

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACTELION PHARMACEUTICALS LTD,
Petitioner,

v.

ICOS CORPORATION,
Patent Owner.

Case IPR2015-00561
Patent 7,182,958 B1

Before SHERIDAN K. SNEDDEN, JAMES A. TARTAL, and
ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

INTRODUCTION

Actelion Pharmaceuticals Ltd (“Petitioner”) filed a Petition (Paper 1, “Pet.”) to institute an *inter partes* review of claims 1–32 of U.S. Patent No. 7,182,958 B1 (Ex. 1003, “the ’958 patent”). On August 4, 2015, the Board instituted a review of the patentability of the challenged claims. Paper 7 (“Dec.”). Thereafter, Patent Owner filed a Response (Paper 16 (“PO Resp.”)), and Petitioner filed a Reply (Paper 20 (“Reply”)). The parties also briefed whether certain exhibits should be excluded from the record. *See* Papers 24, 27, 37–39, 42–45. Oral hearing was held on April 13, 2016. *See* Paper 49 (“Tr.”).

The Board has jurisdiction under 35 U.S.C. § 6(c) and issues this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons provided below, we determine that Petitioner has met its burden of proving the unpatentability of claims 1–32 of the ’958 patent by a preponderance of the evidence. *See* 35 U.S.C. § 316(e).

Related Proceedings

The ’958 patent is the subject of certain district court cases, to which Petitioner is not a party. Pet. 1; Paper 4, 2.

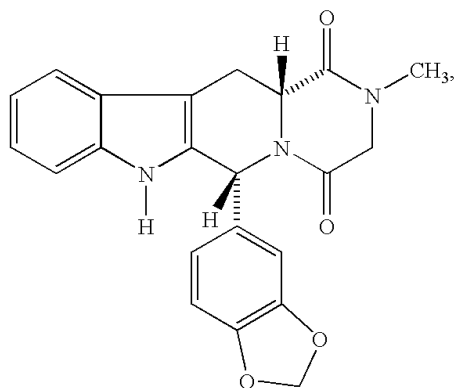
Concurrently with the Petition, Petitioner filed another petition for an *inter partes* review in IPR2015-00562, challenging the claims of U.S. Patent No. 6,821,975 B1, also owned by Patent Owner. We instituted trial in that case, and issue a final decision therein concurrently with this Final Written Decision. *See Actelion Pharm. Ltd. v. ICOS Corp.*, Case IPR2015-00562, (PTAB Aug. 3, 2016) (Paper 50).

The '958 Patent

The '958 patent relates to formulations containing PDE5 inhibitors, specifically, β -carboline compounds, and their use in treating sexual dysfunction. Ex. 1003, Abstract, 1:14–20.

Because of their poor solubility, many β -carboline compounds were developed as co-precipitate preparations before the '958 patent. *Id.* at 1:43–49. According to the '958 patent, however, the co-precipitate products have various drawbacks, and thus, are “less than ideal for pharmaceutical formulations.” *Id.* at 1:50–63.

The '958 patent discloses a pharmaceutical formulation comprising a compound of formula (I) and pharmaceutically acceptable salts and solvates thereof. *Id.* at 2:3–28. Formula (I) has the following structure:



Id. at 2:5–20. In the '958 patent, the compound of formula (I), known as tadalafil, “preferably is provided as a free drug.” *Id.* at 2:28–29. According to the '958 patent, formulating the compound of formula (I) “with a particular combination of pharmaceutical excipients” enhances dosage uniformity, stability, and bioavailability. *Id.* at 3:65–4:4.

Illustrative Claim

Claim 1 is the sole independent claim challenged in the Petition. It reads:

1. A pharmaceutical formulation comprising an active compound having the structural formula [of formula (I),]

wherein said compound is provided as free drug comprising particles wherein at least 90% of the particles of the said compound have a particle size of less than about 40 microns; about 50% to about 85%, by weight, of a water-soluble diluent; a lubricant; a hydrophilic binder selected from the group consisting of a cellulose derivative, povidone, and a mixture thereof; and a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, and a mixture thereof.

Claims 2–32 depend, directly or indirectly, from claim 1.

Specifically, claims 2–19 and 24–26 are directed to pharmaceutical formulations. Claims 20–23 and 27–30 are directed to tablets comprising, or capsules encasing, the formulation of claim 1. Claims 31 and 32 are directed to methods of treating sexual dysfunction using the composition of any one of claims 1–23 and 28–30.

Reviewed Ground of Unpatentability

The Board instituted trial to review whether the combination of Daugan,¹ Seth,² Butler,³ and the common pharmaceutical knowledge

¹ Daugan, WO 97/03675, published Feb. 6, 1997 (Ex. 1006, “Daugan”).

² Seth et al., U.S. Patent No. 4,721,709, issued Jan. 26, 1988 (Ex. 1011, “Seth”).

³ Butler, WO 96/38131, published Dec. 5, 1996 (Ex. 1008, “Butler”).

evidenced in Wadke,⁴ Rudnic,⁵ and Banker,⁶ renders claims 1–32 obvious.
Dec. 13.

ANALYSIS

Claim Construction

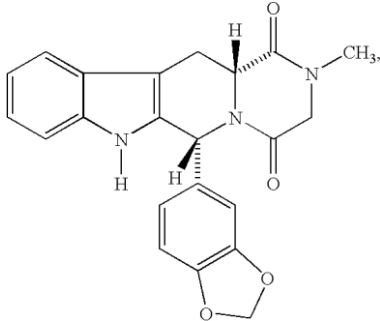
In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

In the Decision to Institute, we determined that the terms “compound having the structural formula” and “free drug” are expressly defined in the ’958 patent Specification as follows:

⁴ Deodatt A. Wadke et al., *Preformulation Testing*, in PHARMACEUTICAL DOSAGE FORMS: TABLETS 1–73 (Herbert A. Lieberman et al. eds., 2d ed., revised and expanded, Marcel Decker 1989) (Ex. 1014, “Wadke”).

⁵ Edward M. Rudnic & Mary Kathryn Kottke, *Tablet Dosage Forms*, in MODERN PHARMACEUTICS 333–94 (Gilbert S. Banker & Christopher T. Rhodes eds., 3d ed., Marcel Decker 1996) (Ex. 1013, “Rudnic”).

⁶ Gilbert S. Banker & Neil R. Anderson, *Tablets*, in THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY, 293, 324–29 (Leon Lachman et al. eds., 3d ed., Lea & Febiger 1986) (Ex. 1018, “Banker”).

Claim Term	Construction
the structural formula 	formula (I), also known as: (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; or (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxymethyl)pyrazino[2',1':6.1]pyrido[3,4-b]indole-1,4-dione (Ex. 1003, 2:3–26)
free drug	solid particles consisting essentially of the compound of structural formula (I), as opposed to the compound intimately embedded in a polymeric coprecipitate (Ex. 1003, 3:11–14)

Dec. 5–6. During trial, the parties did not dispute this determination.

Having considered the complete record developed at trial, we see no reason to change our interpretation of those terms.

Prior Art Disclosures

Daugan

Daugan identifies (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxymethyl)pyrazino[2',1':6.1] pyrido[3,4-b]indole-1,4-dione, also known as compound (A), as a compound of the invention. Ex. 1006, 00005:24–25. Compound (A) is the same as the compound of formula (I) in the '958 patent, i.e., tadalafil.

According to Daugan, tadalafil may be administered orally to treat erectile dysfunction. *Id.* at 00005:30–32. Daugan teaches formulating tadalafil with a pharmaceutically acceptable diluent, carrier, or excipient. *Id.* at 00007:15–26, 32–36. It also teaches that “for a typical adult patient,

individual tablets or capsules contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.”

Id. at 00007:4–7. Specifically, Daugan teaches preparing tablets with 50 mg active compound. *Id.* at 00014:15–00016:16.

