Filed: September 14, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.

Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,

Patent Owner.

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

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

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PATENT OWNER'S EXHIBIT LIST

September 14, 2017

Exhibit Number	**Description**
Ex. 2001	2001 Physicians' Desk Reference ("PDR")
Ex. 2002	Yalkowsky, S.H.; Krzyzaniak, J.F.; and Ward, G.H. "Formulation-Related Problems Associated with Intravenous Drug Delivery," *J. Pharm. Sci.*, 87, 787-796 (1998)
Ex. 2003	James Oeswein & Steven Shire, Physical Biochemistry of Protein Drugs, in Protein and Peptide Delivery, 167, 192-193 (Vincent Lee, ed. 1991)
Ex. 2004	U.S. Patent No. 5,656,722 to Dorschug ("Dorschug")

Patent Owner Sanofi-Aventis Deutschland Gmbh ("Patent Owner") respectfully submits this Preliminary Response in accordance with 35 U.S.C. § 313 and 37 C.F.R. § 42.107, in response to the Petition for *Inter Partes* Review (the "Petition") filed by Mylan Pharmaceuticals Inc. ("Petitioner") regarding Claims 1-25 of U.S. Patent No. 7,476,652 ("the '652 patent").

I. INTRODUCTION

The '652 patent is directed to improved, low-pH insulin glargine ("Glargine") formulations containing polysorbate and/or poloxamers. Glargine is a protein produced by recombinant DNA technology that has improved the lives of millions of patients living with diabetes. Glargine is the first biotherapeutic that allows patients with diabetes to control their blood sugar levels over a 24-hour period through a once-daily injection. Before the development of Glargine, patients with diabetes required multiple daily insulin injections in order to adequately control their blood sugar levels. Patent Owner sells Glargine under the trade name LANTUS®.

Glargine provides this breakthrough therapy because it is a fundamentally different molecule than human insulin—different in its structure (e.g., amino acid sequence), biological and chemical properties, and solubility. Because of those differences, Glargine—in stark contrast to human insulin—has its lowest solubility around the human body's near-neutral pH of 7.4 and its highest solubility around

its storage acidic pH. This means that Glargine—in further stark contrast to human insulin—precipitates (comes out of solution as a solid) rapidly after injection into the body due to the pH change from acidic to neutral. Following injection, Glargine dissolves slowly after it precipitates, allowing for its long-lasting therapeutic effect.

The inventors of the ’652 patent identified and solved a problem in which Glargine molecules sometimes aggregated (came together) and precipitated in the acidic pH range at which Glargine is stored and where complete solubility is desired. The inventors of the ’652 patent solved that problem by providing a new and inventive formulation of Glargine that can enhance stability against aggregation in Glargine’s acidic pH storage environment. They did so through the addition of a nonionic surfactant that unexpectedly prevented Glargine aggregation in its acidic storage environment without interfering with Glargine’s post-injection precipitation properties, thereby allowing Glargine to retain its therapeutic benefits.

Petitioner asserts six grounds on which the formulations claimed in the ’652 patent would have been obvious, each based on the combination of either of two primary references—the 2001 Physicians’ Desk Reference (Ex. 1004) and Owens (Ex. 1005)—with one of three secondary references—Lougheed (Ex. 1006), FASS (Ex. 1007), or Grau (Ex. 1008). As detailed in this Preliminary Response, for multiple independent reasons summarized below, Petitioner has not demonstrated a

reasonable likelihood of success with respect to any of the six proposed obviousness grounds.

First, Grounds 1-6 should be denied because they are premised on Petitioner's unsupported assertion that a person of ordinary skill in the art ("POSITA") would have known of Glargine's aggregation problems at its acidic storage pH, and would have thus been motivated to try to solve that problem. However, neither of Petitioner's primary references, which are directed to Glargine formulations, indicate an aggregation problem. Rather, both suggest the opposite by describing the disclosed Glargine formulations as "clear" and "stabilize[d]" acidic solutions. Petitioner ignores these disclosures and instead makes the unsupported inference that a general patient use instruction in the 2001 PDR that LANTUS® should be used only "if the solution is clear and colorless with no particles visible" would indicate to a POSITA that the Glargine formulation is prone to aggregation. However, Petitioner does not explain why a POSITA would have viewed this general patient use instruction—the substance of which is present on the labels of most, if not all, injectable drugs—as indicating a Glargine aggregation problem rather than warning against microbial or particulate matter contamination. Indeed, Petitioner's expert Dr. Yalkowsky was unwilling to

support Petitioner's assertion, speculating only that "the prevalence of monomeric[1] insulin forms for insulin glargine *could*, in my opinion, increase the *probability* of insulin fibril formation and aggregation." Ex. 1003 at ¶ 126 (emphasis added). Dr. Yalkowsky's speculative assessment is not evidence that a POSITA would have expected or known of an aggregation problem with the Glargine formulations disclosed in the primary references and, as a result, been motivated to solve that problem.

Second, Grounds 1-6 should be denied because Petitioner fails to support its assertion that a POSITA would have been motivated to combine the asserted primary and secondary references to arrive at the claimed invention with a reasonable expectation of success. The invention is an improved Glargine formulation at an acidic pH. As detailed below, Petitioner's primary references disclose clear, stable solutions of Glargine, formulated for subcutaneous injection at acidic pH levels. In contrast, Petitioner's secondary references do not relate to Glargine, but instead relate to human and porcine insulin formulations for delivery

[1] "Monomeric" refers to the state in which Glargine (or any protein) exists as a single isolated molecule, in contrast to states in which a number of protein molecules may exist together (e.g., hexameric form, meaning six molecules of the same protein associated together). Ex. 1014 at 3.

through insulin infusion pumps at a non-acidic pH (or specify no pH at all). Not only does Petitioner fail to provide a motivation to modify the primary references as noted above, Petitioner further fails to explain why a POSITA would have been motivated to make the proposed combinations with a reasonable expectation of success to achieve the claimed invention, in view of these significant differences between the primary and secondary references. Nor does Petitioner address the high degree of complexity and unpredictability in the protein formulation arts.

Third, Grounds 1-6 should also be denied because Petitioner has not accounted for the disclosures in the asserted references that support the nonobviousness of the claimed formulation. For example, Petitioner relies on the disclosure in Lougheed of nonionic surfactants, polysorbate 20 and polysorbate 80, and asserts that it would have been obvious to add those surfactants to the Glargine formulations disclosed in the primary references. But Petitioner does not address the teachings in Lougheed that direct *against* the use of a nonionic surfactant and also suggest that nonionic surfactants would be *unlikely to stabilize* the monomeric form of Glargine (i.e., the form of Glargine that Petitioner contends is prone to aggregation). Thus, Petitioner's secondary reference, Lougheed, directly contradicts Petitioner's alleged motivation to combine the primary and secondary references.

Fourth, Grounds 1-4 should be denied because Petitioner has not presented evidence to support its assertion that the 2001 PDR was publicly accessible more than one year before June 18, 2001. Petitioner asserts that the 2001 PDR was publicly accessible based on the alleged existence of a copy of the 2001 PDR with a date stamp of December 1, 2000. But the copy of the 2001 PDR attached to the Petition (Ex. 1004) includes a copyright year—2001—but no date stamp. Ex. 1004. In fact, no exhibit filed with the Petition corresponds to a copy of the 2001 PDR with such a date stamp. Petitioner's failure to present this evidence to show that the 2001 PDR is even prior art further warrants denial of Grounds 1-3, which use the 2001 PDR as a primary reference, and Ground 4, which relies on the 2001 PDR for an alleged motivation to combine.

Fifth, Grounds 1-6 should also be denied because Patent Owner successfully overcame during prosecution art that is substantially the same as the art presented in Grounds 1-6 of the Petition. During prosecution of the '652 Patent, the Examiner applied art disclosing Glargine in combination with references that disclose human and other animal insulins with a surfactant, such as polysorbate 80. Patent Owner overcame that prior art and the Examiner allowed the claims. The Petition does not address the prosecution history in any meaningful way, and instead presents Grounds that revisit the same substantive teachings addressed during prosecution based on combining Glargine prior art with human/porcine

insulin prior art. Petitioner's failure to address the prosecution history confirms that it does not have a reasonable likelihood of success, and the Board should exercise its discretion to deny the Petition under 35 U.S.C. § 325(d).

