

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.

Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH

Patent Owner.

Patent No. 7,476,652

PETITION FOR *INTER PARTES* REVIEW

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1001	U.S. Patent No. 7,476,652, <i>Acidic Insulin Preparations Having Improved Stability</i> (filed March 25, 2005) (issued January 13, 2009)
1001A Part I	File History for U.S. Patent No. 7,476,652 Part I
1001A Part II	File History for U.S. Patent No. 7,476,652 Part II
1001A Part III	File History for U.S. Patent No. 7,476,652 Part III
1001A Part IV	File History for U.S. Patent No. 7,476,652 Part IV
1001A Part V	File History for U.S. Patent No. 7,476,652 Part V
1001A Part VI	File History for U.S. Patent No. 7,476,652 Part VI
1002	U.S. Patent No. 7,713,930, <i>Acidic Insulin Preparations Having Improved Stability</i> (filed December 4, 2008) (issued May 11, 2010)
1002A	File History for U.S. Patent No. 7,713,930
1003	Expert Declaration of Professor Samuel H. Yalkowsky in Support of Petition for <i>Inter Partes</i> Review of Patent No. 7,476,652 and U.S. Patent No. 7,713,930
1003A	<i>Curriculum Vitae</i> of Professor Samuel H. Yalkowsky
1003B	Materials Reviewed by Professor Samuel H. Yalkowsky
1004	2001 Physician's Desk Reference ("PDR") Entry for LANTUS [®]
1004A	Affidavit of Patricia van Skaik for December 1, 2000 date stamp of 2001 PDR received by the Lloyd Library and Museum (Cincinnati, Ohio)
1005	D.R. Owens et al., "Pharmacokinetics of 125I-Labeled Insulin Glargine (HOE 901) in Healthy Men", <i>Diabetes Care</i> 23:813-19

<u>Exhibit No.</u>	<u>Description</u>
	(June 2000)
1006	W.D. Lougheed et al., “Physical Stability of Insulin Formulations”, <i>Diabetes</i> 32:424-32 (May 1983)
1007	2000 FASS Entry for INSUMAN INFUSAT (January 2000)
1007A	Certified English translation for Ex. 1007 (FASS Entry for INSUMAN INFUSAT)
1008	U. Grau and C.D. Saudek, “Stable Insulin Preparation for Implanted Insulin Pumps”, <i>Diabetes</i> 36:1453-59 (December 1987)
1009	EMA Public Statement on INSUMAN INFUSAT (February 14, 2000), at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/08/news_detail_001094.jsp&mid=WC0b01ac058004d5c1 (accessed June 1, 2017)
1010	FDA Drug Approval for LANTUS® (NDA 02-1081) (April 20, 2000) at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021081 (accessed June 4, 2017)
1011	P. Gillies et al., “Insulin Glargine”, <i>Drugs</i> 59:253-60 (February 2000)
1012	U. Derewenda et al. “Phenol Stabilizes More Helix in a New Symmetrical Zinc Insulin Hexamer”, <i>Nature</i> 338:594-6 (April 1989)
1013	H. Berchtold and R. Hilgenfeld, “Binding of Phenol to R6 Insulin Hexamers”, <i>Biopolymers</i> 51:165-72 (1999)
1014	J. Brange and L. Langkjær, “Insulin Structure and Stability”, in STABILITY AND CHARACTERIZATION OF PROTEIN AND PEPTIDE DRUGS, CASE HISTORIES CHAPTER 11, 315-50 (Vol. 5 of Pharmaceutical Biotechnology) (eds. Y. J. Wang and R. Pearlman) (Plenum Press, New York) (1993)

<u>Exhibit No.</u>	<u>Description</u>
1015	J. Brange et al., "Toward Understanding Insulin Fibrillation", <i>J. Pharm. Sci.</i> 86:517-25 (May 1997)
1016	L.S. Jones et al., "Surfactant-Stabilized Protein Formulations: A Review of Protein-Surfactant Interactions and Novel Analytical Methodologies", in THERAPEUTIC PROTEIN AND PEPTIDE FORMULATION AND DELIVERY, ACS SYMPOSIUM SERIES (eds. Z. Shahrokh et al.) (American Chemical Society, Washington D.C.) (1997)
1017	K. Hallas-Moller, "The Lente Insulins", <i>Diabetes</i> 5:7-14 (1956)
1018	W.D. Loughheed et al., "Insulin Aggregation in Artificial Delivery Systems", <i>Diabetologia</i> 19:1-9 (July 1980)
1019	Excerpts from Handbook of Pharmaceutical Excipients 2 nd Edition (eds. A. Wade and P.J. Weller) (American Pharmaceutical Association, Washington) (The Pharmaceutical Press, London) (1994)
1020	W.R. Ashford and S. Landi, "Stabilizing Properties of Tween 80 in Dilute Protein Solutions", <i>Bull. Parenteral Drug Assoc.</i> 20:74-81 (1966)
1021	H. Thurow and K. Geisen, "Stabilisation of Dissolved Proteins Against Denaturation at Hydrophobic Interfaces", <i>Diabetologia</i> 27:212-18 (1984)
1022	M. Katakam et al., "Effect of Surfactants on the Physical Stability of Recombinant Human Growth Hormone", <i>J. Pharm. Sci.</i> 84:713-16 (June 1995)
1023	U.S. Patent No. 4,153,689 "Stable Insulin Preparation for Nasal Administration" (Issued May 8, 1979) ("Hirai")
1024	U.S. Patent No. 4,839,341 "Stabilized Insulin Formulations" (Issued June 13, 1989) ("Massey")
1025	E.P. Publication No. 0200383 "An Improved Method for

<u>Exhibit No.</u>	<u>Description</u>
	Administering Insulin” (Issued November 5, 1986) (“Su”)
1026	A. Chawla et al. “Aggregation of Insulin, Containing Surfactants, in Contact with Different Materials”, <i>Diabetes</i> 34:420-24 (May 1985)
1027	Y-C Lee et al., “Effect of Brij-78 on Systemic Delivery of Insulin from an Ocular Device” <i>J. Pharm. Sci.</i> 86:430-33 (April 1997)
1028	Y-C Lee et al., “Review on the Systemic Delivery of Insulin via the Ocular Route”, <i>Int’l J. Pharmaceutics</i> 233:1-18 (February 2002)
1029	M. Heile and D. Schneider, “The Evolution of Insulin Therapy in Diabetes Mellitus”, <i>J. Fam. Pract.</i> 61 (5 Suppl.: S6-12 (May 2012)
1030	ADIS R&D Profile “Insulin Glargine: Glargine, HOE 71GT15, HOE 71GT80, HOE 901”, <i>Drugs R&D</i> 2:107-09 (August 1999)
1031	R. Jones, “Insulin Glargine Aventis Pharma”, <i>IDrugs</i> 3:1081-87 (2000)
1032	I.R. Schmolka, “Poloxamers in the Pharmaceutical Industry”, in POLYMERS FOR CONTROLLED DRUG DELIVERY, CHAPTER 10 (CRC Press) (1991)
1033	2001 Rote Liste; Entry for INSUMAN INFUSAT
1033A	Certified Translation of Exh. 1033 (2001 Rote Liste; Entry for INISUMAN INFUSAT)
1033B	Declaration of Hans-Peter Krieger (Deutsche National Bibliothek Librarian) for receipt of 2001 Rote Liste by Deutsche National Bibliothek on February 16, 2001
1034	L. Gatlin and C. Gatlin, “Minimizing Injection Pain & Damage” in INJECTABLE DRUG DEVELOPMENT TECHNIQUES TO REDUCE PAIN AND IRRITATION CHAPTER 17 (eds. P.K. Gupta and G.A. Brazeau) (CRC Press) (1999)

<u>Exhibit No.</u>	<u>Description</u>
1035	2004 CNN Money article regarding Aventis Pharma merger with Sanofi-Synthelabo to create Sanofi-Aventis, the parent corporation of '930 patent assignee Sanofi-Aventis Deutschland GmbH at http://money.cnn.com/2004/04/26/news/international/aventis_sanofi/ (accessed June 2, 2017)

I. INTRODUCTION

Mylan Pharmaceuticals Inc. (“Mylan”) petitions for *Inter Partes* Review (“IPR”) of claims 1-25 of U.S. Patent No. 7,476,652 to Brunner-Schwarz et al., titled “Acidic Insulin Preparations Having Improved Stability” (“the ’652 patent,” Ex. 1001). 37 U.S.C. §311.

By a preponderance of the evidence, this Petition proves the prior art renders unpatentable claims 1-25 of the ’652 patent. An ordinarily skilled artisan (“PHOSITA”¹) would have reason to combine the LANTUS[®] (Insulin Glargine) label [Ex. 1004], which was approved in 2000 and included each component claimed except for a polysorbate or poloxamer, with Lougheed [Ex. 1006], the 2000 FASS Insuman Infusat entry [Ex. 1007 and 1007A] or Grau [Ex. 1008], which provided a reasonable expectation of success that adding a non-ionic surfactant to an insulin formulation would inhibit or eliminate the well-known and recognized tendency for insulin to aggregate. The challenged claims were also obvious to a PHOSITA in view of Owens [Ex. 1005] and Lougheed, the FASS Insuman Infusat entry or Grau.

II. MANDATORY NOTICES

A. Real Parties-In-Interest (37 C.F.R. §42.8(b)(1))

¹ All references herein to the knowledge or understanding of a PHOSITA or a PHOSITA’s interpretation or understanding of a prior art reference are as of the earliest possible priority date unless specifically stated otherwise.

Mylan's real parties-in-interest are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan GmbH, Mylan N.V., Biocon Research Ltd. and Biocon Ltd.

Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan GmbH are subsidiaries of Mylan N.V.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Mylan is not a party to any litigation related to the '652 patent. The '652 patent is related to U.S. Patent No. 7,713,930 and U.S. Patent Application No. 12/773,356 (now abandoned).

C. Identification of Counsel (37 C.F.R. §42.8(b)(3)) and Service Information (37 C.F.R. §42.8(b)(4))

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Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Mylan consents to electronic mail service at jguise@wsgr.com and dcarsten@wsgr.com. A power of attorney pursuant to 37 C.F.R. §42.10(b) accompanies this petition.

III. CERTIFICATIONS (37 C.F.R. §42.104(a))

Mylan certifies that the '652 patent is available for IPR and that Mylan is not barred or estopped from requesting IPR on the identified grounds.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Mylan requests *inter partes* review and cancellation of claims 1-25 of the '652 patent under pre-AIA § 103, as Mylan's detailed statement of the reasons for the relief requested sets forth, supported with exhibit copies, and the Declaration of Dr. Samuel Yalkowsky [Ex. 1003].

