 (1998)
Ex. 2003	James Oeswein & Steven Shire, Physical Biochemistry of Protein Drugs, in Protein and Peptide Delivery, 167, 192-193 (Vincent Lee, ed. 1991)
Ex. 2004	U.S. Patent No. 5,656,722 to Dorschug ("Dorschug")
Ex. 2005	Canadian Patent No. 1,258,427 ("CA 427")
Ex. 2006	Declaration of Dr. Bernhardt Trout
Ex. 2007	Curriculum Vitae of Dr. Bernhardt Trout
Ex. 2008	March 12, 2018, Deposition Transcript of Dr. Samuel H. Yalkowsky
Ex. 2009	Keith R. Campbell et al., "Insulin glargine," 23(12) Clinical Therapeutics 1938-1957 (December 2001)
Ex. 2010	FDA's Office of Clinical Pharmacology and Biopharmaceutics Review, dated March 4, 2005
Ex. 2011	Jens Brange et al., "Chemical Stability of Insulin 1. Hydrolytic Degradation During Storage of Pharmaceutical Preparations," 9(6) *Pharm. Res.* 715-726 (1992)
Ex. 2012	Victoria Sluzky et al., "Kinetics of Insulin Aggregation in Aqueous Solutions Upon Agitation in the Presence of Hydrophobic Surfaces," 88 Proc. Natl. Acad. Sci. 9377-9381 (1991)

Exhibit No.	Description
Ex. 2013	Dean K. Clodfelter et al., "Effects of Non-Covalent Self-Association on the Subcutaneous Absorption of a Therapeutic Peptide," 15(2) Pharm. Res. 254 (1998)
Ex. 2014	Techniques of Solubilization of Drugs 15-89 (Samuel H. Yalkowsky ed., 1981)
Ex. 2015	Ralf H. Rosskamp & Glen Park, "Long-acting Insulin Analogs," 22(2) Diabetes Care 109-13 (March 1999)
Ex. 2016	Ajay K. Banga, Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems, Chapter 3, 63-80 (1995)
Ex. 2017	J. Jaeger et al., "Peroxide Accumulation in Detergents," 29 *J. Biochem. & Biophys. Methods* 77 (1994)
Ex. 2018	Byron J. Hoogwerf et al., "Advances in the Treatment of Diabetes Mellitus in the Elderly: Development of Insulin Analogues," 9(6) Drugs & Aging 438-448 (1996)
Ex. 2019	David L. Nelson and Michael M. Cox, Lehninger Principles of Biochemistry, Chapters 5, 6 & 29 (3rd ed. 2000)
Ex. 2020	Wei Wang, "Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals," 185 *Int'l J. Pharm*. 129 (1999)
Ex. 2021	Lotte Kreilgaard et al., "Effects of Additives on the Stability of Humicola Lanuginosa Lipase During Freeze-Drying and Storage in the Dried Solid," 88(3) *J. Pharm. Sci*. 281 (1999)
Ex. 2022	R.T. Darrington and B.D. Anderson, "Effects of Insulin Concentration and Self-Association on the Partitioning of its A-21 Cyclic Anhydride Intermediate to Desamido Insulin and Covalent Dimer," 12(7) Pharm. Res. 1077-1084 (1995)

Exhibit No.	Description
Ex. 2023	Jens Brange et al., "Chemical Stability of Insulin. 2. Formation of Higher Molecular Weight Transformation Products During Storage of Pharmaceutical Preparations," 9(6) *Pharm. Res.* 727-734 (1992)
Ex. 2024	Maximo Maislos et al., "The Source of the Circulating Aggregate of Insulin in Type I Diabetic Patients is Therapeutic Insulin," 77 *J. Clin. Invest*. 717-723 (1986)
Ex. 2025	Excerpts from the 2001 Physicians' Desk Reference 2 ("PDR 2")
Ex. 2026	Barry V. Fisher & Patricia B. Porter, 33(4) "Stability of Bovine Insulin," *J. Pharm. Pharmacol* 203-206 (1981)
Ex. 2027	V. M. Ingram, "Gene Mutations in Human Hemoglobin: The Chemical Difference Between Normal and Sickle Cell Hemoglobin," 180 *Nature* 326-328 (Aug. 17, 1957)
Ex. 2028	David R. Owens et al., "Insulins Today and Beyond," 358 The Lancet 739-746 (September 1, 2001)
Ex. 2029	Irving Roberts & Harold C. Urey, "The Mechanisms of Acid Catalyzed Ester Hydrolysis, Esterification and Oxygen Exchange of Carboxylic Acids," 61 *J. Am. Chem. Soc*. 2584 (1939)
Ex. 2030	Excerpts from the 2001 Physicians' Desk Reference 3 ("PDR 3")
Ex. 2031	Thomas H. Fife & M. P. Pujari, "Metal Ion Catalysis in the Hydrolysis of Esters of 2-Hydroxy-1,10-phenanthroline: The Effects of Metal Ions on Intramolecular Carboxyl Group Participation," 28 *Bioorganic Chem*. 357 (2000)
Ex. 2032	N. K. Patel & N. E. Foss, "Interaction of Some Pharmaceuticals with Macromolecules I: Effect of Temperature on the Binding of Parabens and Phenols by Polysorbate 80 and Polyethylene Glycol 4000," 53 *J Pharm.*

Exhibit No.	Description
	Sci. 95 (1964)
Ex. 2033	F. D. Pisano & H. B. Kostenbauder, "Interaction of Preservatives with Macromolecules II: Correlation of Binding Data with Required Preservative Concentrations of p-Hydroxybenzoates in the Presence of Tween 80," 48(6) *J. Am. Pharm. Assoc.* 310 (1957)
Ex. 2034	M. Donbrow et al., "Autoxidation of Polysorbates," 67(12) J. of Pharmaceutical Sciences, 1676-81 (December 1978)
Ex. 2035	Wayne V. Moore & Paula Leppert, "Role of Aggregated Human Growth-Hormone (hGH) in Development of Antibodies to hGH," 51(4) *J. of Clinical Endocrinology and Metabolism* 691 (1980)
Ex. 2036	Robert E. Ratner, Terrence M. Phillips & Malcolm Steiner, "Persistent Cutaneous Insulin Allergy Resulting from High Molecular Height Insulin Aggregates," 39(6) *Diabetes* 728 (1990)
Ex. 2037	F. E. Dische, et al., "Insulin as an Amyloid-Fibril Protein at Sites of Repeated Insulin Injections in a Diabetic Patient," 31(3) *Diabetologia* 158 (1988)
Ex. 2038	Claim Construction Chart
Ex. 2039	Dr. Laurence C. Baker's Declaration
Ex. 2040	Curriculum Vitae of Dr. Laurence C. Baker CV
Ex. 2041	Dr. Laurence C. Baker's Prior Testimony
Ex. 2042	Dr. Laurence C. Baker's Documents Relied On
Ex. 2043	U.S. Dollar Sales of Long-Acting Insulin Products
Ex. 2044	U.S. Share of Lantus Vial Among Long-Acting Injectable Insulin Products

Exhibit No.	Description
Ex. 2045	U.S. Total Prescriptions of Long-Acting Insulin Products
Ex. 2046	U.S. Formulary Placement of Long-Acting Insulin Products
Ex. 2047	U.S. Total Marketing Expenditures of Long-Acting Insulin Products
Ex. 2048	U.S. Price per Insulin Unit of Long-Acting Insulin Products

I. INTRODUCTION

The invention claimed in the '652 patent was borne out of an unexpected stability problem that arose with the original LANTUS® formulation that was approved by the FDA in April 2000 and commercially launched in May 2001. The inventors of the '652 patent solved that problem and claimed their solution in the '652 patent, which is directed to an improved acidic pH insulin glargine pharmaceutical formulation containing, *inter alia*, polysorbate and/or poloxamers as a stabilizing agent. This new glargine formulation was approved by the FDA in March 2005, and has enjoyed significant commercial success. As will be demonstrated in this Patent Owner Response, Petitioner's arguments regarding a motivation to modify the original LANTUS® formulation and reasonable expectation of success are the product of hindsight and a deeply flawed conflation of insulin (i.e., human and animal insulin) and insulin glargine.

Insulin glargine, unlike insulin, has a glycine amino acid at the A21 position instead of an asparagine, and also has 53 amino acids because its B-chain has been elongated by the addition of two arginine amino acids. These structural differences result in drastic differences in the physical and chemical properties of glargine as compared to insulin. Thus, unlike insulin, which is stored at a neutral pH, glargine is stored at an acidic pH and precipitates upon injection into the body as a stable hexamer, forming a subcutaneous depot of glargine that slowly dissociates over

time into physiologically-active monomers of glargine. Petitioner and its expert, Dr. Yalkowsky, incorrectly disregard these differences when arguing that (i) a person of ordinary skill in the art ("POSITA") would have known or expected that glargine pharmaceutical formulations were prone to aggregation; and (ii) a POSITA would have a reasonable expectation of success combining insulin pump-related prior art with the original LANTUS® formulation.

First, Petitioner's case hinges on the proposition that a POSITA, in 2002, would have known or expected that the original LANTUS® formulation[1] was prone to aggregate, and therefore, would have been motivated to address that problem by the addition of a stabilizing agent. The testimony of Patent Owner's expert, Dr. Trout, and the cross-examination testimony of Petitioner's expert, Dr. Yalkowsky, confirm that no such problem was recognized in the prior art, and further that a POSITA would not have expected such a problem with the original LANTUS® formulation based on the isolated disclosure of insulin aggregation occurring in the special case of continuous infusion pumps. Indeed, Dr. Yalkowsky's opinion that a POSITA would have expected an aggregation "problem" with the original LANTUS® formulation was proven to be hollow on cross-examination. According to Dr. Yalkowsky, ***all*** proteins are "prone to

[1] Both of Petitioner's primary references—LANTUS Label (Ex. 1004) and Owens (Ex. 1005)—disclose the same original, commercially available LANTUS® formulation.

aggregation" because they can be forced to aggregate upon the application of extreme heat and agitation regardless of whether those conditions occur during normal use.

Moreover, Petitioner's attempts to associate the disclosure in the prior art regarding insulin aggregation in the context of pumps with the original LANTUS formulation fall flat when the differences between insulin and glargine are considered. As explained in detail in this Response, a POSITA would not have expected glargine to be prone to the chemical and physical instabilities based on the disclosures in the prior art regarding insulin aggregation because glargine (i) has a glycine substituted for asparagine at position A21; (ii) has an isoelectric point outside of the acidic range; (iii) is not used in pumps; and (iv) has an elongated B-chain. In addition, Dr. Yalkowsky's theory that glargine is more monomeric, and therefore, prone to aggregation, was proven to be unsupported and contrary to the cited evidence.

Second, Petitioner has failed to show that a POSITA would have had a reasonable expectation of success in arriving at the claimed pharmaceutical formulation. In this regard, the Petition focuses entirely on *in vitro* stabilization and ignores the potential impact the addition of a surfactant could have on the *in vivo* absorption of glargine. Glargine's unique mechanism of action depends upon its aggregation to form hexamers, and its precipitation as a hexamer when injected

into the body. As explained by Dr. Trout, there is ample literature showing that surfactants were known to affect the rates of drug dissolution, aggregation, and precipitation in unpredictable ways. In addition, Petitioner has failed to account for numerous negative consequences that a POSITA would have been aware could occur if a surfactant were added to the original LANTUS® formulation. For example, surfactants such as polysorbates were known to be susceptible to hydrolysis in acidic environments. Surfactants also held the potential to discolor the glargine formulation, interfere with the microbial properties of m-cresol, and undergo autoxidation that could result in the presence of harmful peroxides in the formulation. The failure to consider these negative consequences is fatal to Petitioner's assertion that a POSITA would have had a reasonable expectation of success.