Sixth, at least Grounds 4-6 should further be denied because they are redundant with Grounds 1-3. In Grounds 1-3, Petitioner relies on the 2001 PDR as a primary reference disclosing a Glargine formulation, and attempts to combine its disclosure with one of Lougheed, FASS, and Grau. In Grounds 4-6, Petitioner relies on Owens as a primary reference for the same Glargine formulation disclosure as the 2001 PDR, and attempts to combine Owens with the same three secondary references used in Grounds 1-3. Because Petitioner has failed to articulate a meaningful distinction between Grounds 1-3 and 4-6, institution on at least the latter set of grounds should be denied.

Seventh, at least Grounds 2-4 should be denied for failing to identify with particularity the evidence that Petitioner alleges supports those grounds. As explained herein, Petitioner's presentation of those grounds contains numerous errors that make it unclear which references Petitioner is attempting to rely on, and therefore fails to meet the pleading requirements of 35 U.S.C. § 312(a). Additionally, Petitioner's failure to make a complete identification in its Mandatory Notices of all Related Matters, as required by 37 C.F.R. § 42.8(b)(2), forms a separate basis on which institution should be denied.

For these and the reasons that follow, Patent Owner respectfully requests that the Board deny institution as to all grounds presented in the Petition.

II. THE ’652 PATENT

A. Overview

The ’652 patent is directed to novel and inventive formulations of Glargine in combination with other compounds that can increase stability for Glargine at its storage acidic pH. Ex. 1001 at 3:41-45. Glargine was known in the art as of the filing date of the patent application that led to the ’652 patent, and was known to be different from human insulin in chemical structure (e.g. amino acid sequence), function, and properties. *Id*. at 2:51-65; Petition at 5. In contrast to human insulin, Glargine has two additional arginine amino acids added at the carboxyl end of the B-chain, and a glycine substituted for an asparagine at position 21 of the A-chain. Ex. 1001 at 2:56-58; Petition at 5. These structural differences result in substantial differences in Glargine’s chemical and biological properties. *See* Ex. 1001 at 2:55-65; Petition at 5-6.

As noted, one key difference between human insulin and Glargine is that Glargine is soluble at acidic pH values, and is largely insoluble—meaning it precipitates and comes out of solution—at the near-neutral pH of 7.4 of the human body. Ex. 1001 at 2:58-61 (“Insulin glargine is injected as an acidic, clear solution and precipitates on account of its solution properties in the physiological pH range

of the subcutaneous tissue as a stable hexamer associate."). These unique solubility properties of Glargine are the basis for its distinctive therapeutic benefits. *Id.* Prior to injection, Glargine is stored in acidic solutions. *Id.* at 2:66-3:2. Upon injection into the human body at the physiological pH of around 7.4, the Glargine precipitates due to its decreased solubility. *Id.* at 2:56-65. The precipitated Glargine forms a storage reservoir in the patient's body, allowing a slower and more stable release of the drug. *Id.* at 2:61-65. This is the reason why Glargine can be administered once-daily, in contrast to human insulin, which requires more frequent injections. *Id.*

The '652 patent is directed to Glargine formulations containing polysorbate and/or poloxamer that can increase stability at Glargine's acidic storage pH, while still retaining the post-injection therapeutic benefits of Glargine. *See generally id.* at 5:60-10:63. The '652 patent reports that the addition of surfactant can allow Glargine formulations to remain stable—avoid aggregation—in their acidic pH storage conditions. *Id*. at 3:41-45; 5:58-8:27. For example, the '652 patent reports the results of in use testing involving shaking the tested formulation over a period of time to simulate usage. *Id*. at 5:36-57. The tested Glargine formulations that contained nonionic surfactants showed remarkably improved stability as compared with Glargine without added surfactant. *See id*. at 6:10-9:42. Prior to the invention, the original LANTUS® formulation did not contain surfactant, and

therefore did not exhibit the improved stability seen in certain embodiments of the invention that are exemplified in the '652 patent specification. *See id*. at 6:10-9:42 (reporting the improved stability of tested Glargine formulations containing nonionic surfactant(s), as compared to Glargine formulations that did not contain surfactant). Subsequent to the invention of the '652 patent, LANTUS® was reformulated to embody the '652 invention, and has experienced tremendous commercial success. The FDA approved the new formulation and the '652 patent is listed in the Orange Book for LANTUS®.

The '652 patent has 3 independent claims. Claim 1 recites a pharmaceutical formulation requiring:

- Glargine (referred to as Gly(A21), Arg(B31), Arg(B32)-human insulin)
- at least one chemical entity chosen from polysorbate 20 and polysorbate 80;
- at least one preservative; and
- water,
- wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

Id. at 11:1-9. Independent Claims 7 and 24 are similar to Claim 1, and Claim 7 recites "at least one chemical entity chosen from polysorbate and poloxamers"; and Claim 24 recites "at least one chemical entity chosen from polysorbate and poloxamers." *Id.* at 11:21-28, 12:33-41. Claim 24 also further limits the claimed pH range to 3.5 to 4.5 and specifically requires at least one preservative to be cresol. *Id*. All of the dependent claims depend directly or indirectly from Claim 1,

and further limit the claimed formulation, requiring, among other things, a specific preservative, narrower pH ranges, and other components. *Id.* at 11:10-20, 11:29-12:32, 12:42-44.

B. Claim Construction and Level of Ordinary Skill in the Art

For the purposes of this Preliminary Patent Owner Response, Patent Owner accepts Petitioner's proffered construction of claim terms, and definition of the level of skill of a POSITA. Patent Owner reserves the right to challenge either or both should the Petition be instituted on any ground.

III. OVERVIEW OF THE ALLEGED PRIOR ART AND THE REDUNDANT GROUNDS PROPOSED BY PETITIONER

A. Petitioner's Asserted References

Petitioner's asserted primary and secondary references are summarized below, with a discussion of the redundant grounds of alleged obviousness presented in the Petition.

1. Petitioner's Primary References – 2001 PDR and Owens

As discussed in further detail below, Petitioner relies on the 2001 Physicians' Desk Reference Entry for LANTUS® ("2001 PDR"; Ex. 1004)[2] and D.R. Owens et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901)*

[2] As explained in Section IV.D, Petitioner has not established that the 2001 PDR is prior art to the '652 patent.

in Healthy Men, DIABETES CARE 23:813-19 (June 2000) ("Owens"; Ex. 1005) for the same disclosure of a Glargine formulation – the original formulation of LANTUS® that lacked surfactant. *See* Ex. 1001 at 6:10-9:42 (reporting the improved stability of Glargine formulations with surfactant, as compared to prior Glargine formulations without surfactant). Neither primary reference discloses or suggests the formulation claimed in the '652 patent. Petitioner, therefore, asserts that a POSITA would have had reason to modify the Glargine formulations of the primary references. The Petition, however, fails to address that the 2001 PDR teaches a Glargine formulation that is "completely soluble" at its acidic storage pH (Ex. 1004 at 3) and that Owens likewise discloses a Glargine formulation that is a "clear acidic solution" that achieves "stabilization of the [Glargine] molecule." Ex. 1005 at 1. Thus, rather than indicating to a POSITA that Glargine was prone to aggregation, both references indicate a clear, stable solution at the acidic storage pH.

2. Petitioner's Secondary References – Lougheed, FASS and Grau

Petitioner relies on three secondary references—W.D. Lougheed et al., *Physical Stability of Insulin Formulations*, DIABETES 32:424-32 (May 1983) ("Lougheed"; Ex. 1006); the 2000 FASS Entry for INSUMAN INFUSAT (January 2000) ("FASS"; Ex. 1007); and U. Grau & C.D. Saudek, *Stable Insulin Preparation for Implanted Insulin Pumps*, DIABETES 36:1453-59 (December 1987)

("Grau"; Ex. 1008). As discussed in further detail below, none of these secondary references pertains to Glargine, but instead relate to formulations of human or porcine insulin. In further contrast to both primary references that are directed to acidic Glargine formulations for once-daily subcutaneous injection, each of the secondary references is directed to non-acidic formulations of human/porcine insulin for continuous infusion via pumps.

In particular, Lougheed reports the results of stability investigations in which various surfactants were tested in formulations of "recrystallized porcine insulin" that are "titrated to pH 7.0-7.4." Ex. 1006 at 2. The surfactants were tested only with insulin formulated for continuous infusion via pumps. *Id*. at 1 ("'open-loop' systems … for the continuous infusion of insulin to diabetics"). As detailed in **Section IV.C** below, while both nonionic and anionic surfactants were tested, Lougheed dissuades a POSITA from selecting a nonionic surfactant and teaches that nonionic surfactants do not stabilize the monomeric form of insulin.

Similarly, FASS describes insulin that is "identical with insulin from humans and is manufactured biosynthetically by means of recombinant DNA technology." Ex. 1007A at 7. FASS states that the disclosed insulin formulation for pumps "may only be used in an insulin pump with tetrafluoroethylene or polyethylene catheters" and "may not be used in a peristaltic pump with a silicone catheter." *Id*. at 5.