Butler

Butler teaches the preparation of solid dispersions of poorly water soluble drugs, and their use in pharmaceutical compositions. Ex. 1008, 00003:3–5. According to Butler, tadalafil, also referred to as Compound A, is a poorly water soluble drug. *Id.* at 00006:15–18, 00007:4–5. Butler teaches the process to prepare a solid dispersion of tadalafil, comprising co-precipitating Compound A and a pharmaceutically acceptable carrier or excipient. *Id.* at 00006:15–21, 00007:1–29, 00016:13–00017:16.

Seth

Seth teaches pharmaceutical compositions of hydrophobic drugs adsorbed onto carriers such as starch and/or microcrystalline cellulose. Ex. 1011, Abstract.

Seth explains that when poorly soluble, hydrophobic drug substances are employed in the preparation of solid dosage forms such as tablets or capsules, their rate of dissolution and absorption is slow, which affects the therapeutic utility. *Id.* at 1:66–2:8. Seth teaches methods that “finely grind or ‘micronise’ drug substances so as to reduce their particle size” to 5–10 microns may overcome such problems. *Id.* at 2:9–13. According to Seth, the grinding methods, however, also have some disadvantages. *Id.* at 2:13–20.

Seth teaches that

The problem is solved by providing a dry powder pharmaceutical composition containing a hydrophobic, poorly soluble drug that is adsorbed on to a pharmaceutical carrier preferably an organic pharmaceutical carrier such as starch or cellulose and is characterised in that the drug is present in particulate form and that the drug particles have a mean particle size of less than 10 microns and a particle size distribution such that at least 95% of particles are smaller than 15 microns.

Id. at 4:44–52.

Wadke

Wadke teaches that it is “generally recognized that poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided state than as a coarse material.” Ex. 1014, 00007. According to Wadke, grinding poorly water-soluble materials increases dissolution rate. *Id.* Wadke suggests “[g]rinding should reduce coarse material to, preferably, the 10- to 40- μm range.” *Id.* at 00007–08.

Level of Ordinary Skill

The parties agree that a person of ordinary skill in the art “would have background and experience relating to oral dosage formulations. Such a person would have either a Ph.D. in Chemistry, Pharmaceuticals, or Chemical Engineering (with a few years of experience in the preparation, formulation, and characterization of orally administered formulations), or a Bachelor’s or Master’s degree in Chemistry, Pharmaceuticals, or Chemical Engineering with a proportionately greater degree of work experience.” Pet. 14 (citing Ex. 1002 ¶ 46); PO Resp. 5–6.

In addition, Petitioner contends an ordinary artisan “would also have

to have knowledge of particle size reduction and the expression of particle size distributions, and be able to understand the effect of particle size on the absorption of drug substances.” Pet. 14 (citing Ex. 1002 ¶ 46). Patent Owner does not dispute this assertion. It, however, disagrees with Petitioner’s argument that prior art “patents and printed publications all reflect the understanding in the art that particle size reduction is a general solution to poor drug dissolution.” PO Resp. 6 (citing Pet. 16). According to Patent Owner, the prior art sometimes criticized micronization, for example, as “counterproductive, since the micronized particles may aggregate, which may decrease the surface area.” *Id.* (citing Ex. 1019).

We do not understand the parties’ positions to be inconsistent with each other. Indeed, one of ordinary skill in the art would have understood that micronization “is routinely used to reduce the particle size of active ingredients so that the maximum surface area is exposed to enhance the solubility and dissolution properties of poorly soluble compounds.” Ex. 1019, 00007. At the same time, an ordinary artisan also would have recognized micronization—like any other formulation method—is not a panacea, as “particle size is of importance only when the absorption process is rate-limited by the dissolution rate in gastrointestinal fluids.” Ex. 2060, 6.

Obviousness over the Combination of Daugan, Seth, and Butler

Petitioner contends that claims 1–32 would have been obvious over the combination of Daugan, Seth, Butler, and the common pharmaceutical knowledge evidenced in Wadke, Rudnic, and Banker. Pet. 21–59. In support of its patentability challenges, Petitioner relies on the Declarations

of Dr. Harry G. Brittain. Exs. 1002, 1046.⁷ After reviewing the entire record, we conclude Petitioner has shown by a preponderance of the evidence that the challenged claims are unpatentable as obvious.

Claims 1–19, 24–28, 31, and 32

Petitioner refers to Daugan for teaching free drug tadalafil as an active compound in a tablet or capsule, as recited in claim 1. Pet. 16–17.

Petitioner also points to Daugan for teaching a diluent, a lubricant, a binder, and a disintegrant, as recited in claim 1. *Id.* at 26–33 (citing Ex. 1006, 00014–00016). Petitioner further refers to Seth for teaching a dry powder pharmaceutical composition containing a poorly soluble drug adsorbed onto a pharmaceutical carrier, wherein the drug is present in particulate form with the particle size and the distribution of particles within the range recited in claim 1. *Id.* at 17–18 (citing Ex. 1011, 4:44–52). Petitioner asserts that one of ordinary skill in the art would have had a reason to combine the teachings of Daugan and Seth because Butler teaches tadalafil as a poorly water soluble drug while Wadke teaches reducing particle size to improve the dissolution of a poorly water soluble drug. *Id.* at 23–24. According to Petitioner, an ordinary artisan would have had a reasonable expectation that modifying tadalafil as taught in Daugan with the teachings of Seth and Wadke would have resulted in a pharmaceutical formulation that includes every limitation of claim 1. *Id.* at 21–33, 46–48.

⁷ Patent Owner criticizes Dr. Brittain’s testimony in Exhibit 1002 as inconsistent and fundamentally flawed. PO Resp. 6–14. In addition, Patent Owner moves to exclude Exhibit 1046. Paper 27, 9–14. As explained below, we deny Patent Owner’s Motion to Exclude. For each of Exhibits 1002 and 1046, we consider Dr. Brittain’s testimony and accord it proper weight.

Relying on the Declaration of Dr. Stephen Byrn (Ex. 2075),⁸ Patent Owner contends that the references fail to teach the combination of excipients as claimed. PO Resp. 43–46. In addition, Patent Owner argues that neither the asserted prior art nor the general knowledge in the art would have provided one of ordinary skill in the art a reason to combine the references or the expectation of success in doing so. *Id.* at 18–43. We address each of Patent Owner’s arguments in turn.

Combination of Excipients

Patent Owner does not dispute that the asserted prior art teaches the free drug tadalafil as well as the particle size and the size distribution recited in claim 1. Patent Owner, however, challenges whether the combination of asserted prior art teaches tadalafil with the excipients recited in claim 1. According to Patent Owner, “Petitioner’s relies [sic] on generic disclosure of *Rudnic* and *Bunker* [sic] to argue that ‘there is nothing inventive about employing [commonly used excipients] in a pharmaceutical composition,’ . . . is flawed.” PO Resp. 43. Patent Owner further argues that “even with Petitioner’s proposed selections of components from *Rudnic* and *Bunker* [sic], the prior art is still missing an express limitation—‘about 50 to about 85% weight of diluent.’” *Id.* at 45. We disagree.