Finally, the commercial success of the reformulated LANTUS® vial product is objective evidence of non-obviousness. The reformulated LANTUS® vial product has enjoyed tremendous commercial success and is covered by claims 1-12, 15-21 and 23-25 of the '652 patent. Furthermore, as explained by Dr. Trout and Dr. Baker, the formulation disclosed and claimed in the '652 patent and used in the reformulated LANTUS® vial averted potential regulatory action and negative sales impacts that could have occurred had Patent Owner not remedied the aggregation issues with the original LANTUS® vial. Thus, there is a nexus

between the claimed invention in the '652 patent and the commercial success of the LANTUS® vial product.

For the reasons set forth more fully below, Patent Owner respectfully requests that the Board reject Petitioner's arguments regarding obviousness and find that the claims of the '652 patent are patentable.

II. BACKGROUND

A. Insulin

"Insulin" is described in the '652 patent (and in the prior art) as "a polypeptide of 51 amino acids, which are divided into 2 amino acid chains: the A chain having 21 amino acids and the B chain having 30 amino acids" where "[t]he chains are connected to one another by means of 2 disulfide bridges." Ex. 1001 at 2:9-13; *see also* Ex. 1014 at 3 (Figure 1), 28 ("Insulin is composed of 51 amino acids in two peptide chains (A and B) linked by two disulfide bonds"). Human, bovine, and porcine insulin fall within this description, and have been used for diabetes therapy since well before the filing date of the '652 patent.[2] Ex. 2006, ¶ 52. The figure below depicts the primary structure of human insulin (with black designating the amino acids that are invariant among species of insulin):

[2] Porcine insulin and bovine insulin differ from human insulin in position B30 (alanine instead of threonine). Ex. 1014 at 11 (Figure 1). Bovine insulin additionally differs in position A8 (alanine instead of threonine) and position A10 (valine instead of isoleucine).

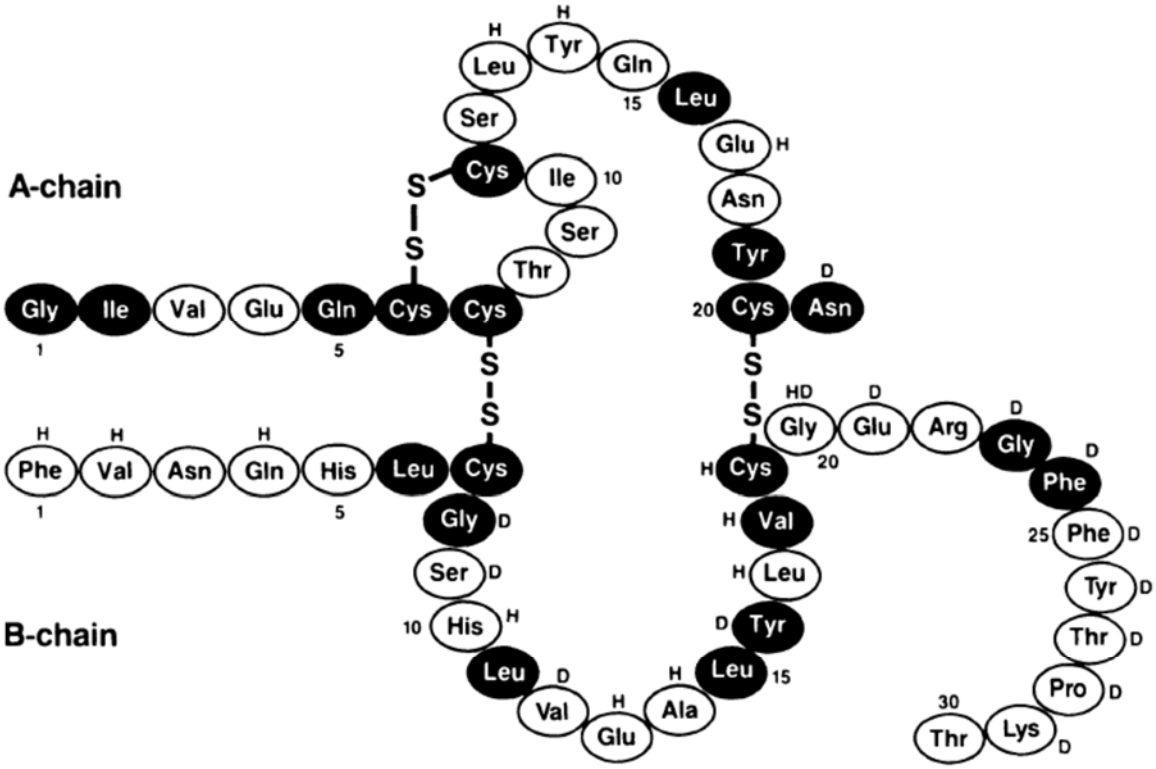


Figure 1. The primary structure of human insulin. The black residues designate the amino acids which are invariant among species of insulin. The letters indicate the residues involved in association of the molecule: D, dimer formation; H, hexamer formation. Porcine insulin only differs in position B30 (Ala instead of Thr). Bovine insulin has the same substitution and contains, in addition, Ala in position A8 and valine in position A10.

Ex. 1014 at 3; *see* Ex. 1003, ¶ 94.

The physiologically active form of insulin is the monomer – a single molecule of insulin. Ex. 2006, ¶ 54. In solution, insulin molecules were known to come together to form several self-association structures (i.e., "native" or desirable aggregates), including dimers (2 molecules), tetramers (4 molecules), and hexamers (6 molecules). Ex. 2006, ¶¶ 55-57. Brange explained that "[i]nsulin exists as a monomer only at low concentration … dimerizes at higher concentrations relevant for pharmaceutical formulation, and in the pH range 4-8, in

the presence of zinc ions, three dimers assemble at concentrations >0.01 mM further into a hexamer." Ex. 1014 at 3; *see also* Ex. 1014 at 5 (Figure 3).

Insulin was also known to aggregate in several non-native (undesirable) ways due to physical or chemical instability. Ex. 2006, ¶ 58. Insulin molecules were known to be susceptible to two main types of chemical degradation – hydrolysis to desamido insulin, and intermolecular reactions such as transamidation forming higher-molecular-weight transformation products (i.e., covalent polymers). Ex. 1014 at 28 ("Chemical deterioration of insulin during storage of pharmaceutical preparations is mainly due to two categories of chemical reactions, hydrolysis and intermolecular transformation reactions leading to insulin HMWT [higher-molecular-weight transformation] products."); Ex. 2006, ¶¶ 59-62. Both types of chemical instabilities occurred in acidic environments, and primarily resulted from the presence of an asparagine amino acid residue at the A21 position in insulin. Ex. 2006, ¶ 62. Because asparagine has an amide group, it is one of two amino acids (the other being glutamine) known to undergo a process called "deamidation" caused by hydrolysis of the amide, which results in the formation of desamido insulin and covalent HMWT products in acidic solution. Ex. 2006, ¶ 60.

The two main types of physical instability that were known to affect insulin were undesirable isoelectric precipitation and fibrillation. Ex. 2006, ¶ 63. "Isoelectric precipitation" of insulin occurs when insulin molecules precipitate out

of solution because the pH of the solution changes to be closer to insulin's isoelectric point, i.e., the point at which the molecules exhibit their lowest solubility. Ex. 2006, ¶ 64. Because native insulins have their isoelectric points in the acidic range (*id*.), "in unbuffered, neutral solutions of insulin, even small amounts of acidic substances, e.g., leachables from polymer materials used in devices for insulin delivery (Melberg et al., 1988), can result in sufficient decrease in pH to bring insulin into its isoelectric precipitation zone (pH 4.5-6.5)." Ex. 1014 at 8. This isoelectric precipitation leads to the "[f]ormation of amorphous or crystalline precipitates from solutions of insulin." *Id*. Isoelectric precipitation was specifically associated with neutral formulations of insulins used in infusion pumps. Ex. 2006, ¶ 65.

Fibrillation—a type of physical instability that may manifest as a viscous gel or insoluble precipitates—was believed to be caused by the unfolding of insulin molecules, which exposes otherwise hidden hydrophobic residues and results in molecules aggregating together. Ex. 2006, ¶ 66. Not all insulins have the same tendency to fibrillate. For example, "bovine insulin is significantly more prone to fibrillation than [human and porcine insulins]." Ex. 1015 at 2. Fibrillation can be induced in some species of insulin by applying extreme conditions of heat, agitation, and exposure to hydrophobic surfaces, for a sufficiently long duration of time. Ex. 2006, ¶ 70.

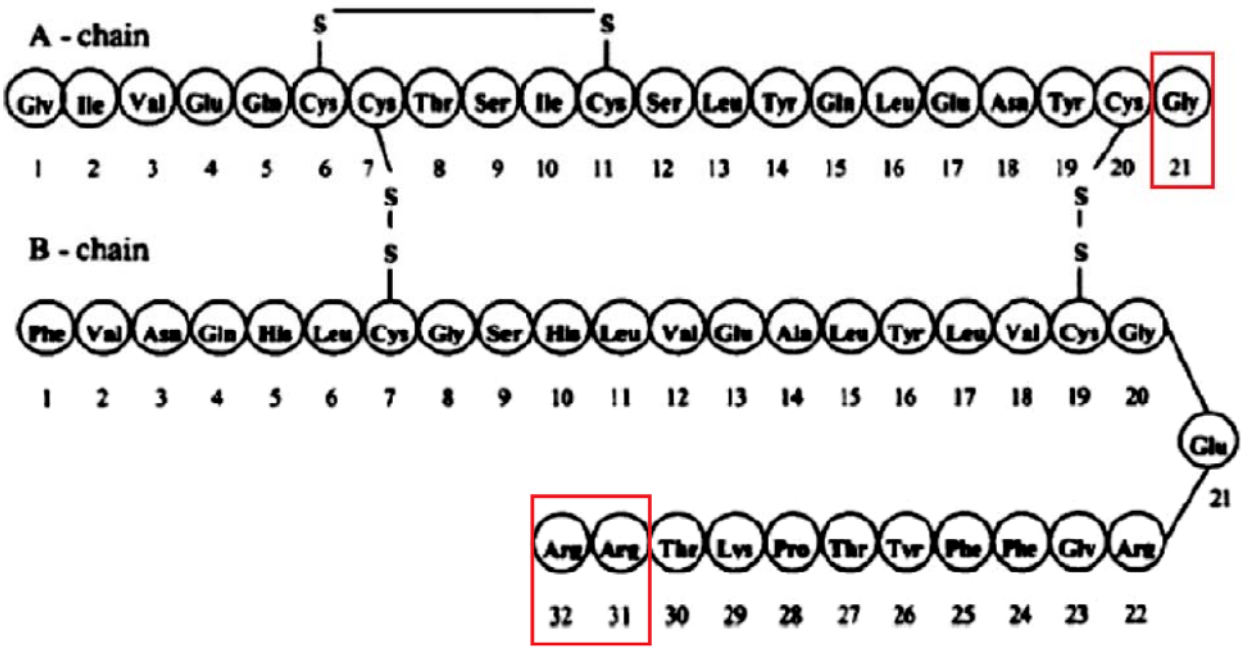
Structurally, it was believed that the C-terminus of the B-chain of insulin had to be "displaced" in order to expose the buried hydrophobic surfaces that cause fibrillation. Ex. 2006, ¶ 67. Thus, Brange explained that increasing truncation, i.e., shortening of the B-chain in the insulin molecule, increases the tendency to fibrillate. *Id*. Brange also discloses that insulin monomers were more prone to denaturation and fibrillation, as compared to dimers and hexamers. Ex. 1015 at 6; Ex. 1014 at 10. Because zinc promotes the formation of hexamers, the addition of zinc achieves a "fibrillation-inhibitory effect" in insulin formulations. Ex. 1015 at 7; Ex. 2006, ¶¶ 68-69.