Grau teaches "an insulin preparation specifically formulated for implanted insulin pumps" that is "semi-synthetic human insulin" which is "pH-neutral buffered." Ex. 1008 at 1. Grau also distinguishes between formulations for subcutaneous injection and formulations for insulin pumps, noting that insulin formulations for "subcutaneous injection are now uniformly stable and highly purified," but in comparison "insulin for implantable infusion pumps requires further steps to ensure stability." *Id*. at 6.

B. Petitioner's Redundant Obviousness Grounds

In Ground 1 (challenging Claims 1-25), Ground 2 (challenging Claims 7 and 24), and Ground 3 (challenging Claims 7 and 24), Petitioner alleges that the claims of the '652 patent would have been obvious based on a combination of the 2001 PDR with Lougheed, FASS, and/or Grau.

In Ground 4 (challenging Claims 1-25), Ground 5 (challenging Claims 7 and 24), and Ground 6 (challenging Claims 7 and 24), Petitioner alleges that the claims of the '652 patent would have been obvious based on a combination of Owens, also in combination with Lougheed, FASS, and/or Grau.

"[M]ultiple grounds, which are presented in a redundant manner by a petitioner who makes no meaningful distinction between them, are contrary to the regulatory and statutory mandates, and therefore are not all entitled to consideration." *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*,

CBM2012-00003, Paper 7 at 2 (P.T.A.B. Oct. 25, 2012). Here, Petitioner presents six grounds, but instead of attempting to articulate a meaningful distinction among them, Petitioner presents the same disclosure and arguments for Grounds 4-6 as presented for Grounds 1-3. As explained above, Petitioner relies on both of its primary references (the 2001 PDR and Owens) for a disclosure of the same Glargine formulation, and then attempts to separately combine each of those primary references with the same set of three secondary references (Lougheed, FASS and Grau). Grounds 1-3 and Grounds 4-6 are thus redundant, and institution should be denied as to the latter set of grounds. *EMC Corp. v. PersonalWeb Techs, LLC*, IPR2013-00082, Paper 33 at 3-4 (P.T.A.B. Jun. 5, 2013) ("The proper focus of a redundancy designation is not whether the applied prior art disclosures have differences, for it is rarely the case that disclosures of different prior art references will be literally identical. Rather, the focus is on whether the petitioner articulated a meaningful distinction in terms of relative strengths and weaknesses with respect to application of the prior art disclosures to one or more claim limitations.").

IV. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD OF SUCCESS FOR ANY GROUND

A. Grounds 1-6: Petitioner Fails To Demonstrate That a POSITA Would Have Had Motivation to Modify the Identified Glargine Formulations

Petitioner's grounds for obviousness are premised on the assertion that a POSITA would have been aware that Glargine was prone to aggregation at its

acidic pH, and, on that basis, would have been motivated to solve that problem by modifying the Glargine formulations disclosed in the primary references. Petition at 27, 42, 44, 46, 57, 59-60. As detailed below, Petitioner cannot demonstrate a reasonable likelihood of success because it has presented no prior art disclosure of a Glargine aggregation problem, and thus no prior art disclosure providing motivation to a POSITA to solve any such problem. *See Novartis Pharm. Corp. v. Watson Laboratories, Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015) ("Watson failed to prove that a rivastigmine formulation was known to be susceptible to oxidative degradation. … Without the knowledge of the problem, one of skill in the art would not have been motivated to modify GB '040 with antioxidants as purportedly disclosed in the [prior art]"); *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377-78 (Fed. Cir. 2012) ("Instead, PCM must prove … that a person of ordinary skill in the meat encasement arts at the time of the invention would have recognized the adherence problem recognized by the inventors and found it obvious to produce the meat encasement structure disclosed in the '148 patent to solve that problem."); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.").

1. Neither The 2001 PDR Nor Owens Identify An Aggregation Problem With Glargine Formulations

Petitioner fails to identify any prior art reference that discloses an aggregation problem of Glargine at its acidic storage pH. Neither of Petitioner's primary Glargine references—the 2001 PDR and Owens—disclose such a problem. To the contrary, the 2001 PDR describes a formulation wherein the Glargine "[a]t pH 4…is *completely soluble*." Ex. 1004 at 3 (emphasis added). Owens likewise states the Glargine is a "*clear* acidic solution" with "*stabilization* of the [Glargine] molecule." Ex. 1005 at 1 (emphasis added). Thus, both primary references on their face contradict Petitioner's assertion that a POSITA would have known that Glargine formulations were prone to aggregation.

Petitioner's only attempt to identify a prior art disclosure of an aggregation problem for acidic formulations of Glargine is the general statement in the 2001 PDR that "LANTUS must only be used if the solution is clear and colorless with no particles visible." Petition at 27; Ex. 1004 at 5. Petitioner, however, provides no explanation for why a POSITA would understand the use-only-when-clear patient instructions in the 2001 PDR as conveying an aggregation problem for Glargine, as opposed to a standard *use* instruction that would apply to any drug that is delivered by injection. Indeed, the 2001 PDR categorizes a large number of drugs that are delivered by injection and likewise instructs that the injection should

not be made if the solution appears cloudy.[3] The 2001 PDR itself offers an alternative explanation for cloudiness: "If LANTUS is diluted or mixed, the solution may become cloudy." Ex. 1004 at 4. Petitioner's proffered expert, Dr. Yalkowsky, has likewise admitted in a published article that "[s]ome of the problems associated with intravenous drug delivery are independent of formulation," and these problems include "microbiological contamination [and] particulate matter," both of which would cause a solution to appear cloudy. Ex. 2002 at 1. Neither Petitioner nor its expert offers evidence or explanation for why a POSITA would read the general patient use instruction as disclosing a problem with Glargine aggregation, rather than providing a standard patient

[3] *See, e.g.*, Ex. 2001 at 43, Lupron ("As with all parenteral product, inspect container's solution for discoloration and particulate matter before each use."); *id.* at 19, Sandostatin Injection ("Do not use if particulates and/or discoloration are observed."); *id.* at 9, Taxol ("Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit."); *id.* at 12, Decadron Phosphate Injection (same); *id.* at 15, Miacalcin (same); *id.* at 32, Intron A (same); *id.* at 26, Procrit (same); *id.* at 41, Gonal-F (same).

instruction to avoid use if cloudy due to microbial contamination or other particulate matter.

Petitioner's attempt to convert this general patient use instruction in the 2001 PDR into a prior art disclosure that Glargine had aggregation problems that would have motivated a POSITA to alter the disclosed Glargine formulation is not supported by evidence. Moreover, Petitioner cites no evidence in its other primary reference, Owens, of any aggregation problem for Glargine. Accordingly, Petitioner has failed to present evidence showing that a POSITA would have known of an aggregation problem in acidic formulations of Glargine and been motivated to solve that problem. *See Coherus Biosciences, Inc. v. Abbvie Biotechnology, Ltd*., IPR2017-01009, Paper 11 at 11, 14-15, 21 (P.T.A.B. Sept. 7, 2017) (denying institution and rejecting petitioner's argument that a statement in the 2003 Physician's Desk Reference Label for Humira that "12% of patients reported injection site pain as an adverse event during clinical trials" would have identified a problem and motivated a POSITA to solve it by eliminating a buffer system from the protein formulation). Thus, while Petitioner asserts that the Glargine formulation disclosed in the 2001 PDR and Owens was commercially available, *see, e.g.*, Petition at 10, "Petitioner identifies no reason why, in the absence of hindsight, one of skill in the art would have changed such a formulation." *Coherus Biosciences, Inc. v. Abbvie Biotechnology, Ltd*., IPR2017-

00822, Paper 14 at 22 (P.T.A.B. Sept. 7, 2017). This failure warrants denial of institution on all asserted grounds. *See id.* at 21 (denying institution where the "[p]etitioner ha[d] failed to identify any problem with Humira (or any problem known in the art generally) that would have prompted one of skill in the art to remove the buffer system from the Humira formulation"); *Securus Techs., Inc. v. Globel Tel*Link Corp*., IPR2016-00267, Paper 8 at 8-9 (P.T.A.B. June 3, 2016) (denying institution where there was "no evidence of record that a person of ordinary skill in the art would have expected the [proposed] problem to exist at all"(citation omitted)); *see also Novartis*, 611 F. App'x at 996; *Mintz*, 679 F.3d at 1377-78.