The challenged claims relate to an insulin glargine formulation, specifically a formulation created through the simple addition of a polysorbate or poloxamer to a then-commercially available insulin glargine formulation. Claims 1-25 of the '652 patent are unpatentable on these grounds:

Ground	Claims and Basis
1	Claims 1-25 as obvious over the LANTUS [®] label [Ex. 1004] and Lougheed [Ex. 1006]
2	Claims 7 and 24 as obvious over the LANTUS [®] label and the 2000 FASS Insuman Infusat entry [Ex. 1007 and 1007A]
3	Claims 7 and 24 as obvious over the LANTUS [®] label and Grau [Ex. 1008]
4	Claims 1-25 as obvious over Owens [Ex. 1005] and Lougheed
5	Claims 7 and 24 as obvious over Owens and the 2000 FASS Insuman Infusat entry
6	Claims 7 and 24 as obvious over Owens and Grau

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

Researchers have been working since the discovery of insulin in the 1920s to provide diabetic patients with therapeutic insulin preparations that allow constant and consistent glycemic control. Ex. 1003 ¶¶92-97. The development of variant insulin

compositions, including long-acting, controlled release basal insulin analogs, and fast-acting insulin was critical for achieving long-term control of blood sugar levels. *Id.*

Basal insulin glargine (LYS2963016 or HOE 901), developed and patented in the early 1990s, is an example of a biosynthetic recombinant human insulin analogue (Gly(A21)-Arg(B31)-Arg(B32)). *Id.* ¶¶124-28. Insulin glargine differs from human insulin at position 21 (glycine substitution for asparagine) and addition of two arginines at the C-terminal, which results in an altered acidic isoelectric point, as well as a predominantly monomeric insulin form in solution. *Id.* Because of its lowered solubility at neutral pH, insulin glargine precipitates upon injection into a subcutaneous tissue (a relatively neutral environment), resulting in controlled release and a longer time of action. *Id.*; Ex. 1004, 3. Insulin glargine was approved as a therapeutic by the U.S. Food and Drug Administration (FDA) in April 2000. *See* FDA Drug Approval for NDA 021081 [Ex. 1010].

Insulin glargine's mechanism of action centers on its altered isoelectric point, resulting in the therapeutic preparation being more soluble in an acidic environment; by contrast, native human insulin formulations are more soluble at neutral pH. *See* Gillies [Ex. 1011], 2; Ex. 1003 ¶125. Thus, insulin glargine is provided and stored as an acidic (pH 4.0) solution with a predominantly monomeric form. *See* Ex. 1004, 3; Ex. 1003 ¶125. Upon administering the acidic insulin glargine solution, the neutral environment of the patient's subcutaneous tissue causes insulin glargine to precipitate

at the site of injection, effectively prolonging its absorption into the bloodstream. *Id.* Adding zinc prolonged the release of active insulin monomers. Preservatives (*e.g.*, m-cresol) and isotonic agents (*e.g.*, glycerol) were extensively used to further stabilize insulin formulations. *See* Owens [Ex. 1005], 3; Derewenda [Ex. 1012], 1; Berchtold [Ex. 1013], 1; Brange and Langkjær [Ex. 1014], 20; Ex. 1003 ¶125. Patients administered insulin glargine display a 24-hour duration of action with a relatively flat profile over the measured time period. Ex. 1004, 3.

While insulin precipitation *in vivo* can be useful for prolonged therapeutic effect, insulin aggregation before injection (such as during storage) can adversely affect its biological activity, including the well-known and inherent tendency of insulin products to aggregate during storage or agitation of the pharmaceutical solution. *See, e.g.*, Loughheed [Ex. 1006], 1 (“Unfortunately, the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to their prolonged clinical use.”); Brange and Langkjoer [Ex. 1014], 8 (“The inherent tendency of insulin to undergo conformational changes resulting in aggregation and formation of a viscous gel or insoluble precipitates was observed early on in the insulin era.”); Ex. 1003 ¶¶103-08. Factors known to contribute to insulin aggregation (or fibrillation) include acidic pH environments, as well as the prevalence of insulin in a monomeric form, primarily due to exposed hydrophobic surface areas. *See, e.g.*, Brange [Ex. 1015], 3 (“[M]onomers [were] the

least stable species and therefore more likely than dimers and hexamers to undergo conformational changes at hydrophobic interfaces.”).

Insulin aggregation, which differs from the formation of relatively stable insulin dimers and hexamers in solution, contributes to the formation of high-molecular weight polymers including desamido insulin, which can lead to decreases in biological activity of the insulin preparation. Ex. 1006, 1. In fact, labels for insulin preparations, such as insulin glargine, have long warned patients not to use the product unless “the solution is clear and colorless with no particles visible”, *i.e.*, no aggregation of insulin has occurred. Ex. 1004, 5-6. Moreover, insulin glargine would have also been expected to aggregate because of the prevalence of monomeric forms of insulin glargine and its acidic pH environment. *See* Ex. 1003 ¶¶105-08, 126.

Thus, it was long and well-known that insulin had a tendency to aggregate. That inherent characteristic, recognized for decades, hampered efforts to develop insulin solutions, for example, for therapeutic mechanical and automatic infusions. Skilled artisans have expended significant effort in researching and testing ways to prevent insulin aggregation during storage and use. Ex. 1003 ¶¶109-23. In the early 1980s, Lougheed and colleagues performed experiments designed to test insulin formulations under the most severe storage conditions, including varying storage materials (such as copper, titanium and rubber), bacteriostatic agents (cresol, phenol and glycerol), and using different non-ionic, anionic and ionic surfactants to combat

insulin aggregation. Lougheed concluded that aggregate formation was inhibited by the tested nonionic detergents, including Brij 35, Lubrol WX, Triton X100, Tween 20 and Tween 80, and the anionic detergent sodium dodecyl sulfate (SDS). Lougheed [Ex. 1006], 7. Other prior art references confirmed the early findings of Lougheed concluding that adding surfactants to insulin formulations would reduce aggregation and have no adverse effect on the biological activity of insulin. Ex. 1003 ¶¶109-23. In fact, Brange et al. concluded that “[s]tabilization of the insulin hexameric structure and blockage of hydrophobic interfaces by addition of surfactants are the most effective means of counteracting insulin fibrillation.” Brange [Ex. 1015], Abstract; Ex. 1003 ¶109. Accordingly, adding a surfactant to known insulin formulations would have been well-known and routine to PHOSITAs. Ex. 1003 ¶¶109-23.

The fact that non-ionic surfactants stabilize and inhibit aggregation in protein solutions is not surprising. Non-ionic surfactants, including polysorbates and poloxamers, have long been used to stabilize commercially available and FDA-approved human protein and polypeptide pharmaceutical formulations because of their stabilizing effects, low toxicity, and pH independence. *See* Ex. 1003 ¶¶111-15. (“Based on their use in reducing aggregation in other protein formulations as well as their safety, one of ordinary skill in the art would consider polysorbates and poloxamers in formulating insulin.”). Jones noted that the Physician’s Desk Reference (“PDR”) in 1994, well before the earliest priority date of September 9,

2002, included commercial formulations incorporating non-ionic surfactants such as the claimed polysorbate 20 and polysorbate 80:

Table I. Nonionic Surfactants Used in the Pharmaceutical Industry

Chemical Name	Commercial Name	Final Formulation Usage	Quantity	Manufacturer
Polysorbate 20	Tween 20	Actimmune (Interferon gamma-1b)	0.1 mg/ml	Genentech
Polysorbate 40	Tween 40			
Polysorbate 60	Tween 60			
Polysorbate 80	Tween 80	Tubersol (Tuberculin purified protein derivative diagnostic antigen)	0.0005%	Connaught Laboratories
Polysorbate 80	Tween 80	RhoGAM (Rh ₀ (D) Immune Globulin)	0.01%	Ortho Diagnostics Systems
Polysorbate 80	Tween 80	Neupogen (Filgrastim)	0.004%	Amgen
Polysorbate 80	Tween 80	Activase (Recombinant Alteplase)	0.11 mg/ml	Genentech
Polysorbate 80	Tween 80	Koate-HP (Factor VIII)	< 25 ppm	Miles Biologicals
Polysorbate 80	Tween 80	Kogenate (Recombinant Antihemophilic Factor)	<600 µg / 1000 IU	Miles Biologicals
Cetomacrogol 1000	Brij			
Polyethylene Glycol	PEG			

(Adapted from Bam) (15). Final Formulation Usage and Quantity data compiled from *Physicians Desk Reference (PDR)*, 48th Edition, 1994 and is by no means complete. Information regarding specifics of these and other approved excipients for pharmaceuticals found in several handbooks (16-19).

See Ex. 1016, 3.

Moreover, Insuman Infusat, an insulin product approved by the EMA (European Medicines Agency) in 1997 and “specially designed for use in external portable insulin pumps”, was a commercially available insulin therapeutic in at least Austria, France, Sweden, Finland and Germany. See EMEA Public Statement [Ex. 1009], 1. Insuman Infusat included a non-ionic surfactant well before the earliest priority date of the '652 patent. See, e.g., 2000 FASS Insuman Infusat Entry [Ex. 1007 and 1007A], 5 (inclusion of poly(oxyethylene, oxypropylene)glycol to biosynthetic human insulin formulation); Insuman Infusat 2001 Rote Liste Entry [Ex.

1033, 1033A], 6 (inclusion of poloxamer 171 in human recombinant insulin solution).

Insuman Infusat was developed by Hoescht AG, and marketed by Sanofi-Aventis.

It is beyond reasonable dispute that non-ionic surfactants were used in commercially-available insulin formulations for inhibiting protein aggregation long before the priority date of the '652 patent's claims. Thus a PHOSITA would have had reason to improve commercially-available insulin glargine formulations (*see, e.g.*, LANTUS[®] 2000 label [Ex. 1004] and Owens [Ex. 1005]) by anti-aggregation additives, such as Brij 35, Lubrol WX, Triton X100, Tween 20, Tween 80, poloxamer 171, poloxamer 181 and other known surfactants, which were used routinely to inhibit aggregation and formation of particles in peptide and protein-containing formulations. Ex. 1003 ¶128. The challenged '652 patent claims were obvious.

B. '652 Patent--Background

1. The '652 Patent

The '652 patent issued January 13, 2009 as a continuation of an earlier-abandoned U.S. patent application (U.S. Patent Appl. No. 10/461,740) (filed June 13, 2003), which claimed priority to U.S. Provisional Appl. No. 60/409,336, filed September 9, 2002, and DE10227232, filed June 18, 2002, the '652 patent's earliest possible priority date.

