Case IPR2016-01096
Patent No. 6,667,061
Petition for *Inter Partes* Review
Attorney Docket No. 9LUYE 7.1R-004

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUYE PHARMA GROUP LTD., LUYE PHARMA(USA) LTD., SHANDONG LUYE PHARMACEUTICAL CO., LTD., and NANJING LUYE PHARMACEUTICAL CO., LTD.
Petitioners

v.

ALKERMES PHARMA IRELAND LTD
Patent Owner

Patent No. 6,667,061 to Ramstack *et al*.
Issue Date: December 23, 2003
Title: PREPARATION OF INJECTABLE SUSPENSIONS HAVING IMPROVED INJECTABILITY

Inter Partes Review No. IPR2016-01096

PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1-13 AND 17-23 OF U.S. PATENT NO. 6,667,061

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EXHIBIT LIST

Exhibit #	Reference
1001	U.S. Patent No. 6,667,061 ("the '061 Patent")
1002	Declaration of Dr. Patrick P. DeLuca
1003	*Curriculum Vitae* of Dr. Patrick P. DeLuca
1004	Intentionally Left Blank
1005	International Publication No. WO 95/13799 ("Ramstack")
1006	U.S. Pharmacopeia Entry re: CMC, viscosity pp.274-75, 1840 (1994)
1007	EP Pharmacopoeia Entry re: CMC, pp.547-48(3d ed. 1997)
1008	Handbook of Pharmaceutical Excipients pp.78-81, 135-38, 294-95, 329-330, 375-78, 420-21, 439-42, 477-80, 481-82 (2nd ed. 1994)
1009	U.S. Patent No. 5,654,010 ("Johnson")
1010	U.S. Patent No. 5,656,299 ("Kino")
1011	International Publication No. WO199714408 ("Gustafsson")
1012	Intentionally Left Blank
1013	Intentionally Left Blank
1014	Herbert A. Lieberman *et al*. (eds.), *Pharmaceutical Dosage Forms: Disperse Systems*, Vol.2, pp.26-35, 40, 43-46, 261, 285-318 (2nd ed. rev. expanded 1996)
1015	U.S. Patent No. 6,495,164 ("the '164 Patent")
1016	Serial No. 10/259,949, Office Action, Apr. 9, 2003
1017	Serial No. 10/259,949, Applicants' Resp., May 14, 2003
1018	Serial No. 09/577,875, Declaration of Mark A. Tracy, May 17, 2002
1019	Serial No. 10/259,949, Notice of Allowability, July 24, 2003
1020	Kenneth E. Avis *et al.* (eds.), 1 (Chs.2, 4, 5) Pharmaceutical Dosage Forms:Parenteral Medications 17-25, 115-16, 140-43, 150-51, 173-75, 190-212 (2nd ed. rev. expanded Marcel Dekker, Inc. 1992)
1021	Leon Lachman, PhD *et al.*, *The Theory and Practice of Industrial Pharmacy* 642-44, 783-84 (Lea & Febiger 3rd ed. 1986)
1022	Herbert A. Lieberman *et al*., *Pharmaceutical Dosage Forms: Disperse Systems*, Vol.1, pp.287-313 (2nd ed. rev. expanded 1996)
1023	Orange Book entries for RISPERDAL®

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Luye Pharma Group Ltd., Luye Pharma (USA) Ltd., Shandong Luye Pharmaceutical Co., Ltd., and Nanjing Luye Pharmaceutical Co., Ltd. (collectively "Luye" or "Petitioners") petition for *Inter Partes* Review ("IPR") seeking cancellation of claims 1-13 and 17-23 of U.S. Patent No. 6,667,061 ("the '061 Patent") (Ex.1001).

I. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Notice Of Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest for this Petition are Luye Pharma Group Ltd., Luye Pharma (USA) Ltd., Shandong Luye Pharmaceutical Co., Ltd., and Nanjing Luye Pharmaceutical Co., Ltd.. The '061 Patent is assigned on its face to Alkermes Controlled Therapeutics, Inc., but by later assignment is owned by Alkermes Pharma Ireland Limited. (collectively "Patent Owner" or "Alkermes").

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

Petitioners have concurrently filed a second petition for *Inter Partes* Review IPR2016- 01095 seeking cancelation of claims 1-13 and 1-23 on other grounds. There are no related litigation matters between the parties involving this patent.

C. Designation Of Lead And Backup Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel:	**Backup Counsel:**
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D. Notice Of Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to the lead and backup counsel at the address shown above. Petitioners also consent to electronic service by e-mail at the above-listed e-mail addresses.

E. Grounds For Standing (37 C.F.R. §42.104(a))

Petitioners certify that (1) the '061 Patent is available for IPR; and (2) Petitioners are not barred or estopped from requesting IPR of the '061 Patent

on the grounds identified herein. The fee for this petition has been paid. The Office is hereby authorized to charge any fee deficiencies to, or credit any overpayments to, Deposit Acct No. 12-1095 in connection with this petition.

II. STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R. § 42.22(a))

For the reasons set forth herein, the information presented shows that there is a reasonable likelihood that Luye will prevail with respect to at least one of the claims challenged in this petition. Petitioners request institution of an IPR and cancellation of claims 1-13 and 17-23 of the '061 Patent. The text of the challenged claims can be found in the claim charts included herein.

III. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. § 104(b))

IPR of claims 1-13 and 17-23 of the '061 Patent is requested on the two separate grounds of unpatentability listed below. Per 37 C.F.R. § 42.6(d), a copy of each of the references is filed herewith. In support of the proposed grounds for unpatentability, this petition includes the declaration of technical expert Patrick DeLuca Ph.D. (Ex.1002), explaining what the art would have conveyed to a person of ordinary skill in the art ("POSA"). Dr. DeLuca's *Curriculum Vitae* is included as well. (Ex.1003.) Dr. DeLuca is an expert in the field of formulations involving risperidone microparticles, pharmaceutics, parenteral dosage form design,

microparticles, sustained release delivery systems, and pharmaceutical patents, among others. (Ex.1002 ¶¶ 4-7.)

Ground	References	Basis	Claims
1	Johnson (Ex.1009) in view of Kino (Ex.1010)	§ 103	1-13 and 17-23
2	Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)	§ 103	1-13 and 17-23

In Ground 1, Petitioners show that claims 1-13 and 17-23 are unpatentable over U.S. Patent No. 5,654,010 to Johnson *et al.* ("Johnson") (Ex.1009) in view of Kino (Ex.1010). Johnson alone renders obvious every element of claims 1-3, 6-9, 12-13, 17-19, and 22-23. Johnson, in combination with Kino, would render claims 4-5, 10-11, and 20-21 obvious to a POSA as of the priority date.

In Ground 2, Petitioners show that claims 1-13 and 17-23 are unpatentable over WO 1997/144408 to Gustafsson *et al.* ("Gustafsson") (Ex.1011) in view of WO 1995/13799 to Ramstack *et al.* ("Ramstack") (Ex.1005), and the Handbook of Pharmaceutical Excipients, 2nd Edition ("the Handbook") (Ex.1005). Gustafsson, in combination with Ramstack, and the Handbook render claims 1-13 and 17-23 obvious to a POSA as of the priority date.

Although Petitioner provides multiple grounds of unpatentability, they are meaningfully distinct. Ground 1 and Ground 2 rely upon different primary and secondary references. All of the Grounds in this Petition also represent meaningfully different arguments than those made in the corresponding IPR Petition filed on the same date as this Petition bearing case number IPR2016-01095.

IV. BACKGROUND

A. Introduction

The allowed claims of the ’061 Patent are directed to a composition suitable for injection through a needle into a host. (Exs.1001 cl.1; 1002 ¶ 14.) The claims require microparticles (which are particles that include an active agent dispersed or dissolved in a polymeric binder) and an injection vehicle. (Exs.1001 cl.1; 1002 ¶ 14.) The microparticles are suspended in the injection vehicle at a concentration of 30mg/ml to form a suspension. (Exs.1001 cl.1; 1002 ¶ 14.) The fluid phase of the suspension has a viscosity of greater than about 20cp and less than about 600cp at 20°C. (Exs.1001 cl.1; 1002 ¶ 14.) This viscosity allows the composition to be injected through an 18-22 gauge needle, according to the ’061 Patent. (Exs.1001 cl.1; 1002 ¶ 14.)

Patent Owner's alleged invention was using known viscosity enhancing agents to increase the viscosity of an injectable composition that includes microparticles to improve injectability of the composition. (Exs.1001 Abstract; 1002 ¶ 15.) Patent Owner alleged that increasing viscosity of the fluid phase was an unexpected improvement in injectability and reduced *in vivo* injection failures. (Exs.1001, at 4:57-60; 1002 ¶ 15.)

But Patent Owner did not invent a new microparticle. (Exs.1005, at 35-36, Examples 2, 3; 1002 ¶ 16.) Nor did Patent Owner invent viscosity enhancing agent or new injection vehicles. (Exs.1009, at 12:42-45; 1002 ¶ 16.) Indeed, Patent Owner did not invent combining a viscous injection vehicle with microparticles. (Ex.1002 ¶16.) Patent Owner did nothing more than combine well-known elements to arrive at a known concentration and viscosity for an injectable composition. (Exs.1009, at 12:39-42; 1008, at 78, 135, 137, 239, 420; 1002 ¶ 16.) Injecting a microparticle suspension through an 18-22 gauge needle was also known in the prior art, together with knowledge of injectables having viscosities greater than about 20cp at 20°C. (Exs.1008, at 78, 135, 137, 239, 420; 1002 ¶ 16, 32.) Accordingly, Petitioners request institution of an IPR of claims 1-13 and 17-23 of the '061 Patent.

