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. 7,713,930

PETITION FOR *INTER PARTES* REVIEW

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1009	EMEA 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)
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1011	P. Gillies et al., "Insulin Glargine", *Drugs* 59:253-60 (February 2000)
1012	U. Derewenda et al. "Phenol Stabilizes More Helix in a New Symmetrical Zinc Insulin Hexamer", *Nature* 338:594-6 (April 1989)
1013	H. Berchtold and R. Hilgenfeld, "Binding of Phenol to R6 Insulin Hexamers", *Biopolymers* 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)

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1015	J. Brange et al., "Toward Understanding Insulin Fibrillation", *J. Pharm. Sci.* 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", *Diabetes* 5:7-14 (1956)
1018	W.D. Lougheed et al., "Insulin Aggregation in Artificial Delivery Systems", *Diabetologia* 19:1-9 (July 1980)
1019	Excerpts from Handbook of Pharmaceutical Excipients 2nd 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", *Bull. Parenteral Drug Assoc.* 20:74-81 (1966)
1021	H. Thurow and K. Geisen, "Stabilisation of Dissolved Proteins Against Denaturation at Hydrophobic Interfaces", *Diabetologia* 27:212-18 (1984)
1022	M. Katakam et al., "Effect of Surfactants on the Physical Stability of Recombinant Human Growth Hormone", *J. Pharm. Sci.* 84:713-16 (June 1995)
1023	U.S. Patent No. 4,153,689 "Stable Iinsulin 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

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	Administering Insulin" (Issued November 5, 1986) ("Su")
1026	A. Chawla et al. "Aggregation of Insulin, Containing Surfactants, in Contact with Different Materials", *Diabetes* 34:420-24 (May 1985)
1027	Y-C Lee et al., "Effect of Brij-78 on Systemic Delivery of Insulin from an Ocular Device" *J. Pharm. Sci.* 86:430-33 (April 1997)
1028	Y-C Lee et al., "Review on the Systemic Delivery of Insulin via the Ocular Route", *Int'l J. Pharmaceutics* 233:1-18 (February 2002)
1029	M. Heile and D. Schneider, "The Evolution of Insulin Therapy in Diabetes Mellitus", *J. Fam. Pract.* 61 (5 Suppl.: S6-12 (May 2012)
1030	ADIS R&D Profile "Insulin Glargine: Glargine, HOE 71GT15, HOE 71GT80, HOE 901", *Drugs R&D* 2:107-09 (August 1999)
1031	R. Jones, "Insulin Glargine Aventis Pharma", *IDrugs* 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)

Exhibit No.	Description
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 1-20 of U.S. Patent No. 7,713,930 to Brunner-Schwarz et al., titled "Acidic Insulin Preparations Having Improved Stability" ("the '930 patent," Ex. 1002). 37 C.F.R. §311.

By a preponderance of the evidence, this Petition proves the prior art renders unpatentable claims 1-20 of the '930 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] 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 2000 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 '930 patent. The '930 patent is related to U.S. Patent No. 7,476,652 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 '930 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 1-20 of the '930 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 polysorbates or poloxamers to a then-commercially available insulin glargine formulation. Claims 1-20 are unpatentable as follows:

Ground	Claims and Basis
1	Claims 1-20 as obvious over the LANTUS® 2000 label [Ex. 1004] and Lougheed [Ex. 1006]
2	Claims 1-18 and 20 as obvious over the LANTUS® 2000 label and the 2000 FASS Insuman Infusat entry [Exs. 1007 and 1007A]
3	Claims 1-18 and 20 as obvious over the LANTUS® 2000 label and Grau [Ex. 1008]
4	Claim 19 as obvious over the LANTUS® 2000 label, and the 2000 FASS Insuman Infusat entry or Grau and Lougheed
5	Claims 1-20 as obvious over Owens [Ex. 1005] and Lougheed
6	Claims 1-18 and 20 as obvious over Owens and the 2000 FASS Insuman Infusat entry
7	Claims 1-18 and 20 as obvious over Owens and Grau
8	Claim 19 as obvious over Owens and the 2000 FASS Insuman Infusat entry or Grau and Lougheed

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 administrating 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.*, Lougheed [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 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 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 cationic 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. 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 Antihemopphilic 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 pharmaceutics 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 '930 patent. *See, e.g.*, 2000 FASS Insuman Infusat Entry [Ex.

1007 and 1007A], 5 (inclusion of poly(oxyethylene, oxypropylene)glycol to biosynthetic insulin formulation); Insuman Infusat 2001 Rote Liste Entry [Ex. 1033], 6 (including 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 '930 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 '930 patent claims were obvious.

B. Background

1. The '930 Patent [Ex. 1002]

The '930 patent issued May 11, 2010 as a continuation of U.S. Patent U.S. Patent No. 7,476,652, filed March 25, 2000, which was a continuation of U.S. Patent Appl. No. 10/461,740) (now abandoned) 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 '930 patent's earliest possible priority date.

The ’930 patent issued with 20 claims. Claim 1 is the sole independent claim, and claims a pharmaceutical formulation comprising:

- Gly(A21), Arg(B31), Arg(B32)-human insulin (*i.e.*, insulin glargine)
- At least one chemical entity chosen from esters and ethers of polyhydric alcohols
- At least one preservative
- Water
- pH of the insulin glargine formulation in the acidic range from 1 to 6.8.

The dependent claims recite specific chemical entities of the insulin glargine formulation of claim 1, such as specific preservatives (claims 2, 3 and 8), addition of zinc (claim 4), addition of “an isotonicizing agent” (claims 5, 9 and 17), a specific pH range (claims 6 and 7), insulin glargine concentrations (claim 12 and 13), polyhydric alcohol amounts (claims 14-16), and additional excipients, including “acids, alkalis and salts” (claim 18), a buffer (claim 10), “chosen from TRIS, phosphate, citrate, acetate, and glycylglycine” (claim 11), “in a concentration of 5-250 mM” (claim 20), and “NaCl which is present in a concentration of up to 150 mM” (claim 19), to the claimed formulation of independent claim 1.

The well-known issues of insulin-aggregation was fully acknowledged by the ’930 patent, where “[e]specially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress,

which can make itself felt in the form of turbidity and precipitation (particle formation)." Ex. 1002 at 3:7-12, citing to Ex. 1015 (Brange). The '930 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. 1002 at 3:13-22.