The '652 patent issued with 25 claims. Claims 1, 7 and 24 are independent claims, all claiming a pharmaceutical formulation comprising:

- Gly(A21), Arg(B31), Arg (B32)-human insulin (*i.e.*, insulin glargine)
- At least one chemical entity chosen from a polysorbate or poloxamer
- At least one preservative
- Water
- pH of the insulin glargine formulation in the range from 1 to 6.8 (claims 1 and 7) or 3.5 to 4.5 (claim 24).

Claim 1 limits the formulation to a polysorbate chosen from polysorbate 20 or polysorbate 80. Claim 24 limits the formulation to the preservative cresol.

Although independent claims 7 and 24 are interspersed within the claim set, all of the dependent claims ultimately depend from independent claim 1 only. The dependent claims recite various chemical entities of the insulin glargine formulation of claim 1, such as polysorbate 20 (claim 2) “in an effective amount to reduce turbidity” (claim 8). Many of the additional chemical entities recited in the dependent claims include compounds that are commonly found in insulin formulations, including a preservative such as phenol (claim 3), cresol (claim 4), or a Markush group of preservatives including “phenol, cresol, chlorocresol, benzyl alcohol, and parabens” (claim 11). Claims 5 and 6 further include other common additives of commercially available insulin formulations, including zinc (claim 5), a buffer (claim 13), including “TRIS, phosphate, citrate, acetate and glycylglycin” (claim 14), “in a concentration of 5-250 mM” (claim 22), sodium chloride (NaCl) in a concentration of

up to 150 mM (claim 21) or “at least one isotonicizing agent”) (claim 6). Claim 12, which depends from claim 6, lists “mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, and glycerol” as isotonicizing agents, common additives in parenteral formulations. Claim 25 further includes “one or more excipients chosen from acids, alkalis and salts” to the claimed formulation of independent claim 1.

Claims 9 and 10 further limit the acidic pH range of independent claim 1 to “3.5 to 6.8” (claim 9) and “3.5 to 4.5” (claim 10). Claims 15 to 18 limit concentrations or amounts of certain agents or excipients in the claimed pharmaceutical formulation, including insulin glargine “in a concentration of 60-6000 nmol/ml” (claim 15) and insulin glargine “in a concentration of 240-3000 nmol/ml” (claim 16). The polysorbate 20 and polysorbate 80 concentrations of claim 1 are limited to 5-200 µg/ml (claim 17), 5-120 µg/ml (claim 18) and 20-75 µg/ml (claim 19).

Claims 20 and 23 recite the excipients and concentrations of claims 12 and 6, respectively. Claim 20 recites “[t]he pharmaceutical formulation as claimed in claim 12, wherein at least one isotonicizing agent is chosen from glycerol and mannitol and wherein said at least one isotonicizing agent is present in a concentration of 100-250 mM.” Claim 23 recites “[t]he pharmaceutical formulation as claimed in claim 6, wherein the at least one chemical entity comprises polysorbate 20, at least one preservative is cresol, and the pharmaceutical formulation has a pH in the acidic range

from 3.5 to 4.5.

The well-known issue of insulin aggregation was fully acknowledged by the '652 patent, where “[e]specially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation on thermal and physicochemical stress, which can make itself felt in the form of turbidity and precipitation (particle formation).” Ex. 1001, 3:2-7, citing to Brange [Ex. 1015]. The '652 patent further describes known sources of insulin aggregation, including hydrophobic surfaces that insulin molecules commonly encounter, such as glass vial walls, rubber or silicone stoppers, and contact with air. Ex. 1001, 3:8-14.

Moreover, while the '652 patent acknowledges such issues, the patent specification fails to acknowledge, and the applicants failed to inform the Patent Office, of the nearly identical prior art insulin glargine formulation that was known and available to the public more than one year before the earliest priority date of the '652 patent, the assignee's prior use of poloxamer in an insulin formulation or the numerous prior art references acknowledging aggregation issues and providing nonionic surfactants as a proven solution to such issues. The only difference between the prior art insulin glargine formulation and the '652 patent claims is the addition of a surfactant, a well-known and proven solution to the well-known and common problem of insulin aggregation.

2. Brief Overview of the '652 Patent's Prosecution History

The '652 patent issued from Application No. 11/089,777 (“the '777 application”). During prosecution, the PTO rejected the '777 application’s claims for anticipation, obviousness and lack of written description. The rejection did not include the Lantus[®] 2000 label [Ex. 1004], Owens [Ex. 1005], Lougheed [Ex. 1006], the FASS Insuman Infusat entry [Ex. 1007] or Grau [Ex. 1008], asserted here. Lougheed was disclosed in an information disclosure statement, but not applied. *See* Ex. 1001A, 67.

C. Level of Ordinary Skill in the Art

The invention’s field involves inhibition of insulin aggregation and increased stability in insulin formulations. A PHOSITA would have held an M.S. or Ph.D. or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations. *See, e.g.*, Ex. 1003 ¶¶31-34. A PHOSITA would have, for example, the educational background above with experience in surfactants commonly used in peptide injection formulation, as well as an understanding of factors that contribute to the molecule’s instability. *Id.* This experience is consistent with the types of problems encountered in the art, which would have included peptide aggregation and instability, impact of stabilizing agents and additives on peptide aggregation, and compatibility with injection or storage equipment materials, for example. *Id.* A PHOSITA may have also consulted

with one or more team members of experienced professionals to develop an insulin formulation resistant to the well-known aggregation propensities of insulin molecules.

Id. A PHOSITA would have been well-versed in the field's literature that was available as of the priority date. *Id.*

D. Claim Construction

The '652 patent claims presumably possess their "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. §42.100(b). Under the broadest reasonable construction, a PHOSITA would understand the claim terms below at least include the following meanings.²

"A Pharmaceutical Formulation". All claims require a "pharmaceutical formulation" Mylan notes that the claims are not limited to a specific use or method related to the claimed pharmaceutical formulation. Accordingly, any pharmaceutical formulation that recites the limitations of the challenged claims, regardless of the

² Without taking a position here on whether the claims are sufficiently definite, Mylan notes that even when the metes and bounds of a claim are indefinite, the Board nevertheless determines whether embodiments plainly within the scope of the claim would have been obvious. *Ex parte Tanksley*, 26 USPQ2d 1384, 1387 (BPAI 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 USPQ2d 1443, 1444 n.* (BPAI 1988) (affirming obviousness despite indefinite claim format).

application or use of the pharmaceutical formulation, would be relevant to the patentability of the challenged claims.

“Polysorbate” or “Poloxamer”. The independent claims each contain reference to a “polysorbate” or a “poloxamer.” A PHOSITA would understand “polysorbate” or “poloxamer” to refer to classes of compounds, which are used as, for example, surfactants, including nonionic surfactants. *See* Ex. 1003 ¶¶53-57. The ’652 patent lists compounds that are “pharmaceutically customary surfactants” as preferred, including:

[P]artial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span®, Tween®, in particular Tween® 20 and Tween® 80, Myrj®, Brij®), Cremophor® or poloxamers.

Ex. 1001, 3:52-56. Because claims 7 and 24 require only “at least one chemical entity chosen from polysorbate and poloxamers”, under the broadest reasonable interpretation of the claim, this limitation would be met by *any* polysorbate or poloxamer.

“Polysorbate 20” or “Polysorbate 80”. Independent claim 1 recites to two polysorbate compounds: polysorbate 20 and polysorbate 80. Polysorbate 20 is a nonionic surfactant formed by the ethoxylation of sorbitan before the addition of lauric acid, and has been commonly used in a number of pharmacological applications, including parenteral formulations. *See* Ex. 1003 ¶¶53-54. Polysorbate 80 is also a nonionic surfactant used in parenteral formulations, and is synthesized

from polyethoxylated sorbitan and oleic acid. *Id.* Furthermore, a PHOSITA would understand that the commercial names for polysorbate 20 and polysorbate 80 include Tween[®] 20 and Tween[®] 80, respectively, among other commercial and chemical names. *Id.*

E. Patents and Printed Publications Relied On In This Petition

Mylan relies on the following patents and printed publications:

1. LANTUS[®] (Insulin Glargine) 2000 Product Label (“LANTUS[®] 2000 Label”) [Ex. 1004 and 1004A]

LANTUS[®] (insulin glargine) was approved on April 20, 2000. The product label submitted with the approval published in a learned periodical more than one year before the earliest priority date of the '652 patent. *See* Ex. 1004A, Affidavit of Patricia van Skaik establishing at least December 1, 2000 publication date; Ex. 1003 ¶¶129-33.

The LANTUS[®] 2000 Label discloses insulin glargine as a recombinant DNA insulin that “differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain,” *i.e.*, Gly(A21)-Arg(B31)-Arg(B32)-human insulin. Ex. 1004, 3. The LANTUS[®] 2000 Label states “[e]ach 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” with a pH of approximately 4. *Id.* The

LANTUS[®] 2000 Label contains two warnings that “LANTUS must only be used if the solution is clear and colorless with no particles visible.” *Id.*, 5-6.

2. **Owens, D.R., et al., “Pharmacokinetics Of ¹²⁵I-Labeled Insulin Glargine (HOE 901) In Healthy Men: Comparison With NPH Insulin And The Influence Of Different Subcutaneous Injection Sites,” *Diabetes Care*. 2000 Jun;23:813-19 (“Owens”) [Ex. 1005]**

Owens published in a learned periodical more than one year before the earliest priority date of the '652 patent. Owens described clinical studies designed to determine the subcutaneous absorption rates of insulin glargine (referred to as HOE 901) with 15, 30, and 80 microgram/mL of zinc. Ex. 1005, Abstract; Ex. 1003 ¶¶134-37.

Owens described insulin glargine, or HOE 901, as “a di-arginine (30^Ba-L-Arg-30^Bb-L-Arg) human insulin analog in which asparagine at position 21^A is replaced by glycine. This achieves an increase in the isoelectric point from pH 5.4 (native insulin) to 7.0 and stabilization of the molecule. When injected as a clear acidic solution (pH 4.0), insulin glargine undergoes microprecipitation in the subcutaneous tissue, which retards absorption.” Ex. 1005, 1.

For one of the clinical studies, Owens disclosed the following preparation of insulin glargine:

The recombinant human insulin analog formulations insulin glargine[15] and **insulin glargine**[80] (Hoechst AG) were also administered from 5-ml vials, with each 1-ml suspension containing **21A-Gly-30^Ba-L-Arg-30^Bb-L-**

Arg-human insulin equimolar to 100 U human insulin, 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., 3 (emphasis added). Thus, Owens disclosed an insulin glargine formulation containing 100 U/mL insulin glargine, m-cresol, and glycerol with 2.295, 4.59 and 12.24 µmol/L zinc at pH 4.0 well before the earliest priority date of the '652 patent. *Id.*, 3-4.