B. Improving Injectability

Injectable suspensions are heterogeneous systems that include a solid phase and a liquid phase. (Exs.1014, at 285; 1001, at 1:17-25; 1002 ¶ 18.) Aqueous and nonaqueous liquid phases were known to be used in injectable suspensions. (Exs.1014, at 285; 1001, at 1:17-25; 1002 ¶ 18.) The solid phase of the suspension are known to include microparticles, which have an active pharmaceutical ingredient encapsulated in a polymeric binder and provides extended release in injectable suspensions. (Exs.1014, at 285; 1001, at 1:17-25; 1002 ¶ 18.)

Injectable suspensions must be syringeable and injectable. (Exs.1014, at 285; 1001, at 1:17-25; 1002 ¶ 19.) A composition is "syringeable" if it is capable of flowing through a needle from a vial. (Exs.1014, at 298; 1001, at 1:53-60; 1002 ¶ 19.) Some common issues associated with syringeability are clogging of the needle, withdrawal of the composition from the vial, and accuracy of the dose to be administered. (Exs.1014, at 298-99; 1001, at 1:61-64; 1002 ¶ 19.) "Injectable" refers to how the suspension performs during the actual injection of the composition. (Exs.1014, at 299; 1001, at 1:53-60; 1002 ¶ 19.) Common issues associated with injectability are force required to administer the injection, evenness of the flow, aspiration, and clogging. (Exs.1014, at 299; 1001, at 1:53-60; 1002 ¶ 19.)

C. Risperidone

Risperidone is a well-known hydrophobic antipsychotic drug, which first gained market approval in 1993. (Exs.1023; 1002 ¶ 20.)

D. The Role of Viscosity In Injectable Formulations

Syringeability is defined as the ability of a parenteral solution or suspension to pass easily through a hypodermic needle and considered one of the most important properties of a suitable parenteral suspension. (Exs.1014, at 33-34; 1002 ¶ 21.) Increases in various characteristics may make the syringeability more difficult. For example, the following should be considered when determining an appropriate syringeability: viscosity of the vehicle, density of the vehicle, size of the suspended particulate, and concentration of the drug. (*Id*.)

Viscosity is a necessary component of injectable formulations. As described by Lieberman, the viscosity measurement is one of the most important factors and the easiest for a formulator to control. (Exs.1014, at 33-34; 1002 ¶ 22.)An injectable formulation must have the proper viscosity to ensure it is capable of being forced through a syringe (*i.e.*, syringeable) and capable of being injected through a needle into a host (*i.e.*, injectable). (*Id*.)

Aqueous injection vehicles primarily include water and require additives if the active particles do not readily dissolve in water. (Exs.1014, at 291; 1002 ¶ 24.)

Accordingly, the formulator must include various substances such as suspending agents, tonicity agents, wetting agents, etc. to arrive at a suitable aqueous injection vehicle capable of satisfying the syringeability and injectability properties required to make a formulation suitable for injection. (Exs.1014, at 288; 1002 ¶ 24.)

Viscosity is a measurement that is also dependent on temperature. (Exs.1022, at 305; 1006, at 1840; 1002 ¶ 25.) As the temperature increases, the viscosity decreases. (Exs.1002, at 305; 1006 at 1840; 1002 ¶ 25.) A POSA would know to create an injectable formulation that was viscous enough to hold the microparticles in solution, but not too viscous that it presents syringeability or injectability problems.

E. The Prior Art Taught Microparticle Suspensions With The Claimed Concentration And Viscosity

Injectable formulations that include microspheres would include a viscosity enhancing or suspending agent. Sodium carboxymethylcellulose (CMC) is one of the most commonly used suspending and viscosity enhancing agents. (Exs.1008, at 78-81; 1022, at 305; 1002 ¶26.)

Johnson is not in the same patent family as the ’061 Patent, but is owned by Patent Owner and shares a common inventor, OluFunmi L(ily) Johnson. (Exs.1001, 1009.) Johnson teaches a formulation suitable for injection, which may include microparticles. (Exs.1009, at 4:54-60, 12:39-45; 1002 ¶ 27.) Johnson also

teaches a microparticle concentration greater than 30mg/ml and an injection vehicle that includes 3% w/w carboxymethylcellulose (sodium salt). (Exs.1009, at 12:42-45; 1002 ¶ 27.) Johnson further teaches incorporating a wetting agent, such as polysorbate, and a tonicity agent, such as sodium chloride. (Exs.1009, at 12:42-45; 1002 ¶ 27.) Johnson states that such formulation may be injected through a 20 gauge needle. (Exs.1009, at 12:40-42; 1002 ¶ 27.)

As mentioned above, the ’061 Patent appeared to disclaim the exact Johnson vehicle in the Summary of the Invention, “the injection vehicle not being the aqueous injection vehicle that consists of 3% by volume carboxymethyl cellulose, 1% by volume polysorbate 20, 0.9% by volume sodium chloride,” but the claims include no such limitation. (Exs.1001, at 3:4-7.) Thus the Johnson injection vehicle directly reads upon the claims. Even if the Johnson injection vehicle were interpreted to be disclaimed by the ’061 Patent, Patent Owner never provided any arguments or supporting documentation to prove that their injection vehicle was anything other than an obvious variation of that the exact injection vehicle taught by Johnson.

Gustafsson teaches a sustained release formulation that includes polymer microparticles in a suspension suitable for injection. (Exs.1011 Abstract; 1002 ¶ 28.) Gustafsson teaches that such formulations can be used for any known active

pharmaceutical ingredient. (Exs.1011, at 6:33-35; 1002 ¶ 28.) Gustafsson teaches that such formulations can include 3% sodium carboxymethylcellulose and microparticles in a concentration of greater than 30mg/ml, and in a suspension that is suitable for injection through a 21 gauge needle. (Exs.1011, at 18:19-24, 19:19-24; 1002 ¶ 28.) Gustafsson further teaches incorporating a physiological sodium chloride solution, which is a well-known tonicity agent. (Exs.1011, at 18:19-24, 19:21-22; 1002 ¶ 28.)

Ramstack teaches the preparation of biodegradable microparticles that include a biologically active agent and specifically identifies risperidone. (Exs.1005 Abstract, 35:1-36:26; 1002 ¶ 29.) Ramstack teaches that a polymer, such as 75:25 dl (polylactide-co-glycolide), may be used for encapsulating risperidone. (Exs.1005, at 5:19-22, 35:1-36:26, Examples 2, 3; 1002 ¶ 29.) The poly(lactide-co-glycolide) may have a molar ratio of lactide to glycolide in a range of 85:15 to 50:50. (Exs.1005, at 16:28-31; 1002 ¶ 29.) Additional polymer materials useful for encapsulation may include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonene, poly(ortho carbonates), poly(acetals), poly(lactic acidcaprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, polyphosphazines, and natural polymers including

albumin, casein, and waxes. (Exs.1005, at 16:7-13; 1002 ¶ 29.) Ramstack teaches an aqueous injection vehicle that includes CMC, mannitol, and polysorbate. (Exs.1005, at 37:6-7; 1002 ¶ 29.)

Kino teaches sustained release microspheres of antipsychotic drugs, including risperidone. (Exs.1010, at 1:65-2:3, 2:41; 1002 ¶ 30.) Kino teaches that such microspheres can be used in aqueous injection solutions that include carboxymethylcellulose. (Exs.1010, at 4:39-41; 1002 ¶ 30.) Kino teaches the inclusion of wetting agents, such as polysorbate, and tonicity agents, such as sodium chloride. (Exs.1010, at 38-51; 1002 ¶ 30.) Kino teaches the addition of sorbitol to an injection vehicle. (Exs.1010, at 4:52:55; 1002 ¶ 30.)

The Handbook of Pharmaceutical Excipients, 2nd Edition, was published in 1994. The Handbook teaches that polysorbates are wetting agents that can be used in parenteral suspensions. (Exs.1008, at 376; 1002 ¶ 32.) And the Handbook teaches that mannitol and sorbitol may be used in injections and can be used to increase the density of an aqueous solution. (Exs.1008, at 294, 477, 479; 1002 ¶ 32.)

V. THE '061 PATENT

A. The Claims

Independent claim 1 is directed to a composition that is suitable for injection through a needle into a host, which includes microparticles with a polymeric binder, and an injection vehicle. (Exs.1001 cl.1; 1002 ¶34.) The microparticles are suspended in the injection vehicle to form a suspension, which includes a fluid phase having a viscosity of greater than about 20cp and less than about 600cp at 20°C and provides injectability of the composition through a needle having a diameter from 18-22 gauge. (*Id*.)

