United States Court of Appeals for the Federal Circuit

JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV,
Plaintiffs-Appellees

v.

TEVA PHARMACEUTICALS USA, INC., MYLAN LABORATORIES LTD.,
Defendants-Appellants

2022-1258, 2022-1307

Appeals from the United States District Court for the District of New Jersey in Nos. 2:18-cv-00734-CCC-LDW, 2:19-cv-16484-CCC-LDW, Judge Claire C. Cecchi.

Decided: April 1, 2024

BARBARA MULLIN, Patterson Belknap Webb & Tyler LLP, New York, NY, argued for plaintiffs-appellees. Also represented by ANDREW D. COHEN, ARON RUSSELL FISCHER, MEGHAN LARYWON.

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DEEPRO MUKERJEE, Katten Muchin Rosenman LLP, for defendant-appellant Mylan Laboratories Ltd. Also represented by LANCE SODERSTROM; JITENDRA MALIK, Charlotte, NC; JILLIAN SCHURR, Chicago, IL; ERIC THOMAS WERLINGER, Washington, DC.

Before DYK, PROST, and HUGHES, *Circuit Judges*.

PROST, *Circuit Judge*.

Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica NV (collectively, "Janssen") sued Teva Pharmaceuticals USA, Inc. ("Teva") for patent infringement in the United States District Court for the District of New Jersey. Janssen asserted U.S. Patent No. 9,439,906 ("the '906 patent"). Teva stipulated to infringement but challenged validity. Relevant here, Teva argued that all representative claims were invalid as obvious and that claims 19–21 were also invalid as indefinite. After a bench trial, the district court found that Teva had not proven invalidity on either basis. Teva appeals.[1] For the reasons below, we affirm the district court's indefiniteness determination but vacate and remand its nonobviousness determination.

BACKGROUND

Janssen markets and sells Invega Sustenna. Invega Sustenna is an extended-release intramuscular injectable of paliperidone palmitate, which is indicated for the treatment of schizophrenia in adults. J.A. 13118. After Teva

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[1] Janssen also sued Mylan Laboratories Ltd. ("Mylan") in a separate action. In that action, the parties stipulated to be bound by the final judgment in the Teva action with respect to infringement and validity. J.A. 49 (final judgment). Although we refer to Teva throughout, Mylan is also an Appellant here.

filed an Abbreviated New Drug Application ("ANDA") seeking FDA approval to sell a generic version of Invega Sustenna, Janssen sued and asserted various claims of the '906 patent. The '906 patent, which generally relates to dosing regimens of paliperidone palmitate, is the last remaining Orange Book patent for Invega Sustenna.

I

The '906 patent is titled "dosing regimen associated with long acting injectable paliperidone esters." '906 patent col. 1 ll. 1–3 (capitalization normalized). It was filed in December 2008 and claims priority to a provisional application filed in December 2007. *Id.* at col. 1 ll. 8–10. For purposes of this appeal, Teva does not contest that the '906 patent is entitled to the December 2007 priority date. Appellants' Br. 19.

The parties agreed that claims 2, 10, 13, and 20–21 were representative. *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 571 F. Supp. 3d 281, 291 n.3 (D.N.J. 2021) ("*Opinion*"). All asserted claims relate to "[a] dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia." '906 patent claims 1 and 8.

Claim 2 (non-renal-impairment claim), which depends from claim 1, relates to a normal or non-renal-impairment dosing regimen. Both claims are reproduced below.

> 1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising
>
> > (1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

> (2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and
>
> (3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.
>
> 2. The dosing regimen of claim 1 wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals.

'906 patent claims 1 and 2.

Representative claims 10 and 13 (renal-impairment claims) claim dosing regimens for renally impaired patients. Claim 10 depends from claim 8. Both claims are reproduced below.

> 8. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder comprising
>
> (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated

> in a sustained release formulation on the first day of treatment;
>
> (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment; and
>
> (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose.
>
> 10. The dosing regimen of claim 8 wherein the sustained release formulation is an aqueous nanoparticle suspension.

'906 patent claims 8 and 10.

Claim 13 differs from claim 10 by requiring that the patient is in need of treatment for schizophrenia and reciting a range of 25 mg-eq. to about 50 mg-eq. for the maintenance dose.

Claims 20 and 21 (particle-size claims) are only representative as they depend from claims 1 and 8. They both further depend from claim 19. Because for our purposes the particle-size limitation of claim 19 is most pertinent, only claim 19 is reproduced below.

> 19. The dosing regimen of claims *1*, 4, *8* or 11 wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of

> (a) *156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm*;
>
> (b) 12 mg/ml of polysorbate 20;
>
> (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);
>
> (d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and
>
> (f) water q.s. ad 100%.

'906 patent claim 19 (emphasis added).

The '906 patent discloses that "[p]aliperidone is the major active metabolite of risperidone," an antipsychotic that was developed in the 1990s. '906 patent col. 1 ll. 36–37. It further explains that due to their chemical properties, "paliperidone esters such as paliperidone palmitate dissolve slowly after an [intramuscular] injection before being hydrolyzed to paliperidone and made available in the systemic circulation." *Id.* at col. 1 ll. 46–49. The specification acknowledges that persons of skill "could easily determine the effective amount of paliperidone to administer," and that for purposes of the '906 patent's invention, "[t]he amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g.[,] 156 mg corresponds to paliperidone 100 mg)." *Id.* at col. 14 ll. 13–26.

A tablet formulation of paliperidone was already on the market and indicated for the treatment of schizophrenia. *Id.* at col. 1 ll. 37–41; *see also* U.S. Patent No. 5,158,952 (compound patent for paliperidone, issued in 1992). However, the specification describes the prevalence of treatment adherence problems when patients are prescribed

oral antipsychotic medications that need to be taken daily, which in turn "often result in worsening of symptoms, suboptimal treatment response, frequent relapses and rehospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies." '906 patent col. 1 ll. 50–57.

The specification explains that an injectable formulation of paliperidone palmitate was previously "developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing." *Id.* at col. 1 ll. 58–63. And, it explains that U.S. Patent Nos. 6,577,545 and 6,555,544 ("the '544 patent") had already described the formulation. *Id.* The '906 specification also describes the preferred particle size as d(50) of preferably "1600 nm to 400 nm" and "most preferably 1400 nm to 900 nm." *Id.* at col. 7 ll. 28–31. In the '906 patent, d(50) means that "at least 50% of the particles have a smaller diameter" than the listed measurement. *Id.* at col. 7 ll. 32–38.

The '906 patent describes several different "dosing regimen[s] for administering paliperidone esters to a psychiatric patient in need of treatment" and emphasizes the plasma concentration of paliperidone reached when different variables are changed and the time frame for reaching it. *See generally id.* at col. 2 l. 11–col. 4 l. 42 (describing embodiments); *id.* at col. 5 ll. 2–5; *id.* at col. 6 ll. 41–59.

