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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.,
Petitioner,

v.

ALKERMES PHARMA IRELAND LTD. and ALKERMES CONTROLLED THERAPEUTICS, INC.,
Patent Owner.

Case IPR2016-01095
Patent 6,667,061 B2

Before LORA M. GREEN, ROBERT A. POLLOCK, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Luye Pharma Group Ltd., Luye Pharma (USA) Ltd., Shandong Luye Pharmaceutical Co., Ltd., and Nanjing Luye Pharmaceutical Co., Ltd. (collectively "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–13 and 17–23 of U.S. Patent No. 6,667,061 B2 (Ex. 1001, "the '061 patent"). Paper 5 ("Pet."). Alkermes Pharma Ireland Limited and Alkermes Controlled Therapeutics, Inc. (collectively, "Patent Owner") filed a Preliminary Response to the Petition. Paper 11 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314; *see* 37 C.F.R. §§ 42.4, 42.108. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–13 and 17–23. Accordingly, we decline to institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner states that it has filed a second request for *inter partes* review seeking cancellation of claims 1–13 and 17–23 of the '061 patent on other grounds. Pet. 1; Prelim. Resp. 1 n.1. That petition for *inter partes* review, IPR2016-01096, is being decided concurrently with the instant proceeding.

B. The '061 Patent (Ex. 1001)

The '061 patent issued on December 23, 2003, with J. Michael Ramstack, M. Gary I. Riley, Stephen E. Zale, Joyce M. Hotz, and Olufunmi

L. Johnson as the listed co-inventors. Ex. 1001. According to the '061 patent, it is drawn "to injectable suspensions having improved injectability." *Id.* at 1:12–14.

The '061 patent discloses:

> Injectable suspensions are heterogeneous systems that typically consist of a solid phase dispersed in a liquid phase, the liquid phase being aqueous or nonaqueous. To be effective and pharmaceutically acceptable, injectable suspensions should preferably be: sterile; stable; resuspendable; syringeable; injectable; isotonic; and nonirritating. The foregoing characteristics result in manufacturing, storage, and usage requirements that make injectable suspensions one of the most difficult dosage forms to develop.

Id. at 1:17–25.

The '061 patent teaches that viscosity enhancers are added to injection vehicles to prevent settling of particles, but notes that viscosity is kept low to facilitate mixing and make the suspension easier to inject. *Id.* at 2:25–30. According to the '061 patent, it was "unexpectedly discovered that injectability is improved, and in vivo injectability failures significantly and unexpectedly reduced, by increasing the viscosity of the fluid phase of an injectable suspension." *Id.* at 4:57–60. The '061 patent teaches that "is in contrast to conventional teachings that an increase in the viscosity hinders injectability and syringeability." *Id.* at 4:60–62.

The '061 patent specifically teaches that "microparticles" and "microspheres" refer to "particles that contain an active agent or other substance dispersed or dissolved within a polymer that serves as a matrix or binder of the particle," wherein the "polymer is preferably biodegradable and biocompatible." *Id.* at 5:14–19.

The ’061 patent specifically teaches the following injection vehicles: Vehicle A: 0.9% saline and 0.1% Tween 20; Vehicle B: 1.5% CMC, 30% sorbitol, and 0.2% Tween 20; and Vehicle C: 3% CMC, 0.1% Tween 20, and 0.9% saline. *Id.* at 9:38–46. According to the ’061 patent, Vehicle A had a viscosity of 1.0 cp , Vehicle B had a viscosity of 24 cp, and Vehicle C had a viscosity of 56 cp. *Id.* at 10:Table 4. The ’061 patent specifically teaches that CMC is a viscosity enhancing agent. *Id.* at 12:14–20.

C. Challenged Claims

Petitioner challenges claims 1–13 and 17–23 of the ’061 patent. Claim 1, the only independent claim of the ’061 patent, is representative:

> 1. A composition suitable for injection through a needle into a host, comprising:
>
> microparticles comprising a polymeric binder; and
>
> an injection vehicle, wherein said microparticles are suspended in said injection vehicle at a concentration of greater than about 30 mg/ml to form a suspension, *wherein a fluid phase of said suspension has a viscosity greater than about 20 cp and less than about 600 cp at 20º 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. 1001, 18:6–16 (emphasis added).