Dependent claims 2 and 3 require the addition of a viscosity enhancing agent, such as sodium carboxymethyl cellulose. (Exs.1001 cls.2-3; 1002 ¶35.) Dependent claims 4 and 5 require the addition of a density enhancing agent, such as sorbitol. (Exs.1001 cls.4-5; 1002 ¶35.) Dependent claims 6 and 7 require the addition of a tonicity adjusting agent, such as sodium chloride. (Exs.1001 cls.6-7; 1002 ¶35.) Dependent claims 8 and 9 require the addition of a wetting agent, such as polysorbate 20, polysorbate 40, or polysorbate 80. (Exs.1001 cls.8-9; 1002 ¶35.) Dependent claims 10 and 11 require the addition of a combination of a density enhancing agent and a wetting agent, such as polysorbate 20, polysorbate 40, or polysorbate 80. (Exs.1001 cls.10-11; 1002 ¶35.) Dependent claims 12 and 13

require the addition of a combination of a tonicity adjusting agent and a wetting agent, such as polysorbate 20, polysorbate 40, or polysorbate 80. (Exs.1001 cls.10-11; 1002 ¶35.) Dependent claims 17, 18, and 19 require the microparticle to include an active agent encapsulated with a polymeric binder, such as poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50. (Exs.1001 cls.17-19; 1002 ¶35.) Dependent claims 20 and 21 require the active agent of claim 17 and 19, respectively, to be risperidone, 9-hydroxyrisperidone, or a pharmaceutically acceptable salt. (Exs.1001 cls.20-21; 1002 ¶35.) Finally dependent claims 22 and 23 require the microparticles to have a mass median diameter of less than about 250μm or from about 20μm to about 150μm. (Exs.1001 cls.22-23; 1002 ¶35.)

B. The Family History Of The '061 Patent

The '061 Patent issued on December 23, 2003, from U.S. Application No. 10/259,949. The patent states on its face that it is a continuation of U.S. Patent Application No. 09/577,875, filed on May 25, 2000, which issued as U.S. Patent No. 6,495,164 ("the '164 Patent") on December 17, 2002. (Exs.1015; 1002 ¶ 36.) The specifications of the '164 Patent and '061 Patent are substantially the same. (Ex.1002 ¶ 36.)

C. The Specification Of The '061 Patent

The '061 Patent discloses injectable suspensions having improved injectability. (Exs.1001 Abstract; 1002 ¶ 37.)

The Background of the Invention admits that adding viscosity enhancers to injection vehicles was known. (Exs.1001, at 2:25-27; 1002 ¶ 37.) The '061 Patent also admits that this was done "in order to retard settling of the particles in the vial and syringe." (Exs.1001, at 2:25-27; 1002 ¶ 37.) The '061 Patent provides an example of a known formulation of microparticles in an aqueous injectable suspension. (Ex.1002 ¶ 38.)For example, the '061 Patent admits that "[t]he fluid phase of a suspension of Decapeptyl . . . mean particle size of 40 μm . . . when prepared as directed, has a viscosity of approximately 19.7 cp." (Exs.1001, at 2:34-37; 1002 ¶ 38.) The Background then states that there is a need in the art to improve the injectability of injectables that include microparticle suspensions. (Ex.1001, at 2:55-61; 1002 ¶ 38.)

The Summary of the Invention and the Detailed Description describes different embodiments of the alleged invention. In one aspect, the injection vehicle is defined as "not being the aqueous injection vehicle that consists of 3% by volume carboxymethyl cellulose, 1% by volume polysorbate 20, 0.9% by volume sodium chloride." (Exs.1001, at 3:4-7; 1002 ¶ 39.) The specification then provides

a preferred embodiment for an injection vehicle that includes "3% sodium carboxymethyl cellulose, 0.9% saline, and 0.1% polysorbate 20." (Exs.1001, at 16:64-67; 1002 ¶ 39.) The Method and Examples section provides various studies, such as an *in vitro* test study, animal studies, *ex vivo* injectability tests, and methods of preparing the injectable compositions. (Exs.1001, at 5:41-17:60; 1002 ¶ 39.)

D. The Pertinent Prosecution History Of The '061 Patent

The prosecution history of the '061 Patent is relatively brief. The only pertinent portion of the petition is that the Examiner issued a nonfinal office action on April 9, 2003, which rejected claims 1-21 and 41-42 under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,656,299 to Kino *et al.* and further in view of U.S. Patent No. 5,540,912 to Roorda *et al.* (Exs.1016; 1002 ¶ 40)

In regards to Kino, the Examiner stated that Kino disclosed sustained release microsphere preparations of antipsychotic drugs that are suitable for injection. (Exs.1016, at 3; 1002 ¶ 41.) The Examiner stated that although "Kino does not disclose the viscosity to be greater than about 60 cp and less than about 600cp," it would have been obvious "to determine the optimal viscosity for application." (Exs.1016, at 4; 1002 ¶ 41.) According to the Examiner:

> Both the prior art and the instant claims are drawn to a composition suitable for injection through a needle host comprising microparticles comprising a polymeric binder in combination with a viscosity enhancing agent, a density enhancing agent, a tonicity enhancing agent, a wetting agent and an active agent. Therefore, absent unexpected results regarding the criticality of the viscosity, Kino discloses all the limitations of the instant claims.

(Exs.1016, at 4; 1002 ¶ 41.)

Applicants filed a response and a terminal disclaimer on May 14, 2003. (Ex.1017, at 3; 1002 ¶ 42.) The response included a declaration from Dr. Mark A. Tracy ("Tracy Declaration"). (Exs.1018; 1002 ¶ 42.) The Tracy Declaration is dated May 17, 2002, and was used in the application for the '164 Patent to overcome a similar rejection based on the Kino reference.

In the response the Tracy Declaration and allowing arguments submitted with the response alleged that Kino does not teach a viscosity greater than 20 and less than 600 cps. (Ex.1002 ¶ 43.) In fact, Applicants did not test the formulation of Kino (Ex.1010), nor did they provide testing that compared their formulation with that of the closest prior art in the Tracy Declaration. (Exs.1018; 1002 ¶ 44.)Instead, Applicants merely used the Tracy Declaration to show that the Applicants' injection vehicle described a composition that included 1.5% carboxymethyl

cellulose ("CMC") and had a viscosity of 27cps while an injection vehicle with 0.75% CMC had a viscosity of 7cps. (Exs.1018 ¶, at 5; 1002 ¶ 44.) The Tracy Declaration also did not address that Test Example 2 of Kino was "isotonized with mannitol" (Exs.1010, at 6:28-33; 1002 ¶44), which would be known to increase the viscosity of the formulation (Ex.1002 ¶ 44). Nor did the Tracy Declaration address the Examiner's request for evidence of any unexpected results. (*Id*.)

A notice of allowance was mailed on July 24, 2003. (Ex.1018.) The Notice of Allowability did not include any reasons for allowance.

VI. PERSON OF SKILL IN THE ART ("POSA")

Factors relevant to determining the level of skill in the art include: the educational level of the inventors, the types of problems encountered in the art, prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1376 (Fed. Cir. 2012).

In certain situations, the POSA "may be a composite of different types of individuals." *Warner Chilcott Co. v. Lupin Ltd*, Civ. Action Nos. 11-5048, 12-2928, 2014 U.S. Dist. LEXIS 6228, at *28 (D.N.J. Jan. 17, 2014).

As explained in the Declaration of Patrick DeLuca, Ph.D., the claimed invention relates to generally well-known and well-understood injectable

suspensions. Adjusting excipients to provide a suitable viscosity for injectability purposes is well within the general knowledge of a skilled artisan. Finally, Petitioner notes that the inventors each have a Ph.D degree in chemical engineering, biomedical engineering, pathology, and chemistry, but no specific degrees in formulation specifically. (Exh.1002 ¶¶ 8-13.) Thus a POSA at the time of the invention had at least a bachelor's degree and/or a number of years of industry training or experience in one or more the following fields: pharmaceutical formulation, chemistry, pharmaceutical science, polymer chemistry, pharmaceutics, pharmaceutical technology, pharmacokinetics, and/or pharmacology. (Ex.1002 ¶¶ 8-13.)

VII. CLAIM CONSTRUCTION

In IPR, a claim term is given its "broadest reasonable construction in light of the specification." 37 C.F.R. § 42.100(b). Here, that standard should be applied as well. But even if that were not the case, the standard applied should not alter the outcome of these proceedings because the challenged claims are unpatentable regardless of whether it is construed pursuant to broadest reasonable interpretation, *Phillips*, or another standard consistent with governing precedent.

A. "Suitable For Injection"

Claim 1 recites a composition that is "suitable for injection" through a needle into a host. Although the term is not explicitly defined by the specification, a POSA would appreciate that a composition is suitable for injection if it is sterile, stable, syringeable, injectable, and isotonic. (Exs.1001, at 1:19-22, 2:66-3:1; 1002 ¶ 47.)

B. "Microparticles"

Claim 1 recites a composition that includes "microparticles." The specification defines "microparticles" and "microspheres" to mean particles that include "an active agent or other substance dispersed or dissolved within a polymer." (Exs.1001, at 5:15-18; 1002 ¶ 48.) A POSA would appreciate that "microparticles" encompasses the terms "microcapsules" and "microspheres." (Ex.1002 ¶48.)

C. "Injection Vehicle"

Claim 1 recites an "injection vehicle." The term is not explicitly defined in the specification but is nonetheless described to a POSA by its constituents that make up the injection vehicle. (Exs.1001, at 16:43-67; 1002 ¶ 49.) The Background of the application states that liquid phases of an injectable suspension can be aqueous or non-aqueous. (Exs.1001, at 1:17-19; 1002 ¶ 49.) Accordingly, the broadest reasonable interpretation of injection vehicle means the aqueous or

non-aqueous fluid medium prior to the addition of microparticles to form a suspension.