Petitioner cites *Rudnic* and *Banker* to explain the knowledge of an ordinary artisan, including, for example, that lactose is a widely employed water-soluble diluent. *See* Pet. 26–27. And in an obviousness inquiry, we must consider the background knowledge possessed by a person having

⁸ Petitioner contends that Dr. Byrn’s testimony in Exhibit 2075 should be given little weight because it contains multiple factual errors and omissions. Reply 2–12. We consider Dr. Byrn’s testimony and accord it proper weight.

ordinary skill in the art. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Moreover, contrary to Patent Owner's allegation, Petitioner does not "pick and choose" the recited excipients based on a generic disclosure of Rudnic and Banker. Instead, Petitioner relies on specific teachings in Daugan. Indeed, Petitioner contends, and we agree, that (1) examples A1 and B2 of Daugan include lactose as a water-soluble diluent and teach tablet formulations with 70% by weight anhydrous lactose and 59% by weight lactose, respectively; (2) all examples in Daugan use magnesium stearate as a lubricant; (3) example B1 of Daugan uses povidone as a hydrophilic binder; and (4) example B1 of Daugan uses croscarmellose sodium and examples A1 and A2 use crospovidone as disintegrants. Pet. 26–33 (citing Ex. 1006, 00014–16). In other words, Daugan teaches the required excipients and the amount of diluent within the range recited in claim 1.

Reason to Combine

Petitioner asserts that (1) Butler teaches tadalafil has poor solubility; (2) poorly soluble drugs have a slow dissolution rate, which results in poor absorption; and (3) both Seth and Wadke teach reducing the particle size of a drug improves the dissolution and absorption of the drug. Pet. 23–24. According to Petitioner, these combined teachings "would have suggested to a person of ordinary skill in the art that this [micronization] process should be carried out with tadalafil." *Id.* at 25–26.

Patent Owner insists that "no [prior art] references teaches that tadalafil free drug absorption would be limited by dissolution rate." PO Resp. 19. Instead, according to Patent Owner, the '958 patent came into being because the inventors recognized that, in the clinic, absorption of

coprecipitated tadalafil, as taught in Butler, “lacked sufficient reproducibility and absorption rate.” *Id.* at 2–3, 22. Patent Owner contends “[t]he inventors’ recognition in this regard is not part of the prior art, but instead evidences the non-obviousness of the claimed subject matter.” *Id.* at 22.

The law “does not require that the references be combined for the reasons contemplated by the inventor.” *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992). Indeed,

[T]he problem motivating the patentee may be only one of many addressed by the patent’s subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR, 550 U.S. at 420.

Such is the case here. Patent Owner may be correct that none of the asserted prior art explicitly identifies slow dissolution rate as a problem for tadalafil. PO Resp. 33. Evidence of the record, however, shows that at the time of the invention, it was known that tadalafil has low solubility.

Ex. 1008, 00007. And it was known that compounds with low solubility generally also have a slow dissolution rate:

It is a common observation that when poorly soluble, hydrophobic drug substances are employed in the preparation of solid dosage forms such as tablets or capsules, their rate of dissolution is rather slow. As a result, their absorption from the gastrointestinal tract into systemic blood of the body is also slow.

Ex. 1011, 1:66–2:8; *see also* Ex. 1014, 00026 (“[F]or relatively insoluble compounds, the rate-determining step in the overall absorption process is generally the rate of dissolution.”). It was also known that “a conventional

method for increasing the rate of dissolution of solids is by reduction of their particle size by micronisation.” Ex. 1011, 3:64–66; *see also* Ex. 1014, 00025 (stating particle size reduction is a “commonly employed practice” to enhance dissolution). Thus, the teachings of Butler, Seth, and Wadke reasonably suggest that tadalafil has slow dissolution, and we are persuaded that one of ordinary skill in the art would have combined the asserted prior art to solve the problem by micronizing tadalafil.

Patent Owner contends that “a thorough preformulation investigation is necessary to determine a putative drug’s unique physical and biological properties, including its solubility and permeability.” PO Resp. 7. According to Patent Owner, “[w]ithout this preformulation information . . . one cannot rationally design a pharmaceutical formulation.” *Id.* We have no reason to doubt the accuracy of this statement. Whether, at the time of the invention, one of ordinary skill in the art would so practice, however, is unclear. Indeed, Yu,⁹ a reference relied on by Patent Owner, laments that “[r]ational formulation design based on pharmaceutical properties of compounds [wa]s far from a reality” in 1999, the apparent time of the ’958 patent invention. Ex. 2071, 1.

In addition, Petitioner contends that at the time of the invention, an ordinary artisan “was not drawing on a blank canvas.” Reply 12. Instead, Petitioner asserts, Daugan “already disclosed multiple oral formulations” of tadalafil, including tablets and capsules. *See id.* (citing Ex. 1006, 00014:15–00018:9). When questioned during the hearing, counsel for Patent Owner

⁹ Lawrence X. Yu, *An Integrated Model for Determining Causes of Poor Oral Drug Absorption*, 16 PHARM. RES. 1883–87 (1999) (Ex. 2071 “Yu”).

argued that “Daugan is all prophetic.” Tr. 34:16. “Under an obviousness analysis, a reference need not work to qualify as prior art; it qualifies as prior art, regardless, for whatever is disclosed therein.” *Geo. M. Martin Co. v. Alliance Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1302 (Fed. Cir. 2010) (citations and internal quotation marks omitted); *see also Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (“Even if a reference discloses an inoperative device, it is prior art for all that it teaches.”). Thus, we agree with Petitioner and find a preponderance of the evidence supports Petitioner’s argument that an ordinary artisan would have been guided by the teachings of Daugan to improve the oral formulations of tadalafil.

Moreover, even if, at the time of the invention, one of ordinary skill in the art would have started from scratch to conduct a preformulation investigation, we disagree with Patent Owner that an ordinary artisan would have expected micronization, an otherwise routine formulation technique, to be unsuitable for tadalafil. *See* PO Resp. 35–43.

Wadke teaches grinding a drug substance to reduce the particle size before conducting in-depth preformulation studies. Ex. 1014, 00007–00008. Counsel for Patent Owner argues that because the title of Wadke is “Preformulation Testing,” it is irrelevant to formulation development. Tr. 25:13–26:11. This distinction, however, does not carry the day. Patent Owner does not explain why, after tadalafil is micronized at an early stage of preformulation, even if only for testing purposes, an ordinary artisan would later, during formulation, abandon that approach entirely. We find the evidence of record suggests otherwise. *See* Ex. 2026, 16 (“[P]article size

determinations should be carried out in preformulation as well in formulation functions.”).

Yu explains that “the absorption of poorly absorbable drugs can be limited by permeability, solubility, and/or dissolution.” Ex. 2071, 2. According to Yu, “poor dissolution can be caused either by particle size . . . or solubility.” *Id.* Wadke also teaches that “for relatively insoluble compounds, the rate-determining step in the overall absorption process is generally the rate of dissolution.” Ex. 1014, 00026. In addition, Wadke states that “[i]nasmuch as the rate of dissolution of a solid is a function of its solubility in the dissolution medium, the latter could influence absorption of the relatively insoluble drugs.” *Id.* at 00015. Furthermore, “[s]ince dissolution precedes absorption in the overall scheme, any change in the process of dissolution would influence the absorption. It is essential, therefore, to investigate the dissolution behavior of drug substances, especially those with moderate and poor solubility. Efforts are then undertaken to alter this process if deemed necessary.” Ex. 1014, 00020–00021.

Patent Owner has not presented sufficient evidence or persuasive argument to show that information from a preformulation analysis would have deterred an ordinary artisan from pursuing micronization to improve the dissolution and absorption of tadalafil. According to Patent Owner, a preformulation investigation would have shown the solubility of tadalafil is 2 µg/ml. PO Resp. 36 (citing Ex. 2065). Such “extremely low solubility,” Patent Owner asserts, would have suggested to a person of ordinary skill that tadalafil would not be suitable as any oral dosage form, including one formulated through micronization. *Id.* at 36–37. We disagree.

Dr. Byrn, Patent Owner's declarant, testifies that "[a]t the time of the ['958 patent] invention, it was known that tadalafil was poorly water soluble, but its exact solubility had not been reported." Ex. 2075 ¶ 135. Instead, citing two post-filing date patent documents, he states that the solubility of tadalafil is "as low as around 2 µg/ml." *Id.* ¶ 139 (citing Ex. 2065, 5:11–13; Ex. 2070, 3:19–21).