3. Lougheed, W.D., at al. “Physical Stability of Insulin Formulations,” *Diabetes*. 1983 May;32(5):424-32. [Ex. 1006]

Lougheed published in May 1983, more than one year before the earliest priority date of the '652 patent, in a learned periodical. Ex. 1003 ¶¶138-46.

Lougheed recognized that “the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to [the] prolonged clinical use [of insulin]”. Ex. 1006, 1. Lougheed recognized that aggregates forming during storage could decrease biological activity “primarily [due] to the formation of high-molecular weight polymers of insulin and desamido insulin.” *Id.* Lougheed thus investigated “the effects of physiologic and nonphysiologic compounds on the aggregation behavior of crystalline zinc insulin (CZI) solutions.” *Id.*

Lougheed found that Tween, a polysorbate, as well as the broader class of “nonionic and ionic surfactants containing the hydrophobic group, CH₃(CH₂)_N,

with N = 7-16,” stabilized crystalline zinc insulin (or CZI) formulations, and further concluded that “anionic and nonionic surfactants containing appropriately long hydrophobic groups demonstrated the greatest degree of stabilization.” *Id.* Lougheed tested “[n]onionic, cationic, and ionic detergents (both physiologic and synthetic) as stabilizers in view of their known protein-solvation characteristics and their potential to constrain the conformation of insulin and other proteins in aqueous solution.” *Id.*, 2.

As depicted in Table 3, Lougheed compared the stabilities of formulations containing various nonionic detergents, including Tween 20 and Tween 80, which are also known as polysorbate 20 and polysorbate 80. Lougheed noted that insulin “aggregate formation was inhibited by the nonionics; Brij 35 (0.1% vol/vol), Lubrol WX (0.1% vol/vol), Triton X 100 (0.02% vol/vol), **Tween 20 (0.01% vol/vol)**, **Tween 80 (1% vol/vol)**, and the anionic; SDS (0.05% wt/vol in 0.9% NaCl) and SDS (1% wt/vol).” *Id.*, 3-4 (emphasis added). Accordingly, Lougheed disclosed at least the use of Tween 20 (*i.e.*, polysorbate 20) and Tween 80 (*i.e.*, polysorbate 80) to reduce insulin aggregation and particle formulation. *Id.*, 7.

**4. FASS 2000 Entry for Insuman Infusat, (January 2000)
 (“Insuman Infusat”) [Ex. 1007 and 1007A]**

Insuman Infusat, a commercially available human insulin product distributed by Aventis Pharma³ in 2001, was published in the Swedish FASS (“Farmaceutiska Specialiteter I Sverige” (Swedish Drug Formulary)) by January 2000, *i.e.*, more than one year before the earliest priority date of the ’652 patent. Ex. 1003 ¶¶147-49.

Insuman Infusat, available in 3.15 milliliter ampules containing 100 international units (I.E.) per milliliter recombinant human insulin, was supplied as an injectable solution for the treatment of diabetes mellitus. Insuman Infusat components included: “Insulin for human use (biosynthetic) 100 units (3.5 mg) zinc chloride 0.058 mg, trometamol 6 mg, glycerol 20 mg, poly(oxyethylene, oxypropylene)glycol 0.01 mg, preservative (phenol 2.7 mg), hydrochloric acid 3.7 mg, water for injection up to 1 ml.” Ex. 1007A, 5.

The FASS Insuman Infusat entry states that the formulation was specially made to inhibit aggregation in insulin pumps: “**Properties of the pharmaceutical**

³ Aventis Pharma merged with Sanofi-Synthelabo in 2004 (*see, e.g.*,

http://money.cnn.com/2004/04/26/news/international/aventis_sanofi/ (accessed

June 2, 2017)) [Ex. 1035] to create Sanofi-Aventis, the parent corporation of ’930 patent assignee Sanofi-Aventis Deutschland GmbH.

form. Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps since the risk of clogging in the catheter with resulting loss of the intended effect is minimized.” *Id.*, 7.

5. Grau, U. and Saudek, C.D., “Stable Insulin Preparation for Implanted Insulin Pumps” Diabetes. 1987 December; 36:1453-59 (“Grau”) (Ex. 1008)

Grau published more than one year before the earliest priority date of the ’652 patent in a learned periodical. Ex. 1003 ¶¶150-57. Like Lougheed, Grau recognized the issues with stability of insulin formulations:

The stability of insulin has been a significant impediment in the development of mechanical medication-delivery devices for diabetes. *An inherently fragile protein, insulin has a tendency to precipitate, aggregate in high-molecular weight forms, and denature.*

Ex. 1008, 1 (emphasis added). Grau investigated the ability of the poloxamer Genapol (polyethylene-polypropylene glycol) to inhibit aggregation of insulin in pump catheters.

Grau used a “pH-neutral buffered insulin formulation containing either 100 or 400 IU/ml semi-synthetic human insulin, 27.8 or 111 µg/ml zinc ions (for U-100 and U-400 insulin, respectively) with 2 mg/ml phenol as a preservative, 16 mg/ml glycerol as an isotonicity agent, 50 mM of tris-(hydroxymethyl)-aminomethane (Tris) buffer, and 10 µg/ml polyethylene-polypropylene glycol (Genapol, Hoechst

AG, Frankfurt, FRG).” *Id.*, 1. The insulin formulations were tested on a shaking platform in a programmable implantable medication system (PIMS), which pumped the test formulations into a glass vial at a constant rate throughout the 10+ months of testing. *Id.*, 2-3. Insulin aggregation in PIMS systems was also tested *in vivo* in dogs implanted with the insulin delivery devices. *Id.* The insulin formulation was analyzed for precipitates using scanning electron microscopy and X-ray microanalysis, as well as for biological activity/potency in rabbits. *Id.*, 3-4.

Grau found that insulin concentration, chemical stability and biological potency were maintained when tested both *in vitro* and *in vivo* in PIMS-implanted dogs. *See, e.g.*, Grau [Ex. 1008], 4-5, Tables 2-3. Grau reported that changes to the poloxamer-containing insulin formulations “were comparable to those seen in insulin stored in a glass vial at 37 °C without movement.” *Id.*, 4. Grau found that the “[s]urfaces were clean of apparent precipitate even in remote corners.” *Id.*, 5. Grau moreover noted that the “[g]lycemic control of [the] diabetic dogs was good ... [with] no trend toward either worse diabetic control or increased insulin dosage between refills ...”. *Id.* Grau concluded that “Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces.... The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills *in vivo*.” *Id.*, 6.

F. The Prior Art Renders The Challenged Claims Obvious

Before the earliest priority date of the '652 patent, Sanofi-Aventis (the patent assignee) published the details of its commercialized LANTUS[®] product, an insulin glargine formulation nearly identical to the claimed formulation: the only ingredient missing from the commercially available formulation was the claimed polysorbate or poloxamer (*e.g.*, polysorbate 20 or polysorbate 80 of claim 1). Ex. 1003 ¶162.

However, the well-known propensity for insulin aggregation especially at acidic pH was a recognized “fundamental obstacle” in the development of commercial insulin, and was studied well before the earliest priority date of the '652 patent. *Id.* ¶¶103-08.

These numerous studies disclosed the use of polysorbates and poloxamers to inhibit insulin aggregation. *Id.* ¶¶109-23. In addition, poloxamer was actually used in a commercially available human insulin formulation sold under the brand name INSUMAN INFUSAT, by Aventis Pharma, for the prevention of insulin aggregation, as disclosed in its Swedish FASS and German Rote Liste label, well before the priority date of the '652 patent. *Id.* ¶122.

In other words, more than a year before the '652 patent's earliest filing date, the details of a commercially available insulin glargine formulation and solutions for inhibiting insulin aggregation of insulin in solution were known, published, and approved for administration as a therapeutic agent for treatment of diabetes. Furthermore, the copious body of work instructing precisely how to solve insulin

aggregation demonstrates that inhibition of insulin aggregation with polysorbates and poloxamers added to a commercially available insulin product, as claimed in each challenged claim, was plainly obvious.

G. Ground 1: Claims 1-25 of the '652 Patent were Obvious Over the LANTUS[®] 2000 Label and Lougheed

1. Claim 1 was Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 1 of the '652 patent recites a “pharmaceutical formulation comprising 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.”

A label for LANTUS[®] described “Gly(A21), Arg(B31), Arg(B32)-human insulin”, or insulin glargine, more than one year before the earliest priority date of the '652 patent. *See* Ex. 1004; Ex. 1003 ¶129. The LANTUS[®] 2000 Label, which was publicly available to PHOSITAs, *see* Ex. 1004A (December 1, 2000 publication date), taught that “[e]ach 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” with a pH of approximately 4.0. Ex. 1004, 1. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS[®] 2000 Label disclosed

the claim elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, the LANTUS[®] 2000 Label taught all the elements recited in claim 1 except “at least one chemical entity chosen from polysorbate 20 and polysorbate 80.” *Id.* ¶¶160-62.

Lougheed disclosed and addressed several known issues with insulin formulations, including the propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1 (“Unfortunately, the tendency of insulin to aggregate during storage in and delivery from these devices remains one of the fundamental obstacles to their prolonged clinical use.”); Ex. 1003 ¶¶163-69. Lougheed addressed the aggregation issue by comparing different nonionic detergents in extreme storage conditions, and measuring the appearance of aggregated particles through time. Ex. 1006, 1. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id.*, 4, 7 and Table 3; Ex. 1003 ¶¶163-69.

It is not surprising that Lougheed chose polysorbate 20 and polysorbate 80 as an excipient for use in insulin formulations. Polysorbates were commonly used to stabilize other protein and peptide formulations well prior to June 2002, including for commercially-available biologic therapeutics. *See* Jones [Ex. 1016],

3, Table I; Ex. 1003 ¶¶163-69. Moreover, certain polysorbate formulations, including polysorbate 20 and polysorbate 80, were GRAS (Generally Recognized as Safe) and already included in the FDA Inactive Ingredients Guide for various pharmaceutical formulations. Ex. 1003 ¶167. The inclusion of “[p]olysorbate 20 and polysorbate 80, thus, would have been obvious [] to use for inhibiting insulin aggregation.” *Id.* ¶172.