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–13 and 17–23 of the ’061 patent on the following grounds (Pet. 4):

References	Basis	Claims Challenged
Goldenheim[1]	§ 102	1–3, 6–9, 12, 13, 17–19, 22, and 23
Goldenheim, Ramstack,[2] U.S. Pharmacopeia,[3] and the European Pharmacopoeia[4]	§ 103	1–3, 6–9, 12, 13, and 17–23
Goldenheim, Kino, [5] U.S. Pharmacopeia, and the European Pharmacopoeia	§ 103	1–13 and 17–23

Petitioner relies also on the Declaration of Patrick P. Deluca, Ph.D. (Ex. 1002).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See* 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–45 (2016) (upholding the use of the broadest reasonable interpretation standard).

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[1] Goldenheim et al., WO 99/01114, published January 14, 1999 (Ex. 1004) ("Goldenheim").

[2] Ramstack et al., WO 95/13799, published May 26, 1995 (Ex. 1005) ("Ramstack").

[3] THE UNITED STATES PHARMACOPEIA;USP 23, NF 18, 274–275, 1840, 2333, 2390 (U.S. Pharmacopeial Convention, Inc. 1994) (Ex. 1006) ("the U.S. Pharmacopeia").

[4] EUROPEAN PHARMACOPOEIA, 547–548, 1780 (Council of Europe 3rd ed. 1996) (Ex. 1007) ("the European Pharmacopoeia").

[5] Kino et al., U.S. Patent No. 5,656,299, issued August 12, 1997 (Ex. 1010) ("Kino").

Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the that term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). *See also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner offers explicit constructions of several claim terms (Pet. 18–21), as does Patent Owner (Prelim. Resp. 10–12). On the present record, we determine that none of the claim terms require explicit construction for purposes of this Decision. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs, Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Anticipation by Goldenheim

Petitioner asserts that claims 1–3, 6–9, 12, 13, 17–19, 22, and 23 are anticipated by Goldenheim. Pet. 21–33. Petitioner presents a claim chart demonstrating where the limitations of the challenged claims may be found in Goldenheim. *Id.* at 28–33. Patent Owner contends that Petitioner has not established a reasonable likelihood that claims 1–3, 6–9, 12, 13, 17–19, 22, and 23 are anticipated by Goldenheim. Prelim. Resp. 15–24.

i. Overview of Goldenheim (Ex. 1004)

Goldenheim relates to "sustained release formulations for the administration of locally active agents and/or diagnostic agents in sustained release form intra articularly or in other body spaces." Ex. 1004, 1:6–8. Goldenheim teaches administration of a formulation of a biocompatible sustained release material into an articular joint, wherein the active agent "can include one or more enzymes, anti-infectives, antibodies, and the like, diagnostic agents, as well as local anesthetics, local anesthesia augmenting agents and combinations thereof." *Id.* at 5:30–6:3. Goldenheim notes that the formulation is suitable also for "administration in all body spaces/cavities." *Id.* at 10:1–3. According to Goldenheim, "the formulation is in a form suitable for suspension in isotonic saline, physiological buffer or other solution acceptable for injection into a patient." *Id.* at 8:16–17.

Specifically, Goldenheim teaches:

> As used herein, the term "microparticles" includes microspheres and microcapsules in a size range suitable for injection into a desired site of administration by injection, infiltration, infusion and the like. For administration by injection and/or infiltration or infusion, the formulations according to the invention may be suspended (e.g., for microparticles), or dissolved (e.g., for immediate release forms), in any art known vehicle suitable for injection and/or infiltration or infusion. Such vehicles include, simply by way of example, isotonic saline, buffered or unbuffered and the like and may optionally include any other art known ingredients or agents, e.g., colorants, preservatives, antibiotics, epinephrine and other art known ingredients.

Id. at 16:19–27.