It further discloses that "deltoid injections result in a faster rise in initial plasma concentration" and that "to facilitate patients' attaining a rapid therapeutic concentration of paliperidone it is preferred to provide the initial loading dose of paliperidone palmitate in the deltoids." *Id.* at col. 5 ll. 2–8. It states that "[a]fter the first or more preferably after the second loading dose injection patients will be approaching a steady state concentration of paliperidone in their plasma and may be injected in either the deltoid or the gluteal muscle thereafter. However, it is

preferred that the patients receive further injections in the gluteal muscle." *Id.* at col. 5 ll. 11–16.

Relatedly, the specification explains that there was an observed relationship between needle length and body mass index ("BMI") and time to reach ideal initial plasma concentrations of paliperidone. Specifically, "[p]atients with high BMI had lower plasma concentration of paliperidone and a lessened treatment response . . . likely due to unintended partial or complete injection into adipose tissue, instead of deep injection into muscle." *Id.* at col. 6 ll. 44–49. As a result, the specification explains that for deltoid injections 1-inch needles are sufficient for patients weighing less than 90kg, but 1.5-inch needles should be used for those who weigh more. *Id.* at col. 6 ll. 51–57. For gluteal injections, the specification simply states that "1.5-inch needle[s] should be used" without specifying a weight-based preference. *Id.* at col. 6 ll. 57–59.

In terms of dosing, the specification states that "[p]referably the first two doses will be loading dose[s] of between from about 100 mg-eq. to about 150 mg-eq.," *id.* at col. 5 ll. 34–36; *see also id.* at col. 5 ll. 8–10, and "[t]he subsequent doses thereafter will drop to a therapeutic maintenance dose of from about 25 mg-eq. to 150 mg-eq. per month (±7 days) . . . most preferably the maintenance dose initially will be about 50 mg[-]eq," *id.* at col. 5 ll. 38–45. It also explains that "[t]hose of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patient['s] condition (response to the medication and renal function)." *Id.* at col. 5 ll. 49–52.

The '906 patent contains three figures. Each of these figures shows both observed and modeled plasma paliperidone concentrations. For all three figures, patients were given a 150 mg-eq. dose in the deltoid on day 1; day 8, 36, and 64 doses were either 25 mg-eq (Figure 1), 100 mg-eq. (Figure 2), or 150 mg-eq. (Figure 3). The day 8, 36, and 64 doses were given in either the deltoid or the gluteus. The

specification indicates that the figures make apparent that "the plasma profiles provided by initiating paliperidone with 150 mg[-]eq. followed by a subsequent dose of 100 *or* 150 for days 1-36 provide a rapid rise to a therapeutic dose level[]." *Id.* at col. 31 ll. 62–65 (emphasis added).

II

The safety of paliperidone, its efficacy for treating schizophrenia, and its recommended dosing were all well established as of the '906 patent's priority date. J.A. 13266–79; J.A. 16209–10; J.A. 16233. Additionally, long acting injectables (LAIs)—administered intramuscularly—of other antipsychotics were on the market. J.A. 16640, 16650–52 (label for haldol decanoate, LAI of haloperidol); J.A. 17911, 17941 (risperdal consta, LAI of risperidone, of which paliperidone is the major metabolite).

To demonstrate obviousness of the paliperidone palmitate LAI dosing regimen claims at issue here, Teva relied on three primary prior-art references at trial: (1) clinical study protocol NCT00210548 ("the '548 protocol"); (2) the '544 patent; and (3) International Publication No. WO 2006/114384 ("WO'384"). We describe each reference below.

A

The '548 protocol, published in 2005, is a protocol for an interventional Phase III clinical trial with the brief title: "A Study to Evaluate the Effectiveness and Safety of 3 Doses of Paliperidone Palmitate in Treating Subjects with Schizophrenia." J.A. 13244–45. The protocol explains that "[t]he hypothesis is that the 3 fixed doses of paliperidone are each more efficacious than placebo in treating subjects with schizophrenia." *Id.* Further, the protocol's dosing is outlined as follows:

> Four injections of paliperidone palmitate 50, 100, or 150 milligrams equivalent administered in the gluteal muscle (buttocks). Injections will be given

> on Days 1, 8, 36, and 64 of the double-blind treatment period of the study.

Id.

Experts on both sides provided testimony about what the Phase III status of the protocol would indicate to them. Dr. Gopal, an inventor of the '906 patent who designed clinical trials for paliperidone palmitate, testified that Phase III studies were expected to meet safety and efficacy endpoints because of the requisite preexisting Phase I and II data. J.A. 11124:8–20; *see also* J.A. 11135:9–11 ("[W]e generally don't like to change too many things going from Phase II to Phase III. We want to extrapolate as much as possible so we try to keep them the same."). Teva's expert, Dr. Wermeling, similarly testified that a person of ordinary skill in the art would understand that Phase III studies "us[ed] doses that are thought to be safe and effective and are going to be confirmed in the larger patient population." J.A. 10316:17–10317:2; *see also* J.A. 10207:5–23.

It is undisputed that the '548 protocol does not contain any results—*Opinion*, 571 F. Supp. 3d at 301—and Teva relied on how a person of ordinary skill in the art ("POSA") would understand the protocol itself considering its Phase III status and other background knowledge in the art. And while the protocol is associated with Janssen's PSY-3003 clinical trial, the results of the PSY-3003 trial were not known in the prior art. As we explain in more detail throughout this opinion, the import of these unknown results influenced the district court's view about what the claims require, what a POSA would need to know before she was motivated to modify the '548 protocol, and what results would be unexpected.

Consequently, although unavailable to a POSA, some information about the PSY-3003 trial results provides helpful context for our discussion. The 50 mg-eq. study arm—50 mg-eq. given on days 1, 8, 36, and 64—did not demonstrate a statistical difference compared to placebo.

J.A. 10895:6–7. In contrast, the 100 mg-eq. study arm did demonstrate efficacy that was significantly better than placebo. J.A. 11061:21–24; J.A. 11147:3–9; J.A. 10893:15–17; J.A. 10895:11–13; J.A. 13130. However, "by [its] own measures," Janssen considered the day 36 onset for efficacy "too late." J.A. 11062:7–11. Finally, for the 150 mg-eq. study arm, because of a randomization error, most patients who were supposed to receive the 150 mg-eq. doses mistakenly received placebo instead. J.A. 11063:24–11064:8; J.A. 10894:6–17. As a result, the data for that study arm was unusable for conducting statistical analyses. J.A. 11064:9–12; J.A. 10895:1–6; J.A. 11169:22–25. Ultimately, Janssen considered this clinical trial a failure—it did not believe it had sufficient data to obtain FDA approval. J.A. 11068:3–17; J.A. 10784:15–20.