In view of at least Lougheed’s experiments, the knowledge that polysorbate 20 and polysorbate 80 were generally regarded as effective and safe in inhibiting aggregation in other biologic products, and knowledge of the LANTUS[®] 2000 Label formulation, a PHOSITA would have had ample reason to add at least nonionic surfactants disclosed in Lougheed, *e.g.*, polysorbate 20 and polysorbate 80, to an insulin glargine formulation, with a reasonable expectation that doing so would successfully inhibit or eliminate insulin’s well-known propensity to aggregate. A PHOSITA would especially have had reason because insulin glargine was likely prone to aggregation as monomeric insulin in an acid pH environment. *See id.* ¶¶126, 168. The LANTUS[®] 2000 Label, in fact, warned users and practitioners not to use the product if aggregation occurred. *See* Ex. 1004, 5-6 (“LANTUS must only be used if the solution is clear and colorless with no particles visible.”). Accordingly, a PHOSITA would have had reason, with a reasonable expectation of success, to combine polysorbate 20 or polysorbate 80, as

encouraged by Lougheed [Ex. 1006], with the known and FDA-approved LANTUS[®] 2000 formulation [Ex. 1004] to inhibit or eliminate insulin aggregation, which was a well-recognized obstacle to the success of insulin as a therapeutic agent.

The use by Lougheed of numerous nonionic surfactants, including the claimed polysorbate 20 and polysorbate 80, to inhibit aggregation and reduce turbidity is simply consistent with the disclosures in the prior art. Ex. 1003 ¶165; *see also* Ex. 1001 3:2-6 (“[I]nsulins, however, show a decreased stability and an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation).”). The ’652 patent, which lists a wide range of “partial and fatty acid esters and ethers of polyhydric alcohols” as useful against aggregation of insulin preparations, is thus simply consistent with what the art already knew. A PHOSITA would not have been surprised at the success of combining the known and available insulin glargine formulation with either of two promising aggregation-inhibiting nonionic surfactants to inhibit the formation of particles and the appearance of turbid solutions, would have worked. A PHOSITA would have reasonably expected nothing less. Claim 1 was obvious over the LANTUS[®] 2000 Label and Lougheed.

2. Independent Claims 7 and 24 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 7 of the '652 patent recites a “pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin, at least one chemical entity chosen from polysorbate and poloxamers; at least one preservative; and water; wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.”

Claim 24 recites a “pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin: at least one chemical entity chosen from polysorbate and poloxamers; at least one preservative chosen from cresol; and water, wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5.” For the same reasons as for claim 1, claims 7 and 24 were obvious over the LANTUS® 2000 label and Lougheed. *See* Ex. 1003 ¶¶175-80.

“Gly(A21), Arg(B31), Arg(B32)-human insulin”, or insulin glargine, was commercially available more than one year before the earliest priority date of the '652 patent as the brand product LANTUS®. The LANTUS® 2000 Label, which was publicly available to PHOSITAs, *see* Ex. 1004A, taught that “[e]ach 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” with a pH of approximately 4.0. Ex. 1004, 3. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS® 2000 Label disclosed the claim elements of water and an acidic

pH of approximately 4.0 for the insulin glargine formulation. Thus, as with claim 1, the LANTUS[®] 2000 Label taught all the elements recited in claims 7 and 24 except “at least one chemical entity chosen from polysorbate and poloxamers.”

As above, Lougheed detailed the use of polysorbate 20 and polysorbate 80, *i.e.*, a polysorbate as claimed in claims 7 and 24, as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶177-79. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), among other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. Ex. 1006, 4, 7 and Table 3; Ex. 1003 ¶178.

These experiments, knowledge of the safety and efficacy of polysorbate 20 and polysorbate 80 in other commercially-available biological therapeutics and knowledge of the LANTUS[®] 2000 Label formulation, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, including the polysorbates polysorbate 20 or polysorbate 80 recited in claims 7 and 24, with a reasonable expectation that doing so would inhibit or eliminate insulin’s well-known propensity to aggregate. *See* Ex. 1003 ¶¶175-80. Given insulin glargine’s increased propensity for aggregation, and the LANTUS[®] 2000 Label’s warning to not use the product if aggregation occurred, a PHOSITA would have

had specific reason to combine a polysorbate, including polysorbate 20 or polysorbate 80 as encouraged by Lougheed [Ex. 1006], with the known and FDA-approved LANTUS[®] 2000 formulation [Ex. 1004], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a recognized obstacle to the success of insulin as a therapeutic agent. *See* Ex. 1004, 5-6; Ex. 1003 ¶¶175-80. Claims 7 and 24 were obvious over the LANTUS[®] 2000 Label and Lougheed. *See In re Slayter*, 276 F.2d 408, 411 (C.C.P.A. 1960) (“A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus.”).

3. Dependent Claims 2, 8 and 17-19 were Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 2 of the '652 patent recites that “the at least one chemical entity comprises polysorbate 20.” Dependent claim 8 further recites that the polysorbate 20 claimed in claim 2 “is present in an effective amount to avoid turbidity.” Dependent claim 17 depends from claim 1, and recites that “the at least one chemical entity is present in a concentration of 5-200 µg/ml.” Claim 18 depends from claim 17, and recites that “the at least one chemical entity is present in a concentration of 5-120 µg/ml.” Claim 19 depends from claim 18, and further recites that “the at least one chemical entity is present in a concentration of 20-75 µg/ml.”

Lougheed detailed the use of polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶182-84. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) was one of several nonionic surfactants that showed significant enhancement of insulin stability through inhibition of insulin aggregation, *i.e.*, to avoid turbidity of the formulation. Ex. 1006, 4, 7 and Table 3; Ex. 1003 ¶183.

Moreover, Lougheed also taught the concentration ranges in claims 17, 18 and 19. For example, Lougheed exemplified polysorbate 20 at concentrations of 0.000001% and 0.01% (vol/vol) and polysorbate 80 at concentrations 0.000001%, 0.00001%, 0.01%, and 1% (vol/vol) in the formulations tested. Lougheed [Ex. 1006], 3, Table 3; Ex. 1003 ¶184. Given that the densities of polysorbate 20 and polysorbate 80 are 1.095 g/mL and 1.06 g/mL, respectively, Lougheed thus used polysorbate 20 at concentrations of 0.01095 µg/mL and 109.5 µg/mL, and polysorbate 80 at concentrations of 0.0106 µg/mL, 0.106 µg/mL, 106 µg/mL, and 10600 µg/mL. *See* Ex. 1003 ¶184. Lougheed, thus, disclosed concentrations for polysorbate 20 and polysorbate 80 within the ranges recited in claim 17 and 18.

Lougheed would have suggested the slightly narrowed range of claim 19, which recites “20-75 µg/ml”. Not only are the polysorbate 20 and polysorbate 80 levels essentially overlapping with the claimed range, *see Titanium Metals Corp. of*

Am. v. Banner, 778 F.2d 775 (Fed. Cir. 1985), a PHOSITA would have tested and optimized the polysorbate 20 and polysorbate 80 levels taught by Lougheed. Ex. 1003 ¶¶184-85; *see also In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955).

Accordingly, a PHOSITA would have had reason to combine polysorbate 20 (claim 2) as encouraged by Lougheed [Ex. 1006], including at the concentrations tested by Lougheed (claims 17-19), with the known and FDA-approved LANTUS[®] 2000 formulation [Ex. 1004], with a reasonable expectation of inhibiting or eliminating insulin aggregation, *i.e.*, avoiding turbidity of the formulation (claim 8). Claims 2, 8 and 17-19 were therefore obvious over the Lantus[®] 2000 Label and Lougheed. Ex. 1003 ¶185.

4. Dependent Claims 3, 4 and 11 were Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 3 depends from claim 2, and requires that “the at least one preservative is chosen from phenols.” Claim 4 depends from claim 3, and recites “wherein the at least one preservative is cresol.” Claim 11 depends from claim 1 and recites “wherein the at least one preservative is chosen from phenol, *cresol*, chlorocresol, benzyl alcohol, and parabens.” Emphasis added.

The LANTUS[®] 2000 Label taught an insulin glargine formulation disclosed with “2.7 mg m-cresol”. Ex. 1004, 3. Cresol was a known preservative and a derivative of phenol. *See* Ex. 1003 ¶¶98-102. That the LANTUS[®] 2000 pharmaceutical formulation contained a preservative such as cresol (a phenolic

derivative) is not surprising. Lougheed also investigated the stabilizing effects of phenol and cresol on insulin solutions, finding that both phenol and m-cresol were capable of stabilizing insulin. Ex. 1006, Table 2.

Accordingly, a PHOSITA would have had reason with a reasonable expectation of success to include cresol, as taught by the LANTUS[®] 2000 Label and as encouraged by Lougheed [Ex. 1006]. Ex. 1003 ¶¶187-89. Claims 3, 4 and 11 were therefore obvious over the Lantus[®] 2000 Label and Lougheed.

5. Dependent Claim 5 was Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 5 depends from claim 4, and recites the formulation “further including zinc.”

The LANTUS[®] 2000 Label taught the inclusion of “30 mcg zinc” in the disclosed insulin glargine formulation. Ex. 1004, 3. Including zinc as a component in the LANTUS[®] 2000 label was not surprising or inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*. *See, e.g.*, Hallas-Moller, Diabetes (1956) [Ex. 1017]; Ex. 1003 ¶¶98-102. In fact, various amounts of zinc were tested in insulin glargine formulations well before the earliest priority date of the '652 patent to determine the zinc amounts that would further prolong insulin release and activity. *See* Ex. 1005, 1. A PHOSITA had reason to include zinc, as taught by the LANTUS[®] 2000

Label, in an insulin pharmaceutical formulation as claimed in claim 5. Ex. 1003 ¶¶191-93.

6. Dependent Claims 6, 12 and 20 were Obvious Over LANTUS[®] 2000 Label and Loughheed

Claim 6 depends from claim 1, and recites “further including at least one isotonicizing agent.” Claim 12 depends from claim 6, and recites “wherein the at least one isotonicizing agent is chosen from mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, and glycerol.” Claim 20 depends from claim 12, and recites “wherein at least one isotonicizing agent is chosen from glycerol and mannitol and wherein said at least one isotonicizing agent is present in a concentration of 100-250 mM.”

The LANTUS[®] 2000 Label taught that the disclosed insulin glargine formulation included “20 mg glycerol 85%”. Ex. 1004, 3. Accordingly, the LANTUS[®] 2000 Label taught including glycerol (an isotonicizing agent) in a commercially available insulin glargine formulation. The molecular weight of glycerol is 92.1, so 20 mg glycerol 85% as taught by the LANTUS[®] 2000 Label is equivalent to 185 mM glycerol, which is within the range as claimed in claim 20. *See* Ex. 1003 ¶197.