Moreover, while the '930 patent acknowledges such issues of insulin, it discusses neither 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 '930 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 challenged claims is the addition of a surfactant, a well-known and proven solution to the well-known and common insulin-aggregation problem.

2. Brief Overview of the '930 Patent's Prosecution History

The '930 patent issued from Application No. 12/328,208 ("the '208 application"). During prosecution, the PTO rejected the '208 application's claims for obviousness and obviousness-type double patenting. The rejection did not include the Lantus® 2000 label [Ex. 1004], Owens [Ex. 1005], Lougheed [Ex. 1006], FASS Insuman Infusat entry [Ex. 1007] or Grau [Ex. 1005], asserted here. Lougheed was

disclosed in an information disclosure statement, but not applied. *See* Ex. 1002A, 124.

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., 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* Ex. 1003 ¶¶31-34. A PHOSITA would have the experience in surfactants commonly used in peptide injection formulation, as well as factors that contribute to peptide 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 consulted with one or more team members of experienced professionals to develop an insulin formulation resistant to the well-known insulin-aggregation propensities. *Id*. A PHOSITA would also have been well-versed in the available world-wide literature as of the priority date. *Id*.

D. Claim Construction

The Board gives the challenged claims their "broadest reasonable construction

in light of the specification of the patent in which it appears." §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 application or use of the pharmaceutical formulation, would be relevant to the patentability of the challenged claims.

"Esters and Ethers of Polyhydric Alcohols". Each claim of the '930 patent contains reference to "esters and ethers of polyhydric alcohols." The '930 patent specification provides examples of esters and ethers of polyhydric alcohols:

> Preferred pharmaceutical formulations of the present invention are those wherein the surfactant is selected from the group consisting of

[2] Without taking a position here on the definiteness of the claims, 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 a 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).

> partial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol and sorbitol, and polyols; the partial and fatty acid esters and ethers of glycerol and sorbitol being selected from the group consisting of Span®, **Tween®**, Myrj®, Brij®, Cremophor®; the polyols being selected from the group consisting of polypropylene glycols, polyethylene glycols, **poloxamers**, **Pluronics®**., and Tetronics®.

'930 patent [Ex. 1002] 4:23-32 (emphasis added).

A PHOSITA would understand that polysorbate 20 (or Tween® 20) and polysorbate 80 (or Tween® 80) are polyoxyethylene sorbitol esters, and are encompassed in the definition of "esters and ethers of polyhydric alcohols," as described by the '930 patent. Ex. 1003 ¶¶79-80. Additionally, a PHOSITA would understand and recognize that poloxamers and Pluronics® are ethers of polyhydric alcohols. *Id*. Thus, a PHOSITA would interpret "esters and ethers of polyhydric alcohols" to include at least polysorbates and poloxamers, amongst many other compounds.

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]

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 '930 patent. *See* Ex. 1004A, Affidavit of Patricia van Skaik (establishing 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 ^{125}I-Labeled Insulin Glargine (HOE 901) In Healthy Men: Comparison With NPH Insulin And The Influence Of Different Subcutaneous Injection Sites," Diabetes Care. 2000 Jun;23:813-9 ("Owens") [Ex. 1005]

Owens published in a learned periodical more than one year before the earliest priority date of the '930 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^{B}a-L-Arg-30^{B}b-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^{B}a-L-Arg-30^{B}b-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 '930 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, $CH_3(CH_2)_N$, 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% NaCI) and SDS (1% wt/vol)." *Id*., 3-4 (emphasis added). Lougheed disclosed at least including 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 Insuman Infusat Entry (January 2000) ("Insuman Infusat") [Ex. 1007 and 1007A]

Insuman Infusat, a commercially available insulin product distributed by Aventis Pharma[3] 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 '930 patent. Ex. 1003 ¶¶147-49.

Insuman Infusat, available in 3.15 milliliter ampules containing 100 international units (I.E.) per milliliter recombinant insulin, was supplied as an injectable solution for the treatment of diabetes mellitus. Insuman Infusat

[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.

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. 1007, 5.

The FASS Insuman Infusat entry states that the formulation was specially made to inhibit aggregation in insulin pumps: "**Properties of the pharmaceutical 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.*, 6.

5. Grau, U. and Saudek, C.D., "Stable Insulin Preparaton for Implanted Insulin Pumps" Diabetes. 1987 December; 36:1453-1459 ("Grau") (Ex. 1008)

Grau published more than one year before the earliest priority date of the '930 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 stabilize insulin formulations by inhibiting 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.

Grau found insulin concentration, chemical stability and biological potency were maintained when tested both *in vitro* and *in vivo* in PIMS-implanted dogs. *Id.*, 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 ^{o}C without movement." *Id.* 1456. Grau concluded "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 '930 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 ester or ether of polyhydric alcohol, *e.g.*, polysorbates or poloxamers. Ex. 1003 ¶310. 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. Ex. 1003 ¶¶103-08. These numerous studies disclosed including polysorbates and poloxamers to inhibit insulin aggregation. *Id.*, ¶¶109-23. In addition, poloxamer was actually used in a commercially available 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 '930 patent. *Id.* ¶122.

In other words, more than a year before the '930 patent's earliest filing date, a commercially available insulin glargine formulation and solutions for inhibiting 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 1-20 of the '930 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 '930 patent recites a "pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin; at least one chemical entity chosen from esters and ethers of polyhydric alcohols; 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. 1004A; Ex. 1003 ¶307. 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, 3. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102, 309; Ex. 1002, 4:27-28. The LANTUS® 2000 Label further disclosed water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, the LANTUS® 2000 Label taught all elements recited

in claim 1 except "at least one chemical entity chosen from polysorbate 20 and polysorbate 80." *Id.*, ¶¶308-10.

Lougheed disclosed and addressed several known issues with insulin formulations, including the propensity for insulin to aggregate upon storage and delivery in, for example, injection devices and infusion pumps. 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 ¶¶308-17. Lougheed compared different nonionic detergents in extreme storage conditions and measuring the appearance of aggregated particles through time. *Id.* Lougheed specifically taught that various esters of polyhydric alcohols, including polysorbate 20 (*i.e.*, Tween 20), polysorbate 80 (*i.e.*, Tween 80) and Brij 35, showed enhancement of insulin stability and decrease of aggregation. Ex. 1006, 4, 6, Table 3; Ex. 1003 ¶¶308-17.