Physical conditions were also known to affect the tendency of an insulin to fibrillate. For example, increasing the surface area of hydrophobic material, along with agitation from "interfacial and shear forces" on insulin molecules had been shown to increase the tendency of bovine insulin to fibrillate. Ex. 2006, ¶¶ 69-71. Thus, as with isoelectric precipitation, nothing in the record suggests that fibrillation in insulin pharmaceutical formulations was an issue outside of pumps, where the amount of rubber tubing and plastic and metal components offered large hydrophobic surfaces that, in combination with the elevated temperatures from being worn close to the body and extreme conditions of mechanical agitation from the constant motion that introduced shear stress on the insulin molecules, resulted

in an increased tendency to fibrillation. Ex. 2006, ¶¶ 72-73; Ex. 2008 at 35:25-36:12.

B. Insulin Glargine

Glargine, in contrast to insulins previously discussed, is a recombinantly produced insulin analog with 53 amino acids and significant modifications to its primary structure. Ex. 2006, ¶ 74. The figure below identifies the differences between glargine's primary structure and that of human insulin. The C-terminal of the B-chain of glargine is elongated as compared to insulin by the addition of two arginine amino acid residues, and glycine is substituted for asparagine at the A21 position. While glargine targets the same receptors in the body as insulin, the modifications in glargine's primary structure makes it exhibit vastly different physical, chemical, and pharmaceutical properties as compared to insulin. Ex. 1001 at 2:55-65; Ex. 2006, ¶¶ 75-78.



Ex. 2006, ¶ 74

For example, the alterations to glargine shift its isoelectric point to a neutral pH around 7.0, making glargine, unlike insulin, soluble in acidic environments, but largely insoluble at the near-neutral environment of the human body. Ex. 2006, ¶ 76. Thus, upon injection into the neutral pH of human subcutaneous tissue, the acidic glargine solution is neutralized, causing glargine to precipitate (come out of solution as a solid). Ex. 1001 at 2:58-61 ("Insulin glargine is injected as an acidic, clear solution and precipitates on account of its solution properties in the physiological pH range of the subcutaneous tissue as a stable hexamer associate."); Ex. 1004 at 3. The precipitated glargine forms a storage reservoir in the patient's body, allowing a slower and more stable release and absorption of the drug into the body. Ex. 1001 at 2:61-65; *see also* Ex. 1011 at 2 ("Alterations to the molecule

also favour the formation of insulin hexamers which further delay absorption from the tissues."). Because of these unique properties, glargine is "not intended for intravenous administration or for use in continuous-infusion insulin pumps." Ex. 2009 at 6; *see also* Ex. 2006, ¶ 77.

III. OVERVIEW OF THE '652 PATENT

A. The Claimed Invention

A problem arose with the stability of the original glargine formulation that the FDA approved in April 2000 and that Sanofi commercially launched in May 2001. Namely, it was found that the LANTUS® formulation unexpectedly exhibited aggregation and precipitation in the acidic pH range at which glargine is stored and at which glargine was previously known to be fully soluble. Ex. 2006, ¶¶ 96, 168. In order to solve this problem, the inventors reformulated glargine to include a nonionic surfactant, which allowed glargine to remain stable (i.e., avoid aggregation and precipitation) in its acidic storage environment but without interfering with glargine's post-injection precipitation properties. Ex. 1001 at 3:41-45; 5:58-10:63; Ex. 2006, ¶¶ 168-169. The '652 patent claims this solution.

In particular, the '652 patent is directed to glargine formulations containing polysorbate and/or poloxamers that increase stability at the acidic storage pH. *See* Ex. 1001 at 6:10-9:42; *see also id.* at 5:36-57 (reporting the results of in-use testing involving shaking the tested formulations over a period of time to simulate usage).

As the original LANTUS® formulation did not contain polysorbate or a poloxamer, it did not exhibit the improved stability seen in certain embodiments of the invention that are exemplified in the '652 patent. Ex. 1004 at 3; Ex. 1001 at 6:10-9:42. Thus, following the invention of the '652 patent, original LANTUS® was reformulated to embody the '652 patent invention, and has enjoyed tremendous commercial success. Ex. 2010 at 41. The FDA approved the new formulation and the '652 patent is listed in the Orange Book for LANTUS®. *Id*.

The '652 patent has 25 total claims, three of which are independent. Claim 1 recites a pharmaceutical formulation comprising glargine (referred to as Gly(A21), Arg(B31), Arg(B32)-human insulin); at least one chemical entity chosen from polysorbate 20 and polysorbate 80; at least one preservative; and water, wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

While similar to claim 1, independent claims 7 and 24 require that the pharmaceutical formulation comprise "at least one chemical entity chosen from polysorbate and poloxamers" rather than the specific "polysorbate 20 and polysorbate 80" recited in claim 1. Ex. 1001 at 11:21-28; 12:33-41. Claim 24 further limits the claimed pH range of the pharmaceutical formulation to an "acidic range from 3.5 to 4.5," and specifically requires at least one preservative to be "chosen from cresol." *Id.* at 12:33-41.

Each of the dependent claims of the ’652 patent depend directly or indirectly from claim 1 and further limit the claimed pharmaceutical formulation, requiring, *inter alia*, a specific preservative, narrower pH ranges, and additional components. For example, dependent claims 3 and 4 require specific preservatives chosen from phenols and cresol, respectively. Ex. 1001 at 11:13-16. Dependent claim 11 requires “at least one preservative is chosen from phenol, cresol, chlorocresol, benzyl alcohol, and parabens.” *Id.* at 11:38-40.

Dependent claim 5 requires the pharmaceutical formulation of claim 4 to include zinc. *Id.* at 11:17-18.

Dependent claims 9 and 10 require a pH in the acidic range from 3.5 to 6.8 (claim 9) and from 3.5 to 4.5 (claim 10). *Id.* at 11:32-37.

Dependent claim 6 directs that the formulation include at least one isotonicizing agent, while dependent claim 12 requires the isotonicizing agent to be chosen from a listed subset of such agents. *Id.* at 11:19-20, 41-44. Dependent claim 20 further specifies a concentration range for the isotonizing agents glycerol and mannitol listed in claim 12. *Id.* at 12:19-22.

Dependent claims 13 and 14 are directed to additional buffer components, and dependent claim 22 requires the buffer to be present within a concentration range of 5-250 mM. *Id.* at 11:45-12:3, 12:25-27.

Dependent claim 23 requires a pharmaceutical formulation comprising an isotonicizing agent, polysorbate 20, the preservative cresol and having a pH in the acidic range from 3.5 to 4.5. *Id.* at 12:28-32.

Dependent claims 15 and 16 require particular concentrations of glargine (*id.* at 12:4-9), and dependent claims 17-19 limit the concentration of the surfactant chemical entity. *Id.* at 12:10-18.

Dependent claim 2 requires "at least one chemical entity comprises polysorbate 20" (*id.* at 11:10-12), while dependent claim 8 requires the polysorbate 20 to be "present in an effective amount to avoid turbidity." *Id.* at 11:29-31.

Dependent claim 21 requires the formulation to include NaCl "in a concentration of up to 150 mM." *Id.* at 12:23-24. Dependent claim 25 requires "one or more excipients chosen from acids, alkalis and salts." *Id.* at 12:42-44.

B. The Specification

In the Institution Decision, the Board characterized the background of the '652 patent as "discuss[ing] properties of insulins generally, including insulin glargine and human or animal insulin, without distinguishing between different types of insulin." Paper No. 13 at 20. The Institution Decision further states that "the '652 patent specification refers to what was known about insulins generally, without distinguishing between glargine (i.e., modified insulin), human, and animal insulin.") *Id*. at 22. Patent Owner respectfully disagrees and submits that

the ’652 patent clearly distinguishes between insulin and glargine when discussing the physical and chemical properties of the molecules in formulation. Ex. 2006, ¶¶ 80-89.

The ’652 patent describes “insulin” as a polypeptide consisting of 51 total amino acids, divided into an A chain of 21 amino acids and a B chain of 30 amino acids that are connected by 2 disulfide bridges, Ex. 1001 at 2:9-12, and provides that insulin analogs are distinguishable from insulin “by substitution of at least one naturally occurring amino acid residue with other amino acids and/or addition/removal of at least one amino acid residue from the corresponding, otherwise identical, naturally occurring insulin.” *Id*. at 2:16-21. The specification identifies glargine as an insulin analog that “is ***distinguished*** compared with other long-acting insulins by its flat serum profile and the reduction of the danger of nightly hypoglycemia associated therewith.” *Id*. at 2:62-64.

The specification also distinguishes between formulations of insulin and formulations of glargine:

> The specific preparation of insulin glargine, which leads to the prolonged duration of action, is characterized, ***in contrast to previously described preparations***, by a clear solution having an acidic pH.

Id. at 2:66-3:2. Immediately after contrasting acid-soluble glargine with non-

acidic preparations of insulin,[3] the '652 patent makes the following statement regarding the increased proneness of insulin to aggregate at acidic pH:

> Especially at acidic pH, ***insulins***, however, show a decreased stability and an increased proneness to aggregation on thermal and physiomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation) (Brange et al., J. Ph. Sci 86:517-525 (1997)).

Id. at 3:2-7. The above sentence in the specification is plainly not an admission by the inventors that it was known in the prior art that glargine formulations would have issues with aggregation or that a POSITA would have expected based on the prior art that glargine would be prone to aggregate in a pharmaceutical formulation. Ex. 2006, ¶¶ 85-86. Indeed, the paper cited—Brange 1997 (Ex. 1015)—was a "paper to survey the biochemical literature on insulin fibril formulation" that does not in any way discuss or relate to glargine. Ex. 2006, ¶ 85.

The specification also cites to a second paper—Ex. 2012, Sluzky et al., Proc. Natl. Acad. Sci. 88:9377-9381 (1991) ("Sluzky")—to support an additional statement that "[t]he proneness to aggregation can additionally be promoted by hydrophobic surfaces which are in contact with the solution." Ex. 1001 at 3:8-11. Like the previous sentence and supporting citation to Brange 1997, this statement

[3] Ex. 2011 at 1, ("Today, virtually all insulin preparations are neutral solutions or suspensions.").

is not an admission regarding what was known in the art or would be expected regarding glargine pharmaceutical formulations. Ex. 2006, ¶¶ 87-88. Sluzky, which reports the results of certain testing on bovine Zn-insulin in near-neutral (pH 7.4) phosphate-buffered saline aqueous solutions, does not discuss or relate to glargine. *Id*.