Including glycerol, an isotonicizing agent, in the LANTUS[®] 2000 insulin formulation was neither surprising nor inventive. Isotonicizing (or isotonic) agents, such as glycerol and sodium chloride (NaCl), were routinely added to

parenteral or subcutaneous formulations to prevent cell lysis and attendant pain upon injection. *See* Ex. 1003 ¶¶195-98. Accordingly, it would have been obvious to a PHOSITA that an isotonicizing agent such as glycerol, as taught by the LANTUS[®] 2000 Label, would be included in an insulin pharmaceutical formulation as claimed in claims 6, 12 and 20.

7. Dependent Claims 9 and 10 were Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 9 depends from claim 5, and recites “wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 6.8.” Claim 10 depends from claim 9, and further narrows the pH to an “acidic range from 3.5 to 4.5.”

The LANTUS[®] 2000 Label taught that the insulin glargine was formulated at a pH of approximately 4.0. Ex. 1004, 3. Having a pH of an insulin glargine formulation fall in the pH range recited in claims 9 and 10 is not surprising or inventive. A PHOSITA would have known well before the earliest priority date of the '652 patent that the amino acid substitutions in insulin glargine make it most soluble in an acidic (pH 4.0) environment. *See, e.g.*, Ex. 1005, 1; Ex. 1003 ¶201. Accordingly, it would have been obvious to a PHOSITA that the pH range of an insulin glargine formulation, as taught by the LANTUS[®] 2000 Label, would be formulated in the range of “from 3.5 to 6.8” (claim 9) or “from 3.5 to 4.5” (claim 10), *i.e.*, an acidic pH environment. Ex. 1003 ¶¶200-02. Claims 9 and 10 were obvious over the LANTUS[®] 2000 Label and Lougheed.

8. Dependent Claims 13, 14 and 22 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 13 depends from claim 1 and recites that the claimed pharmaceutical formulation “further compris[es] a buffer.” Claim 14 depends from claim 13 and recites the buffer as “chosen from TRIS, phosphate, citrate, acetate, and glycylglycine.” Claim 22 depends from claim 13 and recites that the “buffer is present in a concentration of 5-250 mM.”

Lougheed disclosed the use of non-ionic surfactants and commonly used “salts, buffers and alcohols”, including sodium phosphate, sodium bicarbonate with acetic acid and sodium acetate and sodium bicarbonate with sodium phosphate and sodium citrate, in insulin formulations. *See* Lougheed [Ex. 1006], 6, Table 6; Ex. 1003 ¶204. Lougheed specifically taught that of the tested insulin formulations, “[f]ormulations in 25 mM sodium bicarbonate with phosphate-citrate or oxaloacetate buffers demonstrated mildly increased stability with FSRs of 11-20 days”. Ex. 1006, 6, Table 6; Ex. 1003 ¶204. The concentration ranges of the sodium bicarbonate, sodium phosphate, acetic acid, sodium acetate and sodium citrate buffers tested fall within the claimed range of 5-250 mM. *See, e.g.*, Ex. 1006, Table 6.

Accordingly, a PHOSITA would have had reason to combine a buffer, including citrate, phosphate and acetate buffers, as encouraged by Lougheed [Ex. 1006], and at the concentrations tested by Lougheed (claim 22), with the known

and FDA-approved LANTUS[®] 2000 formulation [Ex. 1004] to inhibit or eliminate insulin aggregation with a reasonable expectation of success. Ex. 1003 ¶¶204-06. Claims 13, 14 and 22 were therefore obvious over the LANTUS[®] 2000 Label and Lougheed.

9. Dependent Claim 21 was Obvious over LANTUS[®] 2000 Label and Lougheed

Claim 21 depends from claim 1 and recites “wherein NaCl is present in a concentration of up to 150 mM.”⁴

Lougheed discloses the testing of commonly used “salts, buffers and alcohols”, including sodium chloride at a concentration of 0.9% (equivalent to 154 mM), in insulin formulations, including in combination with sodium dodecyl sulfate (SDS). *See* Lougheed [Ex. 1006], 5-6, Tables 4 and 6; Ex. 1003 ¶208.

While the exemplary NaCl concentration is slightly over the claimed range of “up to 150 mM”, a PHOSITA would have had reason, with a reasonable expectation of success to combine sodium chloride, as encouraged by Lougheed, with the claimed insulin formulation. The '652 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma Labs.* 737 F.3d 739 (reversing non-invalidity holding). Moreover, a PHOSITA would

⁴Under a broadest reasonable interpretation, claim 21 includes the formulation components recited in claim 1 and NaCl in the stated concentration range.

have known to reduce the amount of sodium chloride (*i.e.*, lower than 154 mM NaCl) in order to compensate for other components in the formulation. Ex. 1003 ¶209. In light of the known use of NaCl in Lougheed, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '652 patent nor other knowledge in the art would have suggested a concentration change from 154 mM to 150 mM NaCl would have been critical or unobvious. *Id.*

Claim 21 was therefore obvious over the LANTUS[®] 2000 Label and Lougheed. *Id.* ¶¶208-10.

10. Dependent Claims 15 and 16 were Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 15 depends from claim 1 and recites that the “Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 60-6000 nmol/ml.” Claim 16 depends from claim 15, and further recites “that the Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 240-3000 nmol/ml.”

The LANTUS[®] 2000 Label taught “100 IU (3.6378 mg) insulin glargine in the insulin formulation. Ex. 1004, 3. The LANTUS[®] 2000 Label further provides that insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) has a molecular weight of 6063. *Id.* Accordingly, the concentration of insulin glargine taught by the LANTUS[®] 2000 Label is 600 nmol/mL, which is within the concentration ranges recited in both claims 15 and 16. *See* Ex. 1003 ¶212.

For these reasons, claims 15 and 16 were obvious over the LANTUS[®] 2000 Label and Lougheed. *Id.* ¶¶212-13.

11. Dependent Claim 23 was Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 23 depends from claim 6, and recites “wherein the at least one chemical entity comprises polysorbate 20, at least one preservative is cresol, and the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5.”

For the same reasons as claims 2, 4 and 10, claim 23 was obvious over the LANTUS[®] 2000 Label and Lougheed. The LANTUS[®] 2000 Label included “2.7 mg m-cresol” at a pH of approximately 4.0 for the insulin glargine formulation disclosed. Ex. 1004, 3. Moreover, Lougheed provided a strong reason with a reasonable expectation of success to add polysorbate 20 to improve stability of insulin solutions. *See* Lougheed [Ex. 1006], 1, Table 3; Ex. 1003 ¶¶215-18.

Accordingly, the pharmaceutical formulation of claim 23 would have been obvious over the LANTUS[®] 2000 Label and Lougheed.

12. Dependent Claim 25 was Obvious Over LANTUS[®] 2000 Label and Lougheed

Claim 25 depends from claim 1, and recites the formulation “further comprising one or more excipients chosen from acids, alkalis and salts.”

The LANTUS[®] 2000 Label taught preparing an insulin glargine solution and adjusting the pH of the solution to 4.0 using hydrochloric acid and sodium

hydroxide. Ex. 1004, 3; Ex. 1003 ¶¶220. Moreover, Lougheed further taught the addition of various acids and salts for improving the stability of insulin, including dehydroascorbic acid, hyaluronic acid, n-acetyl neuraminic acid, glutamic acid, sodium chloride, sodium bicarbonate, sodium citrate, and acetic acid, among others. *See* Lougheed [Ex. 1006], Tables 5 and 6; Ex. 1003 ¶¶220.

Accordingly, in view of the teachings of both the LANTUS[®] 2000 Label and Lougheed, it would have been obvious and a PHOSITA would have had a reasonable expectation of success of adding an acid, alkali or salt as recited in claim 25 to an insulin formulation. Ex. 1003 ¶¶220-21. Claim 25 was therefore obvious over the LANTUS[®] 2000 Label and Lougheed.

H. Ground 2: Claims 7 and 24 were Obvious over the LANTUS[®] 2000 Label and the FASS Insuman Infusat Entry

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. The LANTUS[®] 2000 Label, which was publicly available to PHOSITAs well before the earliest priority date of the '652 patent, *see* Ex. 1004A, taught that “[e]ach 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” with a pH of approximately 4.0. Ex. 1004, 3. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS[®] 2000 Label disclosed the claim elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus,

the LANTUS[®] 2000 Label taught all the elements recited in claims 7 and 24 except “at least one chemical entity chosen from polysorbate and poloxamers.” Ex. 1003 ¶223.

The FASS Insuman Infusat entry disclosed the inclusion of poloxamer poly(oxyethylene, oxypropylene)glycol, *i.e.* “at least one chemical entity chosen from polysorbate and poloxamers” as claimed in claims 7 and 24. *See also* Insuman Infusat Rote Liste entry [Ex. 1033 and 1033A], 6 (inclusion of poloxamer-171 to Insuman Infusat formulation). As noted by the FASS entry, “[a]ddition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps.” *See* Ex. 1007A, 7. PHOSITAS recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Loughed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶¶223-29.

Insuman Infusat was commercially available, and established regulatory precedent agency determined that insulin formulations including poloxamer were safe and effective for use in diabetes treatment. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-63 (Fed. Cir. 2007) (citing to investor testimony confirming “‘part and parcel of pharmaceutically accepted[] was to look in pharmacopoeias and compendia’ to find an [excipient] having ‘precedence for use within the

pharmaceutical industry.’’). This knowledge provided a PHOSITA reason to combine a poloxamer as encouraged by the FASS Insuman Infusat entry [Ex. 1007, 1007A], with the Owens insulin glargine formulation [Ex. 1005], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a use specifically recognized for the Insuman Infusat product. *See* Ex. 1005, 3; Ex. 1007, 1007A, 7; Ex. 1003 ¶¶223-29. Claims 7 and 24 were obvious over Owens and the FASS Insuman Infusat entry.

I. Ground 3: Claims 7 and 24 were Obvious over the LANTUS[®] 2000 Label and Grau

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, the LANTUS[®] 2000 Label, which was publicly available to PHOSITAs well before the earliest priority date of the ’652 patent, *see* Ex. 1004A, taught the inclusion of cresol as a preservative, water and a pH within the claimed range of 1 to 6.8 (claim 7) or 3.5 to 4.5 (claim 24) in an insulin glargine formulation. Ex. 1004, 3. (“[e]ach 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” with a pH of approximately 4.0.). Thus, the LANTUS[®] 2000 Label taught all the elements recited in claims 7 and 24 except “at least one chemical entity chosen from polysorbate and poloxamers.”