D. "Suspension"

Claim 1 recites forming a "suspension" by combining microparticles with an injection vehicle. The term "suspension" is not explicitly defined by the specification but would be understood by a POSA to mean "a mixture in which a solid phase is dispersed throughout a liquid phase." (Exs.1001, at 1:17-19; 1002 ¶ 50.) Accordingly, a POSA would appreciate that a suspension is a mixture of microparticles dispersed throughout an injection vehicle. (Ex. 1002 ¶ 50.)

E. "Fluid Phase Of Said Suspension"

Claim 1 recites a "fluid phase of said suspension." One of skill in the art would appreciate that "fluid phase of [the] suspension" requires, as a prerequisite, the existence of a suspension. (Exs.1001, at 12:36-39; 1002 ¶ 51.) The fluid phase of the suspension therefore is not merely the an injection vehicle as the injection vehicle must be combined with the suspended microparticles to form a suspension. (Exs.1001, at 5:5_13, 11:56-64; 12:35-41, 13:40-60; 1002 ¶ 51.) Accordingly, the broadest reasonable interpretation of the "fluid phase of said suspension" is the reconstituted product in a two-phase product formulation. (*Id*.)

F. "Viscosity Greater Than About 20 cp And Less Than About 600 cp"

Viscosity is not expressly defined. However the '061 Patent explains that viscosity is typically determined by a Brookfield viscometer, which measures a fluid's resistance to flow, and is the instrument specified in the '061 Patent. (Exs.1001, at 10:11-12; 1002 ¶ 52.) Viscosity is inversely proportional to temperature — that is, as temperature goes up, viscosity decreases, and vice versa. (Exs.1006, at 1840; 1002 ¶ 52.) Unless otherwise specified, viscosity is typically measured at 20 or 25°C. (Exs.1006, at 275, 1840; 1007, at 547; 1002 ¶ 52.)

The term "about" is also not defined by the specification. A POSA would appreciate the term "greater than about 20" to mean greater than 19.7cp as the background of the '061 Patent clearly teaches with respect to a prior art injectable suspension having a viscosity of approximately 19.7cp when prepared as directed. (Exs.1001, at 2:34-37; 1002 ¶ 53.)

VIII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '061 PATENT IS UNPATENTABLE

As Petitioners explain below in Grounds 1-2, claims 1-13 and 17-23 are invalid as obvious in view of the prior art. Secondary considerations weigh against any finding to the contrary.

A. Ground 1: Claims 1-13 And 17-23 Are Obvious Over Johnson (Ex.1009) In View Of Kino (Ex.1010)

The obviousness inquiry is one of law based on four factual predicates: (1) "the scope and content of the prior art," (2) "[the] differences between the prior art and the claims at issue," (3) "the level of ordinary skill in the pertinent art," and (4) "secondary considerations" such as "commercial success, long felt but unsolved needs, failure of others, etc." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); 35 U.S.C. § 103(a). *KSR* reaffirmed that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. Moreover, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill [in the art] has good reason to pursue the known options within his or her technical grasp." *Id.* at 421.

"Motivation to combine may be found in many different places and forms." *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014) (citations omitted). A challenger is not limited to relying on the same motivation that the patentee had. *See id.* (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012)).

Johnson issued on August 5, 1997, and qualifies as prior art to the '061 Patent under 35 U.S.C. § 102(b). (Ex.1009.) Kino issued on August 12, 1997, and qualifies as prior art to the '061 Patent under 35 U.S.C. § 102(b). (Ex.1010.) Kino was of record and discussed by the Examiner in connection with the claims, but Johnson was not cited and was never discussed by the Examiner.

1. Johnson in View Of Kino Teaches Every Element Of Claims 1-13 And 17-23

a. Claims 1-3

Claim 1 of the '061 Patent is directed to a composition that is suitable for injection through a needle into a host, which includes microparticles with a polymeric binder, and an injection vehicle. (Ex.1001 cl.1.) The microparticles are suspended in the injection vehicle to form a suspension, which includes a fluid phase having a viscosity of greater than about 20cp and less than about 600cp at 20°C and provides injectability of the composition through a needle having a diameter from 18-22 gauge. (*Id*.)

Johnson teaches microspheres suspended in an aqueous injection vehicle. (Exs.1009, at 10:64-66; 1002 ¶ 54, 59.) Indeed, Johnson teaches a solution of 3% w/v carboxymethyl cellulose (low viscosity), polysorbate 20, and sodium chloride used as the injection vehicle; the same components as used in Vehicle C of the '061 Patent. (Exs.1009, at 12:39-42; 1002 ¶ 55, 59.) Johnson teaches that the

concentration of microspheres used was 133mg/ml, which is greater than 30mg/ml as claimed. (Exs.1009, at 12:39-42; 1002 ¶ 54, 59.) Johnson further teaches that the formulation is suitable for injection into a patient via a 20 gauge needle, which is within the claimed range of 18-22 gauge. (Exs.1009, at 12:39-42; 1002 ¶ 54, 59)

Johnson is silent as to the viscosity of the described formulation. But Johnson uses 3% sodium carboxymethyl cellulose and a POSA would know that the viscosity of a sodium carboxymethyl cellulose solution would be tested at 20° C or 25° C. (Exs.1009, at 12:42-45; 1002 ¶ 60, 61.) A POSA would appreciate that sodium carboxymethyl cellulose is a viscosity enhancing agent and would be considered the viscosity-controlling component of an injection vehicle. (Exs.1008, at 78; 1002 ¶ 61.) In response to an office action over Kino, Applicants included the Tracy Declaration and offered the conclusion that Kino taught a viscosity less than 7 cp based solely on the amount of CMC present in the Kino examples. Thus, according to the Tracy Declaration, a solution that includes 1.5% CMC provides viscosity of 27cps. Considering carboxymethyl cellulose is a viscosity-controlling component, a POSA would appreciate that the injection vehicle disclosed in Johnson would have substantially the same viscosity of the preferred embodiment of the ’061 Patent and as a result fall within the scope of claim 1. (Ex. 1002 ¶ 60, 61) Based on the Patent Owner’s admission during prosecution of the ‘061 Patent,

the Tracy Declaration, and what would be known to a POSA, a POSA would reasonably expect the injection vehicle of Johnson — having 3% CMC — to have a viscosity greater than 27cp at 20°C and certainly within the claimed range of 20-600cp at 20°C. Johnson therefore teaches every limitation of claims 1-3. (Ex. 1002 ¶ 60, 61)

b. Claims 4, 5, 10, And 11

Claim 4 of the '061 Patent depends from claim 1 and recites generically "wherein said injection vehicle comprises a density enhancing agent." (Ex.1001 cl.4.) Claim 5 depends from claim 4 and specifies that the density enhancing agent "comprises sorbitol." (*Id.* cl.5.) The '061 Patent defines a density enhancing agent as something "that increases the density of the injection vehicle," and teaches that a "preferred density enhancing agent is sorbitol, although other suitable density enhancing agents may also be used." (*Id.* 16:47-50.)

Claim 10 of the '061 Patent depends from claim 4 and recites generically "wherein said injection vehicle further comprises a wetting agent." (Ex.1001 cl.10.) Claim 11 depends from claim 10 and specifies that the wetting agent is "selected from the group consisting of polysorbate 20, polysorbate, 40, and polysorbate 80." (*Id.* cl.11.) The '061 Patent teaches that "[p]referred wetting

agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80)." (*Id.* 16:57-61.)

Kino teaches incorporating polysorbate 80, which is a known wetting agent, into an aqueous suspension. (Exs.1010, at 4:38-40; 1002 ¶ 56, 62.) Kino teaches that fillers, such as sorbitol, are useful for enhancing the stability of a microparticle suspension. (Exs.1010, at 4:52-56; 1002 ¶ 56, 62.) A POSA, reading Kino, would appreciate that sorbitol would increase the density of an injectable suspension. (Ex.1002 ¶ 62.) Increasing the density of an injectable suspension may be desirable to stabilize the formulation. (*Id*.)

c. Claims 6-9 And 12-13

Claim 6 of the '061 Patent depends from claim 1 and recites generically "wherein said injection vehicle comprises a tonicity adjusting agent." (Ex.1001 cl.6.) Claim 7 depends from claim 6 and specifies that the tonicity adjusting agent "comprises sodium chloride." (*Id.* cl.7.) The '061 Patent teaches that "[a] preferred tonicity adjusting agent is sodium chloride." (*Id.* 16:53-55.)

Claims 8 and 12 of the '061 Patent depend from claims 2 and 6, respectively, and recite generically "wherein said injection vehicle further comprises a wetting agent." (Ex.1001 cls.8, 12.) Claims 9 and 13, in turn, depend from claims 8 and 12 and specify that the wetting agent is "selected from the group

consisting of polysorbate 20, polysorbate, 40, and polysorbate 80." (*Id.* cls.9, 13.) The '061 Patent teaches that "[p]referred wetting agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80)." (*Id.* 16:57-61.)