B

The '544 patent, granted in 2003 and expired in 2018, is owned by Janssen. As the '906 patent is now, the '544 patent was listed in the Orange Book for Invega Sustenna before its expiration. J.A. 17768.

The '544 patent claims "[a] pharmaceutical composition suitable as a depot formulation for administration by intramuscular or subcutaneous injection, comprising," among other things, a "therapeutically effective amount" of paliperidone palmitate. '544 patent claim 1. Additionally, it claims a method of treating schizophrenia, or other disorders, "in a warm-blooded animal in need thereof comprising administering to the animal a therapeutically effective amount of" the claimed composition of paliperidone palmitate. '544 patent claim 7.

Further, the specification emphasizes the ability to space out administrations by three weeks to a month. Specifically, it states that "[t]he present invention results from the investigations into the development of an efficient, well-tolerated, sustained or delayed release (depot) formulation of a [paliperidone] alkanoic acid ester which is

therapeutically effective for at least three weeks or more, in particular about 1 month." *Id.* at col. 2 ll. 38–43; *see also id.* at col. 8 ll. 17–19 ("Typically, said formulation will be administered approximately every three weeks or even at longer intervals where possible."). It further indicates that "effective for at least three weeks or more" means a plasma level of paliperidone above 10 ng/ml and below 100 ng/ml, *id.* at col. 2 ll. 43–50, and that "[t]he dosage should range from about 2 to 4 mg/kg body weight," *id.* at col. 8 ll. 19–20.[2]

The '544 patent discloses specific amounts of active and inactive ingredients for an LAI paliperidone palmitate formulation. *Id.* at col. 8 l. 60–col. 9 l. 7. Most pertinent for our purposes on appeal, the specification discusses the particle size used in the formulations. Specifically, it states that "[t]he pharmacokinetic properties in humans of the aqueous suspensions of [paliperidone] alkanoic acid esters depend on the particle size to a much larger extent than previously held possible." *Id.* at col. 3 ll. 52–55. And it generally provides details related to applying "mechanical means" to reduce the effective average particle size. *Id.* at col. 6 ll. 1–47.

The '544 patent references "an effective average particle size of less than 2,000 nm" several times, *see, e.g.*, *id.* at col. 3 ll. 43–44, col. 5 ll. 15–26, which, as used in the '544 patent, "means that at least 90% of the particles have a diameter of less than 2,000 nm," *id.* at col. 5 ll. 16–18. In other words, "effective average particle size" refers to the d(90) value (90% of the particles have a smaller diameter) in the '544 patent—this is in contrast to the '906 patent which defines effective average particle size as the d(50)

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[2] Dr. Wermeling testified that for a population weighing between 50 and 90 kg, the 2 to 4 mg/kg dosage range would translate to 65 mg-eq. to 230 mg-eq. paliperidone palmitate. J.A. 10284:16–21.

value (50% of the particles have a smaller diameter). *Compare id.*, *with* '906 patent col. 7 ll. 32–36.

The '544 patent discloses the particle sizes of four formulations:

Formulation	Milling Time	Particle Size (nm)			SSA
		d(10)	d(50)	d(90)	
Formulation A	0 hours	2510	6030	7640	1.3
Formulation B	4 hours	620	1380	6830	6.5
Formulation C	7 hours	520	740	1150	13.5
Formulation D	38 hours	430	520	650	>15

See Appellants' Br. 13 (table); '544 patent col. 8 ll. 44–57, col. 9 ll. 24–33 (data).

It further discloses that "[f]ormulations C and D were put on a three month stability test," *id.* at col. 9 ll. 33–34, and that "[e]ach of the four formulations A–D were administered to four beagle dogs intramuscularly," *id.* at col. 9 ll. 48–49.

C

International Publication WO'384 was filed by Janssen and published in 2006. J.A. 13299–321. Although the disclosure is broader, the abstract describes the invention of WO'384 as related to "a process for preparing aseptic crystalline" paliperidone palmitate. J.A. 13299.

As part of an example entitled "[p]reparation of finished form," WO'384 discloses specific amounts of active and inactive ingredients for an LAI paliperidone palmitate formulation. J.A. 13316. Janssen agrees that the composition of this disclosed formulation matches both the composition elements of claims 20 and 21 and the Invega Sustenna formulation. Appellees' Br. 9. Also, as part of this example, WO'384 states that "[t]he suspension was filled aseptically into sterile syringes" in dose volumes

"between 0.25 ml and 1.50 ml depending on the dose needed," J.A. 13317, which corresponds to 25 to 150 mg-eq. of paliperidone, J.A. 12163:15–20.

* * *

Teva argued that all asserted claims were invalid as obvious and that claims 19–21 were also invalid as indefinite. After a bench trial, the district court concluded that Teva had not proven invalidity on either basis. Teva appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Teva first argues that the district court's obviousness analysis, including its analysis of secondary considerations, was legally flawed in several key respects. Some of Teva's arguments relate to all claims while others only relate to a subset of claims. Ultimately, we vacate and remand with respect to all claims.

We address: (1) whether the court required a showing of obviousness that was incongruent with the scope of the claims by requiring—(i) generalized or population-wide dosing (all claims) and (ii) mild renal impairment (claims 10 and 13); (2) whether the court analyzed the prior art with a degree of rigidity foreclosed by *KSR*—(i) generally (all claims) and (ii) teaching away (particle-size claims); and (3) secondary considerations—(i) whether they preclude vacatur and (ii) whether individual secondary considerations were properly analyzed.

Finally, we address Teva's argument that the district court improperly determined that Teva had not demonstrated that claims 19–21 (particle-size claims) were invalid as indefinite. Although the claims may still be invalidated as obvious on remand, we nonetheless reach the question of indefiniteness and affirm the court's determination that claims 19–21 were not shown to be indefinite.

I

Obviousness is a question of law based on underlying factual determinations, "including (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any secondary considerations of non-obviousness." *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018); *see also PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1193–94 (Fed. Cir. 2014). We review the overall determination de novo and the underlying factual findings for clear error. *PAR Pharm.*, 773 F.3d at 1194. Where the court applies an incorrect legal standard in its analysis, it can be appropriate to vacate and remand for factfindings that address the correct legal question. *See id.* at 1196 (remanding where "[t]here [we]re simply no findings of fact addressing th[e correct legal] question" about inherency); *Innovention Toys, LLC v. MGA Ent., Inc.*, 637 F.3d 1314, 1324 (Fed. Cir. 2011) (remanding on determination of nonobviousness where the district court applied an improperly low level of skill in the art for the court to "make a finding on the level of skill in the art and base its obviousness analysis on that level of skill" on remand).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Assessing obviousness is based on an "expansive and flexible approach" that "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 415, 418.

A

Teva makes several arguments about the district court's obviousness analysis, leading with its argument that the district court added unclaimed limitations to the

claims when analyzing obviousness—specifically: (1) *generalized or population-wide* dosing (all claims); and (2) *mild* renal impairment (claims 10 and 13). We address both arguments in turn.