Goldenheim teaches further:

> Microspheres and other injectable substrates described herein may be incorporating an effective amount of the same into

> a pharmaceutically acceptable solution (e.g., water) or suspension for injection. The final reconstituted product viscosity may be in a range suitable for the route of administration. *In certain instances, the final reconstituted product viscosity may be, e.g., about 35 cps*. Administration may be via the subcutaneous or intramuscular route. However, alternative routes are also contemplated, and the formulations may be applied to the localized site in any manner known to those skilled in the art, such that a localized effect is obtained.

Id. at 35:8–16 (emphasis added).

As to administration, Goldenheim teaches:

> A suspension of microspheres prepared in a form suitable for intra articular injection can be injected into a joint using methods well known to the art. For most body spaces, the use of a needle or "skinny needle" is acceptable. The chosen needle is one that is small in bore (large) gauge as possible, and as long as necessary. Commonly, for a joint, epidural, intraperitoneal, intrapleural or bursae, 22-28 gauge, 1-2 inch is used. For the microparticles used in the present invention, one should allow for increased bore size (e.g., to 18 gauge). This also allows for the puncturing needle to be removable, being encased in a plastic infusion catheter. For a few procedures, "skinny needles" are used. Such needles have the same bores but are longer, and hence look "skinny". For locations such as intrapericardial, the gauges for the skinny needle are the same, but the needles can be up to 3 -4 inches long. For epidural, and other locations, there is a metal puncturing needle of the same gauges and up to 3 inches long, often encased in a plastic catheter, through which another catheter, from[ ] 22-28 gauge, and up to 6-12 inches long, can be inserted into the space.

Id. at 41:13–26.

Example 16 of Goldenheim is drawn to in vivo injection of microspheres containing a local anesthetic into elderly male baboons. *Id.* at 51:21–52:4; 53:1–4. As shown in Table 4, the microspheres were

administered at a concentration of 70 mg in 1 ml of vehicle. *Id.* at 54. The vehicle used was 0.5% CMC and 0.1% Tween 80 in water. *Id.* at 52:27–28.

ii. Analysis

Petitioner relies on Goldenheim for teaching "a formulation that includes microparticles suitable for injection," wherein "the active agents are included in or encapsulated by a polymeric binder." Pet. 23 (citing Ex. 1004, Abstract, 26:23–31; Ex. 1002 ¶¶ 54, 58). Petitioner notes that Goldenheim teaches that the formulation may be used with any active agent. *Id.* (citing Ex. 1004, 13:22–27; Ex. 1002 ¶ 54). Petitioner relies also on Goldenheim for its teaching a microparticle concentration of 70 mg/ml, and that such compositions may be administered using a 18 gauge needle. *Id.* at 24 (citing Ex. 1004, 54:Table 4, 41:17–19; Ex. 1002 ¶¶ 54, 60).

In particular, Petitioner contends that "Goldenheim teaches that such final reconstituted product has a viscosity of 35cp." *Id.* at 23 (citing Ex. 1004, 35:8–12; Ex. 1002 ¶¶ 54, 59). Petitioner asserts:

> As explained by Dr. DeLuca, [an ordinary artisan] would understand that viscosity is typically measured at 20 or 25°C. (Ex.1002 ¶¶ 56, 59.) If Goldenheim's reported viscosity was taken at 20°C, then its viscosity is 35cp. If Goldenheim's reported viscosity was taken at 25°C, then the viscosity would only be higher at 20°C given the inverse relationship between viscosity and temperature. (Ex.1002 ¶ 59.) In either event, Goldenheim's viscosity falls within the claimed range of "greater than about 20 cp and less than about 600 cp at 20°C."

Id. at 23.

Thus, Petitioner concludes, Goldenheim teaches all of the limitations of independent claim 1. *Id.* at 24.