2. Petitioner Has Failed to Present Evidence that a POSITA Would Have Expected the Same Aggregation Problem for Glargine as Seen in Human Insulin Formulations

While Petitioner's primary references relate to Glargine, Petitioner's secondary references do not. The asserted secondary references all instead relate to non-Glargine formulations of human or other animal insulins. *See* Ex. 1003 ¶¶103-08; Ex. 1006-1008, 1014-1015, 1018. Yet, Petitioner repeatedly conflates Glargine and non-Glargine insulin, asserting that "insulin's well-known propensity to aggregate" provided a motivation to add surfactants to Glargine. *See* Petition at 27 ("a PHOSITA would have had ample reason to add at least nonionic surfactants disclosed in Lougheed, *e.g.*, polysorbate 20 and polysorbate 80, to an insulin

glargine formulation, with a reasonable expectation that doing so would successfully inhibit or eliminate *insulin's* well-known propensity to aggregate" (emphasis added)); *see also id.* at 41, 44-45.

Petitioner, however, admits that Glargine and human insulin are different molecules having different structures and different chemical and biological properties. For example, Petitioner states:

> **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,[4] 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's mechanism of action centers on its altered isoelectric point, resulting in the therapeutic preparation being more soluble in an acidic environment;

[4] Petitioner defines the isoelectric point as the pH at which a protein exhibits its lowest solubility and for purposes of this filing Patent Owner accepts this definition. *See* Ex. 1003, ¶ 125.

> **by contrast, native human insulin formulations are more soluble at neutral pH**. *See* Gillies [Ex. 1011], 2; Ex. 1003 ¶125.

Petition at 5 (citing Petitioner's expert declaration at Ex. 1003) (emphasis added); *see also* Ex. 1003 ¶¶ 124-28. Petitioner fails to address these admitted differences and explain, in view of them, why a POSITA would have applied prior art regarding non-Glargine insulins to Glargine. This is a fatal flaw of the Petition. *See Coherus*, IPR2017-01009, Paper 11 at 16 ("Petitioner's assertion that an ordinary artisan would have been prompted to combine the Humira® and Gamimune® formulations, because both products are liquid pharmaceutical formulations of IgG antibodies at a concentration of 50 mg/mL … falls short of an articulated reasoning with a rational underpinning to support the conclusion of obviousness." (internal citations omitted)).

By electing not to address these significant and admitted differences between Glargine and non-Glargine insulins, Petitioner presents nothing more than a conclusory statement that a POSITA would attribute problems with respect to a specific human or animal insulin formulation to the Glargine formulations disclosed in the primary references. While Petitioner cites to paragraphs 105-108, 126 and 168 of the Declaration of Samuel Yalkowsky (Ex. 1003), those paragraphs do not connect Glargine and human/animal insulin, or include objective prior art

evidence supporting the assertion that it was known to a POSITA that Glargine was prone to aggregation.

First, Paragraph 126 of the Declaration of Dr. Yalkowsky confirms that Dr. Yalkowsky does not support Petitioner's assertion that Glargine "would have also been expected to aggregate because of the prevalence of monomeric forms." Petition at 7; *see also id*. at 27 ("A PHOSITA would especially have had reason because insulin glargine was likely prone to aggregation...."). Instead, Dr. Yalkowsky concludes only that "the prevalence of monomeric insulin forms for insulin glargine *could*, in my opinion, increase the *probability* of insulin fibril formation and aggregation." Ex. 1003, ¶ 126 (emphasis added). Dr. Yalkowsky's present-tense speculation, years after the '652 invention, that monomeric forms of Glargine *could* increase the probability of aggregation, is unsupported by objective evidence and does not show that a POSITA, at the time of the invention, would have known of and been motivated to solve an aggregation problem with Glargine. *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) ("[S]peculative and tentative disclosure of what 'might' or 'may' [result] does not sufficiently direct or instruct one of skill in this art."); *NPF Ltd. v. Smart Parts, Inc.*, 187 F. App'x 973, 979 (Fed. Cir. 2006) ("Merely knowing, years later, that someone could have successfully made the combination does not aid in determining whether at the time of the invention, one of skill in the art would have

been motivated to do so."); *Nautilus Hyosung Inc. v. Diebold, Inc*., IPR2016-00633, Paper 9 at 21 (P.T.A.B. Aug. 22, 2016) ("An assertion that something *could* be done does not articulate a reason why something *would* be done by one of ordinary skill in the art at the time of the invention and, therefore, raises a specter of impermissible hindsight bias in an obviousness analysis."); *Coalition for Affordable Drugs XI LLC v. Insys Pharma, Inc.*, IPR2015-01797, Paper 9 at 9 (P.T.A.B. Mar. 10, 2016) (denying institution where the "[expert] opinion is conclusory and unpersuasive because it is not keyed to objective proof, regarding the understanding of a person of ordinary skill in the art"). Moreover, even if it were assumed, as Dr. Yalkowsky states, that Glargine *could* possibly aggregate, that speculation is clearly insufficient to support Petitioner's assertion that Glargine "*would* have also been expected to aggregate" and "*would*" have given a POSITA reason to modify the prior art Glargine formulation. *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (holding that expert's testimony could not support a finding of obviousness where "testimony primarily consisted of conclusory references to [the expert's] belief that one of ordinary skill in the art *could* combine these references, not that they *would* have been motivated to do so" (emphasis added)); Petition at 7.

Second, Paragraphs 105 to 108 in the Yalkowsky declaration do not even discuss Glargine, but instead address references that propound hypotheses for

mechanisms of aggregation in insulin. Ex. 1003, ¶¶ 105-08. But Dr. Yalkowsky again does not address why a POSITA would look to non-Glargine insulin art in view of the admitted numerous structural, chemical, and behavioral differences between Glargine and human insulin. *See, e.g.*, Petition at 5; Ex. 1001 at 2:51-65; Ex. 1004 at 3. Petitioner's own cited art explains that structural differences even among various types of insulin are known to affect the corresponding formulations during storage. *See, e.g.*, Ex. 1014 at 28 ("A variety of chemical changes of the primary structure (yielding insulin derivatives), and physical modifications of the secondary to quaternary structures (resulting in 'denaturation,' aggregation, and precipitation) are known to affect insulin and insulin preparations during storage and use (Fig. 8)."); *id.* at 10 ("Human, porcine, and bovine insulins vary in their tendency to form insulin fibrils, bovine insulin being more prone to fibrillation than the other two species of insulin."). Nonetheless, Petitioner fails to explain why a POSITA, at the time of the '652 invention, would have looked to *insulin* references and expected *Glargine* storage or stability problems, given the admitted "variety of chemical changes of the primary structure" and solubility properties between Glargine and human or porcine insulin. *Id*. at 28.

Finally, paragraph 168 of Dr. Yalkowsky's declaration includes no support for Petitioner's assertion that a POSITA would have expected Glargine to be "likely prone to aggregation as monomeric insulin in an acid pH environment."

Petition at 27. Rather, Dr. Yalkowsky states only that Glargine exists in a monomeric form, with no support for what a POSITA would have known at the time of the invention, and repeats the patient use instruction in the 2001 PDR. Ex. 1003, ¶ 168.

In view of the many differences between Glargine and other forms of insulin, Petitioner's failure to explain why a POSITA would have expected factors that can cause aggregation of non-Glargine insulin to cause aggregation of Glargine is a dispositive deficiency in the Petition. The conclusory attorney argument attempting to span that critical gap is entitled to no weight, and fails to show that a POSITA would have had motivation to make the alleged combinations with a reasonable expectation of success. *EMC Corp. v. Intellectual Ventures LLC*, IPR2017-00439, Paper 11 at 41 (P.T.A.B. July 11, 2017) ("conclusory statements and unspecific testimony without evidence on the record cannot satisfy the Petitioner's burden of demonstrating obviousness").

In sum, Grounds 1-6 of the Petition are all premised on Petitioner's assertion that a POSITA would have expected Glargine to be prone to aggregation and would have been motivated to modify the Glargine formulations disclosed in the 2001 PDR and Owens. As detailed above, this assertion is not supported by evidence, and is inconsistent with the speculation of Petitioner's own proffered expert. Institution of Ground 1-6 should be denied.