In sum, the specification distinguishes between insulin and glargine in terms of structure, properties, and preparation.[4] Furthermore, the specification, when citing to Brange 1997 and Sluzky, merely states what was known in the art regarding non-acidic preparations of insulin, and in no way admits that it was known or that a POSITA would have expected that glargine pharmaceutical formulations were prone to aggregate at an acidic storage pH. Ex. 2006, ¶¶ 80-89.

C. Claim Construction

As noted in the Board's Institution Decision, none of the claim limitations Petitioner proposes for construction is necessary to resolve the issues raised in this

[4] The Institution Decision also appears to suggest that originally filed claim 1 is evidence that the '652 patent fails to distinguish between glargine and insulin. *See* Paper 13 at 22 (citing Ex. 1001A at 2817). The originally filed claim identifies human, bovine, and porcine insulin *separately* from an insulin analog, an insulin derivative, and an active insulin metabolite. Ex. 1001A at 2817. Furthermore, the claims of the '652 patent were amended to require glargine, a specific insulin analog, thus distinguishing the claims from "insulin" prior art. *Id*. at 2384.

inter partes review.[5] Paper No. 13 at 9.

IV. THE LEVEL OF ORDINARY SKILL IN THE ART

Patent Owner disputes certain aspects of Petitioner's description of the level of ordinary skill in the art. First, Petitioner describes the field of invention as "inhibition of insulin aggregation and increased stability in insulin formulations." Petition at 14. The claimed invention, however, relates to increasing stability of glargine formulations, which presents unique challenges compared to the broader field identified by Petitioner. *See, e.g.*, Ex. 1001 at 3:32-37 (defining the object of the disclosure as "finding preparations for *acid-soluble insulins*") (emphasis added); *id.* at 11:1-9 (claiming a pharmaceutical formulation for the specific insulin analog glargine).

Second, a person of ordinary skill is "also a person of ordinary creativity." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). In other words, a POSITA is "presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). In contrast, Petitioner asserts

[5] Patent Owner's Preliminary Response noted several district court cases involving the '652 Patent. In each of these cases, the district court issued a claim construction ruling involving one or more terms of the '652 patent. Attached as Ex. 2038, is a table showing the constructions of the terms of the '652 patent adopted by the district court and/or agreed to by the parties. Patent Owner does not believe any of these construed terms bear on the issues in this IPR.

that a POSITA would be more than ordinarily creative because she "may have also consulted with one or more team members of experienced professionals to develop an insulin formulation . . ." Petition at 14-15. Courts have previously found that similar definitions are contrary to the generally accepted definition of a POSITA. *See, e.g., Supernus Pharm., Inc. v. Actavis Inc.*, No. 14-06102, 2016 WL 901837, at *2 (D.N.J. Mar. 9, 2016) ("[A] multidisciplinary 'drug team'…. would be innovative and more than ordinarily creative."). Similarly, Petitioner's statement that a POSITA "would have been *well-versed* in the field's literature" (Petition at 15), appears to go beyond the notion that a POSITA is presumed to have known the relevant art at the time of the invention.

Finally, while a POSITA would have had a general understanding regarding factors that contribute to a molecule's instability, nothing in Petitioner's references suggests that a POSITA would have been aware of or expected that the original LANTUS glargine formulation would be prone to aggregation under normal use conditions. Ex. 2006, ¶¶ 113-115; *see also* Ex. 2008 at 35:25-36:12; 43:25-44:12; 51:2-52:8; 54:21-59:12; 63:20-64:4. In 2001, a POSITA would have understood the significant differences between prior insulins and glargine, including that the unique primary structure of glargine promotes stability in acidic environments with a longer profile of action compared to known non-acidic insulin preparations. Ex. 2006, ¶¶ 74-78. Because of the different structure and properties of glargine, a

POSITA would not have readily applied the literature regarding stability issues sometimes seen in non-acidic insulin pump formulations to the original LANTUS® formulation. Ex. 2006, ¶¶ 122-135.

V. THE PRIOR ART AT ISSUE

A. Primary References: LANTUS Label and Owens

The primary reference for Grounds 1-3 is the 2001 Physicians' Desk Reference Entry for LANTUS ("the LANTUS Label"; Ex. 1004), while the primary reference for Grounds 4-6 is an article by D.R. Owens et al. titled *Pharmacokinetics of 125 I-Labeled Insulin Glargine (HOE 901) in Healthy Men*, Diabetes Care 23:813-19 (June 2000) ("Owens"; Ex. 1005). Petitioner relies on the LANTUS Label and Owens for the same disclosure of a glargine formulation—i.e., the original, commercially available LANTUS® formulation that lacked the chemical entity recited in the '652 patent capable of stabilizing the formulation. Neither primary reference discloses a formulation with a chemical entity that is a nonionic surfactant. Neither primary reference discloses the claimed invention of the '652 patent or suggests any problem with the original LANTUS® formulation.

The LANTUS Label discloses the original, commercially-available formulation of glargine for once-daily injection:

> LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

Ex. 1004 at 3; Ex. 2006, ¶¶ 95-98. It further explains that glargine "has been designed to have a low aqueous solubility at neutral pH" and that at pH 4 "it is completely soluble." *Id*. The LANTUS Label also discloses that "[a]fter injection into subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released." *Id*.

The LANTUS Label contains numerous routine dosage and administration precautions. Ex. 2006, ¶ 97. For example, it warns, "LANTUS is not intended for intravenous administration," explaining "[t]he prolonged duration of activity of insulin glargine is dependent upon injection into the subcutaneous tissue." *Id.* at 4. The LANTUS Label also cautions that "LANTUS must only be used if the solution is clear and colorless with no particles visible" and that the formulation "must not be diluted or mixed with any other insulin or solution." *Id.* at 4-5 (noting that "[i]f LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamics profile (e.g., onset of action, time to peak

effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner"). Nowhere, however, does the LANTUS Label disclose or suggest to a POSITA that glargine in pharmaceutical formulation was prone to physical or chemical instability that could result in turbidity. Ex. 2006, ¶¶ 98, 114. The LANTUS Label's use-when-clear instruction is a typical statement found in numerous labels for injectable drugs. Ex. 2006, ¶¶ 98, 117.

Petitioner's second primary reference, Owens, also discloses the original, commercially-available formulation of glargine which does not contain polysorbate or poloxamer. Owens is a research article with the stated objective of determining "the subcutaneous absorption rates and the appearance in plasma of 3 formulations of the long-acting human insulin glargine (HOE 901) differing only in zinc content (15, 30, and 80 µg/ml)." Ex. 1005 at 1. Like the LANTUS Label, Owens discloses that glargine is "injected as a clear acidic solution (pH 4.0) [and] undergoes microprecipitation in the subcutaneous tissue, which retards absorption." *Id.* at 1. Owens discloses a first study involving formulations of glargine with "100 U human insulin [glargine], together with *m*-cresol and glycerol at pH 4.0, with 15 and 80 µg/ml (2.295 and 12.24 µmol/l) zinc, respectively," (*id.* at 3) and a second study involving the same glargine formulation with a higher zinc content of "30 µg/ml (4.59 µmol/l) zinc." *Id.* at 4. Owens does not disclose

or suggest to a POSITA that the glargine formulation was prone to aggregation that could result in turbidity. Ex. 2006, ¶¶ 113-114.

B. Secondary References: Lougheed, Insuman Infusat, and Grau

In contrast to the primary references, which disclose an acidic glargine formulation for once-daily subcutaneous injection, the three secondary references—Lougheed (Ex. 1006), Insuman Infusat (Ex. 1007), and Grau (Ex. 1008)—do not relate to glargine, but instead disclose near neutral solutions or formulations of human or porcine insulin that were specifically for use in continuous infusion pumps. Ex. 2006, ¶¶ 103-111.

Lougheed is a high-level screening study that reports the results of stability investigations in which various pump materials and additives, including surfactants, were tested with solutions of "recrystallized porcine insulin" at pH 7.4. Ex. 1006 at 2. As Petitioner's expert has admitted, Lougheed "only discusses the problem of insulin aggregation with respect to pumps." Ex. 2008 at 32:18-33:1, 40:25-41:3; Ex. 1006 at 1 ("'open-loop' systems … for the continuous infusion of insulin to diabetics"). The solutions tested in Lougheed had a low insulin concentration of 5 IU/ml, which is a level at which insulin was known to be monomeric, as compared to higher concentrations "relevant for pharmaceutical formulation" where insulin is present in its more stable native aggregate forms. Ex. 1014 at 3; *see* Ex. 2008 at 66:1-8 (Dr. Yalkowsky confirming that 5 IU/ml is a

low concentration); *cf*. Ex. 1004 at 3 (glargine concentration in LANTUS is 100 IU/ml). Moreover, the low-concentration insulin solutions tested in Lougheed lacked zinc and phenol, which were known to be present in pharmaceutical formulations to promote insulin hexamer formation and stability. Ex. 2006, ¶¶ 57, 104. Thus, a POSITA would readily appreciate that Lougheed does not disclose pharmaceutical formulations, but instead selects an anionic surfactant for further testing, even though such a surfactant would be known to have negative consequences if used pharmacologically. Ex. 2006, ¶ 105; Ex. 2008 at 69:15-70:10. The preliminary studies in Lougheed, conducted "under severe conditions," produced inconclusive results, offering at best an invitation to conduct further investigation. Ex. 1006 at 7; Ex. 2006, ¶¶ 103-105.

Insuman Infusat describes insulin that is "identical with insulin from humans and is manufactured biosynthetically by means of recombinant DNA technology." Ex. 1007A at 7. The disclosed insulin formulation is solely for use in a pump. *Id*. at 5 ("may only be used in an insulin pump with tetrafluoroethylene or polyethylene catheters" and "may not be used in a peristaltic pump with a silicone catheter."); Ex. 2006, ¶¶ 108-109; Ex. 2008 at 48:5-20. Insuman states that the "[a]ddition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin." *Id*. at 7.

Grau discloses "an insulin preparation specifically formulated for implanted

insulin pumps" that does not contain glargine, but instead a "semi-synthetic human insulin" which is "pH-neutral buffered." Ex. 1008 at 1. The purpose of the research in Grau was to study insulin stability in pumps. Ex. 2006, ¶ 111; Ex. 2008 at 33:2-9. Grau explains that formulations used in pumps are particularly prone to aggregation because "residence time in the reservoir may be relatively long, thermal exposure is greater, and there is long-term contact with metallic and synthetic surfaces as well as mechanical stresses in the pump itself." Ex. 1008 at 1. Grau also distinguishes between formulations for subcutaneous injection and formulations for insulin pumps, noting that insulin formulations for "subcutaneous injection are now uniformly stable and highly purified," but in comparison "insulin for implantable infusion pumps requires further steps to ensure stability." *Id*. at 6.

C. Brange 1993 and Brange 1997

Petitioner and Dr. Yalkowsky principally rely on two publications—Brange 1993 (Ex. 1014) and Brange 1997 (Ex. 1015)—in support of the argument that a POSITA would have expected glargine to be prone to aggregation. As explained by Dr. Trout, neither of these publications relate to glargine, nor would a POSITA have expected pharmaceutical formulations of glargine to be prone to aggregation based on the teachings in these publications regarding chemical and physical instability of human and animal insulin. Ex. 2006, ¶¶ 85-86; *see also* Ex. 2008 at 59:22-60:2.