Grau disclosed the use of a poloxamer (Genapol) to inhibit insulin aggregation in various test conditions, including with a programmable implantable

medication system (PIMS) which pumped the test formulations into a glass vial at a constant rate throughout the 10+ months of testing, and other *in vivo* and *in vitro* analysis. Ex. 1008, 2-5. Grau found that insulin concentration, chemical stability, and biological potency were maintained when tested both *in vitro* in a shaking platform PIMS rig, as well as *in vivo* in PIMS-implanted dogs. *Id.*, Tables 2-3, 4-5. Grau reported that changes to the poloxamer-containing insulin formulations “were comparable to those seen in insulin stored in a glass vial at 37°C without movement.” *Id.*, 4. Grau found that the “[s]urfaces were clean of apparent precipitate even in remote corners.” *Id.*, 5. Grau moreover noted that the “[g]lycemic control of [the] diabetic dogs was good ... [with] no trend toward either worse diabetic control or increased insulin dosage between refills ...”. *Id.* Grau concluded that “Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces.... The data demonstrate good stability in accelerated laboratory tests and after as long as 5 months between refills *in vivo*.” *Id.*, 6.

Thus, given insulin glargine’s increased propensity for aggregation, and the LANTUS[®] 2000 Label’s warning to not use the product if aggregation occurred, a PHOSITA would have had reason to combine a poloxamer as encouraged by Grau [Ex. 1008], with the known and FDA-approved LANTUS[®] 2000 formulation [Ex. 1004], with a reasonable expectation of success of inhibiting or eliminating insulin

aggregation, which were a recognized obstacle to the success of insulin as a therapeutic agent. Ex. 1003 ¶¶231-37. Claims 7 and 24 were obvious over the LANTUS[®] 2000 Label and the Insuman Infusat reference.

J. Ground 4: Claims 1-25 of the '652 Patent were Obvious Over Owens and Lougheed

1. Claim 1 was Obvious Over Owens and Lougheed

The limitations of claim 1 are recited above. *See* §V.B.1, *supra*.

Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing “21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0,” and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶239. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claim elements reciting water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all the elements recited in claim 1 but for “at least one chemical entity chosen from polysorbate 20 and polysorbate 80.”

Lougheed disclosed and addressed several known issues with insulin formulations, including the propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶241-43. Lougheed addressed the aggregation issue by comparing different

nonionic detergents in extreme storage conditions and measuring the appearance of aggregated particles over time. *Id.* Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id.*, 4, 7 and Table 3; Ex. 1003 ¶242. These experiments, and knowledge of the insulin glargine formulation in Owens, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, including the polysorbates polysorbate 20 or polysorbate 80 recited in claims 7 and 24 of the '652 patent, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶239-46. In fact, a PHOSITA would have had specific reason to add the non-ionic surfactants polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80) given insulin glargine's increased propensity for aggregation, and the LANTUS[®] 2000 Label's warning to not use the product if aggregation occurred. *Id.* ¶126. Claim 1 was obvious over Owens and Lougheed.

2. Claims 7 and 24 were Obvious Over Owens and Lougheed

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*.

Owens recited insulin glargine “together with *m-cresol* and glycerol at pH 4.0,” and 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 815-16 (emphasis added); Ex. 1003 ¶250. Cresol was a known

preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claims elements reciting water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all of the elements recited in claims 7 and 24 but for “at least one chemical entity chosen from polysorbate and poloxamers.”

For the same reason as with claim 1, Lougheed in combination with Owens obviates claims 7 and 24. Lougheed detailed the use of polysorbate 20 and polysorbate 80 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶251-52. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id.*, 427, 430 and Table 3; Ex. 1003 ¶252.

These experiments, and knowledge of the insulin glargine formulation in Owens, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, polysorbate 20 or polysorbate 80 recited in claims 7 and 24 of the '652 patent, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶249-53. Given insulin glargine's increased propensity for aggregation, and the LANTUS® 2000 Label's warning to not use the product if aggregation

occurred, a PHOSITA would have had specific reasons to do so. *Id.* ¶126. Claims 7 and 24 were obvious over Owens and Lougheed.

3. Dependent Claims 2, 8 and 17-19 were Obvious Over Owens and Lougheed

The limitations and dependencies of claims 2, 8 and 17-19 are presented above.

See §V.B.1, *supra*.

Lougheed detailed the use of polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶255-57. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) was one of several nonionic surfactants that showed significant enhancement of insulin stability through inhibition of insulin aggregation, *i.e.*, to avoid turbidity of the formulation. Ex. 1006, 4, 7, Table 3; Ex. 1003 ¶256; Ex. 1001, 3:2-6 (“[I]nsulins, however, show a decreased stability and an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation).”).

Moreover, Lougheed also taught the concentration ranges in claims 17, 18 and 19. For example, Lougheed exemplified polysorbate 20 at concentrations of 0.000001% and 0.01% (vol/vol) and polysorbate 80 at concentrations 0.000001%, 0.00001%, 0.01%, and 1% (vol/vol) in the formulations tested. Ex. 1006, Table 3; Ex. 1003 ¶257. Given that the densities of polysorbate 20 and polysorbate 80 are

1.095 g/mL and 1.06 g/mL, respectively, Lougheed thus used polysorbate 20 at concentrations of 0.01095 µg/mL and 109.5 µg/mL, and polysorbate 80 at concentrations of 0.0106 µg/mL, 0.106 µg/mL, 106 µg/mL, and 10600 µg/mL. *See* Ex. 1003 ¶257. Each of these concentrations for polysorbate 20 and polysorbate 80 are within the ranges recited in claims 17 and 18.

The slightly narrowed range of claim 19, which recites “20-75 µg/ml” was obvious from Lougheed’s teaching. Not only are the polysorbate 20 and polysorbate 80 levels essentially overlapping with the claimed range, *see Titanium Metals*, 778 F.2d 775 (close amounts suggest prima facie obviousness), a PHOSITA would have had reason to test and optimize the polysorbate 20 and polysorbate 80 levels taught by Lougheed. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (optimization is routine); *In re Ethicon, Inc.*, 844 F.3d 1344 (Fed. Cir. 2017); Ex. 1003 ¶ 257; *see also Aller*, 220 F.2d at 456; *Galderma Labs.*, 737 F.3d at 739.

A PHOSITA would have had reason to combine polysorbate 20 (claim 2) as encouraged by Lougheed [Ex. 1006], including at the concentrations Lougheed tested (claims 17-19), with the insulin glargine formulation Owens disclosed [Ex. 1005] to inhibit or eliminate insulin aggregation, *i.e.* avoid turbidity of the formulation (claim 8), with a reasonable expectation of success. Ex. 1003 ¶¶255-57; *see also* Ex. 1001 3:2-6 (“[I]nsulins, however, show a decreased stability and

an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation).”). Claims 2, 8 and 17-19 were obvious over Owens and Lougheed.

4. Dependent Claims 3, 4 and 11 were Obvious Over Owens and Lougheed

The limitations and dependencies of claims 3, 4 and 11 are presented above.

See §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing *m-cresol*. Ex. 1005, 3-4; Ex. 1003 ¶260. Cresol was a known preservative and a derivative of phenol, which was known by PHOSITAs at the time. *See* Ex. 1003 ¶¶98-102.

Owen’s insulin glargine pharmaceutical formulation containing a preservative such as cresol (a phenolic derivative) is not surprising. Lougheed investigated the stabilizing effects of phenol and cresol on insulin solutions, finding that both phenol and m-cresol successfully stabilized insulin. Ex. 1006, Table 2.

A PHOSITA had reason to include cresol (a preservative and phenol derivative), as Owens taught and Lougheed encouraged, with a reasonable expectation of success. Ex. 1003 ¶¶260-61. Claims 3, 4 and 11 were obvious over the Owens and Lougheed.

5. Dependent Claim 5 was Obvious Over Owens and Lougheed

The language of claim 5 is presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4; Ex. 1003 ¶264.

Owen's inclusion of zinc in insulin glargine formulations was not surprising or inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*. *See, e.g.*, Hallas-Moller [Ex. 1017]; Ex. 1003 ¶265. Owens tested the various amounts of zinc to determine the zinc amounts that would further prolong insulin release and activity. *See* Ex. 1005, 1. Accordingly, it would have been obvious to a PHOSITA that zinc, as taught by Owens, would be included in an insulin pharmaceutical formulation as claimed in claim 5. Ex. 1003 ¶¶264-66.

6. Dependent Claims 6, 12 and 20 were Obvious Over Owens and Lougheed

The limitations of claims 6, 12 and 20 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing "... *glycerol* at pH 4.0." Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶268.

Owen's inclusion of glycerol, an isotonicizing agent, in the insulin glargine formulation was not surprising or inventive. Isotonicizing (or isotonic) agents, such as glycerol, are routinely added to parenteral or subcutaneous formulations to

prevent cell lysis and attendant pain upon injection. *See* Ex. 1003 ¶269. Moreover, Lougheed disclosed the use of 1.6% glycerol in an insulin formulation. *See* Ex. 1006, 7, Table 2. A PHOSITA had ample reason to include an isotonicizing agent such as glycerol, as Owens taught, in an insulin glargine pharmaceutical formulation as claimed in claims 6 and 12. Ex. 1003 ¶¶268-71.

7. Dependent Claims 9 and 10 were Obvious Over Owens and Lougheed

The limitations of claims 9 and 10 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations "... at pH 4.0.". Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶273. It is not surprising or inventive that the pH of an insulin glargine formulation would fall in the pH range recited in claims 9 and 10. A PHOSITA would have known that because of the amino acid substitutions in insulin glargine, insulin glargine is most soluble in an acidic (pH 4.0) environment. *See, e.g.*, Ex. 1005, 1; Ex. 1003 ¶¶274-75. A PHOSITA knew that the pH range of an insulin glargine formulation, as Owens taught, would fall in the range of "from 3.5 to 6.8" (claim 9) or "from 3.5 to 4.5" (claim 10). Claims 9 and 10 were obvious over Owens and Lougheed.

8. Dependent Claims 13, 14 and 22 were Obvious Over Owens and Lougheed

The limitations of claims 13, 14 and 22 are presented above. *See* §V.B.1, *supra*.

Lougheed detailed not only the use of non-ionic surfactants, but also commonly used “salts, buffers and alcohols”, including sodium phosphate, sodium bicarbonate with acetic acid and sodium acetate and sodium bicarbonate with sodium phosphate and sodium citrate buffers, in insulin formulations. *See* Ex. 1006, 6, Table 6; Ex. 1003 ¶277. Lougheed specifically taught that “[f]ormulations in 25 mM sodium bicarbonate with phosphate-citrate or oxaloacetate buffers demonstrated mildly increased stability with FSRs of 11-20 days” of the tested insulin formulations. Ex. 1006, 6, Table 6; Ex. 1003 ¶277-78. The concentration ranges of the sodium bicarbonate, sodium phosphate, acetic acid, sodium acetate and sodium citrate buffers tested all fall within the claimed range of 5-250 mM. Ex. 1006, Table 6, ranging from 20 mM to 100 mM (sodium phosphate).