B. Grounds 1-6: Petitioner Has Failed to Present Evidence That a POSITA Would Have Been Motivated to Make the Proposed Combinations With a Reasonable Expectation of Success

Each of the asserted grounds hinges on Petitioner's assertions that a POSITA would have been motivated to combine the primary and secondary references to achieve the claimed Glargine formulation. As discussed, the Petition fails to show that a POSITA would have known of any such problem and been motivated to solve it. But even assuming such a showing, each of the grounds separately fails because the Petition fails to show that a POSITA, even if motivated to modify the primary Glargine references, would have turned to the asserted secondary references for the alleged combination. In particular, the Petition fails to address the numerous differences between the primary and secondary references and explain why a POSITA would have combined these entirely different references to achieve the invention with a reasonable expectation of success. The primary references each involve Glargine, at an acidic pH, delivered by injection. Ex. 1004 at 3-7; Ex. 1005 at 1-3. The secondary references in contrast each involve non-Glargine insulins in a non-acidic pH environment, delivered through an insulin pump. Ex. 1006 at 1-2 ("recrystallized porcine insulin," "titrated to pH 7.0-7.4" "for the continuous infusion of insulin"); Ex. 1007A at 5 (human insulin that can "only be used in an insulin pump with tetrafluoroethylene or polyethylene catheters"); Ex. 1008 ("semi-synthetic human insulin" that is "pH-neutral

buffered" and "specifically formulated for implanted insulin pumps"). The table below summarizes these key differences:

	Primary References		**Secondary References**		
	2001 PDR	**Owens**	**Lougheed**	**FASS**	**Grau**
Protein	Glargine	Glargine	Porcine Insulin	Human insulin	Semi-synthetic human insulin
pH	Acidic (4.0)	Acidic (4.0)	Neutral/Basic (7.0-7.4)	None specified	Neutral (7.0)
Delivery	Injection	Injection	Pump	Pump	Pump

Petitioner "glosses over the differences between the [references] and does not … explain why it would have been obvious for one of ordinary skill to combine the prior art references in the manner recited." *Coalition for Affordable Drugs III LLC v. Jazz Pharm., Inc.*, IPR2015-01018, Paper 17 at 19 (P.T.A.B. Oct. 15, 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (failure to "address these specific differences in how the prior art references are set" contributed to reversal of the Board's finding of obviousness).

First, Petitioner does not account for the differences between Glargine and insulin in the primary and secondary references as discussed above. More specifically, in addition to the admitted differences among human insulin and Glargine, *see supra* **Section IV.A.2**, Petitioner's cited art also discloses the differences between Glargine and porcine insulin. *See* Ex. 1014. In porcine insulin, unlike in Glargine, the amino acid alanine occurs at the thirtieth position of

the B-chain, rather than threonine. *Id.* at 2-3, Fig. 1. Thus, Glargine differs from human insulin by three amino acids, and differs from porcine insulin by four amino acids. Petitioner's cited art indicates that differences in the amino acid chains of human and animal insulins can result in large differences in aggregation tendencies, in unpredictable ways. For example, bovine insulin varies from human insulin by three amino acids, and varies from porcine by two amino acids. Ex. 1014 at 2. Porcine insulin varies from human insulin by two amino acids. *Id.* However, while "there seems to be no significant difference between the tendency to fibrillation of human and porcine insulins[, i]n contrast, bovine insulin is significantly more prone to fibrillation than the other two species of insulin." Ex. 1015 at 2. Despite this unpredictability of protein behavior based on structural changes, Petitioner completely fails to address the structural differences between Glargine, human and porcine insulin, and explain any potential impact on their stability in solution. The failure to address these differences is a significant deficiency. *See Coherus*, IPR2017-01009, Paper 11 at 20 (denying institution where petitioner and its expert "do not account for the differences in the variable regions of the proteins" of the prior art and the claimed formulation).

Second, while the Petition acknowledges the significance of pH to the stability of Glargine and non-Glargine insulins, it fails to address the differing pH environments of the asserted primary and secondary references. Petition at 5

("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.* ("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."). While both the primary references disclose acidic Glargine formulations at pH of 4.0 (Ex. 1004 at 3; Ex. 1005 at 3), the secondary references disclose insulin formulations that are at "pH 7.0-7.4" or "pH-neutral," or do not disclose a pH at all. Ex. 1006 at 2; Ex. 1007A at 7; Ex. 1008. None of Petitioner's references address the stabilization of any protein in an *acidic solution*, which is a part of the problem addressed by the '652 patent with respect to Glargine. The failure to explain why a POSITA would have been motivated to combine Glargine formulations at acidic pH with human/animal insulin formulations at neutral/basic pH with a reasonable expectation of success is a further reason why Petitioner's proposed combinations are deficient.

Third, Petitioner has also failed to address the difference in routes of administration for the primary and secondary references. The 2001 PDR discloses a Glargine formulation "for use as an injection" that is "indicated for once-daily subcutaneous administration." Ex. 1004 at 3-4. Owens discloses the same

formulation for "subcutaneous injection." Ex. 1005 at 1. The secondary references in contrast all relate to formulations for use in insulin pumps involving mechanical and other stresses. Ex. 1006 (Lougheed) at 1 ("'open-loop' systems … for the continuous infusion of insulin to diabetics"); Ex. 1007A (FASS) at 5 ("may only be used in an insulin pump with tetrafluoroethylene or polyethylene catheters" and "may not be used in a peristaltic pump with a silicone catheter"); Ex. 1008 (Grau) at 1 ("an insulin preparation specifically formulated for implanted insulin pumps"). Notably, Grau distinguishes between formulations for subcutaneous injection and formulations for insulin pumps, noting that insulin formulations for "subcutaneous injection are now uniformly stable and highly purified," but in comparison "insulin for implantable infusion pumps requires further steps to ensure stability." *Id*. at 6. Petitioner has not explained why a POSITA would have looked to formulations tested under the mechanical stresses and materials used in insulin pumps for continuous infusion, and have combined these components with those from the once-daily subcutaneous injection Glargine.

Petitioner's failure to address these numerous differences between the primary and secondary references and explain why a POSITA would have combined them despite these differences is further problematic given the high degree of complexity and unpredictability in the protein formulation arts, where "[o]ne must be assured that the combination of [all formulation] ingredients used is

not deleterious to the active compound. This task is all the more difficult when formulating proteins, since the effects of multicomponent systems on the physicochemical properties of proteins are highly diverse and not well understood." Ex. 2003 at 28-29; *see Coherus Biosciences Inc. v. Abbvie Biotechnology Ltd.*, IPR2016-01018, Paper 10 at 13 (P.T.A.B. Nov. 7, 2016) (denying institution and rejecting petitioner's argument of reasonable expectation of success in view of the complexity and unpredictability of formulating proteins). Moreover, as in the instant invention, "when systems involving four or more components are used (as is often the case for protein formulations), predictions on structure cannot be made, since the chemical potentials of all solvent components are interdependent." Ex. 2003 at 28-29*; see Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Paper 37 at 8-9 (P.T.A.B. Dec. 22, 2016) (finding no reasonable expectation of success in arriving at the claimed protein formulations, in light of art disclosing that "for most proteins, maintaining physical and chemical stabilities in aqueous solution for an extended period of time is extremely difficult" (internal quotation and citation omitted)).

Thus, Petitioner's assertion that a POSITA would have combined the primary and secondary references, and had a reasonable expectation of success in modifying the Glargine formulations of the 2001 PDR and Owens by adding a surfactant from the non-Glargine formulations in the secondary references, fails to

account for the significant unpredictability in the protein formulation arts. Petitioner's failure to address this unpredictability further underscores its inability to show a reasonable likelihood of success on the merits. *See P&G Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 996 (Fed. Cir. 2009) ("To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on identified, predictable solutions may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."); *see Coherus*, IPR2017-01009, Paper 11 at 20-21 (denying institution where petitioner had not accounted for the unpredictability in the protein formulation arts and instead advocated "a one-size-fits-all approach"). This failing is compounded by Petitioner's admission that Glargine's unique mechanism of action is different from that of human insulin, and is based on the differences in solubility between the two proteins whereby Glargine "precipitates upon injection," in contrast to "human insulin formulations that are more soluble at neutral pH." Petition at 5.

C. Grounds 1-6: Petitioner Fails to Account for the Prior Art Disclosure That Supports Nonobviousness

Petitioner cannot demonstrate a reasonable likelihood of success with respect to Grounds 1-6 for the additional reason that it has not accounted for the disclosures in the prior art that support nonobviousness. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd*., 719 F.3d 1346, 1365 (Fed. Cir. 2013) ("In the search for scientific truth '[o]ne cannot ... pick and choose among isolated disclosures in

the prior art to deprecate the claimed invention;' it is necessary to consider prior art that supports unobviousness of the claimed invention, as well as that which weighs against it." (internal citations omitted)). Specifically, Petitioner has ignored the teachings in the asserted prior art that would have dissuaded a POSITA from selecting a nonionic surfactant and warns of the negative consequences that could arise from modifying the formulations in the 2001 PDR and Owens to include a nonionic surfactant.