Brange 1993 contains no reference whatsoever to glargine. Instead, a POSITA would understand that the description of "insulin" in Brange 1993 excludes glargine. Ex. 2006, ¶¶ 85-86. Moreover, a POSITA would not have expected glargine to be prone to the chemical and physical instabilities discussed in Brange 1993 because glargine (i) has a glycine substituted for asparagine at position A21; (ii) has an isolectric point outside of the acidic range; (iii) is not used in pumps; and (iv) has an elongated B-chain. Ex. 2006, ¶¶ 76-77, 86, 125-128.

Brange 1997 is a publication regarding fibrillation in human and animal insulin, and like Brange 1993, it contains no reference to glargine. Ex. 2006, ¶¶ 85, 125-129; Ex. 2008 at 59:22-60:2 (Q. There is no reference or analysis in Brange regarding insulin glargine, correct? A. Correct."). While Brange 1997 attempts to ascertain the factors affecting fibrillation and the molecular mechanism of fibril formation in human and animal insulin, it plainly discloses that even in prior insulins, fibrillation was "rarely encountered" outside of the context of pumps:

> During the first 60 years of insulin therapy, fibrillation-related stability problems during normal handling, storage, or use of insulin preparations were ***rarely encountered***. In the late 1970s, however, the endeavors to obtain normoglycemia in diabetes treatment result in the introduction of devices for continuous insulin infusion (insulin pumps), and it soon became evident that commercial insulin

> formulations were ***not sufficiently stable for long-term use in infusion pumps***.

Ex. 1015 at 6.

Petitioner further notes that Brange 1997 discusses inducing fibrillation by heating or by agitation. *Id*. at 2. A POSITA would understand that fibrillation can be induced in glargine under extreme conditions, just as it can be induced for any protein. Ex. 2006, ¶ 112. But stating that a protein can be induced to fibrillate is far different from stating that pharmaceutical formulations containing that protein are prone to or have a tendency to aggregate under normal use conditions. Ex. 2006, ¶¶ 132-135; *cf*. Ex. 2008 at 42:17-44:12. For much the same reason as discussed with respect to Brange 1993, a POSITA would not have expected glargine pharmaceutical formulations to be prone to fibrillation based on the disclosure in Brange 1997. Ex. 2006, ¶¶ 125-129.

VI. PETITIONER HAS FAILED TO DEMONSTRATE A MOTIVATION TO MODIFY THE PRIOR ART GLARGINE FORMULATIONS

Petitioner's entire obviousness case hinges on Dr. Yalkowsky's assertion that a POSITA would have known or expected that glargine pharmaceutical formulations were "prone to aggregation," and would, on that basis alone, have been motivated to solve this "problem" by modifying the commercially available glargine formulation disclosed in LANTUS Label and/or Owens. Petition at 27; *see id*. at 42, 44, 46, 57, 59-60. However, on cross-examination, Dr. Yalkowsky

clarified that Petitioner's alleged "motivation" is not specific to glargine, or even to prior insulin formulations, but rather applies to ***all*** protein formulations, because, in his opinion, all proteins are "prone to aggregation" because they can be forced to aggregate by introducing enough heat and agitation for a sufficiently long time. Ex. 2008 at 42:17-43:10.

Dr. Yalkowsky's generalized assertion that aggregation can be induced in all insulins and all proteins simply would not motivate a POSITA to modify the commercially available glargine formulations disclosed in LANTUS Label and Owens absent an indication in the prior art of a problem specific to the original glargine formulation. Ex. 2006, ¶ 112. As detailed herein, because the prior art does not disclose any such problem with glargine formulations, nor would a POSITA have expected such a problem, Petitioner's case is revealed as based only on impermissible hindsight.

A. There Is No Prior Art Evidence That Glargine Formulations Were Prone to Aggregation

Petitioner's motivation to modify the prior art glargine formulations is based entirely on the existence of a problem—aggregation of glargine at its acidic storage pH. There is, however, no evidence in the prior art of such a problem with glargine formulations, and therefore, Petitioner has failed to prove its case.

Neither the LANTUS Label nor Owens teach or suggest that the original glargine formulation was prone to aggregation. To the contrary, both references

teach the opposite. The LANTUS Label provides that glargine is "dissolved in a clear aqueous fluid" and "[a]t pH 4 . . . it is completely soluble." Ex. 1004 at 3. Owens similarly states that glargine is injected "as a clear acidic solution." Ex. 1005 at 1. Owens also discloses that the structural modifications present in the amino acid chains of glargine achieve "stabilization of the [glargine] molecule." *Id.* Such statements would have indicated to a POSITA that glargine pharmaceutical formulations were stable in an acidic pH storage environment, not that there was a problem. Ex. 2006, ¶¶ 113-116. On cross-examination, Dr. Yalkowsky admitted that no prior art reference discloses an aggregation problem in glargine, and that he did not know "in the absence of data" whether or not insulin glargine would be prone to aggregate. Ex. 2008 at 30:17-31:10. Dr. Yalkowsky further acknowledged that his opinion regarding the tendency of glargine formulations to aggregate was his own hypothesis that is *not* disclosed in the prior art.[6] Ex. 2008 at 63:20-64:4.

Nevertheless, Petitioner attempts to use a general statement in the LANTUS Label that "LANTUS must only be used if the solution is clear and colorless with no particles visible" to suggest that glargine was prone to aggregate. Petition at 27.

[6] Dr. Yalkowsky's 2017 "hypothesis" is flawed for a number of reasons addressed in detail in **Section VI.B**. In addition, the fact that this hypothesis was developed as part of this IPR, as opposed to independent work prior to any involvement in this matter, plainly makes it susceptible to hindsight bias. *See* Ex. 2008 at 45:20-23.

As explained by Dr. Trout, a POSITA would not interpret this standard use-only-when-clear patient instruction as indicating that glargine had an increased tendency to aggregate. Ex. 2006, ¶¶ 117-119. Indeed, there are numerous reasons why a pharmaceutical formulation might become cloudy that are entirely unrelated to physical or chemical instability of the formulation. Ex. 2006, ¶¶ 118-119; *see also* Ex. 2002 at 1 (Publication authored by Petitioner's expert indicating problems with intravenous drug delivery can be "independent of the formulation" and can include "microbiological contamination" and "particular matter"). Thus, the use-only-when-clear instruction is found in most if not all labels for injectable drugs. Ex. 2006, ¶ 117. The LANTUS Label itself offers at least one possible alternative explanation for the cloudiness: "[i]f LANTUS is diluted or mixed, the solution may become cloudy." Ex. 1004 at 4.

The remaining references cited by Petitioner also fail to disclose that glargine formulations had a tendency to aggregate at an acidic storage pH. Ex. 2006, ¶¶ 139-148. All of these remaining references relate to chemical and physical instability of human and animal insulin formulations, and are completely silent regarding glargine formulations. *See* Exs. 1006, 1007A, 1008, 1014, 1015, 1018.

As none of the prior art of record discloses or suggests any stability issues with the LANTUS label and Owens glargine formulations, Petitioner has failed to

prove its case in all asserted grounds that a POSITA would have been motivated to modify those prior art glargine formulations. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) ("The ordinary artisan would first have needed to recognize the problem . . . . Only after recognizing the existence of the problem would an artisan then turn to the prior art and attempt to develop a new formulation for storage stability."); *In re Nomiya,* 509 F.2d 566, 572 (C.C.P.A. 1975) ("The significance of evidence that a problem was known in the prior art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution.").

B. Petitioner's Evidence Does Not Demonstrate That a POSITA Would Have Expected Glargine Pharmaceutical Formulations to Aggregate

As explained above and acknowledged by Dr. Yalkowsky (Ex. 2008 at 30:8-31:10), Petitioner has failed to produce any prior art evidence that a POSITA would have known that glargine formulations were prone to aggregate at an acidic storage pH, and therefore, the Board need not even entertain Petitioner's argument that "insulin glargine would have also been expected to aggregate." Petition at 7; *see Novartis Pharm. Corp. v. Watson Laboratories, Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015) ("Watson failed to prove that a rivastigmine formulation was known to be susceptible to oxidative degradation. … Without the knowledge of the problem, one of skill in the art would not have been motivated to modify GB '040

with antioxidants as purportedly disclosed in the [prior art]"); *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377-78 (Fed. Cir. 2012) ("Instead, PCM must prove … that a person of ordinary skill in the meat encasement arts at the time of the invention would have recognized the adherence problem recognized by the inventors and found it obvious to produce the meat encasement structure disclosed in the '148 patent to solve that problem."). Nevertheless, even assuming Petitioner's obviousness case can proceed in the absence of any actual disclosure in the prior art that glargine had a tendency to aggregate, Petitioner has nonetheless failed to demonstrate that a POSITA "would have also expected" (based on the prior art) that glargine was prone to aggregate.

1. Petitioner Fails to Account for the Differences Between Insulin and Glargine

First, because of the structural differences between insulin and glargine, and the resultant changes in physical and chemical properties of glargine, a POSITA would not have expected glargine to aggregate based on prior art disclosing chemical and physical instability in human and animal insulin. Ex. 2006, ¶¶ 122-135.

Petitioner mistakenly assumes that chemical instability observed in insulins would have been expected in glargine. *See* Petition at 7 ("Insulin aggregation … contributes to the formation of high-molecular weight polymers including desamido insulin"); Ex. 1003, ¶¶ 163-69. However, as previously explained in

Section II.A, the two main types of chemical instability in acidic solutions of insulin—hydrolysis to desamido insulin and covalent polymerization leading to HMWT products—were both primarily caused by chemical reaction with asparagine at position A21. Ex. 2006, ¶¶ 59-62. Glargine does not have an asparagine at A21, and instead has a glycine that cannot undergo deamidation. Ex. 2006, ¶ 78. In fact, the removal of asparagine from the A21 position in glargine was effected "[i]n an attempt to increase the stability in acid medium." Ex. 2004 at 2:51-61. However, rather than understanding, as a POSITA would have known at the critical date, that the substitution of the A21 asparagine would prevent glargine's deamidation or transamidation at that residue, Petitioner's expert has confessed to not knowing which positions on insulin's primary structure are susceptible to deamidation, or which amino acids are capable of undergoing deamidation.[7] Ex. 2008 at 42:5-13. Accordingly, a POSITA would have understood that the chemical instability reported in the prior art, and relied upon by Petitioner, would not be expected in glargine formulations. Ex. 2006, ¶¶ 78, 123-124, 148.

[7] Moreover, although Petitioner relies on Lougheed to argue that "[i]nsulin aggregation … contributed to the formation of high-molecular weight polymers [and] desamido insulin," Petition at 7, 19 (citing Ex. 1006 at 1), Dr. Yalkowsky has admitted to not knowing what desamido insulin is. Ex. 2008 at 41:4-28.

Similarly, a POSITA would not have expected the prior art disclosure of aggregation due to physical instability in human and animal insulin to apply to glargine. As discussed in **Section II.A**, insulin was known to experience two main types of physical instability: isoelectric precipitation in acidic environments, and fibrillation. Ex. 2006, ¶ 63. Regarding isoelectric precipitation, a POSITA would have understood that while insulins experienced isoelectric precipitation in acidic media because their isoelectric points lie in the acidic pH range, glargine would not similarly precipitate because its structural modifications shift the isoelectric point to neutral pH. Ex. 2006, ¶¶ 76-77, 140. Thus, Petitioner's reliance on the prior art teaching of isoelectric precipitation of human and animal insulin in acidic media is misplaced.