Johnson teaches a formulation that includes a sodium chloride solution. (Exs.1009, at 12:42-45; 1002 ¶ 63.) Johnson also teaches that such formulation may also include polysorbate 20. (Exs.1009, at 12:42-45; 1002 ¶ 63.) And Johnson specifically teaches an injection vehicle that includes carboxymethyl cellulose, polysorbate 20, and sodium chloride. (Exs.1009, at 12:42-45; 1002 ¶ 63.) A POSA would appreciate that carboxymethyl cellulose is a viscosity enhancing agent, sodium chloride is a tonicity adjusting agent, and polysorbate is a wetting agent. (Ex.1002 ¶ 63.) Thus, Johnson teaches carboxymethyl cellulose (sodium), a viscosity enhancing agent, sodium chloride, a tonicity agent, and polysorbate 20, a wetting agent, alone or in combination, and therefore teaches every element of claims 6-9 and 12-13. (*Id*.)

d. Claims 17-21

Claim 17 depends from claim 1 and requires that the microparticles "further comprise an active agent encapsulated within said polymeric binder." (Ex.1001 cl.17.) Claim 18 depends from claim 17 and sets out a *Markush* group of polymeric

binder materials, including a copolymer of poly(glycolic acid) and poly-d,l-lactic acid. (*Id.* cl.18.) Claim 19 also depends from claim 17 and specifies that the "polymeric binder is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50." (*Id.* cl.19.)

Claims 20 and 21 depend from claims 17 and 19, respectively, and specify that the "active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof. (Ex.1001 cls.20-21.)

Johnson teaches entrapping active substances to create sustained release microparticles. (Exs.1009, at 1:45-49; 1002 ¶ 64.) Johnson teaches poly(lactide-co-glycolide) as a polymeric binder. (Exs.1009, at 3:55-60; 1002 ¶ 64.)

Kino teaches sustained release microspheres, which include an active and a polymer. (Exs.1010 Abstract; 1002 ¶64.) Kino teaches that poly(lactic-co-glycolic)acid, with a ratio of lactic acid to glycolic acid in the range of 100:0 to 50:50, is a preferred polymer. (Exs.1010, at 3:10-18; 1002 ¶ 64.)

Kino teaches that daily dose maintenance therapy to treat mental disease is undesirable due to patient compliance and that improvements in sustained release antipsychotics are necessary. (Exs.1010, at 1:12-2:13; 1002 ¶ 65.) Kino teaches

improvements to compliance of maintenance therapy with antipsychotic drugs can be obtained with injections of sustained release preparations. (Exs.1010, at 1:65-2:3; 1002 ¶ 65.) Kino discloses risperidone as an active agent used as an antipsychotic drug in such invention. (Exs.1010, at 2:41; 1002 ¶ 65.)

A POSA would be motivated to improve the injectability of the suspension of an antipsychotic microparticles, such as risperidone, to assist in patient compliance of maintenance therapy. (Ex.1002 ¶ 66.) A POSA would look to combine sustained release microparticles, which include sustained release microparticles, to improve the injectability of the suspension. (*Id*.) Accordingly, a POSA would expect to combine the risperidone microspheres of Kino and the injection vehicle of Johnson with a reasonable expectation of success. (*Id*.)

e. Claims 22-23

Claim 22 of the ’061 Patent depends from claim 1 and specifies that the “mass median diameter of said microparticles is less than about 250 μm.” (Ex.1001 cl.22.) Claim 23 depends from claim 1 and specifies that the “mass median diameter of said microparticles is in the range of from about 20 μm to about 150 μm.” (Ex.1001 cl.23.)

In determining whether a claimed range is anticipated, “the disclosure in the prior art of any value within claimed range is an anticipation of the claimed range.”

In re Wertheim, 541 F.2d 257, 267 (C.C.P.A. 1976); *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) ("when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim.")

Johnson teaches sustained release microparticles that include a polymer, such as poly(lactide-co-glycolide). (Exs.1009, at 1:45-49, 3:55-60; 1002 ¶ 67.) Johnson teaches that such microparticles have a diameter between 1 to about 180 microns. (Exs.1009, at 4:60-62; 1002 ¶ 67.) Johnson does not describe how the microparticles are measured, but a POSA would reasonably expect that the mass median diameter of the Johnson microparticles would fall within the range recited by claims 22 and 23. Kino teaches microparticles having a diameter of 0.5 to about 400 μm, or preferably 0.5-200 μm and most preferably 15-50 μm. (Exs.1010, at 4:34-37; 1002 ¶68.) Kino explains that their microspheres are screened to remove any oversized particles. (Exs.1010, at 4:29-30; 1002 ¶68.) A POSA would reasonably expect that the mass median diameter of the Kino microparticles would fall within the range recited by claims 22 and 23.

For the purposes of injectability, the claimed particle size range of the '061 Patent falls within or at least overlaps the ranges taught by Johnson and Kino. Accordingly, a POSA would reasonably expect that the mass median diameters of

the microparticles recited in claims 22 and 23 fall within the range described by Johnson and Kino and therefore claims 22-23 are obvious.

2. Claims 1-13 And 17-23 Are Obvious

As detailed above and in the supporting declaration of Dr. DeLuca, as well as outlined in Claim Chart 1 below, Johnson in view of Kino teaches all the elements of claims 1-13 and 17-23, thus anticipating or rendering obvious those claims.

CLAIM CHART 1

U.S. Patent No. 6,667,061	**Johnson (Ex.1009) in view of Kino (Ex.1010)**
1.A composition suitable for injection through a needle into a host, comprising:	Ex.1009, at 10:28-29 ("Each rat was injected with an entire vial of microspheres using 18 to 21 gauge needles.")*id.* 12:40-42 ("administered to each monkey in 1.2 ml of injection vehicle through a 20 gauge needle.") Ex.1002 ¶¶ 27, 54, 59
microparticles comprising a polymeric binder; and	Ex.1009 Abstract ("The sustained release composition of this invention comprises a polymeric matrix of a biocompatible polymer and particles of biologically active, stabilized hGH, wherein said particles are dispersed within the biocompatible polymer.") Ex.1002 ¶¶ 27, 54, 59
an injection vehicle,	Ex.1009, at 10:64-66 ("Rats were injected subcutaneously with approximately 7.5 mg hGH in 50 mg of microspheres, suspended

	in 0.75 ml of an aqueous injection vehicle.") Ex.1002 ¶¶ 27, 54, 59
wherein said microparticles are suspended in said injection vehicle at a concentration of greater than about 30 mg/ml to form a suspension,	Ex.1009, at 12:39-42 ("A dose of 160 mg of hGH sustained release microspheres (24 mg of hGH) was administered to each monkey in 1.2 ml of injection vehicle through a 20 gauge needle.") Ex.1002 ¶¶ 27, 54, 59
wherein a fluid phase of said suspension has a viscosity greater than about 20 cp and less than about 600 cp at 20° C,	Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶¶ 27, 54, 59, 61 (Patent Owner admits that a 1.5% CMC solution has a viscosity greater than 27cp, so the viscosity of the suspension of Ex.1009 would be greater than 27cp at 20°C.)
wherein the viscosity of said fluid phase of said suspension provides injectability of the composition through a needle ranging in diameter from 18-22 gauge.	Ex.1009, at 12:39-42 ("A dose of 160 mg of hGH sustained release microspheres (24 mg of hGH) was administered to each monkey in 1.2 ml of injection vehicle through a 20 gauge needle.") Ex.1002 ¶¶ 27, 54, 59
2.The composition of claim 1, wherein said injection vehicle comprises a viscosity enhancing agent.	See claim 1 above Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶¶ 27, 54, 59
3.The composition of claim 2,	See claim 2 above

wherein said viscosity enhancing agent comprises sodium carboxymethyl cellulose.	
4.The composition of claim 1, wherein said injection vehicle comprises a density enhancing agent.	See claim 1 above Ex.1010, at 4:55 ("a filler . . . ") Ex.1002 ¶ 62 (A POSA would appreciate that a filler would increase the density of the injection vehicle.)
5.The composition of claim 4, wherein said density enhancing agent is sorbitol.	See claim 4 above Ex.1010, at 4:55 ("sorbitol . . . ") Ex.1002 ¶ 62 (A POSA would appreciate that sorbitol would cause an increase in density of the injection vehicle.)
6.The composition of claim 1, wherein said injection vehicle comprises a tonicity adjusting agent.	See claim 1 above Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶ 63
7.The composition of claim 6, wherein said tonicity adjusting agent comprises sodium chloride.	See claim 6 above
8.The composition of claim 2, wherein said injection vehicle further comprises a wetting agent.	See claim 2 above Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶ 63
9.The composition of claim 8, wherein said wetting agent is selected	See claim 8 above Ex.1009, at 12:42-45 ("The injection

from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶ 63
10.The composition of claim 4, wherein said injection vehicle further comprises a wetting agent.	See claim 4 above Ex.1010, at 4:40-41 ("polysorbate 80 . . . "); *id*. 4:54-55 ("further mixing the above composition with a filler...sorbitol") Ex.1002 ¶ 62 (A POSA would appreciate that polysorbate 80 acts as a wetting agent in an aqueous suspension and a filler, such as sorbitol, would increase the density of the injection vehicle.)
11.The composition of claim 10, wherein said wetting agent is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	See claim 10 above Ex.1010, at 4:40-41 ("and a polysorbate 80 . . . ") Ex.1002 ¶ 62
12.The composition of claim 6, wherein said injection vehicle further comprises a wetting agent.	See claim 6 above Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶ 63
13.The composition of claim 12, wherein said wetting agent is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	See claim 12 above Ex.1009, at 12:42-45 ("The injection vehicle was an aqueous vehicle containing 3% w/v Carboxymethyl Cellulose (sodium salt), 1% v/v Tween 20 (Polysorbate 20) and 0.9% sodium chloride.") Ex.1002 ¶ 63