It is not surprising that Lougheed chose esters of polyhydric alcohols as an excipient for use in insulin formulations. Polysorbates and Brij non-ionic surfactants 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 ¶¶314-17. Moreover, many non-ionic surfactnats were GRAS (Generally Recognized as Safe) and already included in the FDA Inactive Ingredients Guide for various pharmaceutical

formulations. Ex. 1003 ¶315. Including esters of polyhydric alcohols used in Lougheed would have thus been obvious. *Id.* ¶317.

Lougheed's experiments, the knowledge that polysorbates were generally regarded as effective and safe in inhibiting aggregation in other biologic products, and knowledge of the LANTUS® 2000 formulation, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *i.e.*, including esters of polyhydric alcohols (such as polysorbate 20, polysorbate 80 and Brij 35) as claimed in claim 1 of the '930 patent to the LANTUS® 2000 formulation, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶317, 320.

A PHOSITA would especially have had reason because insulin glargine was prone to aggregation as monomeric insulin in an acid pH environment. *See* Ex. 1003 ¶126, 316. 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."). 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.

Thus, the '930 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 simply consistent with what the art already knew. Ex, 1003, ¶313. A PHOSITA would not have been surprised at the success of combining the known and available insulin glargine formulation with nonionic surfactants to inhibit the formation of particles and the appearance of turbid solutions. A PHOSITA would have reasonably expected nothing less. Claim 1 was obvious over the LANTUS® 2000 Label and Lougheed.

2. Dependent Claims 2, 3 and 8 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 2 of the '930 patent depends from claim 1, and recites "wherein the at least one preservative is chosen from phenols." Claim 3 of the '930 patent depends from claim 1, and recites "wherein the at least one preservative is cresol." Claim 8 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 disclosed including "2.7 mg m-cresol" in the insulin glargine formulation. Ex. 1004, 3. Cresol was a known preservative and a derivative of phenol, as the '930 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1002, 4:32-34. That the LANTUS® 2000 formulation contained 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 was capable of stabilizing insulin. Ex. 1006, Table 2.

A PHOSITA would have had reason to include cresol, as taught by the LANTUS® 2000 Label and as encouraged by Lougheed, with a reasonable expectation of success. Ex. 1003, ¶¶322-24. Claims 2, 3 and 8 are obvious over the Lantus® 2000 Label and Lougheed.

3. Claim 4 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 4 of the '930 patent depends from claim 3, recites the pharmaceutical formulation "further including zinc."

The LANTUS® 2000 Label included "30 mcg zinc" in the insulin glargine formulation. Ex. 1004, 3. Including zinc as a component in the LANTUS® 2000 is 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 '930 patent to determine the zinc amounts that would further prolong insulin release and activity. *See* Ex. 1005, 1. A PHOSITA had reasons to include zinc, as taught by the LANTUS® 2000 Label, in an insulin pharmaceutical formulation as claimed in claim 4. Ex. 1003 ¶¶326-28.

4. Dependent Claims 5, 9 and 17 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 5 depends from claim 1, and recites the formulation "further including at least one isotonicizing agent." Claim 9 depends from claim 5, and recites "wherein the at least one isotonicizing agent is chosen from mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride and glycerol." Claim 17 depends from claim 9 and recites "wherein the 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 including "20 mg glycerol 85%" in the insulin glargine formulation. Ex. 1004, 3. The molecular weight of glycerol is 92.1 g/mol, 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 17. *See* Ex. 1003 ¶332.

Including glycerol, an isotonicizing agent, to the LANTUS® 2000 insulin formulation was neither surprising nor 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 ¶¶330-33. A PHOSITA had reason to include an isotonicizing agent such as glycerol, as taught by the LANTUS® 2000 Label, in an insulin pharmaceutical formulation as claimed in claims 5, 9 and 17.

5. Dependent Claims 6 and 7 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 6 depends from claim 4, and recites "wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 6.8." Claim 7 depends from claim 6, and recites "wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5."

The LANTUS® 2000 Label disclosed the insulin glargine formulation as a pH of approximately 4.0. Ex. 1004, 3. Having a pH of an insulin glargine fall in the pH range recited in claims 6 and 7 is not surprising or inventive. A PHOSITA would have known well before the earliest priority date of the '930 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 ¶336. A PHOSITA had reason to use the pH range of an insulin glargine formulation, as taught by the LANTUS® 2000 Label, which falls in the range of "from 3.5 to 6.8" (claim 6) or "from 3.5 to 4.5" (claim 7). Ex. 1003 ¶¶335-37. Claims 6 and 7 were obvious over the LANTUS® 2000 Label and Lougheed.

6. Dependent Claims 10, 11 and 20 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 10 depends from claim 1 and recites that the claimed pharmaceutical formulation "further compris[es] a buffer." Claim 11 depends from claim 10, and recites the buffer as "chosen from TRIS, phosphate, citrate, acetate, and

glycylglycine." Claim 20 depends from claim 10, and recites that the "buffer is present in a concentration of 5-250 mM."

Lougheed disclosed including 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* Ex. 1006, Table 6; Ex. 1003 ¶339. 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. 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.*, *id.*, Table 6.

A PHOSITA had reason to combine a buffer, including citrate, phosphate and acetate buffers, as encouraged by Lougheed, and at the concentrations tested by Lougheed (claim 20), with the known and FDA-approved LANTUS® 2000 formulation to inhibit or eliminate insulin-aggregation with a reasonable expectation of success. Ex. 1003 ¶¶339-41. Claims 10, 11 and 20 were therefore obvious over the LANTUS® 2000 Label and Lougheed.

7. Dependent Claims 12 and 13 were obvious Over LANTUS® 2000 Label and Lougheed

Claim 12 depends from claim 1, and recites "wherein the Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 60-6000 nmol/ml." Claim 13 depends from claim 12, and recites "wherein the Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 240-3000 nmol/ml."

The LANTUS® 2000 Label included "100 IU (3.6378 mg) insulin glargine" in the pharmaceutical 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 g/mol. *Id*, 3. 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 12 and 13. *See* Ex 1003 ¶¶342-44.

For these reasons, claims 12 and 13 were obvious over the LANTUS® 2000 Label and Lougheed.

8. Dependent Claims 14, 15 and 16 were obvious Over LANTUS® 2000 Label and Lougheed

Claim 14 depends from claim 1, and recites "wherein the at least one chemical entity is present in a concentration of 5-200 μg/ml." Claim 15 depends from claim 14, and recites "wherein the at least one chemical entity is present in a concentration of 5-120 μg/ml." Claim 16 depends from claim 15, and recites

"wherein the at least one chemical entity is present in a concentration of 20-75 μg/ml."