1. Lougheed Would Have Dissuaded a POSITA From Selecting a Nonionic Surfactant

Petitioner relies on Lougheed (Ex. 1006) for Grounds 1 and 4, arguing that "Lougheed specifically taught that polysorbate 20 (i.e., Tween 20) and polysorbate 80 (i.e., Tween 80), amongst other nonionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation." Petition at 26. Petitioner further contends (after making the unsupported assertion that "insulin glargine was likely prone to aggregation") that a POSITA would look to combine those nonionic surfactants discussed in Lougheed with the Glargine formulations in the 2001 PDR and Owens. *Id*. at 27. However, as explained below, Petitioner fails to account for the disclosure in Lougheed that would have *dissuaded* a POSITA from selecting a nonionic surfactant. Thus, Petitioner and its expert "fail to account for the prior art as a whole and improperly pick and choose from the references in their reasoning to support their contention that the proposed combination … renders the claims

obvious." *Oracle Corp. v. Crossroads Sys., Inc.*, IPR2014-01209, Paper 77 at 22-23 (P.T.A.B. Jan. 29, 2016).

a. Lougheed Would Have Directed a POSITA to the Anionic Surfactant Sodium Dodecyl Sulfate and Not Nonionic Surfactants

The claimed chemical entities recited in the independent claims of the '652 patent, i.e., polysorbates, polysorbate 20, polysorbate 80, and poloxamers, are all *nonionic*. *See* Ex. 1001 at 1:4-5, 1:23-24, 12:36-37. However, Lougheed, on its face, would have directed a POSITA towards the use of *anionic* surfactants, specifically sodium dodecyl sulfate (SDS), and away from nonionic surfactants.

Lougheed "report[s] the results of stability studies conducted with selected additives for protracted periods of up to 150 days," and characterizes stability in terms of formulation stability (FS) in days, for continuous rotation (FSR) and shaking (FSS). Ex. 1006 at 2, 3. Additives tested included "[n]onionic, cationic, and ionic detergents (both physiologic and synthetic)," and "[t]he effect of various 'medical grade' pump materials on the stability of these formulations was also investigated." *Id*. at 2. Specifically, with respect to the anionic SDS, Lougheed reports that while "the stability of the preparation containing 1% SDS was unaffected by all pump materials tested and remained clear for the duration of testing (150 days) ... *all other detergent preparations* when rotated in the presence of typical pump materials … *showed markedly reduced stabilities*." *Id*. at 3

(emphasis added). In this respect, Lougheed notes that "[w]ith the exception of the 1% SDS solution, the stability of these detergent-insulin formulations was most severely and repetitively reduced in the presence of silicone rubber (FSR < 10 days)." *Id*. at 4. Given these results, the researchers picked only SDS to pursue for further testing with pump materials – "The apparent success of the anionic detergent, sodium dodecyl sulphate (SDS) at 0.05% wt/vol in 0.9% NaCl led to the testing of this formulation in combination with pump materials." *Id*. at 5.

Thus, in contrast to Petitioner's assertion that "Lougheed specifically taught that polysorbate 20 (i.e., Tween 20) and polysorbate 80 (i.e., Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation," Petition at 26, Lougheed actually teaches away from the use of polysorbate in insulin formulations. Specifically, Lougheed reported that "the nonionic detergent Tween 60 did not reduce the rate of aggregate formation," and that Tween 80 did not increase formulation stability in rotational stability testing. Ex. 1006 at 4. In the paragraph on page 426 of Lougheed where the researchers report FSR values for "formulations containing nonionic and anionic detergents," the values for Tween 80 and Tween 20 are the second lowest and third lowest, respectively, out of the seven surfactants listed in that paragraph. *Id*. at 3.

Petitioner and its expert have failed to account for the teachings in Lougheed that direct a POSITA towards use of anionic SDS and away from the claimed nonionic surfactants such as polysorbate, which were disclosed to "not reduce the rate of aggregate formation" and "not significantly increase FSR values." *Id*. at 4.

b. Lougheed's Disclosure of The Mechanism of Action Contradicts Petitioner's Proposed Combinations

Petitioner argues that a POSITA would have employed certain nonionic surfactants from Lougheed in Glargine formulations in order to overcome Glargine's alleged "aggregation as *monomeric* insulin in an acid pH environment." Petition at 27 (emphasis added). However, Lougheed discloses that it is the anionic surfactants (e.g., SDS) that stabilize the monomeric form of insulin, whereas the nonionic surfactants likely work by stabilizing dimers and higher order structures. *See* Ex. 1006 at 8.

Lougheed makes this hypothesis by citing to the work of "Wu and Yang," and explaining that because previous work in the field had "attributed the change in the CD [circular dichroism] spectrum of native insulin seen with the addition of SDS to the disruption of dimers[, t]he stabilization observed in [Lougheed's] studies may well be the result of this stabilization of the monomer." *Id*. at 8. On the other hand, Lougheed hypothesizes that the only "partial success with the polyoxyethylene-type detergents (Brij, Tween, Triton) might therefore be

attributed to stabilization of the dimer or higher polymers *rather than the monomer*." *Id*. (emphasis added).

Thus, even assuming that Petitioner had produced evidence that a POSITA, at the time of the invention, would have expected Glargine to aggregate based on aggregation of the monomeric form of insulin (as explained in **Section IV.A** it has not provided such evidence), Petitioner fails to explain why a POSITA would have attempted to stabilize the monomeric form of Glargine with nonionic surfactants disclosed in Lougheed, when in fact Lougheed teaches the opposite—that nonionic surfactants *do not stabilize* the monomeric form. "This type of reasoning—where relevant parts of the reference are disregarded for the proposed combination without sufficient explanation of why a person of ordinary skill would do so—is precisely the type of hindsight reasoning that must be rejected." *Oracle Corp*, IPR2014-01209, Paper 77 at 26.

2. Petitioner Has Failed to Account for the Disclosure of Negative Consequences in Other Proffered References

Petitioner also fails to account for the teachings in its cited references that disclose certain negative consequences that a POSITA would have expected to arise if the Glargine formulations of the 2001 PDR and/or Owens were modified by addition of a nonionic surfactant.

For example, in Grounds 1 and 4, Petitioner alleges that a POSITA would have been motivated to modify the acidic Glargine formulations of the 2001 PDR

and/or Owens (pH of 4), with polysorbate(s) from Lougheed. Petition at 25-40, 45-55. However, the "Stability and Storage Conditions" section of the polysorbates entry in the 1994 Handbook of Pharmaceutical Excipients ("Handbook"), which Petitioner has presented as Ex. 1019, warns that "gradual saponification occurs with strong acids," i.e., polysorbates were known to experience hydrolysis in an acidic environment. Ex. 1019 at 30, 50. Petitioner has not explained why, in view of that disclosure, a POSITA would have expected success in adding polysorbate to the acidic formulations of the primary references, which contain a strong acid. Ex. 1004 at 3; *see* Ex. 1005 at 3. Petitioner's failure to address this teaching in the prior art is especially pertinent given that the inventors of the '652 patent attempted this warned-against combination of polysorbates with acidic Glargine formulations, and reported their findings that "[a] decline in the stabilizing action due to possible hydrolysis of the polysorbate in the acidic medium of the solution cannot be detected" after the tested 1 month storage. Ex. 1001 at 9:49-51; *see also id.* at 8:23-26.

Additionally, the polysorbates entry in the Handbook relied on by Petitioner warns that, when using polysorbates, "discoloration and/or precipitation occurs with … phenols." Ex. 1019 at 30, 50. The Glargine formulations in the 2001 PDR and Owens contain cresol (Ex. 1004 at 3; Ex. 1005 at 3), and the Handbook entry for cresol confirms that cresol is a phenol. *See* Ex. 1019 at 5 (stating that "[c]resol

consists of a mixture of cresol isomers and other phenols" and cresol's chemical name is "methylphenol"). Given that both the 2001 PDR and Owens state that the Glargine formulations disclosed therein are colorless (Ex. 1004 at 3, Ex. 1005 at 1), and given that Petitioner has relied on the statement in the 2001 PDR that the formulation "must only be used if the solution is clear and colorless with no particles visible" as an alleged motivation to combine (Petition at 27; Ex. 1004 at 5), Petitioner has failed to explain why the Handbook's warning on discoloration would not in fact have *dissuaded the combination* of polysorbates with the Glargine formulations of the 2001 PDR and/or Owens.