Petitioner challenges this as a "mistaken factual premise" for Patent Owner's argument. Reply 8. According to Dr. Brittain, the witness for Petitioner, the values reported in Exhibits 2065 and 2070 not only are unsupported by experimental evidence (Ex. 1046 ¶ 17), but also contradict each other (*id.* ¶ 16). He points out that Exhibit 2065 reports the water solubility of tadalafil is 2 µg/ml at 25°C, whereas Exhibit 2070 reports the solubility is the same at 37°C. *Id.* (citing Ex. 2065, 4:20–22; Ex. 2070, 3:20–21). Dr. Brittain testifies that because the solubility of a compound is often highly dependent on the temperature at which the measurement is made, "it is extraordinarily unlikely that tadalafil would exhibit exactly the same solubility in water at both 25°C and 37°C." *Id.* In addition, Dr. Brittain points to several peer-reviewed, post-filing date publications, which show that the water solubility of tadalafil is 13.6 µg/mL at 25°C, 18.2 µg/mL at 32°C, and 20 µg/ml at 37°C. *Id.* ¶ 17 (citing Ex. 1043), ¶ 18 (citing Exs. 1036, 1045). We find Dr. Brittain's explanation reasonable.

On the whole, we find that a preponderance of the evidence shows that, at the time of the invention, an ordinary artisan, even after conducting a preformulation analysis, would not have avoided formulating tadalafil

through micronization because it is so insoluble that it is not suitable for developing an oral dosage form.¹⁰

Our finding is supported by the teachings of Daugan. Patent Owner asserts “Daugan teaches that crystalline free drug tadalafil has an extremely high melting point of 302-303°C” (*id.* at 18 (citing Ex. 1006, 11:7)), which indicates “potentially serious solubility problems” (*id.* (citing Ex. 2075 ¶¶ 96–98)). Yet Daugan teaches various oral formulations of tadalafil, including tablets and capsules. Ex. 1006, 00014:15–00018:9. Patent Owner has not presented sufficient evidence or persuasive argument to show that one of ordinary skill in the art would not have pursued micronization to improve those formulations.

Similarly, we find that an ordinary artisan, at the time of the invention, and even after conducting a preformulation analysis, would not have avoided formulating tadalafil through micronization due to the alleged concern that the absorption is permeability-limited. Dr. Byrn opines that “[i]f tadalafil was understood to have low permeability and permeability-limited absorption,” or even if it has medium permeability, micronization would not be effective to increase absorption. Ex. 2075 ¶ 144. Evidence of the record, however, does not support the assumption

¹⁰ Dr. Byrn opines that tadalafil’s absorption would become solubility limited at doses higher than 3.82 mg. Ex. 2075 ¶ 148. He reaches this conclusion, however, using 2 µg/ml as the solubility of tadalafil and assuming tadalafil has a medium permeability. *Id.* Because reports on both the solubility and permeability appear inconsistent (*see supra* at 17, *infra* at 19–20), we do not need to address Patent Owner’s argument based on Dr. Byrn’s calculation of 3.82 mg as the resulting saturation dose. *See, e.g.*, PO Resp. 39.

that, at the time of the invention, an ordinary artisan would have understood tadalafil to have low or medium permeability, or its absorption to be permeability-limited.

Dr. Byrn testifies that “[t]he permeability of tadalafil was also apparently unreported at the time of the invention.” *Id.* ¶ 143. According to Dr. Byrn, the teaching in Dugan that “50 mg of tadalafil forms a suspension (and not a solution) in 1 ml of Labrafil M1944CS,” an organic solvent, indicates “potential permeability problems for lacking lipophilicity.” Ex. 2075 ¶¶ 98, 135. Petitioner disputes this conclusion. Reply 6. According to Petitioner, both Dugan (Ex. 1006, 00013:3–5, 00013:11, 00018:18) and post-filing date references (Exs. 1036, 2065) show that tadalafil is “readily soluble” in a variety of organic solvents, including Labrafil. *Id.* at 6–7. Even long after the invention, reports on the permeability of tadalafil appear to be inconsistent. *See, e.g.*, Ex. 1044 (high permeability), Exs. 2041, 2070 (low permeability). Thus, we are not persuaded that at the time of the invention, one of ordinary skill in the art, even after conducting a preformulation analysis, would have understood tadalafil to have low or medium permeability.

Moreover, in its submissions to the FDA, Patent Owner itself characterized tadalafil as having high permeability. *See* Ex. 1037, 8 (stating tadalafil “is very soluble in ethanol and classified as a low soluble highly permeable drug”); Ex. 1038, 26. Given that Exhibit 1037 appears to be the Chemistry Review Data Sheet submitted by Patent Owner in seeking regulatory approval of the new drug application for tadalafil (Ex. 1037, 2), we find the information contained therein credible. We find that, at the time of the invention, one of ordinary skill in the art, after conducting a

preformulation analysis, would have understood tadalafil to have high permeability.

Of course, the more relevant question here is not the absolute permeability of tadalafil, but rather, whether its absorption is permeability-limited. According to Yu, “[p]ermeability-limited absorption occurs for highly soluble drugs or drugs dosed in solutions.” Ex. 2071, 3. Wadke also teaches that “for relatively soluble compounds, the rate of permeation across biological membranes is the rate-determining step.” Ex. 1014, 00026. Despite the parties’ quarrel over whether it should be 2 or 20 µg/ml, there is no dispute that the solubility of tadalafil is low. See Ex. 1008, 00007. Thus, we are not persuaded that at the time of the invention, one of ordinary skill in the art, even after conducting a preformulation analysis, would have understood tadalafil absorption is permeability-limited.

Patent Owner further argues that prior art teaches away from micronizing. PO Resp. 20–32. According to Patent Owner, micronizing is going in “the opposite direction” of Butler (*id.* at 22), which “teaches against maintaining a low solubility drug in free drug state and instead creating an enhanced solubility coprecipitate” (*id.* at 21). Patent Owner contends, “given *Butler*’s focus on increasing solubility, it is not conceivable that one skilled in the art would have been motivated to go backwards in technology to micronize free drug when that would be expected to increase the particle size and *decrease* solubility relative to *Butler*’s coprecipitate.” *Id.* at 23. We disagree.

As evident from Butler, in the pharmaceutical industry, “overcom[ing] the problem of poor water solubility” is rarely the ultimate goal; rather,

improving the “resultant low bioavailability” is. Ex. 1008, 00003; *see also* Ex. 1011, 2:6–8 (“[T]he slow rate of dissolution and slow rate of absorption can put very great limitations on their therapeutic utility.”). Thus, even though Butler may have successfully increased solubility through coprecipitation, which “provides the ‘ultimate’ in particle size reduction” (PO Resp. 3), it would not have discouraged an ordinary artisan from pursuing other common methods to improve dissolution and absorption.

Indeed, “just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” Dec. 11 (quoting *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)). Patent Owner contends that *Mouttet* is distinguishable. According to Patent Owner, in *Mouttet*, the inferiority was “for **certain** purposes.” PO Resp. 40. In contrast, Patent Owner argues, coprecipitation “would be expected to be superior to micronization for **all purposes**.” *Id.* (citing Ex. 1014, 7; Ex. 2060, 6; Ex. 2075 ¶¶ 176–188). As support, Patent Owner points out that Dr. Brittain personally prefers coprecipitation over micronization. *Id.* at 41 (citing Ex. 1033, 145:23–146:8).