Regarding fibrillation, Petitioner and Dr. Yalkowsky principally rely on Brange 1997. But this reference is plainly about human and animal insulin solutions, and makes no suggestion regarding the tendency of glargine formulations to fibrillate. Ex. 2006, ¶¶ 85-86, 125-128; *see also id*. at ¶¶ 129-131. Even among human and animal insulins, Brange reported significant differences in the tendency to fibrillate based on their primary structure (amino acid sequence). Ex. 1015 at 2 ("In contrast, bovine insulin is significantly more prone to fibrillation than the other two species of insulin."). Significantly, Brange 1997 explains that "fibrillation-related stability problems during normal handling, storage, or use of

insulin preparations were rarely encountered" outside of the context of insulin pumps, *id*. at 6, and Dr. Yalkowsky has admitted that while insulin had been delivered in vials for almost a hundred years, he has no evidence that insulin fibrillation was ever reported to be a problem outside of pumps. Ex. 2008 at 48:21-49:6, 51:25-52:8. Glargine is not used in pumps. Ex. 2006, ¶ 77; *see also* Ex. 2008 at 36:19-37:19, 38:14-39:3.

On cross-examination, when asked to produce prior art evidence to support his opinion that insulin aggregation was a major obstacle outside of the context of pumps (Ex. 1003, ¶ 103), Dr. Yalkowsky raised a new and credulity-straining argument that it was an obstacle because insulin has to be refrigerated and has an expiration date. Ex. 2008 at 50:17-51:17. The Board should reject this far-fetched argument as premised on a lack of understanding of protein therapeutics, all of which carry an expiration date and invariably instruct that the product be refrigerated. Ex. 2006, ¶ 120. A POSITA would not have been motivated to modify the glargine formulations disclosed in LANTUS Label and Owens because those formulations had to be refrigerated and had an expiration date. *Id*.

Petitioner also disregards the structural difference in glargine when citing to the portion of Brange 1997 that states that "the propensity to fibril formation increases with increasing truncation" of the B-chain in insulin. Ex. 1003, ¶ 105 (citing Ex. 1015 at 6); Ex. 2008 at 64:25-65:8. Rather than a "truncation," glargine

has an *elongation* of its B-chain by two amino acids as compared to insulin. Ex. 2006, ¶¶ 127-128. Moreover, Brange 1997 suggests that the C-terminal of the B-chain played an important role in how fibrillation occurs, because, according to Brange 1997, "displacement of the B-chain COOH-terminal from its normal position … is a prerequisite for formulation of insulin fibrils." Ex. 1015 at 6. Petitioner offers no explanation why a POSITA would expect the same mechanics of fibrillation for glargine given the modification of the B-chain, C-terminal.

Rather than account for the differences between insulin and glargine, Dr. Yalkowsky has testified that, in his understanding, glargine behaves in the same way as human and animal insulins because "if you count amino acids as an arbitrary measure of what [glargine] is composed of, it's about 92 percent insulin," and "[t]here's only less than a 10 percent difference in the number, in the amino acids." Ex. 2008 at 61:20-62:25. Dr. Yalkowsky further suggests that insulin and glargine behave in the same way because of the existence of the same disulfide bridges. *Id*. This reasoning similarly lacks a scientific basis given that it is well known that even a single amino acid difference can result in vast differences in physical and chemical properties. Ex. 2006, ¶ 132. Furthermore, the literature shows that insulin analogs such as insulin lispro (which Dr. Yalkowksy is not familiar with, Ex. 2008 at 57:12-19) and insulin aspart also share the same disulfide linkage as insulin, but were known to have a significantly diminished

ability to aggregate. Ex. 2006, ¶¶ 133-135.

2. The Evidence Does Not Support Petitioner's Assertion Regarding the Monomeric Form of Glargine

Second, Petitioner's argument that glargine "would also have been expected to aggregate because of the prevalence of monomeric forms of insulin glargine" is not supported by the references relied upon. Petition at 6-7, 27 (citing Ex. 1003, ¶¶ 105-113, 126 and Ex. 1015 at 3).

Specifically, the Petition relies on Dr. Yalkowsky, who in turn bases his entire opinion regarding the "prevalence of monomeric forms" of glargine on an article by Jones (Ex. 1031). *See* Ex. 1003, ¶ 126; Ex. 2008 at 54:21-55:7. Jones makes a statement that "insulin analogs, such as insulin glargine, are also monomeric compared to pharmacological insulin preparations in which insulin is usually present as a hexamer." Ex. 1031 at 1. The Jones article, in turn, bases this statement regarding the "monomeric" nature of glargine entirely on an article by Hoogwerf (Ex. 2018). Ex. 2006, ¶¶ 136-137; Ex. 2008 at 55:8-20. Hoogwerf, however, does not support the position that glargine is monomeric (or more monomeric than insulin). Ex. 2006, ¶ 138. Rather, Hoogwerf states that insulin analogs which are monomeric, such as insulin lispro, will be *fast-acting*, but clearly makes no such statement regarding glargine, which is not a fast-acting insulin analog. Ex. 2018 at 1 ("Insulin analogues, which are monomeric, will have a faster onset of action (more closely approximating endogenous insulin) and

greater reproducibility of effect."), 7 ("The insulin analogue that has been studied most extensively in clinical trials is insulin lispro. This is a monomeric insulin…"); *see also* Ex. 2006 at ¶ 138. Accordingly, a POSITA would understand that the statement in Jones is based on a misreading of Hoogwerf, which only describes fast-acting insulin analogs as monomeric. Ex. 2006, ¶¶ 136-138. Indeed, Dr. Yalkowsky admitted that he formed his opinion regarding glargine being more monomeric based entirely on Jones, and without having read Hoogwerf. Ex. 2008 at 54:21-55:22. However, after reviewing Hoogwerf during the deposition, Dr. Yalkowsky acknowledged that it does not support the proposition that glargine is monomeric. *Id*. at 56:12-58:14.

Furthermore, and contrary to Dr. Yalkowsky's unsupported conclusion, a POSITA would expect glargine to be more hexameric than insulin, because in glargine, "[a]lterations to the molecule also favour the formation of insulin hexamers which further delay absorption from the tissues." Ex. 1011 at 2; *see also* Ex. 2006, ¶ 116. The glargine formulation in the LANTUS Label and Owens included zinc and m-cresol, which were both known to promote the formation of hexamers and thus shift the equilibrium in solution away from the monomeric state. Ex. 2006, ¶¶ 116, 159. Glargine, in fact, was known to known to have a higher affinity for m-cresol than insulin, resulting in increased stability for the glargine hexamer in pharmaceutical formulations. *Id*. Accordingly, Petitioner's

argument that glargine would have been expected to aggregate because it was known to be more "monomeric" is contrary to the evidence.

3. The Prior Art Does Not Teach or Suggest That Glargine Formulations are Prone to Aggregation Because of Their Acidic Storage pH

Third, Petitioner suggests that glargine would be expected to aggregate because it is stored at an acidic pH. Petition at 7. In support, Petitioner cites to the declaration of Dr. Yalkowsky, who in turn cites to Brange 1997, a 1980 paper from Lougheed regarding insulin aggregation in pump systems ("Lougheed 1980") (Ex. 1018), and a 1979 patent disclosing a fast-acting insulin preparation for nasal administration ("Hirai") (Ex. 1023). *See* Ex. 1003, ¶¶ 106-108, 117. These references do not provide a POSITA with an expectation that the glargine pharmaceutical formulation disclosed in LANTUS Label and Owens would be prone to aggregation at the acidic storage pH. Ex. 2006, ¶¶ 139-148.

As already explained above, Brange 1997 in no way relates to glargine, and discloses that fibrillation-related instability in prior insulins was only an issue in the context of pumps. Ex. 1015 at 6 ("During the first 60 years of insulin therapy, fibrillation-related stability problems during normal handling, storage, or use of insulin preparations were rarely encountered…[I]t soon became evident that commercial insulin formulations were not sufficiently stable for long-term use in infusion pumps."). With respect to effect of acidic pH on insulin fibrillation,

Brange 1997 theorizes that "fibril formation is mainly driven by nonpolar and entropic effects." Ex. 1015 at 4. Based on this theory in Brange, a POSITA would *not* expect glargine to exhibit the same fibrillation tendency as insulin, because glargine in acidic solution is *less* nonpolar than insulin. Ex. 2006, ¶¶ 144-146. That is, because glargine has two arginines added to its B-chain, a POSITA would understand that those arginines would add a net positive charge of +2 to the glargine molecule in acidic solution, and thereby change the nonpolar and entropic effects acting upon glargine. *Id*. Petitioner and Dr. Yalkowsky have failed to consider the modifications in glargine when conflating glargine with human and animal insulins.

Petitioner's reliance on Lougheed 1980 and Hirai is also misplaced. As Dr. Yalkowksy confirmed at his deposition, "the only instability caused by pH drop that is discussed in Lougheed Ex. 1018 is isoelectric precipitation." Ex. 2008 at 66:14-67:9. A POSITA would have known that such isoelectric precipitation, which occurred in neutral formulations of pump insulin, would not occur in acidic formulations of glargine because of glargine's altered isoelectric point. Ex. 2006, ¶¶ 140-141. Hirai, on the other hand, refers to the chemical degradation of insulin in an acid medium, which is the specific disclosure of instability that Dr. Yalkowsky quotes and relies on in his declaration. Ex. 1023 at 1:64-66 ("However, insulin in an aqueous solution is very unstable and tends to degrade in

an acid medium to deamidated products"); Ex. 1003, ¶ 117. As previously explained, a POSITA would not have expected this type of chemical degradation in glargine in the same way as insulin, due to the substitution of the asparagine at position A21 in glargine. Ex. 2006, ¶¶ 78, 148.

4. A POSITA Would Not Expect Glargine Formulations to Aggregate Based on Prior Art Relating to Insulin Pumps

Fourth, Petitioner incorrectly relies on prior art disclosing aggregation problems for insulin used in infusion pumps as evidence that glargine pharmaceutical formulations would be expected to aggregate. Each of Petitioner's secondary references—Lougheed, Insuman Infusat, and Grau—are directed to formulations (or, in the case of Lougheed, screening studies) for use in insulin pumps. Ex. 1006 at 1 ("'open-loop' systems … for the continuous infusion of insulin to diabetics"); Ex. 1007A at 5 ("may only be used in an insulin pump with tetrafluoroethylene or polyethylene catheters" and "may not be used in a peristaltic pump with a silicone catheter"); Ex. 1008 at 1 ("an insulin preparation specifically formulated for implanted insulin pumps"); *see also* Ex. 2008 at 32:18-33:1 and 40:25-41:3 (Lougheed only relates to pumps), 48:5-20 (same for Insuman), 33:2-9 (same for Grau). Moreover, Brange 1997 discloses that "stability problems during normal handling, storage or use of insulin preparations were rarely encountered" outside of the context of pumps. Ex. 1015 at 6. As explained below, a POSITA would not have expected pharmaceutical glargine formulation to be prone to

aggregation based on the disclosure in the prior art of aggregation in the context of insulin pumps. Ex. 2006, ¶¶ 65, 72-73, 106-111.