17.The composition of claim 1, wherein said microparticles further comprise an active agent encapsulated within said polymeric binder.	See claim 1 above Ex.1009 Abstract ("The sustained release composition of this invention comprises a polymeric matrix of a biocompatible polymer and particles of biologically active, stabilized hGH, wherein said particles are dispersed within the biocompatible polymer.") Ex.1010 Abstract ("sustained release microsphere…including a hydrophobic antipsychotic drug…into a based composed of a high molecular weight polymer") Ex.1002 ¶ 64
18.The composition of claim 17, wherein said polymeric binder is selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, polyphosphazines, albumin, casein, and waxes.	See claim 17 above Ex.1009, at 3:59 ("poly(lactide-co-glycolide . . . ") Ex.1010, at 3:14 ("poly(lactic-co-glycolic) acid") Ex.1002 ¶ 64
19.The composition of claim 17, wherein said polymeric binder is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50.	See claim 17 above Ex.1009, at 3:60 ("lactide:glycolide ratio of about 1:1") Ex.1010, at 3:16-18 ("ratio of lactic acid and glycolic acid may be in the range of from about 100:0 to 50:50")

	Ex.1002 ¶ 64
20.The composition of claim 17, wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.	See claim 17 above Ex.1010, at 2:41 ("risperidone") Ex.1002 ¶ 63
21.The composition of claim 19, wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.	See claim 19 above Ex.1010, at 2:41 ("risperidone") Ex.1002 ¶ 65
22.The composition of claim 1, wherein the mass median diameter of said microparticles is less than about 250 μm.	See claim 1 above Ex.1009, at 4:60-62 ("A preferred size range for microparticles is from about 1 to about 180 microns in diameter.") Ex.1010, at 4:29-37 ("microspheres are gently ground and screened to remove oversized microspheres…0.5 to about 400μm…most preferably 15 to 50 μm.") Ex.1002 ¶ 67, 68 (A POSA would reasonably expect that microparticles disclosed in Ex.1009 and Ex.1010 to fall within the range recited in claim 22.)
23.The composition of claim 1, wherein the mass median diameter of said microparticles is in the range of from about 20 μm to about 150 μm.	See claim 1 above Ex.1009, at 4:60-62 ("A preferred size range for microparticles is from about 1 to about 180 microns in diameter.") Ex.1010, at 4:29-37 ("microspheres are gently ground and screened to remove oversized microspheres…0.5 to about 400μm…most preferably 15 to 50 μm.") Ex.1002 ¶ 67, 68 (A POSA would

	reasonably expect that microparticles disclosed in Ex.1009 and Ex.1010 to fall within the range recited in claim 23.)

B. Ground 2: Claims 1-13 And 17-23 Are Obvious Over Gustafsson (Ex.1011) In View Of Ramstack (Ex.1005), and the Handbook (Ex.1008)

Gustafsson published on April 24, 1997, and qualifies as prior art to the '061 Patent under 35 U.S.C. § 102(b). (Ex.1011.) Ramstack published on May 26, 1995, and qualifies as prior art to the '061 Patent under 35 U.S.C. § 102(b). (Ex.1005.) The Handbook published in 1994, and qualifies as prior art to the '061 Patent under 35 U.S.C. § 102(b). (Ex.1008.) Gustafsson, Ramstack, and the Handbook were not of record and were never discussed by the Examiner in connection with the claims.

The level of ordinary skill in the art recited in Part VI above and the legal standards for obviousness, as recited in connection with Ground 2, are equally applicable here and are therefore not repeated.

1. Gustafsson In View Of Ramstack, And The Handbook Teaches Every Element Of Claims 1-13 And 17-23

a. Claim 1

Claim 1 of the '061 Patent is directed to a composition that is suitable for injection through a needle into a host, which includes microparticles with a

polymeric binder, and an injection vehicle. The microparticles are suspended in the injection vehicle to form a suspension, which includes a fluid phase having a viscosity of greater than about 20cp and less than about 600cp at 20°C and provides injectability of the composition through a needle having a diameter from 18-22 gauge.

Gustafsson teaches a sustained release formulation that includes microparticles. (Exs.1011 Abstract; 1002 ¶ 57, 69.) Gustafsson teaches that such formulation may be used with any active. (Exs.1011, at 6:33-35; 1002 ¶ 57, 69.) Gustafsson teaches a vehicle that includes a sodium chloride solution containing carboxymethyl cellulose and microparticles in a concentration of greater than 30mg/ml, wherein the resulting suspension is suitable for suspension in a solution suitable for injection into a patient via a 21 gauge needle. (Exs.1011, at 18:19-24; 1002 ¶ 57, 69.)

Although Gustafsson does not specify viscosity, Gustafsson teaches 3% sodium carboxymethyl cellulose and a POSA would appreciate that the viscosity of a CMC solution would be taken at 20 or 25°C. (Exs.1011, at 18:21-24:l; 1002 ¶ 70.) According to the Tracy Declaration and as confirmed by Dr. DeLuca, a POSA would appreciate that sodium carboxymethyl cellulose is the viscosity-controlling component of an injection vehicle. (Ex.1002 ¶ 70.) According

the Tracy Declaration, a solution that includes 1.5% CMC provides viscosity of 27cps. (Ex.1002 ¶ 70.) Based on the Patent Owner's admission during prosecution of the '061 Patent, the Tracy Declaration, and what would have be understood to a POSA, a POSA would reasonably expect the injection vehicle of Gustafsson — having 3% CMC — to have a viscosity greater than 27cp at 20°C and certainly within the claimed range of 20-600cp at 20°C. (*Id*.).

b. Claims 2-3

Claim 2 of the '061 Patent depends from claim 1 and recites generically "wherein said injection vehicle comprises a viscosity enhancing agent." (Ex.1001 cl.2.) Claim 3 depends from claim 2 and specifies that the viscosity enhancing agent "comprises sodium carboxymethyl cellulose." (*Id.* cl.3.) The '061 Patent teaches that "suitable viscosity enhancing agents include sodium carboxymethyl cellulose." (*Id.* 13:15-16.)

Gustafsson teaches that such formulation may include sodium carboxymethyl cellulose. (Exs.1011, at 18:19-23; 1002 ¶ 71.) Thus, Gustafsson teaches a viscosity enhancing agent comprising sodium carboxymethyl cellulose and therefore teaches every element of claims 2 and 3.

c. Claims 4, 5, 10, And 11

Claim 4 of the ’061 Patent depends from claim 1 and recites generically “wherein said injection vehicle comprises a density enhancing agent.” (Ex.1001 cl.4.) Claim 5 depends from claim 4 and specifies that the density enhancing agent “comprises sorbitol.” (*Id.* cl.5.) The ’061 Patent defines a density enhancing agent as an agent “that increases the density of the injection vehicle,” and teaches that a “preferred density enhancing agent is sorbitol, although other suitable density enhancing agents may also be used.” (*Id.* 16:47-50.)

Claim 10 of the ’061 Patent depends from claim 4 and recites generically “wherein said injection vehicle further comprises a wetting agent.” (Ex.1001 cl.10.) Claim 11 depends from claim 10 and specifies that the wetting agent is “selected from the group consisting of polysorbate 20, polysorbate, 40, and polysorbate 80.” (*Id.* cl.11.) The ’061 Patent teaches that “[p]referred wetting agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80).” (*Id.* 16:57-61.)

Ramstack teaches an aqueous vehicle that includes CMC, mannitol, and Tween 80. (Exs.1005, at 37:6; 1002 ¶58, 72.) A POSA would appreciate that ingredients, such as mannitol or sorbitol, would increase the density of the injectable suspension. (Ex.1002 ¶ 72-74.)

The Handbook teaches that wetting agents (Exs.1008, at 375; 1002 ¶¶ 32, 72-74), mannitol and sorbitol (Exs.1008, at 294, 477; 1002 ¶¶ 32, 72-74) are commonly used in intramuscular injections. A POSA would appreciate that mannitol and sorbitol are isomers, have the same molecular weight, and empirical formula. (Exs.1008, at 294, 477; 1002 ¶¶ 32, 72-74.) The Handbook teaches that sorbitol increases the density of aqueous solutions.

Table I: Physical properties of sorbitol in water solutions.

Concentration (% w/w) at 25°C	Density (g/cm^3) at 25°C	Viscosity (mPa s) at 25°C	Refractive index	Freezing point (°C)
10	1.034	1.2	1.348	-1.1
20	1.073	1.7	1.365	-3.8
30	1.114	2.5	1.383	-8.0
40	1.155	4.4	1.400	-13.0
50	1.197	9.1	1.418	-26.0
60	1.240	26.0	1.437	—
70*	1.293	110.0	1.458	—
80	1.330	900.0	1.478	—

* Sorbitol solution PhEur 1985.

(Exs.1008, at 479; 1002 ¶¶ 72-74.)