Patent Owner responds the portion of Goldenheim relied upon by Petitioner to meet the viscosity limitation of challenged claim 1 "includes

only the general statement that '[i]n certain instances, the ***final reconstituted product viscosity*** may be, e.g., about 35 cp.'" Prelim. Resp. 20 (quoting Ex. 1004, 35:11). Patent Owner contends that "Goldenheim offers no information on what those 'certain instances' might be." *Id.* Patent Owner asserts, therefore, that Petitioner has "failed to offer any evidence that such "certain instances" are ones that meet all the other claim limitations of the '061 patent." *Id.*

Patent Owner contends further that Petitioner has improperly picked and chosen from unrelated disclosures of Goldenheim to arrive at the subject matter of challenged claim 1. *Id.* at 22. Specifically, according to Patent Owner:

> Petitioners combine the concentration of microspheres disclosed in Goldenheim's Example 16 with Goldenheim's alleged viscosity disclosure. However, Petitioners provide no reason [an ordinary artisan] would have picked the concentration from Example 16, which relates to the injection of "EDLA [Extended Duration Local Anesthetic] microparticles into the knee joints of adult baboons" (Exh. 1004 at 53:7-8) and combined it with a different portion of Goldenheim that mentions a final reconstituted product viscosity "may be, e.g., about 35 cp" in "certain" unidentified instances. Further, Goldenheim's Example 16 teaches a concentration of 70 mg/ml and there is nothing in Goldenheim or the cited art that suggests combining such a concentration with a viscosity of 35 cp. Petitioners do not provide any reason for such a combination.

Id.

We agree with Patent Owner that Petitioner has failed to sufficiently establish a reasonable likelihood that claims 1–3, 6–9, 12, 13, 17–19, 22, and 23 are anticipated by Goldenheim.

> [U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited

> in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102. . . . [I]t is not enough that the prior art reference . . . includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.

Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1371 (Fed. Cir. 2008)).

Here, as noted by Patent Owner, Petitioner is using disparate teachings of the Goldenheim reference to attempt to establish that the claims of the challenged patent are anticipated by that reference. The disclosure of Goldenheim of a viscosity of 35 cp in certain instances is a single sentence from that document, and Goldenheim provides no guidance as to what those circumstances may be. Petitioner has not sufficiently established that the ordinary artisan would have read that viscosity limitation into the formulation used by Example 16, which Petitioner relies upon to meet the concentration of microparticles required by challenged claim 1. In that regard, we note that Example 16 does not mention viscosity, and specifically teaches the use of an injection vehicle of 0.5% CMC and 0.1% Tween 80 in water. Ex. 1004, 52:27–28

Therefore, after considering the Petition and Preliminary Response, we determine that Petitioner has failed to sufficiently demonstrate a reasonable likelihood that claims 1–3, 6–9, 12, 13, 17–19, 22, and 23 are anticipated by Goldenheim.

C. Obviousness over Goldenheim

Petitioner asserts that claims 1–3, 6–9, 12, 13, and 17–23 are rendered obvious by the combination of Goldenheim, Ramstack, and the two Pharmacopoeia (Pet. 33–43), and that claims 1–13 and 17–23 are rendered obvious by the combination of Goldenheim, Kino, and the two Pharmacopoeia (Pet. 43–52). Patent Owner responds that Petitioner has

failed to establish that the challenged claims are rendered obvious by the cited prior art. Prelim. Resp. 24–42. As the issues are similar for these two challenges, we address them together.

i. Overview of Ramstack (Ex. 1005)

Ramstack is drawn to the preparation of microparticles that encapsulate an active agent. Ex. 1005, 1:14–17. Ramstack teaches that a wide variety of active agents may be encapsulated in the microparticles (*id.* at 30:1–32:18), including antibodies and enzymes (*id.* at 32:6–7), and specifically teaches that the active agent may be risperidone (*id.* at 8:21–22). According to Ramstack the "most preferred polymer for use in the practice of this invention is poly(dl-lactide-co-glycolide)," wherein "the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 85:15 to about 50:50." *Id.* at 16:28–31.