Glargine, as disclosed in LANTUS and Owens, is intended for once-daily subcutaneous administration. Ex. 2006, ¶¶ 77, 96-97, 111. Because glargine achieves a prolonged *in vivo* time action profile on account of its structural modifications, a POSITA would have understood that glargine is incompatible with pumps, which try to achieve a prolonged time action through mechanical means. *Id*. at ¶ 77. Thus, a POSITA would have known that glargine is "not intended for intravenous administration or for use in continuous-infusion insulin pumps." Ex. 2009 at 6.

A POSITA would also appreciate that the extreme factors that may lead to instability in a pump would not be present in the delivery device for glargine. Specifically, insulin in pumps experienced isoelectric precipitation due to acidification of the formulations from carbon dioxide precipitating through the rubber tubing, or acid substances leaching from the rubber and plastic components. Ex. 2006, ¶¶ 65, 140. Similarly, the large amount of rubber tubing and plastic and metal components presented significant amounts of hydrophobic surfaces, which in combination with the elevated temperatures from being worn close to the body and extreme conditions of mechanical agitation from the constant motion that introduced constant shear stress on the insulin molecules, all resulted in an

increased tendency to fibrillation in pumps. *Id*. at ¶ 72. For these reasons, the prior art clearly distinguishes between insulin for pump formulations, and makes clear that it is a special case requiring stabilization that is not needed in other insulin formulations. *Id*. at ¶¶ 65, 72-73, 106-111, 140. Accordingly, a POSITA would not have expected glargine pharmaceutical formulations to be prone to aggregation based on the disclosure in the prior art of aggregation of insulin used in continuous infusion pumps.

C. The ’652 Patent Cannot be Used to Supply the Motivation to Modify Glargine Pharmaceutical Formulations

As explained in the previous sections, the prior art fails to disclose a motivation to modify the prior art glargine formulations disclosed in the LANTUS Label and Owens. Any attempt by Petitioner to fill this gap in the prior art by referring to the disclosure in the ’652 patent must be rejected because (i) the specification does not make any admission that a POSITA would have known or would have expected that glargine formulations have a tendency to aggregate; and (ii) the teaching in the ’652 patent that goes beyond the disclosure in the prior art cannot be used to make a case of obviousness.

First, the ’652 patent plainly distinguishes between glargine and insulin, and does not ever admit that it was known or would be expected by a POSITA that glargine or glargine formulations have a tendency to aggregate at glargine’s acidic storage pH. Rather, as explained in **Section III.B**, the specification simply recites

what was known in the art, specifically in Brange 1997 and Sluzky, regarding *insulin* aggregation. Indeed, neither of these prior art references, nor any other prior art reference of record, discloses that glargine was prone to aggregation at its acidic storage pH. Ex. 2006, ¶¶ 79-89; Ex. 2008 at 30:17-31:10, 63:20-64:4.

Second, given the absence of any disclosure in the prior art that glargine had a tendency or would have been expected to aggregate at its acidic storage pH, the disclosure in the '652 patent regarding glargine aggregation goes beyond what was known in the prior art. This knowledge of the inventors, as disclosed in the specification and claims of the application, may not be used to make out a case of obviousness. *See In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969) ("The court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is, we must view the prior art without reading into that art appellant's teachings. The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious.") (internal citations omitted); *In re Ruff*, 256 F.2d 590, 598 (C.C.P.A. 1958) ("To rely on an equivalence known only to the applicant to establish obviousness is to assume that his disclosure is part of the prior art. The mere statement of this proposition reveals its fallaciousness."); *see also Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is

hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.").

Patent Owner thus submits that Petitioner has failed to come forward with evidence in the prior art that would have motivated a POSITA to modify the original glargine formulations disclosed in the LANTUS Label and Owens. Accordingly, Petitioner has not demonstrated by a preponderance of the evidence that claims 1-25 of the '652 patent are unpatentable as obvious.

VII. PETITIONER HAS FAILED TO DEMONSTRATE A REASONABLE EXPECTATION OF SUCCESS

In an attempt to convince the Board that the use of polysorbates and poloxamers in an insulin formulation would have been routine for a POSITA, Petitioner and Dr. Yalkowsky suggested that polysorbates and poloxamers have long been used to stabilize commercially available, regulatory approved insulins.[8] However, when confronted about this position on cross-examination,

[8] Petitioner also seems to imply that because polysorbates and poloxamers were allegedly used in other protein formulations such as tuberculin and human growth hormone, a POSITA would look to use them with insulin. Petition at 8 (citing Ex. 1003, ¶¶ 111-15). However, Petitioner has provided no scientific basis for a POSITA to expect success in using a surfactant employed in one protein formulation with a completely different protein with different structure, function, and physical and chemical properties. Ex. 2006, ¶¶ 46-51, 131, 152. The burden on Petitioner is not to show what can possibly be used in formulation, or what has been considered safe for use, but rather to identify and articulate specific teachings that would motivate a POSITA to combine the cited references with a reasonable expectation of success. Petitioner has not done so.

Dr. Yalkowsky conceded that he had ***no support*** for opining that polysorbates and poloxamers have long been used to stabilize commercially available and regulatory agency-approved insulins:

> Q: So my question is specific to that. You don't have any support for your opinion that polysorbates and poloxamers have long been used to stabilize commercially available and regulatory agency-approved insulins, correct?
>
> A: Yes. That is correct.

Ex. 2008 at 50:6-15. Moreover, Petitioner's suggestion that a POSITA would have modified the commercially available LANTUS formulation with nonionic surfactants from facially disparate insulin references with a reasonable expectation of success ignores the unpredictability of protein formulation. *See P&G Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 996 (Fed. Cir. 2009) ("To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on identified, predictable solutions may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

The formulation of proteins is especially complex, even as compared to that of small molecule drugs, because the myriad physical and chemical interactions between amino acid residues along the peptide chains cause (and are, in turn, influenced by) the complex folding structures of proteins in solution. Ex. 2006, ¶¶ 43-44. This results in highly unpredictable properties in protein formulations, in

which formulation stability, safety, and efficacy are difficult to predict. Dr. Yalkowsky, who has admitted that the vast majority of his experience is in small molecule formulation rather than proteins, attempted to downplay the complexity of protein formulations and argued that "the principles, they're still chemicals, whether it's a bunch of small molecules strung together or individual molecules." Ex. 2008 at 15:25-16:2. Patent Owner submits that the evidence, as explained by Dr. Trout, shows otherwise. *See generally* Ex. 2006, ¶ 149-166.

Indeed, a POSITA would have understood that creating the claimed pharmaceutical protein formulation was a complex task, because in order to have utility, i.e., regulatory approval and commercialization, pharmaceuticals must achieve desired levels of safety and efficacy, both of which require sufficient stability. *Id*. at ¶¶ 43-45. "This task is all the more difficult when formulating proteins, since the effects of multicomponent systems on the physicochemical properties of proteins are highly diverse and not well understood." Ex. 2003 at 28-29.

The claimed multi-component glargine formulation is particularly complex, because each component of the formulation may interact with the protein and other excipients, and the competing considerations must all be taken into account when choosing to introduce an additional component such as the claimed chemical entity. *See* Ex. 2006, ¶ 44; Ex. 2003 at 28-29. Moreover, the prior art shows the highly

unpredictable effects of surfactants in formulations, including their tendency to destabilize protein formulations and cause negative consequences including promoting aggregation, increasing toxicity, and provoking immunological responses. Ex. 2006, ¶¶ 46-51. For example, a POSITA would know that surfactants could lead to enhanced exposure of hydrophobic groups in proteins and thereby potentially enhance non-native aggregation. As such, for the reasons set forth in detail below, Petitioner has failed to demonstrate a reasonable expectation of success.

1. Petitioner Did Not Evaluate the Impact of a Nonionic Surfactant on Glargine's Mechanism of Action

A POSITA would understand that preserving glargine's mechanism of action is essential to maintaining its efficacy and bioavailability, and would know that "when formulating a therapeutic peptide … [e]ven the seemingly innocuous selection of a widely used 'standard physiological diluent' may have a dramatic effect on bioavailability." Ex. 2013 at 8; Ex. 2006, ¶ 152. Petitioner, however, has failed to address whether the addition of a surfactant would interfere with glargine's unique mechanism of action. As explained below, a POSITA would not have had a reasonable expectation of success when adding a surfactant to the commercial glargine formulation because of the unpredictable affect the surfactant could have on the native aggregation, precipitation, absorption, and efficacy of glargine. Ex. 2006, ¶¶ 149-152.

First, Dr. Yalkowsky has described nonionic surfactants (such as Brij-78) as "absorption enhancers" that "enhance" the absorption of insulin by "inhibition of the aggregation of insulin from monomer to dimer or hexamer." Ex. 1028 at 14; Ex. 2008 at 19:22-20:1. However, unlike insulin, glargine's unique mechanism of action depends upon its aggregation to form hexamers, and precipitation as a hexamer when injected into the body. Ex. 2006, ¶ 151; Ex. 1004 at 3 ("The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of absorption and supports once-daily subcutaneous administration."). Accordingly, Dr. Yalkowsky's own work, which he cites in his declaration (Ex. 1003, ¶ 123), would have left a POSITA uncertain as to whether addition of a nonionic surfactant would inhibit the native (i.e., desirable) aggregation that provides the long-acting profile of glargine. Ex. 2006, ¶ 150.

The art warns about the unpredictable nature of nonionic surfactants, and their tendency to increase or decrease the absorption of a drug:

> Surfactants cannot be considered to be 'inert' pharmaceutical adjuvants which can be used indiscriminately in formulations . . . nonionic surfactants can sometimes act synergistically with a drug substance to promote its absorption or activity, or may decrease activity by entrapping the drug in micelles which diffuse slowly and which cannot cross cell membranes intact."

Ex. 2014 at 51; *see also* Ex. 1025 at 5:9-11; Ex. 2013 at 261. Surfactants were known to alter drug absorption, dissolution, and transportation across membranes, in unpredictable ways. Ex. 2006, ¶¶ 46-51. This could suppress glargine's precipitation upon injection or prevent the formation of hexamers, resulting in faster onset pharmacokinetics. Ex. 2006, ¶¶ 150-152; *see* Ex. 2014 at 5 (noting "the ability of the micellar phase to alter the transport properties of solubilized drug molecules"); Ex. 2013 at 260-61 ("solution conditions that alter the effective size of the drug entity may impact its absorption profile").

Petitioner's obviousness analysis focuses exclusively on whether a POSITA would reasonably expect a nonionic surfactant to inhibit aggregation. Even assuming Petitioner is correct that a nonionic surfactant would be expected to inhibit aggregation, this analysis is incomplete because it fails to address whether the surfactant would interfere with glargine's efficacy. Ex. 2006, ¶¶ 149-152. When taking into account the unique way in which glargine achieves its long-lasting effect, a POSITA would have lacked an expectation of success when combining a nonionic surfactant with the commercial glargine formulation because of the unpredictability regarding how the surfactant would interfere with glargine's aggregation and precipitation post-injection. *Id*.