1

First, Teva argues that the district court's analysis of obviousness required Teva to show that it would have been obvious to use the recited dosing regimens for the general population of patients—i.e., a generalized dosing regimen. The court found that the prior art did not demonstrate population-wide safety and efficacy and thus did not teach a generalized dosing regimen. Teva contends that the claims were not directed to a generalized dosing regimen and therefore the district court asked for a showing of obviousness that went beyond what was claimed. We agree.

The non-renal-impairment dosing regimen claims recite a dosing regimen for "*a* psychiatric patient in need of treatment for schizophrenia"[3]: (1) a 150 mg-eq. loading dose on day 1 administered into the deltoid; (2) a 100 mg-eq. loading dose on day 6 to 10 administered into the deltoid; and (3) a maintenance dose of 25 to 150 mg-eq. given a month (±7 days) after the second loading dose administered into the deltoid or gluteal muscle. '906 patent claim 2 (emphasis added). Likewise, the renal-impairment claims recite a dosing regimen for "*a* renally impaired psychiatric patient in need of treatment for schizophrenia": (1) a 75 mg-eq. loading dose on day 1 administered into the deltoid; (2) a 75 mg-eq. loading dose on day 6 to 10 administered into the deltoid; and (3) a maintenance dose of 25 to about 75 mg-eq. (or 25 to about 50 mg-eq.) given a month (±7 days) after the second loading dose administered into

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[3] Some claims also contemplate that the patient is in need of treatment for a different psychiatric disorder, but the parties focus on schizophrenia, so we do the same.

the deltoid or gluteal muscle. '906 patent claims 10 and 13 (emphasis added).

Nothing in the claims requires that the regimen be used for—let alone be ideal for—the patient population generally or a certain percentage of the patient population. On their face, the claims only recite a dosing regimen for *a* psychiatric patient. Because "[w]hat matters is the objective reach of the claim," *KSR*, 550 U.S. at 419, the district court erred to the extent it effectively defined its obviousness inquiry as one concerning the "generalized" suitability of the dosing regimens.

At the district court, Janssen emphasized arguments and evidence related to its clinical-study design and approval process with the FDA—both of which were keyed to concerns about generating population-wide data. It seems that the court ended up conflating Janssen's purported difficulties in generating data to gain approval for a "universal" or "generalized" dosing regimen with the scope of the *claims* themselves.[4] Given the scope of the claims here, it was important for the court to recognize the distinction and focus its findings on single patient administration. The district court did not do so.

We are persuaded that this misunderstanding about the claims impacted the district court's overall obviousness analysis. Certain portions of the court's discussion provide

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[4] Because we agree with Teva that it was improper to read this limitation into the claims, we need not assess what it would mean for the claimed dosing regimens to be "generalized" or "universal." For example, it is unclear whether that requirement would indicate that physicians typically (or always) dose that way or that some (or all) patients achieve a certain level of a particular unnamed result.

examples of how this legal error affected the district court's analysis and factfinding here.

For example, the district court assessed whether a POSA would be motivated to use the deltoid (shoulder) as an injection site. Teva argued that the deltoid was one of only three finite choices for an intramuscular injection site (the deltoid, gluteal muscle, or thigh), J.A. 11719:9–17, and some patients preferred the deltoid, so using the deltoid as an injection site was obvious. The district court concluded that injecting at the deltoid was not obvious because "such preferences would suggest at most using deltoid administration on an individualized basis." *Opinion*, 571 F. Supp. 3d at 305. As a result, the district court concluded that Teva had not met its burden even by pointing to evidence that, when given a choice, certain populations of patients tend to prefer a deltoid injection over a gluteal one. *Id.*

Likewise, while assessing whether a POSA would be motivated to use unequal loading doses (even where the loading dosage *amounts* were undisputedly disclosed in the prior art, both as a particular dose and as a point within a disclosed range), the district court dismissed Teva's reliance on references related to administering unequal loading doses because they "t[aught] individualized, rather than generalized, dosing." *Id.* at 306.

Additionally, although the court's analysis of reasonable expectation of success has minimal explanation, there too it seemed to require an expectation of success not for administering paliperidone palmitate to *a* patient according to the dosing regimen claimed, but rather success in achieving the goals a POSA would have across an (undefined) average population of patients, such that a POSA would expect to use the regimen as a "generalized multidose regimen." *Id.* at 310. The court also appeared to conflate the invention or the claims with Janssen's approval process when it referred to the difficulties Janssen

encountered with the PSY-3003 clinical trial as an indication of unpredictability in the "invention process." *Id.* at 311.

Janssen makes two arguments about why the district court's framing was not erroneous. First, it argues that the district court simply followed Teva's lead in referring to the claims as "general dosing regimens." Second, it argues that the court was simply analyzing the obviousness theory that Teva presented, not adding limitations to the claims. Neither argument is persuasive.

While it is true that Teva used the phrase "general dosing regimens" to describe the non-renal-impairment claims, Janssen has not pointed to anything showing that Teva used the term "general" in the same way the district court used the term "generalized"—as a comparison between individual and population-wide. Further, Teva's use of the word general is far from a concession that the facts to be found for the obviousness inquiry should be facts about some (unarticulated) percentage of patients in general.

Further, we are not persuaded that Teva's motivation theory based on "reach[ing] therapeutic plasma levels faster," J.A. 1426, or "accelerat[ing] the onset of effect," J.A. 10311, justifies how the court framed its analysis. That theory does not imply a population-wide objective. And, to the extent Teva's theory was predicated on knowledge of some therapeutic effect, the court required far more than that.

In sum, as discussed above, the court's framing led it to ask the wrong questions about important aspects of the obviousness inquiry. This error requires a remand as to all claims because as it currently stands, the record does not contain underlying obviousness factfindings that are cued to the "a psychiatric patient" claims at issue here. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1373 (Fed. Cir. 2005) (reversing and remanding where "the

district court committed legal error in establishing certain factual predicates to its non-obviousness determination").

2

Teva argues that the court also read a "mild" limitation into the renal-impairment claims, whereas the claims do not specify a level of renal impairment. Janssen counters that Teva presented an obviousness theory that was predicated on dosing a patient with mild renal impairment.

We agree that many of the district court's statements suggest that it understood the claims themselves to require administration to a patient with mild renal impairment. *See, e.g.*, *Opinion*, 571 F. Supp. 3d at 307 (noting "the dosing regimens address patients with mild renal impairment"). And we agree that there is no such requirement in the claims. Thus, we remand for the district court to analyze obviousness without a "mild" limitation added to the renal-impairment claims.

B

Next, Teva argues that the court's analysis was impermissibly rigid and does not comport with *KSR* or otherwise reflect this court's obviousness jurisprudence. We first address this argument as it pertains to the court's obviousness analysis more generally. Then, we address Teva's specific argument about the court's teaching-away finding related to particle size (claims 20 and 21).