Ramstack teaches that the microparticles are stored as a dry material, but are suspended in a suitable pharmaceutical liquid vehicle before administration, such as a 2.5 wt. % solution of CMC. *Id.* at 29:27–31. Ramstack provides an example of an aqueous vehicle comprising 0.75% CMC, 5% mannitol, and 0.1% Tween 80, wherein after the microparticles are suspended in that vehicle, they are quickly frozen, and lyophilized. *Id.* at 37:5–9. For injection into dogs, the "dry microparticles were syringe-loaded and resuspended in the syringe with an injection vehicle comprised of 2.5 wt% carboxymethyl cellulose (CMC)." *Id.* at 38:6–8.

iii. Overview of Kino (Ex. 1010)

Kino teaches:

> With the aim of improvement in compliance at the time of maintenance therapy with hydrophobic antipsychotic drugs, the present inventors have conducted intensive studies on the

> development of a sustained release pharmaceutical preparation in which a drug itself is used as an active ingredient without modification. As the result, it was found that a drug can be released at an almost constant rate extending over 1 week or more by including a hydrophobic antipsychotic drug in the form of microcrystals having an average particle size of 10 μm or less, desirably 5 μm or less, into a base comprising a biodegradable high molecular weight polymer having in vivo histocompatibility to make a sustained release microsphere preparation and administrating it by subcutaneous or intramuscular injection.

Ex. 1010, 1:66–2:12.

Kino teaches that the microspheres may be made into a sustained release injection by preparing an aqueous suspension along with a dispersing agent, such as polysorbate 80 or CMC, a preservative, and an isotonic agent, such as sodium chloride or sorbitol. *Id.* at 4:38–44. In addition, according to Kino, the sustained release injection may be made more stable by adding a filler such as sorbitol or mannitol, drying to form a solid preparation, which is then used by adding a dispersion medium, such as water, before injection. *Id.* at 4:52–60.

Kino teaches also that when used as a suspension for injection, the particle size of the microparticles "may be a range which can satisfy their dispersibility and needle-passing property, for example, in the range of from about 0.5 to about 400 μm, more preferably from about 0.5 to about 200 μm, most preferably from about 15 to 50 μm as an average particle size." *Id.* at 4:32–37.

iv. Overview of U.S. Pharmacopeia (Ex. 1006)

The U.S. Pharmacopeia discusses carboxymethyl cellulose sodium, and discusses methods of determining its viscosity. Ex. 1006, 274–275. The U.S. Pharmacopeia discusses also methods of measuring viscosity generally. *Id.* at 1840.

v. Overview of European Pharmacopoeia (Ex. 1007)

The European Pharmacopoeia discusses carboxymethyl cellulose sodium, and discusses methods of determining its viscosity. Ex.1007, 547.

vi. Analysis

Petitioner relies on Goldenheim as it did in its anticipation challenge. Pet. 34–35, 43–44. Petitioner contends "[t]o the extent that Goldenheim's disclosure of the temperature at which viscosity is measured is not considered inherent or within the knowledge of the [ordinary artisan], then the U.S. Pharmacopoeia and the European Pharmacopoeia explicitly disclose that information and render these claims obvious." *Id.* at 35–36; *see also id.* at 45 (noting that the combination of Goldenheim "with the U.S. and European Pharmacopoeias teaches all of the elements of claim 1").

Petitioner has not explained, however, how the additionally cited references remedy the deficiencies discussed above with respect to the anticipation rejection. As the Supreme Court pointed out in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 418. Rather, the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the

known elements *in the fashion claimed* by the patent at issue") (emphasis added).

In the instant proceeding, Petitioner has not provided a reason, however, as to why the ordinary artisan would have taken Goldenheim's one mention of a viscosity of 35 cp and applied it to the formulation in Example 16 relied upon by Petitioner to meet the concentration limitation of independent challenged claim 1. Specifically, as noted by Patent Owner (Prelim. Resp. 20), Goldenheim teaches that "[i]n certain instances, the final reconstituted product viscosity may be, e.g., about 35 cps" (Ex. 1004, 35:11) but does not explain what those instances may be, much less tying that disclosure to the concentration of microparticles used in Example 16, which makes no mention of viscosity.

Thus, after considering the Petition and Preliminary Response, we determine that Petitioner has not sufficiently established a reasonable likelihood that claims 1–13 and 17–23 are rendered obvious by the cited prior art.

III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–13 and 17–23 patent are unpatentable under either 35 U.S.C. § 102 or 35 U.S.C. §103.

IV. ORDER

In consideration of the foregoing, it is

ORDERED that the Petition is DENIED and no trial is instituted.

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