Considering mannitol and sorbitol are structurally similar and have the same molecular weight, a POSA would reasonably conclude that mannitol and sorbitol are interchangeable in terms of enhancing the density of an aqueous solution. (Ex.1002 ¶¶72-74.) Further, Tween 80 is a well-known wetting agent and pharmaceutical excipient. (*Id*.) Thus, in view of Ramstack, claims 4, 5, 10, and 11 would have been obvious to one of ordinary skill in the art.

d. Claims 6 and7

Claim 6 of the ’061 Patent depends from claim 1 and recites generically “wherein said injection vehicle comprises a tonicity adjusting agent.” (Ex.1001 cl.6.) Claim 7 depends from claim 6 and specifies that the tonicity adjusting agent “comprises sodium chloride.” (*Id.* cl.7.) The ’061 Patent teaches that “[a] preferred tonicity adjusting agent is sodium chloride.” (*Id.* 16:53-55.)

Gustafsson teaches that their injection vehicle may include a physiological sodium chloride solution. (Exs.1011, at 18:19-23; 1002 ¶ 75.) A POSA would appreciate that a physiological sodium chloride solution is a tonicity adjusting agent. Thus Gustafsson teaches a tonicity adjusting agent comprising sodium chloride and therefore teaches every element of claims 6-7. (Ex.1002 ¶ 75.)

e. Claims 8 and 9

Claims8 of the ’061 Patent depend from claim 2, respectively, and recites generically “wherein said injection vehicle further comprises a wetting agent.” (Ex.1001 cl.8.) Claim 9, in turn, depends from claim 8 and specifies that the wetting agent is “selected from the group consisting of polysorbate 20, polysorbate, 40, and polysorbate 80.” (*Id.* cls.9, 13.) The ’061 Patent teaches that “[p]referred wetting agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80).” (*Id.* 16:57-61.)

Gustafsson and Ramstack both teach an injection vehicle that includes CMC. (Ex.1005, at 37:6.) A POSA would appreciate that CMC is a viscosity enhancing agent and Tween 80 is a wetting agent. (Ex.1002 ¶ 76.) A POSA would be motivated to add a wetting agent, such as Tween 80, to an injection vehicle to assist in suspendability. (*Id*.) Accordingly, Gustafsson, in in view of Ramstack, teaches an injection vehicle that includes both a viscosity enhancing agent and a wetting agent.

f. Claims 12 and 13

Claim 12 of the '061 Patent depend from claim 6 and recite generically "wherein said injection vehicle further comprises a wetting agent." (Ex.1001 cl.12.) Claim 13, in turn, depends from claim 12 and specifies that the wetting agent is "selected from the group consisting of polysorbate 20, polysorbate, 40, and polysorbate 80." (*Id.* cl.13.) The '061 Patent teaches that "[p]referred wetting agents include polysorbate 20 (Tween 20), polysorbate 40 (Tween 40), and polysorbate 80 (Tween 80)." (*Id.* 16:57-61.)

As set forth above, Gustafsson teaches each of the elements in claims 1 and 6. And Ramstack teaches an injection vehicle that includes the addition of 0.1% Tween 80. (Exs.1005, at 37:6; 1002 ¶77.) A POSA would appreciate that Tween 80 is a wetting agent. (Ex.1002 ¶ 77.) A POSA would be motivated to add a

wetting agent, such as Tween 80, to an injection vehicle to assist in suspendability. (*Id*.) Accordingly, Gustafsson, in view of Ramstack, teaches an injection vehicle that includes both a tonicity adjusting agent and a wetting agent.

g. Claims 17-21

Claim 17 depends from claim 1 and requires that the microparticles "further comprise an active agent encapsulated within said polymeric binder." (Ex.1001 cl.17.) Claim 18 depends from claim 17 and sets out a *Markush* group of polymeric binder materials, including a copolymer of poly(glycolic acid) and poly-d,l-lactic acid. (*Id.* cl.18.) Claim 19 also depends from claim 17 and specifies that the "polymeric binder is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50." (*Id.* cl.19.)

Claims 20 and 21 depend from claims 17 and 19, respectively, and specify that the "active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof. (Ex.1001 cls.20-21.)

Gustafsson teaches entrapping active substances to create sustained release microparticles. (Exs.1011, at 7:11-20; 1002 ¶ 78.) Gustafsson teaches "poly(D,L lactide) . . . poly(lactide-co-glycolide 75/25)" is a useful polymeric binder. (Exs.1011, at 17:21-22; 1002 ¶ 78.) A POSA would appreciate that

poly(lactide-co-glycolide 75/25) has a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50. (Ex.1002 ¶ 78.) Thus, Gustafsson teaches all of the elements of claims 17-19.

Gustafsson teaches that the active may be any substance desirable for sustained or controlled release as a microparticle. (Exs.1011, at 6:33-35; 1002 ¶ 79.)

Ramstack teaches the preparation of biodegradable microparticles that include a biologically active agent and specifically identifies risperidone. (Exs.1005 Abstract, 35:1-36:26; 1002 ¶ 80.) Ramstack teaches that a polymer, such as 75:25 dl (polylactide-co-glycolide), may be used for encapsulating risperidone. (Exs.1005, at 5:19-22, 35:1-36:26, Examples 2, 3; 1002 ¶ 80.) The poly(lactide-co-glycolide) may have a molar ratio of lactide to glycolide in a range of 85:15 to 50:50. (Exs.1005, at 16:28-31; 1002 ¶ 80.) Additional polymer materials useful for encapsulation may include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonene, poly(ortho carbonates), poly(acetals), poly(lactic acidcaprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, polyphosphazines, and natural polymers including albumin, casein, and waxes. (Exs.1005, at 16:7-13; 1002 ¶ 80.) Accordingly, a

POSA would expect to combine the risperidone microspheres of Ramstack and the injection vehicle of Gustafsson with a reasonable expectation of success. (Ex.1002 ¶ 80.)

h. Claims 22-23

Claim 22 of the '061 Patent depends from claim 1 and specifies that the "mass median diameter of said microparticles is less than about 250 μm." (Ex.1001 cl.22.) Claim 23 depends from claim 1 and specifies that the "mass median diameter of said microparticles is in the range of from about 20 μm to about 150 μm." (*Id.* cl.23.)

Gustafsson teaches that the microparticles should be smaller than 200 μm so they can pass through an injection needle. (Exs.1011, at 1:19-23; 1002 ¶ 81.) Gustafsson states that the preferred average diameter for microparticles is 10-200 μm and most preferably, 40-60 μm. (Exs.1011, at 7:30-33; 1002 ¶ 81.).Gustafsson describes a process for preparing microparticles, which includes sieving the microparticles through a 160μm mesh. (Exs.1011, at 15:8-9; 1002 ¶ 81.) Thus Gustafsson teaches microparticles having a mass median diameter at least falling within the scope of claims 22 and 23. (Ex.10002 ¶81.) A POSA would appreciate that the mass median diameter of the Gustafsson microparticles would fall within the range recited by claims 22 and 23. (Ex.1002 ¶81.)

Ramstack teaches microparticles having a diameter of 1-500 microns, or preferably 25-180 microns. (Exs.1005, at 29:21-22; 1002 ¶ 82.) Ramstack describes a process for preparing risperidone microparticles that involves sieving the microparticles through a 25 and 180 micron stainless-steel sieve column. (Exs.1005, at 35:24-25, 36:24-25; 1002 ¶ 82.) A POSA would appreciate that the mass median diameter of the Ramstack microparticles would fall within the range recited by claims 22 and 23. (Ex.1002 ¶ 82.)

For the purposes of injectability, the claimed particle size range of the '061 Patent falls within or at least overlaps the ranges taught by Gustafsson and Ramstack. Accordingly, a POSA would reasonably expect that the mass median diameters of the microparticles recited in claims 22 and 23 fall within the range described by Gustafsson and Ramstack and therefore claims 22-23 are obvious.

2. <u>Claims 1-13 And 17-23 Are Obvious</u>

As detailed above and in the supporting declaration of Dr. DeLuca, as well as outlined in Claim Chart 2 below, Gustafsson in view of Ramstack, and the Handbook, teaches all the elements of claims 1-13 and 17-23, thus anticipating or rendering obvious those claims.

CLAIM CHART 2

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
1.A composition suitable for injection through a needle into a host, comprising:	Ex.1011, at 18:21 ("injected subcutaneously in the neck.") Ex.1002 ¶¶ 28, 57, 69
microparticles comprising a polymeric binder; and	Ex.1011 Abstract, 18:21-24 ("200 µl of a suspension containing 163 mg/ml of microparticles . . . The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid. The injection was made using a 21 G needle.") Ex.1002 ¶¶ 28, 57, 69
an injection vehicle,	Ex.1011, at 18:19-24 ("200 µl of a suspension containing 163 mg/ml of microparticles . . . The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid. The injection was made using a 21 G needle.") Ex.1002 ¶¶ 28, 57, 69
wherein said microparticles are suspended in said injection vehicle at a concentration of greater than about 30 mg/ml to form a suspension,	Ex.1011, at 18:19-24 ("200 µl of a suspension containing 163 mg/ml of microparticles . . . The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid. The injection was made using a 21 G needle.") Ex.1002 ¶¶ 28, 57, 69