1

We agree with Teva that the district court's analysis was erroneously rigid in several respects. The district court analyzed the prior art without giving the needed weight to the perspective of a POSA capable of deducing what references fairly suggest or employing ordinary creativity. Instead of considering the prior art in context or in combination, the court's analysis seems to tackle the express statements of each reference one-by-one—identifying

each difference or dissimilarity between an individual reference and the claims, but not fully assessing the teachings in toto. This seemingly siloed and inflexible approach left insufficient room for consideration of how background knowledge in the art would have impacted a POSA's understanding of, or motivation to modify, the primary references at issue, thereby inflating the significance of minor variations between the prior art and the claims. We vacate and remand on this basis too because it also seems to have prevented the court from carrying out its factfinding role, irrespective of claim scope.

Janssen argues that the court's rigid consideration of prior art references related to modifications—i.e., unequal loading doses, injection sites, and dose reduction for a patient with renal impairment—is justified by the court's determination that there was no motivation to make any modifications to the '548 protocol. Appellees' Br. 44–46.

The district court's obviousness analysis does begin by looking to the '548 protocol and, largely without referring to the evidence offered specific to the modifications at issue, concluding that (1) there were issues with starting from the '548 protocol because "it contains no information about the safety of the dosing regimen or its efficacy"; and (2) without knowledge of the results of the trial that Janssen considered a failure, a POSA would not be motivated to modify the protocol. *Opinion*, 571 F. Supp. 3d at 301–03. To the extent the court's analysis about a POSA's motivation to start with the '548 protocol was not entirely based on its misunderstanding of the claims, it too was not in accordance with law.

First, the district court concluded that in the pharmaceutical context, if a prior art reference does not contain safety and efficacy data, there is no reason to combine it with other prior art references. *Id.* at 301 ("As Dr. Sinko credibly testified, without such safety and efficacy information, a POSA would have had no reason to alter the

regimen disclosed in the ['548 Protocol]."); *Id.* at 310 ("Therefore, to successfully arrive at a multi-dose regimen based on the prior art, a POSA would need safety, efficacy, and pharmacokinetic data in order to evaluate how a generalized dosing regimen would perform in patients."). Whatever role safety and efficacy data may play in assessing the strength of a motivation or a lack of motivation to combine, *see Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1360–61 (Fed. Cir. 2017), absence of such safety and efficacy data in the '548 Protocol cannot justify simply discarding that prior art particularly where, as here, the claims do not have any safety and efficacy requirement. In *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1369 (Fed. Cir. 2023), we found that "the claim language 'treating pulmonary hypertension' does not import any additional efficacy limitations or any safety limitations" and "[w]e decline to insert the FDA's responsibilities into claims by importing requirements where they do not recite such limitations." *Id.* The district court cannot employ a different standard when analyzing prior art for obviousness than would be used to determine infringement. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001). The district court's treatment of the prior art protocol was therefore in error.

Additionally, the court emphasized the protocol's lack of results but failed to consider what the '548 protocol would fairly suggest to a POSA. For example, the court did not discuss evidence related to the significance a POSA would assign to the Phase III status of the protocol, J.A. 11124:8–20; J.A. 11135:9–11, or that paliperidone was already on the market and prescribed to patients in need of treatment for schizophrenia, J.A. 16209. More importantly, the claims of the '906 patent do not recite any particular result or outcome, nor do they recite a need for population-wide statistically significant data. And, although we recognize that obtaining specific results or

outcomes in a population of patients could have been one motivation for modifying the protocol—indeed, it seems that it was Janssen's motivation—the motivation analysis does not look only to the data the patentee found significant. *Cf. KSR*, 550 U.S. at 420; *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) ("There is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval."). While we do not make an initial finding about the level of background information a POSA would require to be motivated to modify an existing dosing regimen for *a* psychiatric patient in need of treatment, it is different from (and almost certainly less demanding than) the level of information desired by a POSA in deciding whether to redesign a Phase III clinical trial to obtain approval for a dosing regimen's use across a population of patients of varying weights.

Second, contrary to the court's assumptions, the '548 protocol did not need to hold itself out as flawed for a POSA to alter it.[5] Again, Janssen's narrative that internal information about the PSY-3003 trial's results caused *it* to alter the regimen used for subsequent trials did not prevent Teva from demonstrating a different motivation based on publicly available information. Further, although identifying a recognized problem or need in the prior art is one way to demonstrate motivation, Teva was not required to demonstrate that there was an explicit problem with the '548 protocol itself. For one thing, the motivation analysis

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[5] Although we address the flaws on both sides of the analysis, we also note the conundrum—the court seemed to conclude both that a POSA would not have looked to the protocol until there was data confirming that the doses were, on average, safe, efficacious, and fast-acting and simultaneously that a POSA would not have modified it until she knew that the protocol had "failed."

is not limited by the problem or need recognized by the inventors. *See PAR Pharm.*, 773 F.3d at 1197. Further, a motivation "may be found in many different places and forms," *Allergan,* 726 F.3d at 1292, and it need not be expressly stated in the references at all, *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006), let alone originate from the reference to be modified. A motivation "may be found explicitly or implicitly in market forces; design incentives; the interrelated teachings of multiple patents; any need or problem known in the field of endeavor at the time of invention and addressed by the patent; and the background knowledge, creativity, and common sense of the person of ordinary skill." *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1365 (Fed. Cir. 2022) (cleaned up).

The court's determination that the '548 protocol simply would not be modified carried through the remainder of its obviousness analysis. This reasoning, contrary to Janssen's suggestion, did not provide a sufficient basis to support the court's entire nonobviousness determination, and instead evidences another reason to vacate the decision.

The district court also made erroneous findings regarding modifications to loading doses and injection sites. Without considering whether the differences in the '548 protocol would be significant to a POSA, the court labeled the equal loading doses and gluteal injection site *material* differences between the '548 protocol and the claims. *Opinion*, 571 F. Supp. 3d at 301; *see also id.* at 303 (calling deltoid administration "a key component of [c]laim 2"); *id.* at 305 (naming unequal loading doses a "key feature").

The district court first looked to the claimed requirement that the first and second doses are given in the deltoid—as opposed to the gluteal muscle, where the day 1 and 8 doses of the '548 protocol are given. The court disregarded evidence related to patient preferences and

injection sites. A POSA can be motivated to do more than one thing (in other words, there was motivation both for the deltoid and gluteal muscle) and Teva did not need to show that a POSA would be singularly motivated to use the deltoid injection site. *See Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) ("[O]bviousness does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away." (emphasis in original) (cleaned up)).