Similarly, the Handbook entry for cresol states that its "[a]ntimicrobial activity is reduced in the presence of nonionic surfactants." Ex. 1019 at 5. This constitutes a further reason why a POSITA would be dissuaded from combining nonionic surfactants, such as polysorbates, with the components of the 2001 PDR and Owens formulations, both of which include cresol as a preservative. Ex. 1004 at 3; Ex. 1005 at 3. Petitioner has failed to explain why the Handbook's warning on the reduction in antimicrobial activity would not dissuade a POSITA from combining polysorbates with the Glargine formulations of the 2001 PDR and/or Owens.

Petitioner's failure to address the disclosures in its cited references that *warn against combining* the components of the asserted primary and secondary

references is a further reason why Petitioner fails to demonstrate a reasonable likelihood of success. *See Novo Nordisk*, 719 F.3d at 1365.

D. Grounds 1-4: Petitioner Has Failed to Present Evidence That the 2001 PDR Reference is Prior Art to the '652 Patent

Grounds 1-3 rely on the 2001 PDR (Ex. 1004) as the primary reference. In addition, Ground 4 relies on the 2001 PDR as purportedly disclosing a motivation to add a surfactant. Petition at 46. However, Petitioner has failed to carry its "initial burden … to come forward with sufficient evidence to make a threshold showing that the reference relied upon is available prior art." *Coalition for Affordable Drugs IV LLC v. Pharmacyclics, Inc*., IPR2015-01076, Paper 33 at 5 (P.T.A.B. Oct. 19, 2015). In order to make a "threshold showing" that the 2001 PDR is a "'printed publication[]' within the meaning of 35 U.S.C. §§ 102(b) [pre-AIA] and 311(b)," Petitioner must show that the reference was "publicly accessible" more than one year before the earliest priority date of the challenged patent. *Servicenow, Inc. v. Hewlett-Packard Co*., IPR2015-00716, Paper 13 at 9 (P.T.A.B. Aug. 26, 2015) (citing *Kyocera Wireless Corp. v. ITC*, 545 F.3d 1340, 1350 (Fed. Cir. 2008)). Petitioner has failed to make this showing.

First, the 2001 PDR reference attached to the Petition (Ex. 1004) contains no indicia showing that it was publicly accessible before the critical date of June 18, 2001. The only temporal indication in Ex. 1004 is a copyright notice that identifies a year–2001–but no month. Ex. 1004 at 2. Irrespective of whether a copyright

notice is even admissible or probative evidence of publication, it certainly does not indicate whether the reference was publicly accessible before June 18, 2001, which is one year before Petitioner's asserted earliest priority date of the '652 patent. *See* Petition at 10; *Servicenow*, IPR2015-00716, Paper 13 at 17 ("we are not persuaded that the presence of a copyright notice, without more, is sufficient evidence of public accessibility as of a particular date").

Second, the affidavit of Patricia van Skaik does not establish a December 1, 2000 publication as asserted by Petitioner. Ex. 1004A. The van Skaik affidavit is premised on a document the affiant claims is attached to the affidavit as Exhibit A– but no such document is attached. *Id*. at ¶ 5. That missing Exhibit A document was purportedly from "the Lloyd Library and Museum" in Cincinnati, Ohio and had "a date stamp on the cover page" which was December 1, 2000. *Id*. An inspection of Ex. 1004, which is the only PDR reference submitted with Petition, shows that it bears no date stamp on the cover page, and instead carries a bar code from the University of California, San Diego. Ex. 1004 at 1. As the van Skaik affidavit is premised entirely on an exhibit that is not in the record purportedly having a date stamp of December 1, 2000, the affidavit cannot establish the public accessibility on that same date of a different document (Ex. 1004) lacking that date stamp.

Petitioner "was fully aware of the need to prove [this] element of its case at the time it filed its Petition, and, thus, evidence of that nature should have been submitted with the Petition had [Petitioner] wanted it considered for purposes of institution." *Intex Recreation Corp. v. Bestway Inflatables & Materials Corp*, IPR2016-00180, Paper 9 at 2 (P.T.A.B Mar. 25, 2016). Accordingly, Grounds 1-4 should be denied institution.

V. THE PETITION FAILS TO ADDRESS THE PROSECUTION HISTORY OF THE '652 PATENT

Petitioner's asserted Grounds present substantially the same arguments as were previously considered by the Office, and successfully overcome by the applicant, during years of rigorous prosecution of the '652 patent. Yet Petitioner notably fails to substantively address the prosecution history, providing only a three-sentence overview (Petition at 13-14) with no mention of the applicants' arguments and amendments that successfully overcame art with substantially the same disclosure as Petitioner's proffered references.

As discussed above, each of Petitioner's Grounds is based on alleged combinations of either of two primary references (2001 PDR or Owens) teaching a single Glargine formulation, with one of three secondary references (Lougheed, FASS or Grau), each of which disclose the use of surfactant(s) in formulations of human or porcine insulins. Similar substantive disclosures were addressed by the Examiner during prosecution.

Regarding the primary references, during prosecution of the ’652 patent, the Examiner rejected the pending claims over a combination of art that included U.S. Patent No. 5,656,722 to Dorschug (“Dorschug”). Dorschug discloses a plasmid for the preparation of Glargine, and also discloses various components, including between 1 µg and 2 mg of zinc, a tonicity agent that can be glycerol, a preservative that can be m-cresol, and an acid that can be HCl, at a pH of “between about 2.5 and 8.5,” in aqueous solution. Ex. 2004 at 4 (5:27-57, 6:1-31). Thus, the list of components disclosed in Dorschug substantially overlaps with the list of components that Petitioner asserts are taught by the 2001 PDR and Owens. *See*, *e.g.*, Petition at 25-26, 45-46. Arguments based on Dorschug were explicitly set forth by the Examiner during prosecution, and successfully overcome by the patentee.[5]

Similarly, during prosecution, the Examiner also applied and considered prior art that is substantively aligned with Petitioner’s secondary references. For example, the Examiner relied on U.S. Patent No. 4,839,341 to Massey et al. (“Massey,” attached to the Petition as Ex. 1024) and U.S. Patent No. 4,153,689 to

[5] The disclosure of Dorschug was also before the Examiner as part of the ’652 patent specification, which cites a European patent corresponding to Dorschug. Ex. 1001 at 2:45-46.

Hirai et al. ("Hirai," attached to the Petition as Ex. 1023) as the basis for obviousness rejections, in substantially the same way as Petitioner attempts to use its secondary references—Lougheed, FASS and Grau. Ex. 1001A at 2406-2411. All of these references disclose the use of surfactant(s) in formulations of human or other animal insulins.

More specifically, Petitioner's Grounds 1 and 4 rely on Lougheed, which discloses compositions of "porcine insulin" that are "titrated to pH 7.0-7.4," in which a number of nonionic and anionic surfactants are tested. Ex. 1006 at 2. Petitioner relies on Lougheed for a teaching of non-Glargine insulin in combination with nonionic surfactants. *See* Petition at 19-20, 25-40, 45-55. In much the same way, during prosecution the Examiner relied on Massey for its teaching of a solution "comprising pork or human insulin, glycerol, and a Pluronic surfactant" with a "pH range of about 3.2 to about 3.8," and relied on Hirai for a teaching of "beef or porcine insulin, polysorbate 80 or polyethylene glycol, and glycerine or glucose." Ex. 1001A at 2407-2408. Moreover, not only is Lougheed listed on the face of the Massey reference, but Massey also relies on Lougheed 1980 (a previous publication which is cited and incorporated by reference in Lougheed) for the specific disclosure of factors that affect insulin aggregation, and for the use of surfactants in non-Glargine insulin formulations. *See* Ex. 1024 at 2.

Similarly, Petitioner proffers both FASS and Grau (Grounds 2-3 and 5-6) for an alleged teaching of a formulation containing insulin and a poloxamer. Petition at 41, 44-45; Exs. 1007A and 1008. This is also no different than the teachings for which Massey was used during prosecution, because "Pluronic," which is the type of surfactant disclosed in Massey, is a trade name for a poloxamer. Ex. 1019 at 17. Similar disclosures of surfactants in combination with non-Glargine insulin were also before the Examiner as part of the '652 patent specification itself, and therefore considered. *See* Ex. 1001 at 3:8-31. In describing one such prior art formulation of non-Glargine insulin containing a surfactant, the '652 patent specification specifically states that the prior art "describes insulin preparations stabilized using polysorbate 20 or poloxamer 188 for pulmonary administration, but does not describe the stabilization in an ***acidic solution against aggregation*** nuclei." *Id*. at 3:22-25 (emphasis added).