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
wherein a fluid phase of said suspension has a viscosity greater than about 20 cp and less than about 600 cp at 20° C.,	Ex.1011, at 18:19-24 ("200 µl of a suspension containing 163 mg/ml of microparticles . . . The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid. The injection was made using a 21 G needle.") Exs.1002 ¶¶ 28, 57, 70 (Patent Owner admits that a 1.5% CMC solution has a viscosity greater than 27 cp, so the viscosity of the suspension of Ex.1011 would be greater than 27cp at 20 or 25°C.)
wherein the viscosity of said fluid phase of said suspension provides injectability of the composition through a needle ranging in diameter from 18-22 gauge.	Ex.1011, at 18:19-24 ("200 µl of a suspension containing 163 mg/ml of microparticles . . . The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid. The injection was made using a 21 G needle.") Ex.1002 ¶¶ 28, 57, 69
2.The composition of claim 1, wherein said injection vehicle comprises a viscosity enhancing agent.	See claim 1 above Ex.1011, at 18:19-23 ("The vehicle for injection was physiological sodium chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid.") Ex.1002 ¶ 71
3.The composition of claim 2, wherein said viscosity enhancing agent	See claim 2 above

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
comprises sodium carboxymethyl cellulose.	
4.The composition of claim 1, wherein said injection vehicle comprises a density enhancing agent.	See claim 1 above Ex.1005, at 37:5-7 ("an aqueous vehicle composed of 0.75% CMC, 5% Mannitol, and 0.1% Tween was added to the vials.") Ex.1008, at 294 ("Mannitol . . . IM injections . . . ") Ex.1002 ¶¶ 29, 58, 72-74-73 (A POSA would appreciate that sorbitol and mannitol are used in intramuscular injections. A POSA would appreciate that mannitol, which is an isomer of sorbitol, can increase the density of an aqueous solution. Thus Gustafsson, in view of Ramstack, and the Handbook, teach a density enhancing agent..)
5.The composition of claim 4, wherein said density enhancing agent is sorbitol.	See claim 4 above Ex.1002 ¶__ (A POSA would appreciate that sorbitol and mannitol are isomers and have the same molecular weight. A POSA would appreciate that sorbitol and mannitol can be used interchangeably. Thus a POSA would appreciate that Gustafsson in view of Ramstack, and the Handbook, teach a density enhancing agent that includes sorbitol.)
6.The composition of claim 1, wherein said injection vehicle comprises a tonicity adjusting agent.	See claim 1 above Ex.1011, at 18:19-23 ("The vehicle for injection was physiological sodium

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
	chloride solution containing 3% of sodium carboxymethylcellulose as suspension aid.") Ex.1002 ¶¶ 75
7.The composition of claim 6, wherein said tonicity adjusting agent comprises sodium chloride.	See claim 6 above
8.The composition of claim 2, wherein said injection vehicle further comprises a wetting agent.	See claim 2 above Ex.1002 ¶ 75
9.The composition of claim 8, wherein said wetting agent is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	See claim 8 above Ex.1002 ¶ 75
10.The composition of claim 4, wherein said injection vehicle further comprises a wetting agent.	See claim 4 above Ex.1008, at 375-6 ("polysorbate . . . wetting agent") Ex.1002 ¶¶ 29, 72-74
11.The composition of claim 10, wherein said wetting agent is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	See claim 10 above Ex.1008, at 375 ("Polysorbate 20 . . . Tween 20") Ex.1002 ¶¶ 29, 72-74
12.The composition of claim 6, wherein said injection vehicle further comprises a wetting agent.	See claim 6 above
13.The composition of claim 12, wherein said wetting agent is selected from the group consisting of polysorbate 20, polysorbate 40, and polysorbate 80.	See claim 12 above Ex.1002 ¶ 75

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
17.The composition of claim 1, wherein said microparticles further comprise an active agent encapsulated within said polymeric binder.	See claim 1 above Ex.1011, at 7:11-20 ("method . . . of preparing . . . sustained release microparticles . . . the biologically active substance being entrapped therein . . . coating the core particles with a film-forming, biodegradable, release-controlling polymer") Ex.1002 ¶¶ 29, 58, 78
18.The composition of claim 17, wherein said polymeric binder is selected from the group consisting of poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, polyphosphazines, albumin, casein, and waxes.	See claim 17 above Ex.1011, at 17:21-22 ("poly(D,L lactide) . . . poly(lactide-co-glycolide 75/25) ") Ex.1002 ¶ 78
19.The composition of claim 17, wherein said polymeric binder is poly(d,l-lactide-co-glycolide) having a molar ratio of lactide to glycolide in the range of from about 85:15 to about 50:50.	See claim 17 above Ex.1011, at 17:21-22 ("poly(D,L lactide) . . . poly(lactide-co-glycolide 75/25) ") Ex.1002 ¶ 78
20.The composition of claim 17, wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and	See claim 17 above Ex.1011, at 6:33-35 ("the invention is useful for all active substances which

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
pharmaceutically acceptable salts thereof.	may be utilized in parenteral administration.") Ex.1005, at 30:20 ("risperidone"); *id*. at 35-36, Examples 2 and 3. Ex.1002 ¶¶ 79-80
21.The composition of claim 19, wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.	See claim 19 above Ex.1011, at 6:33-35 ("the invention is useful for all active substances which may be utilized in parenteral administration.") Ex.1005, at 30:20 ("risperidone"); *id.* at 35-36, Examples 2, 3 Ex.1002 ¶¶79-80
22.The composition of claim 1, wherein the mass median diameter of said microparticles is less than about 250 μm.	See claim 1 above Ex.1011, at 1:19-23 ("particulate drugs intended for injection have to be small enough to pass through the injection needle . . . should be smaller than 200 μm."); *id.* 7:30-33 ("the microparticles preferable have an average diameter in the range of 10-200 μm . . . most preferably . . . 40-60μm . . . "); 15:8-9 ("dry microparticles are sieved through a 160 μm mesh.") Ex.1005, at 29:21-22 ("microparticles 1-500 microns, more preferably, 25-180 microns"); *id*. at 36:23-25 ("the microparticles are isolated and size fractionated by sieving through a

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
	stainless-steel sieve column composed of 25 and 180 micron mesh sizes.") Ex.1002 ¶¶29, 58, 79, 81, 82 (A POSA would reasonably expect that microparticles having a diameter in the range of 10-200 μm, as disclosed in Gustafsson, or the microparticles having a diameter of 25-180 μm, as disclosed in Ramstack, would fall within the range recited in claim 22.)
23.The composition of claim 1, wherein the mass median diameter of said microparticles is in the range of from about 20 μm to about 150 μm.	See claim 1 above Ex.1011, at 1:19-23 ("particulate drugs intended for injection have to be small enough to pass through the injection needle . . . should be smaller than 200 μm."); *id.* 7:30-33 ("the microparticles preferable have an average diameter in the range of 10-200 μm . . . most preferably . . . 40-60μm . . . ") Ex.1005, at 29:21-22 ("microparticles 1-500 microns, more preferably, 25-180 microns"); *id*. at 36:23-25 ("the microparticles are isolated and size fractionated by sieving through a stainless-steel sieve column composed of 25 and 180 micron mesh sizes.") Ex.1002 ¶¶ 29, 58, 81, 82 (A POSA would reasonably expect that microparticles having a preferred diameter in the range of 40-60 μm, as disclosed in Gustafsson, or the

U.S. Patent No. 6,667,061	**Gustafsson (Ex.1011) in view of Ramstack (Ex.1005), and the Handbook (Ex.1008)**
	microparticles having a diameter of 25-180μm, as disclosed in Ramstack, would fall within the range recited in claim 23.)

IX. SECONDARY CONSIDERATIONS

It is the Patent Owner's burden to establish secondary indicia of nonobviousness, if any. Of the several objective indicia of nonobviousness, such as commercial success, copying, long-felt but unmet need, skepticism, and industry acclaim, Patent Owner did not offer any such evidence during prosecution of the '061 Patent. The Patent Owner will also be unsuccessful in proving the existence of unexpected and superior results, or that there is a nexus between any secondary indicia such as commercial success and the claims of the '061 Patent.

"We have held on a number of occasions that evidence of commercial success alone is not sufficient to demonstrate nonobviousness of a claimed invention." *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008). "[T]he proponent must offer proof 'that the sales were a direct result of the unique characteristics of the claimed invention — as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter.'" *Id.* (citations omitted).

To prove nexus, Patent Owner will have to establish that any commercial success it enjoyed was based on patentable features — features of its invention that were not disclosed in the prior art. *See Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997).

The commercial success of any of Patent Owner's products are meaningless unless it can be attributed to the claimed features of the '061 Patent. Patent Owner will not be able to show that the '061 Patent fulfilled a long-felt, but unmet need. And Patent Owner will not be able to show that there was any skepticism in the art that microparticles could be injectable in a suspension in the claimed viscosity range.

X. CONCLUSION

For the foregoing reasons, Petitioners request that *inter partes* review be instituted for claims 1-13 and 17-23 of the '061 Patent and that those claims be held unpatentable over each of the grounds discussed herein.

Dated: May 31, 2016 By: s/ William L. Mentlik /
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CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION

Pursuant to Rule 37 C.F.R. 42.24(d), the undersigned hereby certifies that, based upon the word count of the word-processing system used to prepare this petition, the number of words in this petition is 11,299. Pursuant to 37 C.F.R. § 42.24(a), this word count does not include "a table of contents, a table of authorities, a certificate of service or word count, exhibits, appendix, or claim listing."

Dated: May 31, 2016

By: s/ William L. Mentlik /
William L. Mentlik
Reg. No. 27,108

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1-13 AND 17-23 OF U.S. PATENT NO. 6,667,061**, was served on May 31, 2016, as follows.

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