Next, the court considered unequal loading doses. The '548 protocol expressly disclosed administration of 100 mg-eq. loading doses on days 1 and 8 and administration of 150 mg-eq. loading doses on days 1 and 8. J.A. 13244–45. However, the claims require a 150 mg-eq. dose on day 1 and a 100 mg-eq. dose on day 6–10. The court presumed significance based on the unequalness itself but nonetheless discounted potential teachings related to unequal dosing generally because the references presented other dissimilarities from the claims. For example, in addition to discounting certain references because they related to individualized dosing, the court also seems to have discounted them for involving the administration of a different antipsychotic LAI. *Opinion*, 571 F. Supp. 3d at 305–06. While it is true that the specific *amounts* of medication given in these references would not correlate to the amount of paliperidone palmitate claimed, that should not have led to disregarding the references' teachings related to the concept of dose variation itself. On remand, the court should address these concerns.

Finally, the court considered the renal-impairment claims, which involve two equal loading doses of 75 mg-eq. paliperidone followed by a maintenance dose in the range of 25 mg-eq. to 75 mg-eq. (or 25 mg-eq. to 50 mg-eq. in claim 13). Teva argued that a POSA would have halved the 150 mg-eq. paliperidone palmitate loading dose for renally impaired patients because the prior art taught a 50% dose

reduction for renal impairment. Here too, the court cut short the analysis required *after* identifying differences between the claims and each reference, an analysis that must focus on what the references might fairly suggest to an ordinarily creative POSA or might provide in the way of background knowledge.

For example, Cleton 2007 expressly disclosed that "[p]aliperidone plasma exposure was higher in subjects with renal impairment compared to healthy subjects" and that "[b]ased on the pharmacokinetic data, a lower dose of paliperidone ER should be considered for subjects with moderate and severe renal impairment." J.A. 14112. The prior-art Invega ER label states that the maximum recommended dose for patients with mild renal impairment is 6 mg/day and 3 mg/day for patients with moderate to severe renal impairment, whereas the maximum recommended dose for non-renally impaired patients is 12 mg/day. J.A. 16233. The court appears to have found Teva's reliance on Cleton 2007 and the Invega ER label unavailing, at least in part, simply because the references did not involve injectable paliperidone palmitate. *Opinion*, 571 F. Supp. 3d at 307. The court did not explain why information about oral paliperidone dosing for renally impaired patients would not be meaningful to a POSA considering doses of paliperidone palmitate, which are expressed in equivalents of paliperidone. Similarly, the court's analysis placed significance on the fact that the '591 application[6] was titled "use of paliperidone for the treatment of a mental disorder in a psychiatric patient with reduced hepatic [liver] function" even though it was pointed to as evidence of a POSA's understanding that paliperidone is cleared through the kidneys. *Id.* It is unclear how the '591 application's title could impair a POSA's ability to understand its separate teachings about renal

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[6] U.S. Patent Application No. 2007/0197591 A1.

clearance. Ultimately, the court determined that the references' failure to "*expressly* teach LAI paliperidone palmitate dose reductions for mild renal impairment" was sufficient to reject Teva's arguments.[7] *Id.* at 308 (emphasis added).

Overall, the court's analysis ran afoul of *KSR*'s basic mandate in a number of ways. It failed to consider the "interrelated teachings of multiple" references, "the background knowledge possessed by a person having ordinary skill in the art," or "the inferences and creative steps that a person of ordinary skill in the art would employ." *See KSR*, 550 U.S. at 418. Instead, the court sought an explicit indication in the '548 protocol that an improvement was required—at times also suggesting that it was searching for an indication that the claims captured *the* singular way the protocol would be modified.

2

Teva also argues that the district court erroneously found a teaching away with respect to the "(d50) of from about 1600 nm to about 900 nm" particle-size limitation (claims 20 and 21). Appellants' Br. 57–58. We agree that the district court did not apply the correct test for teaching away.

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[7] The court also appears to have independently rejected Teva's theory because the two claimed 75 mg-eq. loading doses would not result "if the 150/100 mg-eq. loading doses of Claim 2 were reduced by half." *Opinion*, 571 F. Supp. 3d at 308. This was the wrong question. The question was whether halving the '548 protocol's 150 mg-eq. loading doses or selecting 75 mg-eq. loading doses from the disclosed range was obvious when administering to a renally impaired patient, not whether the renally impaired claims were obvious when starting from the non-renally impaired claims.

The prior art '544 patent discloses the particle sizes of four formulations of paliperidone palmitate. '544 patent col. 8 ll. 44–57, col. 9 ll. 24–33. Its formulation B has a d(50) particle size within the claimed range of 1600 nm to 900 nm. *Id.* The court found an "express[] teach[ing] away" from formulation B's d(50) value of 1380 nm (50% of the particles were smaller than 1380 nm) because formulation B's d(90) value was 6830 nm (90% of the particles were smaller than 6830 nm), and the '544 patent's specification emphasized a d(90) value of 2000 nm. *Opinion*, 571 F. Supp. 3d at 309 (citing '544 patent col. 3 ll. 42–44, col. 5 ll. 16–21, col. 9 ll. 25–31, col. 10 ll. 27–29). A teaching that a d(90) value of 2000nm was optimal is not a criticism of all other particle sizes. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738–39 (Fed. Cir. 2013). In fact, the '544 patent stated that "[m]ost preferably, *essentially all of the particles* have a size of less than 2,000 nm." '544 patent col. 5 ll. 25–26 (emphasis added). That the '544 patent did not disclose a preferred d(50) value does not amount to a teaching away either. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 964 (Fed. Cir. 2014) ("[S]ilence does not imply teaching away."). The court should have analyzed whether the d(50) value was "criticize[d], discredit[ed], or otherwise discourage[d]." *Galderma*, 737 F.3d at 739. Instead, it merely assessed what the '544 patent taught about the optimal or standard d(90) value.[8]

We do not address Teva's argument about optimization of a result-effective variable because, as Janssen's brief suggests, *see* Appellees' Br. 51, were the teaching away

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[8] The court can reassess its reliance on expert testimony on remand. However, as it stands, we are not persuaded that the court looked to expert testimony for more than an indication that a different d(90) value was preferred by the '544 patent itself. *See, e.g.*, J.A. 11785:2–13, J.A. 11529:24–11530:8.

analysis sound, the court may have deemed it unnecessary to address optimization, and we do not discern an analysis of this issue in the court's opinion. On remand, the court will reassess the obviousness of these claims in light of our opinion. The court can address optimization as part of that renewed analysis.

C

We agree with Teva that the district court's determinations related to secondary considerations do not disturb our conclusion that vacatur is required here.