2. Petitioner Fails to Account For Potential Negative Consequences From Adding a Nonionic Surfactant

The prior art reports numerous potential negative consequences that a POSITA would have been aware were possible from adding a nonionic surfactant to the glargine formulations disclosed in the LANTUS Label and Owens. Petitioner's failure to consider these negative consequences undercuts its theory of obviousness. *See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd*., 719 F.3d 1346, 1365 (Fed. Cir. 2013) ("In the search for scientific truth '[o]ne cannot ... pick and choose among isolated disclosures in the prior art to deprecate the claimed invention;' it is necessary to consider prior art that supports unobviousness of the claimed invention, as well as that which weighs against it." (internal citations omitted)).

First, a POSITA would have been aware of the potential hydrolysis or saponification of polysorbate in acidic environments. In Grounds 1 and 4, Petitioner alleges that a POSITA would have been motivated to modify the acidic glargine formulations (pH 4) with polysorbate(s) from Lougheed. Petition at 25-40, 45-55. However, the "Stability and Storage Conditions" section of the polysorbates entry in the 1994 Handbook of Pharmaceutical Excipients ("Handbook"), which Petitioner has presented as Ex. 1019, warns that "gradual saponification occurs with strong acids," i.e., polysorbates were known to

experience hydrolysis in an acidic environment. Ex. 1019 at 30, 50; Ex. 2006, ¶¶ 153-154.

A POSITA would also have believed that adding an ester-containing surfactant such as a polysorbate to the glargine formulation in the LANTUS Label or Owens, which are acidic, could potentially cause the polysorbate to hydrolyze. Ex. 2006, ¶¶ 153-156. Specific to the LANTUS formulation, a POSITA would have known that zinc could catalyze ester hydrolysis. *Id*. at ¶ 155. In addition to reducing the effectiveness as a stabilizing agent, this could also create chemical degradation products of the polysorbate which would act as impurities in the formulation. *Id*. at ¶ 156.

Second, a POSITA would have been aware that addition of a nonionic surfactant could discolor the pharmaceutical formulation. *Id*. at ¶ 157. For example, the polysorbates entry in the Handbook relied on by Petitioner warns that, when using polysorbates, "discoloration and/or precipitation occurs with … phenols." Ex. 1019 at 30, 50. The glargine formulations in the LANTUS Label and Owens contain cresol (Ex. 1004 at 3; Ex. 1005 at 3), and the Handbook entry for cresol confirms that cresol is a phenol. *See* Ex. 1019 at 5 (stating that "[c]resol consists of a mixture of cresol isomers and other phenols" and cresol's chemical name is "methylphenol"). Thus, the addition of polysorbate to the prior LANTUS formulation could cause discoloration, which a POSITA would have wanted to

avoid given the statement in the LANTUS Label that the formulation "must only be used if the solution is clear and colorless with no particles visible." Ex. 1004 at 5.

Third, the addition of the suggested surfactants could interfere with the antimicrobial properties and hexamer-stabilizing effects of m-cresol. Ex. 2006, ¶¶ 158-163. For example, a POSITA would have avoided combining nonionic surfactants, such as polysorbates, with the components of the LANTUS Label and Owens formulations (both of which include cresol as a preservative, Ex. 1004 at 3; Ex. 1005 at 3), because the Handbook entry for cresol states that its "[a]ntimicrobial activity is reduced in the presence of nonionic surfactants." Ex. 1019 at 5. Moreover, interactions between m-cresol and poloxamer surfactants could cause the surfactant to precipitate. *See* Ex. 1019 at 43 ("Polyoxyethylene Alkyl Ethers") ("[P]recipitation occurs with … phenolic substances."); *id*. at 46 ("Polyoxyethylene Castor Oil Derivatives") ("Some organic substances may cause precipitation … especially compounds containing phenolic hydroxyl groups, e.g. phenol… ").

Additionally, phenols such as m-cresol were thought to play a role in stabilizing the hexameric form of glargine in solution. Ex. 1012 at 1; Ex. 1013. Glargine specifically was known to have a higher affinity for phenolic molecules than unmodified insulin, resulting in increased stability for the glargine hexamer.

See Ex. 1013 at 7 ("Most interestingly, we have observed binding of the additional phenol molecule only with [Glargine] and with two other insulin analogues . . . carrying a glycine residue in place of Asn A21 . . ."); Ex. 2015 at 4; Ex. 2028 at 4. A POSITA would have understood that m-cresol's incompatibility with surfactants could result in the cresol being unavailable for stabilizing glargine hexamers, thereby pushing the equilibrium in solution toward the monomer. Ex. 2006, ¶¶ 159, 162-163. Thus, under Petitioner's theory that monomers of glargine are responsible for aggregation, the interaction between surfactant and m-cresol could increase the proportion of monomers and thereby increase aggregation. *Id*.

Finally, a POSITA would have avoided adding polysorbate because of the potential for polysorbate to undergo autooxidation reactions to form harmful peroxides in the formulation. Ex. 2006, ¶¶ 164-165. This is because nonionic surfactants such as polysorbates were known to undergo autoxidation during storage. *Id*. Specific to protein formulations such as glargine, a POSITA would have understood that the accumulation of peroxides generated in the course of autoxidation could damage the peptide. *See* Ex. 2017 at 1; Ex. 1019 at 41 ("Polyoxyethylene Alkyl Ethers") ("Polyoxyethylene alkyl ethers are also incompatible with . . . oxidizable drugs."). Surfactants such as polysorbate were also known to cause oxidative instability to the very protein molecules being allegedly stabilized. Ex. 2006, ¶ 166. The glargine molecule, with its histidine,

cysteine, and tyrosine, residues, would have been expected to be prone to oxidative instability with surfactants because those amino acids were known to be prone to oxidation. *Id*. Thus, a POSITA would have been concerned that the inclusion of a nonionic surfactant would lead to potential toxicity and oxidative instability in glargine formulations. *Id*. at ¶¶ 164-166.

For the reasons set forth above, Petitioner has failed to demonstrate that a POSITA would have had a reasonable expectation of success modifying the commercially available glargine formulation disclosed in the LANTUS Label and Owens because of the myriad negative consequences that could have resulted from the inclusion of a nonionic surfactant.

VIII. OBJECTIVE INDICIA SUPPORT A FINDING OF NON-OBVIOUSNESS

As detailed above, Petitioner has failed to establish a *prima facie* case of obviousness of the ’652 patent. In addition, objective evidence of commercial success supports a finding of nonobviousness. Indeed, the Petition does not account for the well-known commercial success of Patent Owner’s reformulated LANTUS® vial. This real world evidence supporting non-obviousness must be considered as an integral part of the obviousness analysis—not merely as rebuttal evidence. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (“Indeed, we have repeatedly stressed that objective considerations of non-obviousness must be considered in *every* case.” (emphasis in original)); *see also In*

re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1075-77 (Fed. Cir. 2012) (requiring consideration of all objective evidence before reaching a conclusion on obviousness, even under the "prima facie" and "rebuttal" language framework).

A problem arose with the stability of the original LANTUS® vial formulation that the FDA approved in April 2000 and Sanofi commercially launched in May 2001. Ex. 2006, ¶¶ 168-171. Specifically, the original LANTUS® vial formulation exhibited unexpected aggregation and precipitation during storage, resulting in the normally clear formulation becoming visibly cloudy. Driven to solve this problem, the inventors of the '652 patent reformulated the original LANTUS® vial to include a nonionic surfactant aimed at stabilizing the formulation without interfering with the glargine's unique profile of action. This solution is claimed in the '652 patent and Patent Owner's reformulated LANTUS® vial practices claims 1-12, 15-21, and 23-25 of the '652 patent. *Id*. at ¶ 170.

The FDA approved the reformulated LANTUS® vial—which included the addition of a stabilizing nonionic surfactant—in March 2005. Ex. 2039, ¶ 21. The reformulated LANTUS® vial has achieved significant commercial success, with U.S. sales growing from $1.1 billion at its introduction to approximately $2.6 billion in 2017. *Id*., ¶ 29. In fact, since June 2006 sales of reformulated Lantus®

Vial have accounted for approximately 33% of all sales of long-acting injectable insulin and/or insulin analog therapies. *Id*., ¶ 30.

There is a nexus between the commercial success of the reformulated LANTUS® vial and the invention disclosed and claimed in the '652 patent. First, because reformulated LANTUS® vial is the invention that is disclosed and claimed in the '652 patent (Ex. 2006 at ¶ 170), the commercial success of Patent Owner's reformulated LANTUS® vial is directly attributable to the claimed invention of the '652 patent. *See WBIP*, 829 F.3d at 1329 ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." (internal quotations/citation removed)); *see also id.* at 1330 (explaining when "the allegedly obvious patent claim is a combination of prior art elements, we have explained that the patent owner can show that it is the claimed combination as a whole that serves as nexus for the objective evidence"); *Gator Tail, LLC v. Mud Buddy LLC*, 618 F. App'x 992, 999 (Fed. Cir. 2015) ("Where the marketed product is coextensive with the claimed features, then the court should presume that commercial success of the product is due to the patented invention."). In addition, as explained by Dr. Trout and Dr. Baker, the formulation disclosed and claimed in the '652 patent, and used in the reformulated LANTUS® vial averted potential regulatory action and negative sales impacts that could have

occurred had Patent Owner not remedied the aggregation issues with the original LANTUS® vial. Ex. 2006 at ¶¶ 168-172; Ex. 2039, ¶¶ 36-39.

To the extent Petitioner argues that Patent Owner's evidence of commercial success is not due to the claimed invention, but rather, to factors beyond the claimed invention such as, *e.g.*, marketing or product price, such arguments should be rejected. In particular, Dr. Baker analyzed marketing expenditures for long-acting insulin products and determined that sales of reformulated LANTUS® vial exceeded sales for other well-marketed long-acting insulin products despite the fact that "[t]otal marketing expenditures for [reformulated] Lantus® Vial were in line with, or were lower than, many other long-acting insulin products." Ex. 2039, ¶ 43. Dr. Baker also analyzed pricing data and found that, although the price of reformulated LANTUS® vial is "in line with the price" of comparable long-acting vial products, "sales and prescriptions for [reformulated] Lantus® Vial have been substantially higher." *Id.*, ¶ 46. Neither Patent Owner's marketing nor the price of reformulated LANTUS® vial explains the commercial success of reformulated LANTUS® vial. *Id.*, ¶¶ 41-46.

Thus, the commercial success of reformulated LANTUS® vial, which is covered by claims 1-12, 15-21, and 23-25 of the '652 Patent, confirms the non-obviousness of the '652 Patent.

IX. CONCLUSION

For the reasons stated above, Petitioner has failed to prove that claims 1-25 of the '652 patent are unpatentable. The Board should accordingly uphold the validity of all challenged claims.[9]

Dated: March 27, 2018

Respectfully submitted,

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[9] Should the Board find any claim of the '652 patent to be invalid, Patent Owner expressly reserves the right to challenge that decision on Constitutional grounds.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 *et seq*., the undersigned certifies that this document complies with the type-volume limitations. This document contains fewer than 13,320 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

Dated: March 27, 2018

/Elizabeth Stotland Weiswasser/
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CERTIFICATE OF SERVICE

I hereby certify that on March 27, 2018, a copy of the foregoing **PATENT OWNER'S RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,476,652** pursuant to 37 CFR § 42.107 was served by filing this document through the Patent Office's electronic systems as well as delivering a copy via electronic mail upon the following counsel of record for Petitioner:

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