Lougheed detailed including polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in, for example, injection devices and infusion pumps. *See* Ex. 1006, 1; Ex. 1003 ¶346. 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 ¶346; Ex. 1002, 3:7-12.

Moreover, the concentration ranges in claims 14, 15 and 16 were taught in Lougheed. 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 ¶¶347-48. 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. Ex. 1003 ¶¶346-49. Each of these concentrations for polysorbate 20 and polysorbate 80 are within the ranges recited in claims 14 and 15.

The slightly narrowed range of claim 16, 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 Corp. of America v. Banner,* 778 F.2d 775, 783 (Fed. Cir. 1985) (close amounts suggest prima facie obviousness), a PHOSITA would have had reason, and would have tested and optimized 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.*, App. 2015-1696, slip op. 12 (Fed. Cir. 2017); Ex. 1003 ¶¶346-49; *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955); accord *Galderma Labs., LP v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

A PHOSITA had reason to combine polysorbate 20 or polysorbate 80 as encouraged by Lougheed, including at the concentrations tested by Lougheed (claims 17-19), with the known and FDA-approved LANTUS® 2000 formulation, with a reasonable expectation of success to inhibit or eliminate insulin-aggregation. Claims 14, 15 and 16 were obvious over the LANTUS® 2000 Label and Lougheed.

9. Dependent Claim 18 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 18 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 ¶351. 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* Ex. 1006, Tables 5-6; Ex. 1003 ¶¶351-52.

In view of the teachings of both the LANTUS® 2000 Label and Lougheed, it would have been obvious to add an acid, alkali or salt as recited in claim 18 to an insulin formulation with a reasonable expectation of success. Claim 18 was obvious over the LANTUS® 2000 Label and Lougheed.

10. Dependent Claim 19 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 19 depends from claim 18, and recites "wherein NaCl is present in a concentration of up to 150 mM."

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 ¶354. 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 '930 patent provides no evidence of the criticality of the

NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma*, 737 F.3d at 739 (reversing non-invalidity holding). Moreover, a PHOSITA would 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 ¶¶354-56. In light of Lougheed's use of NaCl, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '930 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.* ¶355.

Claim 19 was obvious over the LANTUS® 2000 Label and Lougheed.

H. Grounds 2 and 3: Claims 1-18 and 20 of the '930 Patent were Obvious Over the LANTUS® 2000 Label and Insuman Infusat or Grau

1. Claim 1 was Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

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

The LANTUS® 2000 Label disclosed 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 '930 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1002, 4:32-34. The LANTUS® 2000 Label disclosed 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."

The FASS Insuman Infusat entry disclosed including 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. 1007, 6. PHOSITAs recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Lougheed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶362.

Similarly, Grau disclosed including a poloxamer (Genapol; poloxamer 181) to inhibit insulin-aggregation in various test conditions, including with a programmable implantable medication system (PIMS). Ex. 1008, 2-5; Ex. 1003 ¶¶365-70. 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. Ex. 1008, 4-5, Tables 2-3. 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 "[g]enapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces." *Id.*, 6.

A PHOSITA would have had reason, with reasonable expectation of success, to use either poloxamer 171 or Genapol (poloxamer 181) as "at least one chemical entity chosen from esters and ethers of polyhydric alcohols" as claimed in claim 1. The Insuman Infusat product was and is commercially available, which demonstrates that a regulatory agency determined that insulin formulations including poloxamer were safe and effective for use in diabetes treatment.[4] Moreover, Grau's work would have informed a PHOSITA that poloxamer 181 would have inhibited or eliminated insulin's propensity to aggregate. *See* Ex. 1003 ¶¶359-71.

[4] *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-63 (Fed. Cir. 2007) (Citing to investor testimony that "'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.'").

Including a surfactant to inhibit or eliminate insulin aggregation would have been especially evident to PHOSITAs where insulin glargine was likely prone to aggregation as monomeric insulin in an acid pH environment. *See* Ex. 1003 ¶¶359-71. 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."). A PHOSITA had reason to combine a poloxamer as encouraged by the Insuman Infusat FASS entry and Grau, with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004], with a reasonable expectation of success to inhibit or eliminate insulin-aggregation issues, which were a recognized obstacle to the success of insulin as a therapeutic agent.

Claim 1 was obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

2. Dependent Claims 2, 3 and 8 were Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

Claims 2, 3 and 8 are recited above. *See* §V.B.1, *supra*.

The LANTUS® 2000 Label disclosed "2.7 mg m-cresol" in the insulin glargine formulation. Ex. 1004 at 1. Cresol was a known preservative and a derivative of phenol, as confirmed by the '930 patent. *See* Ex. 1003 ¶373; Ex. 1002, 4:32-34. That the LANTUS® 2000 pharmaceutical formulation contained a preservative such as cresol (a phenolic derivative) is not surprising. The insulin

formulations of the FASS Insuman Infusat entry and Grau included phenol (claims 2 and 8) as a preservative. *See* Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶¶373-75.

A PHOSITA had reason to include a phenolic preservative such as cresol as taught by the LANTUS® 2000 Label. Claims 2, 3 and 8 were obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

3. Claim 4 was Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The limitations of claim 4 are recited above. *See* §V.B.1, *supra*.

The LANTUS® 2000 Label included "30 mcg zinc" with the insulin glargine formulation. Ex. 1004, 3. Including zinc as a component in the LANTUS® 2000 is not surprising or inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*, including the insulin formulations in the FASS Insuman Infusat entry and Grau. Ex. 1007, 5; Ex. 1008, 3; Ex. 1003 ¶¶98-102. In fact, various amounts of zinc were tested in insulin glargine formulations well before the earliest priority date of the '930 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, Insuman Infusat or Grau, as claimed in claim 4. Ex. 1003 ¶¶ 377-79. Claim 4 was obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

4. Dependent Claims 5, 9 and 17 were Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The limitations of claims 5, 9 and 17 are recited above. *See* §V.B.1, *supra*.

The LANTUS® 2000 Label included "20 mg glycerol 85%" in the insulin glargine formulation. Ex. 1004, 3. The molecular weight of glycerol is 92.1 g/mol, 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 17. *See* Ex. 1003 ¶383.