On remand, the district court will need to reassess the significance of the secondary considerations as part of its renewed obviousness analysis. Even if the district court's consideration of individual secondary considerations had been error free—and it was not, for at least the reasons discussed below—those same conclusions, left undisturbed, might well be inadequate to support a conclusion of nonobviousness when considered in conjunction with a proper assessment of the other *Graham* factors. *See, e.g., Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011) ("A strong case of prima facie obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness."); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("While secondary considerations must be taken into account, they do not necessarily control the obviousness determination."); *ZUP*, 896 F.3d at 1373 ("[M]inimal evidence of secondary considerations does not create a genuine dispute of fact sufficient to withstand summary judgment on the question of obviousness."). Moreover, as Teva correctly notes, the district court here did not explain in the first instance what significance it assigned to secondary considerations within its overall assessment of obviousness.

Additionally, with respect to individual secondary considerations, the district court will necessarily need to reevaluate nexus because, as discussed above, the court's

misunderstanding of claim scope carried throughout its obviousness analysis. And a proper nexus analysis must "consider the correspondence between the objective evidence and the claim scope." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019); *see also Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015) ("Where objective indicia result from something other than what is both *claimed* and *novel* in the claim, there is no nexus to the merits of the claimed invention." (cleaned up) (first emphasis added)).

Teva also presents specific arguments related to the district court's analysis of certain subcategories of secondary considerations. For at least the sake of judicial efficiency, we address some of those specific arguments as well.[9]

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[9] Because the court only afforded evidence of copying "some limited weight," *Opinion*, 571 F. Supp. 3d at 319, we do not envision the factor playing a large role on remand. As a result, we find it unnecessary to address the parties' dispute about this consideration in detail. However, we do note that the court relied on a case that involved copying a claimed manufacturing process for preparation of a drug. *Id.* (citing *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728, 731 (Fed. Cir. 2017)). The claims here do not recite the process of manufacturing a drug. Further, it was undisputed that particle size, which the court focused on for copying, impacted the pharmacokinetic properties of the paliperidone palmitate LAI. *See, e.g.*, '544 patent col. 3 ll. 52–55; J.A. 11777:18–21 (Janssen's expert agreeing that the '544 patent's statements teach that particle size impacts pharmacokinetics, "and that's consistent with scientific principles"). In previous ANDA cases, this court has emphasized that "a showing of bioequivalence is required for FDA approval" when discussing

1

We first address the district court's treatment of unexpected results. "In considering unexpected results, courts ask whether the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" compared to the prior art as of the priority date. *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (cleaned up). The starting reference point for evaluating unexpectedness is the closest prior art. *See Bristol-Myers*, 752 F.3d at 977; *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006).

The district court found that "the [r]epresentative [c]laims led to unexpected results" and that the "unexpected results indicator weigh[ed] in favor of nonobviousness." *Opinion*, 571 F. Supp. 3d at 315–16. Teva argues that the district court erred because, among other things, it did not make the correct comparisons. We agree.

First, the district court compared the claims to "the conventional wisdom," related to antipsychotics generally, that dosing should "start low and go slow." *Id.* at 315 (citing expert testimony related to the dosing of risperidone, haloperidol decanoate, and risperdal consta). The court then cited a prior-art reference that provided an overview of drug delivery by injection, infusion, or implantation for the proposition that LAIs are "indicated for maintenance treatment rather than initiation of therapy." *Id.* (citing J.A. 14134). The court concluded that "[t]he claimed dosing regimens run contrary to these prior art teachings

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why evidence of copying was not probative. *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013); *see also Adapt Pharma*, 25 F.4th at 1374–75.

because they use depot injections of high, rather than low, loading doses to initiate treatment." *Id*.

To the extent this analysis related to *results* (unexpected or otherwise), it clearly does not involve a comparison of the closest prior art.[10] All the testimony cited for the "start low and go slow" proposition relates to medications with active ingredients other than paliperidone. Risperidone was used as a reference, and it does not have the active ingredient of paliperidone, and is not an injectable medication. J.A. 16244. Similarly, the reference discussing LAIs generally is not about paliperidone palmitate. In contrast, the prior art '548 protocol discloses administering a paliperidone palmitate injection of 150 mg-eq. on days 1 and 8. J.A. 13244. Evaluating unexpectedness via a comparison of the "start low and go slow" paradigm for other medications was improper. There is simply nothing unexpected about starting with a dose of the paliperidone palmitate LAI that was already disclosed simply because other medications were dosed differently.

Next, the district court concluded that the results were unexpected in view of the '548 protocol too. Although the '548 protocol is the closest prior art, the court did not use the required reference point for evaluating unexpectedness. The question was whether, as of the priority date, using the claimed dosing regimens yielded unexpected results when compared with a POSA's expectations based on the state of the prior art. The court instead based its finding of unexpectedness on two different comparisons: (1) a comparison between Janssen's expectations of the '548 protocol results and its disappointment in the results of the PSY-3003 clinical trial (including the lack of data generated by one study arm); and (2) a comparison between the

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[10] Janssen itself acknowledges that the '548 protocol is the closest prior art. Appellees' Br. 62.

unknown results of the PSY-3003 clinical trial and the results of Invega Sustenna.

As to the first comparison, the court found that the "inventors expected the Phase III clinical trials to be a success, especially because they built on the promising results of the SCH-201 study, which showed rapid efficacy." *Opinion*, 571 F. Supp. 3d at 315. Then, instead of comparing this expectation to the results achieved with the claimed regimens, the court looked to the unexpectedness of "the inventors encounter[ing] several clinical failures during Phase III." *Id.* It is unclear how, if at all, the unexpectedness of these failures relates to the claims. In addition, the court did not address the extent to which these failures related to the dosing regimen used in the trial as opposed to the fact that certain patients were *not* dosed in accordance with the protocol or study design.

As to the second comparison, the court found unexpectedness based on "*Invega Sustenna* improv[ing] patient treatment adherence through its use of high initial loading doses that rapidly achieved therapeutic concentrations of paliperidone palmitate and monthly loading doses which maintained these concentrations," compared with the data generated from the PSY-3003 clinical trial. *Id.* (emphasis added). Regardless of whether the clinical trial was later considered unsuccessful—and whether this was tied to the dosing regimens used instead of how the trial was conducted—the results of the clinical trial were not known or in the prior art. A POSA could not have been surprised by results of the claimed regimens compared with the '548 protocol results because a POSA would not have been aware of those results. *See Forest Labs.,* 918 F.3d at 937 ("At the time of the claimed invention, a person of ordinary skill could not have been surprised that the sublingual route of administration did not result in cardiotoxic effects because the person of ordinary skill would not have been aware that other routes of administration do result in cardiotoxic effects.").

Even if the correct comparison had been made between expectations based on information available to a POSA and the claimed regimens' results, it is still not entirely clear what result the district court was evaluating. For example, it is unclear whether the district court intended to analyze the unexpectedness of the level of treatment adherence achieved by the claimed regimen, the time required to reach therapeutic concentrations of paliperidone palmitate, or some combination of both. Likewise, the court labelled the '548 protocol a "failure" and the claimed regimens a "success" without explaining what metrics it was considering in its assessment of success and failure.