Dr. Brittain’s personal preference, however, does not suggest coprecipitation is superior to micronization. *See* Ex. 1033, 146:3–147:4 (stating “it’s formulator’s preference” and some formulators “would never do [coprecipitation], and they would mill everything, because that’s what they do”). Further, Patent Owner does not cite any authority that draws a line between inferiority for certain purposes versus for all purposes. For example, Patent Owner does not argue that any case it relies on held a claim unobvious merely because the claimed subject matter is inferior to prior art teachings for all purposes. As a result, we are not persuaded that Butler’s

disclosure of coprecipitation teaches away from micronization.

Patent Owner also contends that Seth teaches “*drug-plus* formulation and points away from micronized *free drug* formulations.” PO Resp. 24. Thus, according to Patent Owner, Petitioner, when asserting Seth teaches micronization, has either misunderstood or misrepresented the teachings of Seth. *Id.* at 26 (citing Pet. 17).

We agree with Patent Owner that the invention of Seth relates to “precipitating the dissolved drug from solution directly onto the carrier.” PO Resp. 25. Petitioner does not dispute this. *See* Pet. 17 (summarizing that “Seth discloses dry powder pharmaceutical compositions of a hydrophobic poorly soluble drug adsorbed onto an inert pharmaceutical carrier”). Petitioner, however, cites the background section of Seth to support its argument that “Seth discloses that micronization was typically employed when drugs were known to have poor solubility, and that the milling techniques in use would typically reduce the particle size to below 10 microns.” *Id.* (citing Ex. 1011, 2:9–13). We are also persuaded that Petitioner relies on Seth for teaching the particle size, and not the micronization process. Reply 14; *see also* Pet. 22 (citing Seth for teaching the drug in particulate form, the drug particle size, and the particle size distribution).

Pointing out that Seth only discusses micronization in its background, Patent Owner further argues that Seth teaches away because it “expressly criticizes micronization and instead suggests a ‘drug plus’ formulation for a poorly water soluble drug.” PO Resp. 26–28 (citing Ex. 1011, 2:9–23, 3:65–4:2). We disagree.

Patent Owner is correct that Seth refers to micronization in the

background section. A person of ordinary skill, however, would read a reference for all that it teaches, including uses beyond its primary purpose. *KSR*, 550 U.S. at 418–21. Regarding the teaching-away argument, “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Here, as Dr. Byrn testified, despite the disadvantages mentioned in Seth, at the time of the ’958 patent invention, an ordinary artisan did not stop using micronization to address dissolution problems associated with low solubility. Ex. 2104, 126:12–21. In fact, Dr. Byrn added, micronization is still used in some marketed drugs, even today. *Id.* at 125:22–126:3. In other words, one of ordinary skill in the art, upon reading Seth, would not have been discouraged from pursuing micronization. Thus, we do not find Seth teaches away from micronization.

Patent Owner similarly contends Wadke teaches away because it expressly discloses the drawbacks of micronization and micronized particles. PO Resp. 31–32. For the same reason explained above as related to Seth, we do not find Wadke teaches away from micronization.

The parties also dispute the teachings of an excerpt of Wadke, each emphasizing a different portion thereof. The entire passage reads:

When dissolution is considered to be slow, a means of enhancing it may be sought. In the absence of a more soluble physical or chemical form of the drug, particle size reduction is the most commonly employed practice. Enhanced surface area, with a concomitant increase in the dissolution, can also be accomplished by adsorbing the drug on an inert excipient with a high surface area, such as fumed silicon dioxide. Comelting, *coprecipitating*, or triturating a relatively insoluble drug with some excipients *can also result in faster dissolution*.

Ex. 1014, 00025 (internal citations omitted, emphases added).

Petitioner relies on the language that particle size reduction is a common practice. Pet. 23. Highlighting the sentence “[i]n the absence of a more soluble physical or chemical form of the drug,” Patent Owner argues that Wadke teaches particle size reduction is only appropriate if solubility cannot be increased. PO Resp. 30. We do not read Wadke as narrowly as Patent Owner does.

Indeed, Wadke, after suggesting a more soluble form of the drug and particle size reduction to improve dissolution, states that coprecipitation, “can also result in faster dissolution.” Ex. 1014, 00025. If we were to, as Patent Owner insists we must, read Wadke as teaching increasing solubility must be pursued before particle size reduction (Tr. 35:4–25), then in the same vein, we would also need to read Wadke as teaching that coprecipitation is not a method to increase solubility and may only be pursued *after* particle size reduction. This conclusion, logically drawn from Patent Owner’s position, however, contradicts Patent Owner’s contentions elsewhere that the tadalafil coprecipitate taught in Butler increases solubility and would be expected to be superior to micronization for all purposes. See, e.g., PO Resp. 20–21, 40. Thus, we determine that when read in its entirety, Wadke does not imply a sequential practice; rather, it teaches increasing

solubility and particle size reduction as alternative means to increase dissolution. As the “mere disclosure of alternative designs does not teach away,” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004), we are not persuaded by Patent Owner’s argument that Wadke further teaches away from micronization and towards coprecipitation.

For the foregoing reasons, we determine that Petitioner has shown by a preponderance of the evidence that the teachings of the asserted prior art (that tadalafil has poor solubility; that poorly soluble drugs have a slow dissolution rate, which results in poor absorption; and that reducing the particle size of a drug is a known, common practice to improve the dissolution and absorption of a drug) would have suggested to a person of ordinary skill in the art to micronize tadalafil.

Reasonable Expectation of Success

The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Patent Owner argues that without preformulation information, rational design would not have been possible.¹¹ PO Resp. 16. According to Patent Owner, had a preformulation analysis been conducted or had the known properties, such as the melting point, been properly considered, “the expectation would have been that micronized free drug tadalafil would **not** have been successful at least because micronization

¹¹ Motivation to combine and reasonable expectation of success are two legal issues not to be conflated. *Intelligent Bio-Sys.*, 821 F.3d at 1367. We note that, in this case, Patent Owner appears to advance the same arguments for both issues. See PO Resp. 14–42.

would not overcome the expected solubility and/or permeability limited absorption.” *Id.* at 17. We disagree.

Daugan teaches formulating tadalafil into oral dosage forms, including tablets and capsules. Ex. 1006, 00014:15–00018:9. As explained above, an ordinary artisan would have been guided by the teachings of Daugan to improve the oral formulations of tadalafil. *See supra* at 14–15. As such, for the obviousness analysis here, preformulation studies would not have been essential. And even if they were, as we further explained, the preformulation tests would not have deterred an ordinary artisan from pursuing micronization to improve the absorption of tadalafil. *See supra* at 15–20. Because the asserted prior art teaches that reducing the particle size of a drug improves the dissolution and absorption of a poorly soluble drug, and tadalafil is such a drug, we find that a person of ordinary skill would have had a reasonable expectation of success for the micronized tadalafil formulation.

Patent Owner further contends that micronizing free drug does not predictably lead to increased dissolution rate. PO Resp. 42. According to Patent Owner, micronized particles tend to agglomerate and agglomerates will have the effect of decreasing the surface area such that the agglomeration dissolves more slowly than predicted from the size of the micronized particle. *Id.*

Agglomeration is indeed a disadvantage of micronization, as acknowledged in Seth. *See, e.g.*, Ex. 1011, 2:15–18. Dr. Brittain, however, testified that “since this is a generally recognized phenomenon, the solution to the problem is also generally recognized.” Ex. 1033, 45:18–46:22. According to Dr. Brittain, an ordinary artisan would have known that adding

a surfactant typically “is sufficient to overcome any of these agglomeration problems and electrostatics.” *Id.* He points out that even the two references cited in Seth when discussing the agglomeration issue teach the solution to the problem. Ex. 1046 ¶¶ 34, 35 (citing Ex. 1034, 7; Ex.1035, 4 (“It is well known that the presence of a surfactant greatly enhances the deaggregation of these types of powders.”)). We find Dr. Brittain’s opinion in this aspect well supported and persuasive.