Including glycerol, an isotonicizing agent, to the LANTUS® 2000 insulin formulation was neither surprising nor 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, including to the insulin formulations of Insuman Infusat and Grau. *See* Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶¶381-84. A PHOSITA had reason to include an isotonicizing agent such as glycerol, as taught by the LANTUS® 2000 Label, in an insulin pharmaceutical formulation as claimed in claims 5, 9 and 17.

5. Dependent Claims 6 and 7 were Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The language of claims 6 and 7 are recited above. *See* §V.B.1, *supra*.

The LANTUS® 2000 Label disclosed the insulin glargine formulation 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 6 and 7 is not surprising or inventive. A PHOSITA would have known well before the earliest priority date of the '930 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 ¶387. A PHOSITA had reason to use the pH range of an insulin glargine formulation, as taught by the LANTUS® 2000 Label, which falls in the range of "from 3.5 to 6.8" (claim 6) or "from 3.5 to 4.5" (claim 7). Ex. 1003 ¶¶386-88. Claims 6 and 7 were obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

6. Dependent Claims 10, 11 and 20 were Obvious over LANTUS® 2000 Label and Insuman Infusat or Grau

The limitations of claims 10, 11 and 20 are recited above. *See* §V.B.1, *supra*.

Grau and Insuman Infusat disclosed including a Tris buffer in the insulin formulations. *See* Ex. 1008, 1 (50 mM of tris-hydroxymethyl)-aminomethane (Tris)); Ex. 1007, 5 (trometamol component). The purpose of a buffer compound in a pharmaceutical formulation is to maintain a specific pH environment, the same purpose fulfilled by the Tris buffer of Grau and Insuman Infusat. *See* Ex. 1003 ¶390. A PHOSITA had reason, with a reasonable expectation of success, to combine a buffer with the known and FDA-approved LANTUS® 2000 formulation to inhibit or eliminate insulin-aggregation. *Id.* ¶¶390-91. Claims 10, 11 and 20 were obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

7. Dependent Claims 12 and 13 were Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The limitations of claims 12 and 13 are recited above. *See* §V.B.1, *supra*.

As set forth, the LANTUS® 2000 Label included "100 IU (3.6378 mg) insulin glargine" in its pharmaceutical 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 g/mol. *Id.*, 3. 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 12 and 13. *See* Ex. 1003 ¶¶393-95.

For these reasons, claims 12 and 13 were obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

8. Dependent Claims 14, 15 and 16 were Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The limitations of claims 14, 15 and 16 are recited above. *See* §V.B.1, *supra*.

Insuman Infusat and Grau disclosed including a poloxamer to inhibit insulin-aggregation in various test conditions, and found that insulin concentration, chemical stability and biological potency were maintained in the presence of the poloxamer. Ex. 1007, 5-6 ("Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin."); Ex. 1008, 4-5, Tables 2-3. Grau concluded that "[g]enapol, 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.

The claimed concentration ranges of "5-200 μg/ml" and "5-120 μg/ml" are taught in Insuman Infusat and Grau, which disclosed including "poly(oxyethylene oxypropylene)glycol 0.01 mg" (*i.e.*, 10 μg/ml) or "10 μg/ml polyethylene-polypropylene glycol (Genapol)," respectively. Ex. 1007, 5; Ex. 1008, 1. The slightly narrowed range of claim 16, which recites "20-75 μg/ml" was obviated by Insuman Infusat and Grau's 10 μg/ml poloxamer levels. Not only is the 10 μg/ml poloxamer levels essentially overlapping with the claimed range, *see Titanium Metals,* 778 F.2d at 783, a PHOSITA would have reason, and would have tested and optimized the poloxamer levels taught by Insuman Infusat or Grau. *Peterson*, 315 F.3d at 1330; *Ethicon*, App. 2015-1696, slip op. 12; Ex. 1003 ¶¶397-401; *see also Aller*, 220 F.2d at 456; *Galderma*, 737 F.3d at 739.

A PHOSITA had reason to combine a poloxamer at the concentration taught by Insuman Infusat [Ex. 1007] or Grau [Ex. 1008] with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004] with a reasonable expectation of success to inhibit or eliminate insulin-aggregation. Claims 14, 15 and 16 were obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

9. Dependent Claim 18 was Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau

The language of claim 18 is recited above. *See* §V.B.1, *supra*.

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 ¶403. Moreover, Insuman Infusat and Grau further taught the addition of a Tris base as a buffering or stabilising agent. *See* Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶¶403-04.

In view of the teachings of both the LANTUS® 2000 Label and Insuman Infusat or Grau, it would have been obvious to add an acid, alkali or salt as recited in claim 18 to an insulin formulation with a reasonable expectation of success. Claim 18 was as obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau.

I. Ground 4: Dependent Claim 19 was Obvious Over LANTUS® 2000 Label and Insuman Infusat or Grau and Lougheed

The language of claim 19 is recited above. *See* §V.B.1, *supra*.

Lougheed disclosed 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). Ex. 1006, 5-6, Tables 4 and 6; Ex. 1003 ¶406. 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 ’930 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d 454 at 456; accord *Galderma*, 737 F.3d at 739. Moreover, a PHOSITA would 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 ¶407. In light of Lougheed’s use of NaCl, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the ’930 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.* ¶¶406-08.

Claim 19 was obvious over the LANTUS® 2000 Label and Insuman Infusat or Grau and Lougheed.

J. Ground 5: Claims 1-20 of the ’930 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^{B}a-L-Arg-30^{B}b-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 ¶410. Cresol

was a known preservative, as the '930 patent confirms. *See* Ex. 1002, 4:32-34; Ex. 1003 ¶¶98-102. Owens disclosed water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all the elements recited in claim 1 except 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, for example, injection devices and infusion pumps. *See* Ex. 1006, 1; Ex. 1003 ¶¶412-13. 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, Table 3. Lougheed disclosed polysorbate 20 (*i.e.*, Tween 20), polysorbate 80 (*i.e.*, Tween 80) and Brij 35 showed enhancement of insulin stability. Ex. 1006, 4, 7 and Table 3; Ex. 1003 ¶¶412-13. 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 polyhydric alcohols polysorbate 20 and polysorbate 80 as claimed in claim 1 of the '930 patent, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶412-17. A PHOSITA had reason to combine polysorbate 20 or polysorbate 80, as encouraged by Lougheed, with the

insulin glargine formulation of Owens, to inhibit or eliminate insulin-aggregation, a recognized obstacle to the success of insulin as a therapeutic agent with a reasonable expectation of success. Claim 1 was obvious over Owens and Lougheed.