2

Next, Teva challenges the court's industry praise findings, arguing that the court relied on industry praise with no nexus to the claims. We do not address whether it would have been appropriate to find a nexus between the praise and the claims because we do not discern any analysis of nexus in this part of the court's opinion. *See Opinion*, 571 F. Supp. 3d at 317–18. Although the court generally stated that the secondary considerations evidence "is linked to the high loading dose deltoid injections and subsequent maintenance injections" before it addressed the specific secondary considerations, *id.* at 314, its industry praise analysis did not address this supposed link.[11] On

[11] To the extent the court's nexus analysis consists of the mere observation that Invega Sustenna is a product that embodies the claims and the praise related to Invega Sustenna, that was insufficient. For example, Janssen clearly asserts that the '906 patent covers an invention different from the '544 patent; however, both read on the Invega Sustenna product. *Cf. Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1377 (Fed. Cir. 2019) ("Where a product embodies claims from two patents, a presumption of

remand, the court should assess whether the praise "result[ed] from something . . . [that] is both claimed and *novel*." *See Merck & Cie*, 808 F.3d at 837 (cleaned up) (emphasis in original).

3

Finally, Teva argues that the district court improperly disregarded the impact of blocking patents when assessing long-felt need and commercial success. This court has explained that "if all other variables are held constant, a blocking patent diminishes possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing, therefore reducing incentives for innovations in the blocked space by non-owners and non-licensees of the blocking patent." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018). In turn, this decrease in incentives "can discount the significance of evidence" of commercial success and long-felt need (among other secondary considerations not addressed in this appeal) because the failure for others to achieve the claim may be more indicative of deterrence than inventiveness. *Id.* However, the degree of disincentive and its resultant deterrence (or lack of deterrence) is a fact-specific inquiry. *Id.*

We do not address the court's factual evaluation of the level of disincentive or corresponding deterrence present based on the blocking patents in this case. *See id.* (listing at least six variables that are generally relevant to the deterrence inquiry). And we do not address Teva's arguments about the court's assessment of the foundation for Teva's expert testimony. However, we do agree with Teva that the blocking-patent analysis rested on two faulty premises.

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nexus can be appropriate only if the claims of both patents generally cover the same invention.").

First, the consideration of the impact of the blocking patents should have focused on the blocked space that related to Invega Sustenna because that is what Janssen contended was commercially successful and filling an unmet need. The observation that there was testimony that "it was possible to practice [c]laim 2 of the '906 [p]atent . . . without infringing the claims of the '544 and '843 [p]atents," presumably by dosing a different formulation of paliperidone palmitate (i.e., not Invega Sustenna), *Opinion*, 571 F. Supp. 3d at 324, was therefore not pertinent.

Second, to the extent the determination of no deterrence rested on the existence of the safe harbor provision alone, that was error. *See id.* at 324–35. "[A] potential innovator might or might not be willing to research in the blocked space without a license to a blocking patent—even if the research itself is within the safe harbor provided by 35 U.S.C. § 271(e)(1)." *Acorda*, 903 F.3d at 1338. The existence of the safe harbor provision is a single aspect—one that is always present in the ANDA context—of the commercial realities that might impact whether blocking patents deter. If it were true that the existence of the safe harbor provision mitigates any deterrence from blocking patents, the fact-specific inquiry previously described would be unnecessary in every case implicating § 271. The ability to avoid infringement liability for conduct related to preparing FDA submissions does not end the inquiry into the potential deterrence associated with the risk of market entry preclusion once those submissions are complete.

We therefore remand for the district court to conduct its analysis of secondary considerations consistent with this opinion.

II

We now address Teva's indefiniteness arguments. Indefiniteness, like claim construction, is a question of law that can involve underlying factfindings based on extrinsic

evidence. We review the overall determination de novo and any underlying factual determinations for clear error. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1370 (Fed. Cir. 2017). Because the district court's indefiniteness determination here rests on factual findings that Teva has not shown to be clearly erroneous, we affirm.

To satisfy the definiteness requirement, "a patent's claims, viewed in light of the specification and prosecution history, [must] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). This court has held that claim scope is not reasonably certain where a claimed characteristic can be measured in multiple ways, those different measurements "would typically yield a different result" when applied to the same sample, and the intrinsic record fails to provide reasonable certainty about which measurement was intended by the claims. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341, 1345 (Fed. Cir. 2015).

Claim 19 contains a particle-size limitation for the paliperidone palmitate used in the formulations administered: "paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm." '906 patent claim 19. In turn, representative claims 20 and 21—which are representative only as they depend from claims 1 and 8—both depend from claim 19.

The claims do not specify what measurement technique should be used to determine whether the average particle size d(50) is from 1600 nm to 900 nm. Similarly, the specification states that particle size can be "measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation." *Id.* at col. 7 ll. 36–38. Example 1 provides particle-size distributions "measured by laser diffraction." *Id.* at col. 14 l. 52–col. 15 l. 14.

Teva argued that the different particle-size measurement techniques, which were all allowed by the claims, would yield meaningfully different results, creating a situation where the same physical samples of paliperidone palmitate would simultaneously fall inside and outside the claim depending only on how its particle-size measurement is taken. And it did point to evidence that, for particles in general, different particle-size measurement techniques *can* yield different results. J.A. 16306 (explaining how the particle size of imperfect spheres are defined "using the concept of equivalent spheres" and that "different measurement techniques use different equivalent sphere models and therefore will not necessarily give exactly the same result for the particle diameter"); J.A. 16434 ("[E]quivalent particle diameter is defined not only by the physical particle attribute measured, geometric or behavioral, but also by the measurement technique."). However, the district court found that the actual discrepancy in particle-size measurement of paliperidone palmitate that Teva relied on was "an outlier measurement taken with a defective device," i.e., was not based on a discrepancy typical of the measurement technique used. *Opinion*, 571 F. Supp. 3d at 335 n.52.

Teva has not shown that the court's outlier finding was clearly erroneous. As a result, the district court correctly determined that, on this record, Teva did not meet its burden to show that claims 20 and 21 are invalid as indefinite. Specifically, if the measurement discrepancy is an outlier, Teva did not present evidence that different measurement techniques would typically yield different particle-size measurements of paliperidone palmitate. *See Takeda Pharm. Co. v. Zydus Pharms. USA*, 743 F.3d 1359, 1366–67 (Fed. Cir. 2014) (explaining that the "mere possibility of different results" is insufficient for indefiniteness). As a result, we need not reach the parties' arguments about whether, were it typical, this measurement discrepancy—which caused the particle-size measurement to fall both

inside and outside the claimed range—would be significant or meaningful.

CONCLUSION

We vacate and remand the district court's determination of nonobviousness for proceedings consistent with this opinion. We affirm the court's determination on indefiniteness.

AFFIRMED-IN-PART AND VACATED AND REMANDED-IN-PART

COSTS

No costs.