A PHOSITA had reason, with a reasonable expectation of success, to combine a buffer, including citrate, phosphate and acetate buffers, as Lougheed encouraged, including at the concentrations Lougheed tested (claim 22), with Owens [Ex. 1005] to inhibit or eliminate insulin aggregation. Ex. 1003 ¶¶277-79. Claims 13, 14 and 22 were obvious over Owens and Lougheed.

9. Dependent Claim 21 was Obvious Over Owens and Lougheed

The limitations of claim 21 are presented above. *See* §V.B.1, *supra*.

Lougheed discloses the testing of commonly used “salts, buffers and alcohols”, including sodium chloride at a concentration of 0.9% (equivalent to 154

mM), in insulin formulations, including in combination with sodium dodecyl sulfate (SDS). *See* Ex. 1006, 5-6, Tables 4 and 6; Ex. 1003 ¶285. While the exemplary NaCl concentration is slightly over the claimed range of “up to 150 mM”, a PHOSITA would have had reason, with a reasonable expectation of success to combine sodium chloride, as encouraged by Lougheed, with the claimed insulin formulation. The ’652 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma Labs.*, 737 F.3d at 739 (reversing non-invalidity holding). In light of the common use of physiological saline (0.9% or 154 mM), as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the ’652 patent nor other knowledge in the art would have suggested a concentration change from 154 mM to 150 mM NaCl would have been critical. Ex. 1003 ¶¶285-87.

Claim 21 was therefore obvious over Owens and Lougheed.

10. Dependent Claims 15 and 16 were Obvious Over Owens and Lougheed

The limitations of claims 15 and 16 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine formulations containing “21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin equimolar to 100 U human insulin” Ex. 1005, 3-4; Ex. 1003 ¶290. A PHOSITA would have known that insulin glargine has a molecular weight of 6063, and that 100 U of insulin glargine is equivalent to about

3.6 mg insulin glargine per mL. Ex. 1003 ¶¶289-92. Accordingly, a PHOSITA would recognize that 100 U of insulin glargine is equivalent to 600 nmol/mL, which is within the concentration ranges recited in both claims 15 and 16.

For these reasons, claims 15 and 16 were obvious over Owens and Lougheed.

11. Dependent Claim 23 was Obvious Over Owens and Lougheed

The limitation of claim 23 is presented above. *See* §V.B.1, *supra*.

For the same reasons as claims 2, 4, 6 and 10, claim 23 was obvious over Owens and Lougheed. Owens taught insulin glargine suspension formulations containing “*m-cresol* and glycerol at *pH 4.0*.” Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶290. Moreover, Lougheed provided a strong reason with a reasonable expectation of success to add polysorbate 20 to an insulin glargine formulation to improve the stability of insulin solutions. *See* Ex. 1006, 1, Table 3; Ex. 1003 ¶¶289-92.

Accordingly, the pharmaceutical formulation of claim 23 would have been obvious over Owens and Lougheed.

12. Dependent Claim 25 was Obvious Over Owens and Lougheed

The limitation of claim 25 is presented above. *See* §V.B.1, *supra*.

Adjusting the pH using hydrochloric acid and sodium hydroxide, a standard procedure recognized by any PHOSITA, is explicitly disclosed by Lougheed. *See* Ex. 1006, 2. Moreover, Lougheed taught the addition of various acids and salts for improving the stability of insulin, including dehydroascorbic acid, hyaluronic acid, n-acetyl neuraminic acid, glutamic acid, sodium chloride, sodium bicarbonate, sodium citrate, and acetic acid, among others. *See id.*, Tables 5 and 6; Ex. 1003 ¶¶294-95.

Accordingly, in view of the teachings of both Owens and Lougheed, it would have been obvious and a PHOSITA would have had a reasonable expectation of success of adding an acid, alkali or salt as recited in claim 25 to an insulin glargine formulation. Claim 25 was obvious Owens and Lougheed.

K. Ground 5: Claims 7 and 24 were Obvious over Owens and the Insuman Infusat Reference

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, as above, Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing “21^A-Gly-30^{Ba}-L-Arg-30^{Bb}-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0,” and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶297. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102, 297; Ex. 1001, 4:27-28. Owens disclosed the claimed elements of water and

an acidic pH of approximately 4.0 for the insulin glargine formulation. Ex. 1005, 3. Thus, Owens taught all the elements recited in claims 7 and 24 except “at least one chemical entity chosen from polysorbate and poloxamers.”

The FASS Insuman Infusat entry disclosed the inclusion of poloxamer poly(oxyethylene, oxypropylene)glycol, *i.e.* “at least one chemical entity chosen from polysorbate and poloxamers” as claimed in claims 7 and 24. *See also*, Insuman Infusat Rote Liste entry [Ex. 1033 and 1033A], 6 (inclusion of poloxamer-171 to Insuman Infusat formulation); Ex. 1003, ¶¶298-99. As noted by the FASS entry, “[a]ddition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps...” *See* Ex. 1007A, 7. PHOSITAs recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Loughed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶299.

Insuman Infusat was commercially available, and established regulatory precedent agency determined that insulin formulations including poloxamer were safe and effective for use in diabetes treatment. *See Pfizer*, 480 F.3d at 1362-63 (citing to investor testimony confirming “‘part and parcel of pharmaceutically accepted[] was to look in pharmacopoeias and compendia’ to find an [excipient] having ‘precedence for use within the pharmaceutical industry.’”). This knowledge

provided a PHOSITA reason to combine a poloxamer as encouraged by the FASS Insuman Infusat entry [Ex. 1007, 1007A], with the Owens insulin glargine formulation [Ex. 1005], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a use specifically recognized for the Insuman Infusat product. *See* Ex. 1005, 3; Ex. 1007A, 7; Ex. 1003 ¶¶297-300. Claims 7 and 24 were obvious over Owens and the FASS Insuman Infusat entry.

L. Ground 6: Claims 7 and 24 were Obvious over Owens and Grau

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, as above, Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing “21^A-Gly-30^{Ba}-L-Arg-30^{Bb}-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0,” and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶303. Cresol was a known preservative, as the ’652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claims elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Ex. 1005, 3. Thus, Owens taught all the elements recited in claims 7 and 24 except “at least one chemical entity chosen from polysorbate and poloxamers.”

Grau disclosed the use of a poloxamer (Genapol) to inhibit insulin aggregation in various test conditions, including with a programmable implantable

medication system (PIMS) which pumped the test formulations into a glass vial at a constant rate throughout the 10+months of testing, as well as other *in vivo* and *in vitro* analysis. Ex. 1008, 2-5; Ex. 1003 ¶¶304-05. Grau found that insulin concentration, chemical stability, and biological potency were maintained when tested both *in vitro* in a shaking platform PIMS rig, as well as *in vivo* in PIMS-implanted dogs. *See, e.g.*, Ex. 1008, Tables 2-3 and 4-5. Grau reported that changes to the poloxamer-containing insulin formulations “were comparable to those seen in insulin stored in a glass vial at 37°C without movement.” *Id.*, 4. Grau found that the “[s]urfaces were clean of apparent precipitate even in remote corners.” *Id.*, 5. Grau moreover noted that the “[g]lycemic control of [the] diabetic dogs was good ... [with] no trend toward either worse diabetic control or increased insulin dosage between refills ...”. *Id.* Grau concluded that “Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces.... The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills *in vivo*.” *Id.*, 6.

From Grau’s work, and with knowledge of Owen’s base insulin glargine formulation, a PHOSITA had reason to add at least the poloxamer disclosed in Grau as claimed in claims 7 and 24, to inhibit or eliminate insulin’s well-known propensity to aggregate with a reasonable expectation of success. *See* Ex. 1003 ¶¶302-06. A PHOSITA would have had reason, with a reasonable expectation of

success to combine a poloxamer as encouraged by Grau [Ex. 1008], with the Owens formulation [Ex. 1005] to inhibit or eliminate insulin aggregation issues, a recognized obstacle to the success of insulin as a therapeutic agent. Claims 7 and 24 were therefore obvious over Owens and Grau.

M. Secondary Considerations Cannot Preclude Obviousness.

Although the patentee may offer secondary considerations of nonobviousness, any such evidence would be “insufficient” to “overcome the strong [case] of obviousness” here. *Pfizer*, 480 F.3d at 1372. Sanofi-Aventis has the burden of production for any evidence of patentability. *Id.*, 1360. Mylan nonetheless preliminarily addresses some positions Sanofi-Aventis might take.

1. Addition of a Nonionic Surfactant as Recited in the ’652 Patent Was Completely Expected

While the ’652 patent claims that it “surprisingly found that the addition of surfactants can greatly increase the stability of acidic insulin preparations,” Sanofi-Aventis’ surprise was unfounded. Not only did the prior art disclose tests with species within the broadly claimed polysorbates and poloxamers disclosed in the ’652 patent, the ’652 patent in experimental examples used the same two polysorbates: polysorbate 20 (Tween 20) and polysorbate 80 (Tween 80), that worked in the prior art. See Ex. 1006; Ex. 1003 ¶503. Sanofi-Aventis cannot reasonably assert that the addition of surfactant to the known and available prior art LANTUS[®] 2000 insulin glargine formulations achieved any unexpected result. Ex.

1003 ¶503. On the contrary, it was entirely expected that the addition of nonionic surfactants as claimed in the '652 patent would have worked, as shown by the prior art. *In re Skoll*, 523 F.2d 1392, 1397 (C.C.P.A. 1975) (expected results indicate obviousness). Similarly, there is no evidence of record of a long-felt need, failure of others or industry acclaim for an insulin glargine formulation with a polysorbate or poloxamer. *Id.* ¶¶504-08.

2. Copying By Generic Drug Makers Is Irrelevant.

If Sanofi-Aventis argues that Mylan and other generic drug companies seek to copy the invention of the '652 patent by commercializing generic versions of insulin glargine, this would fail to support non-obviousness. Copying “is required for FDA approval” of generic drugs, any “evidence of copying in the [generic drug] context is not probative of nonobviousness.” *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Dated: June 5, 2017

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

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Inter Partes Review totals 13,028, which is less than the 14,000 allowed under 37 C.F.R. 42.24(a)(i). In accordance with 37 C.F.R. 42.24(a), this word count does not include table of contents, table of authorities, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.

Dated: June 5, 2017

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,476,652 and Exhibits 1001-1035** by Federal Express Next Business Day Delivery on this day, June 5, 2017 on the Patent Owner's correspondence address of record for the subject patent as follows:

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