As such, the Office has previously considered the patentability of the challenged claims over Glargine and non-Glargine insulin art, and concluded that the claimed Glargine formulation would not have been obvious. The Examiner reached this conclusion and allowed the claims following the applicant's claim amendments narrowing the claims to Glargine-specific formulations. *See* Ex.1001A at 2817 (patent application that led to '652 patent, as filed); *id.* at 2383-93 (Office Action dated October 3, 2006; Amendment dated March 21, 2007); *id.*

at 2374 (Examiner acknowledged that the claim amendments narrowing claims to Glargine and human and other animal insulins to Glargine only were "effective to overcome the prior art rejections set forth in the Office action mailed October 3, 2006"). In support of patentability of these amendments, the applicants argued that the cited references to human or porcine insulin were distinct from the claimed Glargine and that the cited references "fail [to] disclose the additional recited chemical entities in combination with the recombinant [Glargine] and claimed preservatives." *Id*. at 2389-2391. The Examiner then allowed the claims. *Id*. at 2374.

The Petition does not discuss the prosecution history, and therefore, effectively asks the Board to "second-guess the Office's previous decision on substantially the same issue." *Neil Ziegman, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper 11 at 13 (P.T.A.B. Feb. 24, 2016). This is at odds with the Board's statutory directive for a "just, speedy and inexpensive resolution." 37 C.F.R. § 42.1(b). Patent Owner thus respectfully submits that the Board should exercise its discretion to deny institution under Section 325(d). *See Ziegman*, IPR2015-01860, Paper 11 at 13 (denying institution where the petitioner's grounds employed arguments similar to those used during prosecution, even though the primary reference used in the grounds was not used in any rejection during prosecution); *Funai Elec. Co. v. Gold Charm Ltd.*, IPR2015-01491, Paper 15 at 20 (P.T.A.B.

Dec. 28, 2015) (denying institution for rehashing arguments from prosecution that did not "shed[] a substantially different light on" the asserted reference).

Independently, Petitioner's failure to discuss the relevant prosecution history arguments in the Petition evinces its inability to meet the "reasonable likelihood of success on the merits" standard, which separately warrants denial. *Praxair Distribution, Inc. v. INO Therapeutics, Inc.*, IPR2015-00522, Paper 12 at 17 (P.T.A.B. July 29, 2015) ("Given the Examiner found these arguments persuasive and allowed the claims, we agree with Patent Owner that Petitioner and its declarant should have addressed these arguments in the Petitions to show a reasonable likelihood of success on the merits."). Thus, all of Petitioner's asserted grounds should be denied under 35 U.S.C. § 325(d).

VI. THE PETITION FAILS TO MEET PLEADING REQUIREMENTS

A Petition is required "(1) to identify clearly the grounds and references on which Petitioner is relying to assert that the challenged claims are not patentable; (2) to specify sufficiently where the limitations of the challenged claims are taught or suggested by the cited references; and (3) to provide a sufficiently detailed explanation of the significance of the citations…." *Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I) Corp.*, IPR2015-00488, Paper 14 at 18 (P.T.A.B. July 24, 2015); 35 U.S.C. §312(a)(3); 37 C.F.R. §§42.22(a)(2) and 42.104(b)(2), (4)-(5). At least Grounds 2-4 should be denied for failing to meet these requirements.

A. Grounds 2-4 of the Petition Do Not Identify With Particularity the Evidence that Petitioner Attempts to Rely Upon

"It is [of] the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'" *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (quoting 35 U.S.C. § 312(a)). Petitioner's Petition fails this requirement by including several inadequately pled grounds of alleged invalidity that obscure Petitioner's arguments and require the Board to play detective with the record.

For example, Petitioner switches between the 2001 PDR and Owens in articulating Ground 2. Ground 2 is titled "Claims 7 and 24 were Obvious over the LANTUS® 2000 Label [i.e., the 2001 PDR, Ex. 1004] and the FASS Insuman Infusat Entry," and the opening part of the Ground analysis discusses those two references. Petition at 41-42 (citing Exs. 1004 and 1007A). However, midway through the argument for Ground 2, Petitioner switches to discussing the combination of Owens and FASS. *Id*. at 42-43 (citing Exs. 1005 and 1007A). Moreover, Petitioner does not identify a motivation to combine the 2001 PDR and FASS, and instead suggests a combination of Owens and FASS. *Id*. at 42-43. Petitioner then concludes Ground 2 by alleging that "Claims 7 and 24 were obvious over Owens and the FASS Insuman Infusat entry." *Id*. at 43.

Petitioner also obfuscates the nature of its challenge in Ground 3 by initially styling that ground as alleging that Claims 7 and 24 are obvious over a combination of the 2001 PDR and Grau (Ex. 1008), but then concluding in argument that "Claims 7 and 24 were obvious over the LANTUS® 2000 Label [i.e., the 2001 PDR, Ex. 1004] and the [FASS] Insuman Infusat reference." *Id*. at 43, 45.

Similarly, Ground 4, while initially presented as being based on the combination of Owens and Lougheed, injects the 2001 PDR reference into Ground 4 as the basis for adding polysorbate 20 and polysorbate 80 to the Owens formulation. *Id*. at 46. Thus, it is unclear whether Ground 4 is the combination of Owens and Lougheed, or the combination of Owens, Lougheed, and the 2001 PDR reference.

Thus, institution should be denied for at least Grounds 2-4 because the Petition fails to "identify clearly the grounds and references on which Petitioner is relying." *Whole Space*, IPR2015-00488, Paper 14 at 18; *see Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12 at 10 (P.T.A.B. Aug. 29, 2014) ("A brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record.").

B. Petitioner Fails to Identify Required "Related Matters" Information

Petitioner was required to identify in the Petition "any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding." 37 C.F.R. § 42.8(b)(2) (titled "Related matters"). However, Petitioner has failed to disclose three publicly-known district court cases involving the '652 patent, and also an IPR petition filed by Petitioner against the related '930 patent (IPR2017-01528). That failure "could be grounds for denial of the Petition." *Apple, Inc., v. Contentguard Holdings, Inc*., IPR2015-00356, Paper 9 at 5-6 (P.T.A.B. June 26, 2015).

Specifically, Petitioner failed to disclose the following cases involving the '652 patent and the related '930 patent: *Sanofi-Aventis US LLC et al v. Eli Lilly and Company*, DED-1-14-cv-00113 (concluded), *Sanofi-Aventis US LLC et al v. Eli Lilly and Company*, DED-1-14-cv-00884 (concluded), and *Sanofi-Aventis US LLC et al. v. Merck Sharp & Dohme Corp.*, DED-1-16-cv-00812 (pending).[6] The district court in the *Eli Lilly* cases issued two claim construction rulings involving the '652 patent and its related '930 patent. Moreover, the *Eli Lilly* cases resulted in

[6] Since the filing of the Petition, the '652 patent has been asserted in another district court action, styled *Sanofi-Aventis US LLC et al. v. Merck Sharp & Dohme Corp.*, No. 17-5914 (D.N.J.). *See* Paper 7.

Eli Lilly taking a patent license under the ’652 patent. These failures to disclose related matters provide an independent ground for denial of institution. *See, e.g.*, *Apple, Inc.*, IPR2015-00356, Paper 9 at 8 (failure to identify related matters “could be grounds for denial of the Petition”); *Zoll Lifecor Corp. v. Philips Elec. N. Am. Corp.*, IPR2013-00618, Paper 15 at 16 (P.T.A.B. Mar. 20, 2014) (loss of filing date for failure to include real-party-in interest information).

VII. CONCLUSION

For the reasons set forth above, Petitioner’s unsupported and conclusory assertions do not establish that there is a reasonable likelihood that any of Claims 1-25 of the ’652 patent are unpatentable. *See* 37 C.F.R. § 42.108(c). Accordingly, the Petition should be denied in its entirety.[7]

[7] Should the Board institute review on any ground and find any claim of the ’652 patent to be invalid, Patent Owner expressly reserves the right to challenge that decision on Constitutional grounds, including for denying Patent Owner its Seventh Amendment rights and because Petitioner lacked Constitutional standing to challenge patentability at the time it filed the Petition.

Dated: September 14, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 *et seq*., the undersigned certifies that this document complies with the type-volume limitations. This document contains fewer than 11,847 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

Dated: September 14, 2017

/s/ Elizabeth Stotland Weiswasser
Elizabeth Stotland Weiswasser

CERTIFICATE OF SERVICE

I hereby certify that on September 14, 2017, a copy of the foregoing **PRELIMINARY RESPONSE TO PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,476,652** pursuant to 37 CFR § 42.107 was served by filing this document through the Patent Office's electronic systems as well as delivering a copy via electronic mail upon the following counsel of record for Petitioner:

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