2. Dependent Claims 2, 3 and 8 were obvious Over Owens and Lougheed

The language of claims 2, 3 and 8 are recited above. *See* §V.B.1, *supra*.

Owens disclosed "m-cresol" as included with the insulin glargine formulations. Ex. 1005, 3-4; Ex. 1003 ¶420. Cresol is a preservative and a derivative of phenol, as confirmed by the '930 patent. *See* Ex. 1003 ¶¶98-102; Ex. 1002, 4:32-34.

That the Owens insulin glargine pharmaceutical formulation contained a preservative such as cresol (a phenolic derivative) is not surprising. Lougheed [Ex. 1006] investigated the stabilizing effects of phenol and cresol on insulin solutions, finding that both phenol and m-cresol was capable of stabilizing insulin. *Id.,* Table 2.

A PHOSITA had reason to include cresol (a preservative and derivative of phenol), as taught by Owens and as encouraged by Lougheed with a reasonable expectation of success. Ex. 1003 ¶¶420-22. Claims 2, 3 and 8 were obvious over Owens and Lougheed.

3. Dependent Claim 4 was Obvious Over Owens and Lougheed

The limitations of claim 4 are recited above. *See* §V.B.1, *supra*.

Owens included 15, 30, or 80 μg/ml zinc (or 2.295, 4.59, and 12.24 μmol/L, respectively) with the insulin glargine formulation. Ex. 1005, 3-4; Ex. 1003 ¶424.

Owen's inclusion of zinc in the insulin glargine formulations was neither surprising nor inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*. Ex. 1014; Ex. 1003 ¶425. Owens tested the various amounts of zinc to determine the zinc amounts that would further prolong insulin release and activity. Ex. 1005, 1. A PHOSITA had reason to include zinc, as taught by Owens, in an insulin pharmaceutical formulation as claimed in claim 4. Ex. 1033 ¶¶424-26.

4. Dependent Claims 5, 9 and 17 were obvious Over Owens and Lougheed

The limitations of claims 5, 9 and 17 are recited above. *See* §V.B.1, *supra*.

Owens included glycerol in the insulin glargine formulations disclosed. Ex. 1005, 3-4; Ex. 1003 ¶428.

Owen's inclusion of glycerol, an isotonicizing agent, to the insulin glargine formulation was neither surprising nor 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

¶¶101, 429. Although Owens does not teach the exact concentration of glycerol to use in insulin glargine formulations, Lougheed disclosed including 1.6% glycerol, which is equivalent to 173 mM, *i.e.*, within the glycerol range recited in claim 20. *See* Ex. 1006, 7, Table 2; Ex. 1003 ¶¶428-32. Thus, a PHOSITA had reason to include an isotonicizing agent such as glycerol, as taught by Owens, in an insulin glargine pharmaceutical formulation as claimed in claims 5, 9 and 17.

5. Dependent Claims 6 and 7 were obvious Over Owens and Lougheed

The limitations of claims 6 and 7 are recited above. *See* §V.B.1, *supra*.

Owens disclosed insulin glargine formulations at an acidic pH 4.0. Ex. 1005, 3-4; Ex. 1003 ¶434. Having a pH of an insulin glargine formulation fall in the pH range recited in claims 6 and 7 is not surprising or inventive. A PHOSITA would have known well before the earliest priority date of the '930 patent that the amino acid substitutions in insulin glargine make it most soluble in an acidic (pH 4.0) environment. Ex. 1005, 1; Ex. 1003 ¶435. A PHOSITA had reasons to use the pH range of an insulin glargine formulation, as taught by Owens, which falls in the range of "from 3.5 to 6.8" (claim 6) or "from 3.5 to 4.5" (claim 7). Ex. 1003 ¶¶434-36. Claims 6 and 7 were obvious over Owens and Lougheed.

6. Dependent Claims 10, 11 and 20 were Obvious Over Owens and Lougheed

The limitations of claims 10, 11 and 20 are recited above. *See* §V.B.1, *supra*.

Lougheed detailed not only including 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 ¶438. 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 ¶438. 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.

A PHOSITA had reason to combine a buffer, including citrate, phosphate and acetate buffers, as encouraged by Lougheed, at the concentrations tested by Lougheed (claim 22), with the insulin glargine formulation of Owens to inhibit or eliminate insulin-aggregation with a reasonable expectation of success. Ex. 1003 ¶¶438-39. Claims 10, 11 and 20 were obvious over the Owens and Lougheed.

7. Dependent Claims 12 and 13 were Obvious Over Owens and Lougheed

The limitations of claims 12 and 13 are recited above. *See* §V.B.1, *supra*.

Owens disclosed "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin" formulations. Ex. 1005, 3-4; Ex. 1003 ¶441. A

PHOSITA would have known that that insulin glargine has a molecular weight of 6063 g/mol, and that 100 U of insulin glargine is equivalent to about 3.6 mg insulin glargine per mL. Ex. 1003 ¶442. 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 12 and 13. *Id.* ¶¶441-43.

For these reasons, claims 12 and 13 were obvious over Owens and Lougheed.

8. Dependent Claims 14, 15 and 16 were Obvious Over Owens and Lougheed

The limitations of claims 14, 15 and 16 are recited above. *See* §V.B.1, *supra*.

Lougheed detailed including polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. Ex. 1006, 1; Ex. 1003 ¶445. 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 ¶446.

Moreover, Lougheed also taught the concentration ranges in claims 14, 15 and 16. 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 ¶447. 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. Each of these concentrations for polysorbate 20 and polysorbate 80 are within the ranges recited in claims 14 and 15.

Lougheed would have suggested the slightly narrowed range of claim 16, which recites "20-75 μg/ml". Not only are the polysorbates amounts essentially overlapping with the claimed range, *see Titanium Metals,* 778 F.2d at 783, a PHOSITA would have reason, and would have tested and optimized the polysorbate levels Lougheed tested. *Peterson*, 315 F.3d at 1330; *Ethicon*, App. 2015-1696, slip op. 12; Ex. 1003 ¶¶445-48; *see also Aller*, 220 F.2d at 456; *Galderma*, 737 F.3d at 739.