Patent Owner further contends that other factors must be considered in micronizing a free drug. *See, e.g.*, PO Resp. 35. We understand that here, as generally in pharmaceutical development, there are some “unpredictable variables at play.” *See id.* at 34. An obviousness inquiry, however, does not require absolute predictability. *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985). Indeed, as the Federal Circuit has explained, simply because the formation and properties of a new formulation must be verified through testing does not mean that the formulation would have not been obvious, “since the expectation of success need only be reasonable, not absolute.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). In sum, we find Petitioner has shown by a preponderance of the evidence that an ordinary artisan would have had a reasonable expectation of success for the micronized tadalafil formulation.

Secondary Considerations

Patent Owner contends that unexpected results support a conclusion that micronizing tadalafil would not have been obvious. PO Resp. 49–54. We are not persuaded.

Patent Owner repeats that had a preformulation analysis been conducted, an ordinary artisan would have expected tadalafil’s absorption to

be solubility-limited, at least when the dose is over 3.82 mg, the saturation dose. PO Resp. 49. According to Patent Owner, because micronization cannot overcome solubility-limited absorption, it would be expected that any dose larger than 3.82 mg would not be absorbed. *Id.* at 50. Reducing the particle size of tadalafil, however, Patent Owner points out, increases both the rate and extent of tadalafil's absorption, even at a 10 mg dose. *Id.* (citing Ex. 1001, 11:55–62). This, Patent Owner argues, is an unexpected result. *Id.*

First, as explained above, we do not find sufficient evidence regarding tadalafil's solubility and permeability to support 3.82 mg as the saturation dose. *See supra* at 18 n.10. Second, both Seth and Wadke teach reducing the particle size of a drug improves the dissolution and absorption of the drug. Ex. 1011, 2:9–11; Ex. 1014, 00007. Third, also as explained above, evidence of the record establishes that one of ordinary skill in the art, even after conducting preformulation tests, would not have been deterred from pursuing micronization, a commonly employed method to improve dissolution, to improve the absorption of tadalafil. *See supra* at 15–20. As a result, we are not persuaded that the increased absorption of tadalafil associated with smaller particle size qualifies as unexpected results.

Patent Owner next repeats that coprecipitation, as taught in Butler, is superior over micronization. PO Resp. 50. Micronized tadalafil, however, according to Patent Owner, “achieved substantially faster (T_{max} of 2.0 hours v. 3.0 hours) and greater (blood level 51 ng/ml v. 29 ng/ml after 30mins) tadalafil absorption than tadalafil coprecipitate.” *Id.* at 51 (citing Ex. 1001, 10:33–61). We are not persuaded by this argument, either.

A coprecipitate formulation may dissolve, depending on the carrier or

excipient selected, either “rapidly (within about 15 to 60 minutes),” or “over a relatively prolonged period of time (typically, 2 to 4 hours) so as to achieve sustained release” of the drug. Ex. 1008, 00007:34–00008:3. Patent Owner compares micronized tadalafil with tadalafil coprecipitate formulated using hydroxypropylmethylcellulose phthalate (“HPMCP”). Ex. 1001, 10:39–40. Dr. Byrn testified during his deposition that HPMCP is used for formulating a slow-dissolving, sustained-release drug. Ex. 2104, 98:13–99:10. He also testified that the fact that it takes three to four hours for tadalafil coprecipitate to reach the maximum blood concentration “could be related for sure” to the use of the slow-release HPMCP. Ex. 2104, 106:8–107:2. Thus, even assuming coprecipitation is superior over micronization, we are not persuaded that Patent Owner has shown that the allegedly better absorption of tadalafil is due to the micronization of the free drug, and not the use of a slow-release polymer in the coprecipitate.

Patent Owner also relies on the Declaration of Dr. Martha A. Kral (Ex. 2012), proffered during the patent prosecution. PO Resp. 53–54. The Kral Declaration allegedly compares the formulation of the ’958 patent invention with that of Daugan Examples A2 and B2. Ex. 2012 ¶ 9. Daugan teaches tablet formulations with 50 mg tadalafil. Ex. 1006, 00015, 00016. For the comparison, that amount of tadalafil was decreased to 10 mg, while the amount of diluent (microcrystalline cellulose in Example A2 and lactose in Example B2) was increased to maintain the total weight of the tablet. Ex. 2012 ¶¶ 10–12. According to Dr. Kral, compared with the modified Daugan formulations, the ’958 patent invention is superior in “providing a rapid onset of the therapeutic effect and enhanced bioavailability, as well as providing tablets with uniform potency and desirable stability.” *Id.* ¶ 20.

Petitioner points out that “none of the claims is limited to the 4 micron particle size drug that was used in Dr. Kral’s dissolution tests.” Pet. 43; Reply 23. As a result, Petitioner contends, the Kral Declaration is not commensurate in scope with the full breadth of the formulation covered by the challenged claims. Pet. 43; Reply 23.

Patent Owner is not required to test every embodiment within the scope of the challenged claims. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). If Patent Owner demonstrates that “an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims.” *Id.* For purposes of this Decision, we assume Patent Owner has established that the tested formulation is commensurate with the scope of the claims. We, nevertheless, do not find the Kral Declaration constitutes sufficient evidence of unexpected results to outweigh the evidence of obviousness.

First, Dr. Kral testified that tablets with Daugan Example B2 formulation dissolved quickly and completely. *Id.* ¶¶ 15, 19. Those tablets, however, according to Dr. Kral, were soft and “not sufficiently robust for a further manufacturing step, such as film coating, without significant breakage or erosion.” *Id.* ¶ 15. None of the challenged claims, however, require the claimed formulation to be a coated tablet. In fact, most composition claims merely recite a formulation (claims 1–19 and 24–26), while claim 23 recites “[a] capsule comprising a hard shell encasing the formulation of claim 1 as dry, free-flowing particles.” Claims 31 and 32 are method claims comprising administering to a patient “an effective amount of

a formulation or a tablet.” Claims 20–22 and 27–30 are directed to tablets; but they do not require further coating. *See* Ex. 1006, 00014, 00016 (teaching “FILM COATED TABLETS” separate from “TABLETS FOR ORAL ADMINISTRATION”); *see also* Ex. 1003, 6:4 (disclosing tablets can be with or without film coating). Thus, we are not persuaded that the formulation allegedly prepared according to the ’958 patent showed unexpected results.

Moreover, for objective evidence of secondary considerations, including unexpected results, to be accorded substantial weight, Patent Owner must establish a nexus between the evidence and the merits of the claimed invention. *In re Kao*, 639 F.3d at 1068. For the formulation allegedly made according to the ’958 patent that showed unexpected results, Dr. Kral explained:

The use of a water-soluble diluent, i.e., lactose monohydrate, with a hydrophilic cellulosic binder (hydroxypropylcellulose), provided a good granulation. The addition of spray dried lactose monohydrate enhanced the compressibility of the final granulation, as did the outside powder addition of microcrystalline cellulose, resulting in tablets that were sufficiently hard to withstand the coating process, packaging, and shipping.

Id. ¶ 16.

As explained above, Daugan teaches using water-soluble diluent and hydrophilic binder to formulate a tablet. *See supra* at 11–12. In addition, as Petitioner pointed out, which we agree, none of the challenged claims recite spray dried lactose monohydrate. Pet. 43; Reply 23. Further, only claims 2, 12, and 18 require adding microcrystalline cellulose as an excipient. Pet. 43; Reply 23. None of these claims, however, requires the formulation in a

tablet form. *Compare* claim 2 (reciting “[t]he formulation of claim 1”), with claim 20 (reciting “[a] tablet comprising the formulation of claim 1”). As a result, the addition of microcrystalline cellulose to enhance the compressibility is irrelevant. Pet. 43; Reply 23. Thus, Patent Owner has not established a nexus between the alleged unexpected results and the challenged claims.