A PHOSITA had reason to combine polysorbate 20 or polysorbate 80 as encouraged by Lougheed, at the concentrations tested by Lougheed (claims 14-16), with the insulin glargine formulation disclosed in Owens [Ex. 1005] to inhibit or eliminate insulin-aggregation with a reasonable expectation of success. Claims 14, 15 and 16 were obvious over Owens and Lougheed.

9. Dependent Claim 18 was Obvious Over Owens and Lougheed

The limitations of claim 18 are recited 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 also 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.

In view of the teachings of both Owens and Lougheed, a PHOSITA had reason to add an acid, alkali or salt as recited in claim 18 to an insulin glargine formulation with a reasonable expectation of success. Ex. 1003 ¶¶ 450-51. Claim 18 was obvious over Owens and Lougheed.

10. Dependent Claim 19 was Obvious Over LANTUS® 2000 Label and Lougheed

The limitations of claim 19 are recited above. *See* §V.B.1, *supra*.

Lougheed disclosed 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 ¶453. 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. Ex. 1003 ¶ 453. The '930 patent provides no evidence of the

criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma*, 737 F.3d at 739. Moreover, a PHOSITA would 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 ¶454. In light of Lougheed's use of NaCl, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '930 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.* ¶¶453-55.

Claim 19 was obvious over Owens and Lougheed.

K. Grounds 6 and 7: Claims 1-18 and 20 of the '930 Patent was obvious Over Owens and Insuman Infusat or Grau

1. Claim 1 was Obvious Over Owens and Insuman Infusat or Grau

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

Owens taught insulin glargine 1 ml. suspension formulations containing "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-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 ¶457. Cresol was a known preservative, as confirmed by the '930 patent. *See* Ex. 1003 ¶¶98-102; Ex. 1002, 4:32-34. Owens disclosed

water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all the elements recited in claim 1 except "at least one chemical entity chosen from polysorbate 20 and polysorbate 80."

The FASS Insuman Infusat entry disclosed including 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. 1007, 6. PHOSITAs recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Lougheed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶¶459-61.

Similarly, Grau disclosed including a poloxamer (Genapol; poloxamer 181) to inhibit insulin-aggregation in various test conditions, and concluded that "[g]enapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces." Ex. 1008, 6; Ex. 1003 ¶¶462-63.

A PHOSITA would have had reason to combine either poloxamer 171 or Genapol (poloxamer 181) as the "at least one chemical entity chosen from esters

and ethers of polyhydric alcohols" as claimed in claim 1. Given the commercial availability of the Insuman Infusat product, and thus the established precedence by a regulatory agency that insulin formulations including poloxamer were safe and effective for use in diabetes treatment and with knowledge of the base formulation taught in Owens, a PHOSITA would have had ample reason to add at least a poloxamer as disclosed in the Insuman Infusat FASS entry. Moreover, Grau's work would have informed a PHOSITA that poloxamer 181 would have also inhibited or eliminated insulin's propensity to aggregate. *See* Ex. 1003 ¶¶457-64.

Claim 1 was obvious over Owens and Insuman Infusat or Grau.

2. Dependent Claims 2, 3 and 8 were Obvious Over Owens and Insuman Infusat Reference or Grau

The limitations of claims 2, 3 and 8 are recited above. *See* §V.B.1, *supra*.

As set forth, Owens disclosed the inclusion of m-cresol in the insulin glargine formulations. Ex. 1005, 3-4; Ex. 1003 ¶466. Cresol was a known preservative and a derivative of phenol, as confirmed by the '930 patent. *See* Ex. 1003 ¶¶98-102; Ex. 1002, 4:32-34.

That the Owens insulin glargine pharmaceutical formulation contained a preservative such as cresol (a phenolic derivative) is not surprising. The insulin formulations in Insuman Infusat and Grau included phenol (claims 2 and 8) as a preservative. *See* Ex. 1007, 5; Ex. 1008, 1.

A PHOSITA had ample reason to include cresol (a preservative and derivative of phenol), as taught by Owens. Claims 2, 3 and 8 were obvious over Owens and Insuman Infusat or Grau.

3. Dependent Claim 4 was Obvious Over Owens and Insuman Infusat Reference or Grau

The language of claim 4 is recited above. *See* §V.B.1, *supra*.

Owens disclosed including 15, 30, or 80 μg/ml zinc (or 2.295, 4.59, and 12.24 μmol/L, respectively), the insulin glargine formulations. Ex. 1005, 3-4; Ex. 1003 ¶470.

Owen's inclusion of zinc in the 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*, including to the commercially available Insuman Infusat formulation and the insulin formulation in Grau. Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶¶471-72. Owens tested the various amounts of zinc 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 Owens, in an insulin pharmaceutical formulation as claimed in claim 4.

4. Dependent Claims 5, 9 and 17 were Obvious Over Owens and Insuman Infusat Reference or Grau

The limitations of claims 5, 9 and 17 are recited above. *See* §V.B.1, *supra*.

Owens included glycerol in the disclosed insulin glargine formulations. Ex. 1005, 3-4; Ex. 1003 ¶474.

Owen's inclusion of glycerol, an isotonicizing agent, to the insulin glargine formulation was neither surprising nor inventive. Isotonicizing (or isotonic) agents, such as glycerol, are routinely added to parenteral or subcutaneous formulations, including to the insulin formulations disclosed in Insuman Infusat and Grau, to prevent cell lysis and the attendant pain. *See* Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶¶474-77. Although Owens does not teach the exact concentration of glycerol to use in insulin glargine formulations, Grau teaches a 16 mg/ml glycerol content (or 173 mM) for the poloxamer insulin formulation, and Insuman Infusat teaches 20 mg/mL glycerol (or 217.1 mM), *i.e.,* within the claimed range of 100-250 mM in claim 17. *See* Ex. 1008, 1; Ex. 1003 ¶476.

A PHOSITA thus had reason to include an isotonicizing agent such as glycerol, as taught by Owens and Insuman Infusat or Grau, in an insulin glargine pharmaceutical formulation as claimed in claims 5, 9 and 17. Ex. 1003 ¶¶474-77.

5. Dependent Claims 6 and 7 were Obvious Over Owens and Insuman Infusat or Grau

The limitations of claims 6 and 7 are recited above. *See* §V.B.1, *supra*.