In sum, we find that the combination of Daugan, Seth, Butler, and the common pharmaceutical knowledge evidenced in Wadke, Rudnic, and Banker teaches or suggests each limitation in claims 1–19, 24–28, 31, and 32. We also find that Petitioner has articulated a reason with rational underpinning for one of ordinary skill in the art to combine the teachings in the asserted prior art and that an ordinary artisan would have had a reasonable expectation of success in arriving at the claimed formulation of micronized tadalafil. We further find that Patent Owner has not provided sufficient evidence of secondary considerations to outweigh the evidence of obviousness. As a result, we hold that claims 1–19, 24–28, 31, and 32 would have been obvious over the asserted prior art.

Claims 20–23, 29, and 30¹²

Claims 20–23, 29, and 30 depend from claim 1 and further recite tadalafil dosage in the amount of “about 1 to about 20 mg,” “about 5 to about 15 mg,” “about 5 mg,” “about 2.5 mg,” or “about 20 mg” per unit. Petitioner refers to Daugan for teaching “individual tablets or capsules contain from 0.2-400mg” of tadalafil. Pet. 35 (citing Ex. 1006, 00007). Petitioner contends that because the recited drug amounts fall within the ranges disclosed in Daugan, claims 20–23, 29, and 30 would have been obvious. Pet. 35.

Patent Owner criticizes that Dr. Brittain did not “consider the pharmacology or toxicology of tadalafil that would be relevant to the claimed doses.” PO Resp. 47. Whether Dr. Brittain did or did not do so, however, is of little import to our analysis because ordinarily, “where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.” *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

Of course, Patent Owner is correct that where there is a range disclosed in the prior art, and the claimed invention falls within that range, a

¹² Claims 27 and 28, similar to claims 20–23, 29, and 30, also recite dose ranges for tadalafil. Patent Owner, however, does not additionally argue nonobviousness of claims 27 and 28 based on the dose range. See PO Resp. 46–49. As we cautioned in the Scheduling Order, “any arguments for patentability not raised in the response will be deemed waived.” Paper 8, 3. Thus, we deem that Patent Owner has waived the argument for nonobviousness of claims 27 and 28 based on the recited dose ranges. Nevertheless, even if Patent Owner did not waive this argument, for the same reasons explained in this section, we find Petitioner has met its burden in showing the unpatentability of claims 27 and 28.

relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges. PO Resp. 47 (citing *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1304–05 (Fed. Cir. 2015)). Patent Owner, however, fails to mention that the *Allergan* court continued to explain that, in those circumstances, “the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.” *Allergan*, 796 F.3d at 1305; *see also Iron Grip Barbell*, 392 F.3d at 1322 (stating a patent owner may rebut the presumption of obviousness by showing teaching away or unexpected results).

Here, as Dr. Brittain points out, Daugan teaches tablet and capsule formulations with 50 mg tadalafil. Ex. 1002 ¶ 31 (citing Ex. 1006). According to Daugan, tablets of other strengths may be prepared by altering the ratio of active ingredient to excipients. Ex. 1006, 00016. For capsules, other doses may also be prepared by altering “the fill weight and if necessary changing the capsule size.” *Id.* at 00016. With this guidance, optimization of the range taught in Daugan “flows from the ‘normal desire of scientists or artisans to improve upon what is already generally known.’” *Pfizer*, 480 F.3d at 1368 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

Patent Owner asserts that “one skilled in the art would not have expected that low doses of *micronized* tadalafil could have achieved full efficacy with minimized side effects.” PO Resp. 55 (emphasis added). Patent Owner argues that U.S. Patent No. 6,943,166 (Ex. 2066, “the ’166 patent”), cited on the face of the ’958 patent, as well as two declarations submitted during the prosecution thereof (Exs. 2062, 2063), constitute part

of the “intrinsic record.”¹³ *Id.* at 55–57. According to Patent Owner, the additional evidence shows “therapeutic efficacy does not increase at higher doses above the claimed 1-20 mg range but that side effects, which are minimal in the 1-20 mg range, do continue to increase.” *Id.* This, Patent Owner argues, is an unexpected result. *Id.* We disagree.

As explained above, Patent Owner must establish a nexus between the unexpected result and the merits of the claimed invention. *In re Kao*, 639 F.3d at 1068. “Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention.” *Id.* Here, Patent Owner does not argue, and we find no evidence to show, that the ’166 patent and the two related declarations relate to *micronized* tadalafil, the subject matter of the challenged claims. As a result, Patent Owner has not presented sufficient evidence to rebut the presumption that claimed tadalafil doses and dose ranges would have been obvious.

Motions to Exclude

Petitioner’s First Motion to Exclude (Paper 24)

Petitioner filed a Motion to Exclude Exhibits 2041, 2051, 2062, 2063, 2065, 2066, and 2070. Paper 24. Exhibits 2041, 2051, 2065, and 2070 relate to the solubility and permeability—the inherent properties—of tadalafil. Exhibit 2066 (the ’166 patent) and Exhibits 2062 and 2063 (two declarations submitted during the prosecution of the ’166 patent) purportedly show an unexpected result of low dose tadalafil.

¹³ For purpose of this Decision, we assume, without deciding, that Exhibits 2062, 2063, and 2066 constitute part of the “intrinsic record.”

According to Petitioner, Exhibits 2041, 2051, and 2070, being non-prior art, should be excluded as irrelevant and their admission would cause unfair prejudice to Petitioner. *Id.* at 5–9, 13–14. A post-filing date publication is not automatically excluded from consideration as irrelevant. *See, e.g., Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). In addition, similar to a district court in a bench trial, the Board, sitting as a non-jury tribunal with administrative expertise, is well-positioned to determine and assign appropriate weight to evidence presented. In this *inter partes* review, the better course is to have a complete record of the evidence to facilitate public access as well as appellate review. Thus, we deny Petitioner’s Motion to Exclude as to Exhibits 2041, 2051, and 2070.

Petitioner argues that Exhibits 2065 and 2066, two U.S. patents, should be excluded because Patent Owner fails to comply with 37 C.F.R. § 42.61(c). Paper 24, 11–13. Rule § 42.61(c) prescribes:

A specification or drawing of a United States patent application or patent is admissible as evidence only to prove what the specification or drawing describes. If there is data in the specification or a drawing upon which a party intends to rely to prove the truth of the data, an affidavit by an individual having first-hand knowledge of how the data was generated must be filed.

Regarding Exhibit 2065, Patent Owner counters that the safeguarding purpose of the rule against unreliable data has been satisfied because other references reported similar data regarding tadalafil’s solubility. Paper 38, 8 (citing Exs. 2091, 2092). Regarding Exhibit 2066, Patent Owner asserts that it was offered for the “proper purpose” of showing the “unexpected observation” described therein. *Id.* at 15. We do not find either assertion

persuasive. Nevertheless, 37 C.F.R. § 42.61(c) specifically states that U.S. patents are admissible. As a result, we decline to exclude Exhibits 2065 and 2066, but accord them little weight.

Petitioner also contends that Exhibits 2062 and 2063 should be excluded because Patent Owner fails to comply with 37 C.F.R. § 42.65 and because the declarant lacks personal knowledge under Federal Rule of Evidence 602. Paper 24, 9–11. Patent Owner asserts that Dr. Byrn’s reliance on Exhibits 2062 and 2063 is proper because Federal Rule of Evidence 602 does not apply to expert testimony. Paper 38, 12. Petitioner, however, does not challenge Dr. Byrn’s reliance on those exhibits. Rather, Petitioner challenges the admissibility of those exhibits themselves. Nevertheless, we find Exhibits 2062 and 2063 qualify as expert testimony.¹⁴ See Ex. 2062 ¶¶ 1–5; Ex. 2063 ¶¶ 1–5. As a result, Federal Rule of Evidence 602 does not apply. See Fed. R. Evid. § 703 (“An expert may base an opinion on facts or data in the case that the expert has been made aware of or personally observed.”).