Owens disclosed the insulin glargine formulations as an acidic pH 4.0 formulation. Ex. 1005, 3-4; Ex. 1003 ¶479. Having a pH of an insulin glargine formulation fall in the pH range recited in claims 6 and 7 is not surprising or

inventive. A PHOSITA would have known well before the earliest priority date of the '930 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 ¶¶479-81. A PHOSITA had reason to use the pH range of an insulin glargine formulation, as taught by Owens, which falls in the range of "from 3.5 to 6.8" (claim 6) or "from 3.5 to 4.5" (claim 7). Claims 6 and 7 were obvious over Owens and Insuman Infusat or Grau.

6. Dependent Claims 10, 11 and 20 were Obvious over Owens and Insuman Infusat or Grau

The limitations of claims 11, 12 and 20 are recited above. *See* §V.B.1, *supra*.

Grau and Insuman Infusat disclosed including a Tris buffer in the insulin formulations. *See* Ex. 1008, 1 (50 mM of tris-hydroxymethyl)-aminomethane (Tris)); Ex. 1007, 5 (trometamol component). The purpose of a buffer compound in a pharmaceutical formulation is to maintain a specific pH environment, the same purpose fulfilled by the Tris buffer of Grau and Insuman Infusat. *See* Ex. 1003 ¶¶483-84. A PHOSITA had reason to combine a buffer with Owens to inhibit or eliminate insulin-aggregation with a reasonable expectation of success. Claims 10, 11 and 20 were obvious over Owens and Insuman Infusat or Grau.

7. Dependent Claims 12 and 13 were Obvious Over Owens and Insuman Infusat or Grau

The limitations of claims 12 and 13 are recited above. *See* §V.B.1, *supra*.

Owens disclosed "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin" formulations. Ex. 1005, 3-4; Ex 1003 ¶486. A PHOSITA would have known that insulin glargine has a molecular weight of 6063 g/mol, and that 100 U of insulin glargine is equivalent to about 3.6 mg insulin glargine per mL. Ex. 1003 ¶¶486-88. A PHOSITA would have recognized that 100 U of insulin glargine is equivalent to 600 nmol/mL, which is within the concentration ranges recited in both claims 12 and 13.

For these reasons, claims 12 and 13 were obvious over Owens and Insuman Infusat or Grau.

8. Dependent Claims 14, 15 and 16 were Obvious Over Owens and Insuman Infusat or Grau

The limitations of claims 14, 15 and 16 are recited above. *See* §V.B.1, *supra*.

Insuman Infusat and Grau disclosed including a poloxamer to inhibit insulin-aggregation in various test conditions, and found that insulin concentration, chemical stability and biological potency were maintained in the presence of the poloxamer. Ex. 1007, 5-6 ("Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin."); Ex. 1008, 4-5, Tables 2-3; Ex. 1003 ¶¶490-91. Grau concluded that "[g]enapol, 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." Ex. 1008, 4-5.

The claimed concentration ranges of "5-200 μg/ml" and "5-120 μg/ml" are taught in Insuman Infusat and Grau, which disclosed including "poly(oxyethylene oxypropylene)glycol 0.01 mg" (*i.e.*, 10 μg/ml) or "10 μg/ml polyethylene-polypropylene glycol (Genapol)," respectively. Ex. 1007, 5; Ex. 1008, 1. The slightly narrowed range of claim 16, which recites "20-75 μg/ml" was obviated by Insuman Infusat and Grau's 10 μg/ml poloxamer levels. Not only is the 10 μg/ml poloxamer levels essentially overlapping with the claimed range, *see Titanium Metals,* 778 F.2d at 783, a PHOSITA would have reason, and would have tested and optimized the poloxamer levels taught by Insuman Infusat or Grau. *Peterson*, 315 F.3d at 1330; *Ethicon*, App. 2015-1696, slip op. 12; Ex. 1003 ¶¶490-94; *see also Aller*, 220 F.2d at 456; *Galderma*, 737 F.3d at 739.

Accordingly, a PHOSITA had reason to combine a poloxamer at the concentration taught by Insuman Infusat and Grau with the insulin glargine formulation disclosed in Owens to inhibit or eliminate insulin-aggregation with a reasonable expectation of success. Ex. 1003 ¶¶490-94. Claims 14, 15 and 16 were obvious over Owens and Insuman Infusat or Grau.

9. Dependent Claim 18 was Obvious Over Owens and Insuman Infusat or Grau

The language of claim 18 is recited above. *See* §V.B.1, *supra*.

Owens taught preparing an insulin glargine solution and adjusting the pH of the solution to 4.0 using hydrochloric acid and sodium hydroxide. Ex. 1005, 3-4. Moreover, Insuman Infusat and Grau further taught the addition of a Tris base as a buffering agent for the insulin formulation. Ex. 1007, 5; Ex. 1008, 1; Ex. 1003 ¶496.

Accordingly, in view of the teachings of Owens and Insuman Infusat or Grau, it would have been obvious to add an acid, alkali or salt as recited in claim 18, with a reasonable expectation of success. Ex. 1003 ¶¶496-97. Claim 18 was obvious over Owens and Insuman Infusat or Grau.

L. Ground 8: Dependent Claim 19 was Obvious Over Owens and Insuman Infusat or Grau and Lougheed

The language of claim 19 is recited above. *See* §V.B.1, *supra*.

Lougheed disclosed 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). Ex. 1006, 5-6, Tables 4 and 6; Ex. 1003 ¶499. 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 '930 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma*, 737 F.3d at

739. Moreover, a PHOSITA would 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 ¶500. In light of Lougheed's use of NaCl, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '930 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.* ¶500.

Claim 19 was obvious over Owens and Insuman Infusat or Grau and Lougheed. Ex. 1003 ¶¶497-501.

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, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1372 (Fed. Cir. 2007). 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. The Addition of a Nonionic Surfactant as Recited in the '930 Patent Was Completely Expected

While the '930 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 test species within the broadly claimed polysorbates and poloxamers disclosed in the '930 patent, but the '930 patent in experimental examples used the same two polysorbates: polysorbate 20 (Tween20) and polysorbate 80 (Tween 80), that worked optimally in the prior-art. *See* Ex. 1006 at 4. Sanofi-Aventis cannot reasonably assert that that the addition of known pharmaceutical surfactants 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 '930 patent would have worked, as shown by the prior-art. *In re Skoll*, 523 F.2d 1392, 1397 (CCPA 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. Ex. 1003 ¶¶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 '930 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 Pharms., Inc. v. Watson Pharms., 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 13,736, 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. 7,713,930 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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