As expert testimony, Exhibits 2062 and 2063 are subject to Rule 42.65, which provides (a) “[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight”; and (b) “[i]f a party relies on a technical test or data from such a

¹⁴ Petitioner states that Patent Owner “did not file the Sides declarations (Exs. 2062 and 2063) as expert testimony subject to cross-examination in these proceedings.” Paper 42, 4. Petitioner does not point to any evidence or authority to support this assertion. In fact, even though Exhibits 2062 and 2063 were submitted to the Patent Office during the prosecution of the ’166 patent, because Patent Owner relies on them substantively, Petitioner was entitled to cross-examine the declarant.

test, the party must provide an affidavit explaining” all “information necessary for the Board to evaluate the test and data.” Patent Owner asserts that the Rule is to determine the weight of the evidence, and not its admissibility. Paper 38, 12. We agree. As a result, we decline to exclude Exhibits 2062 and 2063.

Petitioner’s Second Motion to Exclude

Petitioner filed a second Motion to Exclude, with respect to Exhibits 2083–2102 and portions of the transcript of the second deposition of Dr. Brittain (Exhibit 2103) that relate to those exhibits. Paper 37. It is undisputed that none of these references qualifies as prior art.

According to Petitioner, Exhibits 2083–2102 were introduced during the cross-examination of Dr. Brittain regarding the declaration he submitted in support of Petitioner’s Reply. *Id.* at 1–2. Petitioner asserts that these exhibits are improper rebuttal evidence. *Id.* at 4–7. Patent Owner counters that these exhibits are offered to impeach Dr. Brittain’s credibility. Paper 43, 2–8. For purposes of this Decision, we accept that Exhibits 2083–2102 are admissible, but solely for impeachment purposes.¹⁵ As a result, we also deny Petitioner’s Motion to Exclude portions of Exhibit 2103.

Patent Owner also contends that Exhibits 2091 and 2092, reporting the solubility of tadalafil is 2–3 µg/ml at 37°C, are further admissible. Paper 43, 9–10. This is a response to Petitioner’s argument that these two exhibits should also be excluded for additional reasons. *See* Paper 37, 8–10. We do

¹⁵ Alternatively, because we do not rely on Exhibits 2083–2102, we dismiss Petitioner’s Motion to Exclude regarding these exhibits as moot.

not find Exhibits 2091 and 2092 admissible for substantive purposes. Indeed, together with its Response, Patent Owner filed Exhibits 2065 and 2070 to show tadalafil's solubility is 2 µg/ml. See PO Resp. 36 (citing Ex. 2065); see also Ex. 2075 ¶ 139 (citing Ex. 206[5], 5:11–13; Ex. 2070, 3:19–21). Patent Owner could have filed Exhibits 2091 and 2092 at that same time, but chose not to do so. Had it done so, Petitioner (and Dr. Brittain) would have had a chance to properly consider the references and address them in Petitioner's Reply. Instead, Patent Owner introduced these exhibits for the first time during the second deposition of Dr. Brittain. Patent Owner argues that Dr. Brittain testified during the deposition that these articles "are convincing." Paper 43, 8 (citing Ex. 2103, 118:15–119:5). Exhibits 2091 and 2092, however, are 11 and 10 pages long, respectively. We doubt anyone, even an expert, can thoroughly review and opine on references of such length during the limited time to answer a question during deposition. Thus, it is improper for Patent Owner to rely on these exhibits for anything other than impeachment purposes.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude Exhibits 1036–1038 and 1043–1045, as well as Dr. Brittain's Reply Declaration (Ex. 1046), which relies on those exhibits. Paper 27. Exhibits 1036, 1043, and 1045 relate to tadalafil's solubility. Exhibits 1037, 1038, and 1044 relate to tadalafil's permeability.

According to Patent Owner, Exhibits 1036–1038 and 1043–1045 should be excluded because they do not qualify as prior art. *Id.* at 1–5. As explained above in relation to Petitioner's Motion to Exclude Exhibits 2041, 2051, and 2070, we decline to exclude exhibits showing inherent properties

of tadalafil, whether or not they are prior art. *See supra* at 36.

Patent Owner further contends that Exhibits 1037, 1038, and 1044, showing tadalafil as a BCS Class II drug, should be excluded because the absorption of “BCS class II drugs can be permeability and/or solubility limited,” in which case micronization would not be effective to increase absorption. Paper 27, 5–9. We note, however, it is Patent Owner who, in the Patent Owner Response, first relies on post-filing date references to show tadalafil has low permeability and introduces BCS classification. *See, e.g.*, PO Resp. 38 (citing Ex. 2041, 2070). As Petitioner states, it relies on the challenged exhibits solely for rebuttal purpose and only to the extent the Board considers Patent Owner’s similar, post-filing date exhibits showing tadalafil’s solubility and permeability. We, thus, deny Patent Owner’s Motion to Exclude in this regard too.

Patent Owner argues that because Dr. Brittain relies on Exhibits 1036–1038 and 1043–1045 in the Reply Declaration (Exhibit 1046), that Declaration should be excluded. Paper 27, 10. We disagree. First, as explained above, we deny Patent Owner’s Motion to Exclude as to Exhibits 1036–1038 and 1043–1045. Second, as Petitioner correctly points out, an expert witness may rely on otherwise inadmissible evidence in forming his opinions. Fed. R. Evid. § 703. We, thus, deny Patent Owner’s Motion to Exclude as to Exhibit 1046 for this reason.

Patent Owner further asserts that Exhibit 1046 should be excluded because it “goes beyond [Dr. Brittain’s] admitted limited expertise in *in vivo* absorption, is not based on sufficient facts or data, and fails to rely on or apply reliable principles and methods.” Paper 27, 10. Specifically, Patent Owner argues that paragraphs 2–6 of Exhibit 1046 “address *in vivo* drug

absorption, including solubility-limited absorption and ‘sink’ conditions.”
Id. We do not rely on paragraphs 2–6 of Exhibit 1046 in rendering this Decision. Thus, we dismiss this aspect of Patent Owner’s Motion to Exclude as moot.

Patent Owner further argues that Dr. Brittain, instead of conducting any experiments, relied on non-prior art reports of the solubility of tadalafil. *Id.* at 12. In addition, according to Patent Owner, Dr. Brittain failed to address many problems of micronization. *Id.* at 13. These issues, however, relate to the weight, not the admissibility of Exhibit 1046. Thus, we deny Patent Owner’s Motion to Exclude as to Exhibit 1046 for this reason too.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–32 of the ’958 patent are unpatentable for obviousness over the combination of Daugan, Butler, Seth, and Wadke.

ORDER

Accordingly, it is

ORDERED that claims 1–32 of the ’958 patent are held unpatentable;

FURTHER ORDERED that Petitioner’s Motions to Exclude are denied;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is denied-in-part and dismissed-in-part; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2015-00561
Patent 7,182,958 B1

PETITIONER:

Mark Waddell
Warren MacRae
Kathleen Gersh
LOEB & LOEB LLP
mwaddell@loeb.com
wmacrae@loeb.com
kgersh@loeb.com

PATENT OWNER:

Mark Feldstein
Charles Lipsey
Yieyie Yang
Joshua Goldberg
Megan Johns
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
mark.feldstein@finnegan.com
charles.lipsey@finnegan
yieyie.yang@finnegan.com
joshua.goldberg@finnegan.com
megan.leinenjohns@finnegan.com

Dan Wood
Mark Stewart
ELI LILLY AND COMPANY
stewart_mark@lilly.com
wood_dan_l@lilly.com