

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACTELION PHARMACEUTICALS LTD,
Petitioner,

v.

ICOS CORPORATION,
Patent Owner.

Case IPR2015-00562
Patent 6,821,975 B1

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

SNEDDEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

Actelion Pharmaceuticals Ltd (“Petitioner”) filed a Petition (Paper 1; “Pet.”) to institute an *inter partes* review of claims 1–11 of U.S. Patent No. 6,821,975 B1 (Ex. 1001; “the ’975 patent”). ICOS Corporation (“Patent Owner”) filed a Patent Owner Preliminary Response. Paper 6 (“Prelim. Resp.”). Based on these submissions, we instituted trial on the following ground of unpatentability asserted by Petitioner:

Reference[s]	Basis	Claims challenged
Daugan, Butler , Seth, and Wadke	§ 103(a)	1–11

Decision to Institute (Paper 7, “Dec.”).

After institution of trial, Patent Owner filed a Patent Owner Response (Paper 16, “PO Resp.”), to which Petitioner filed a Reply (Paper 20, “Pet. Reply”).

Petitioner relies upon the Declarations of Dr. Harry Brittain (“Brittain Decl.” (Ex. 1002) and “Brittain Reply Decl.” (Ex. 1046)) in support of its Petition.

Patent Owner relies upon the Declarations of Dr. Steven Byrn (“Byrn Decl.”) (Ex. 2075) and Dr. Martha Kral (“Kral Decl.”) (Ex. 2012) in support of its Patent Owner Response.

Petitioner filed a first motion to exclude certain of Patent Owner’s evidence. Paper 24. Patent Owner filed an opposition (Paper 38), and Petitioner filed a reply (Paper 42).

Petitioner filed a second motion to exclude certain of Patent Owner’s evidence. Paper 37. Patent Owner filed an opposition (Paper 43), and Petitioner filed a reply (Paper 45).

Patent Owner filed a motion to exclude certain of Petitioner's evidence. Paper 27. Petitioner filed an opposition (Paper 39), and Patent Owner filed a reply (Paper 44).

Oral argument was conducted on April 13, 2016. A transcript is entered as Paper 49 ("Tr.").

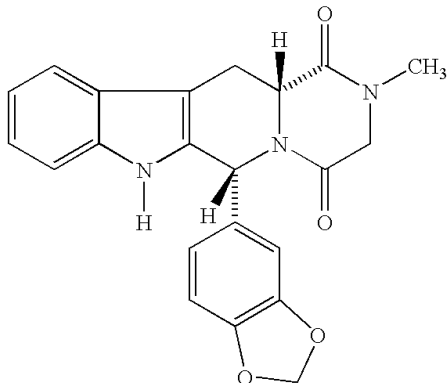
This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). We conclude for the reasons that follow that Petitioner has shown by a preponderance of the evidence that claims 1–11 of the '975 patent are unpatentable.

A. Related Proceedings

The parties inform us of no related litigation between them. Pet. 1; Paper 4. Concurrent with the present *inter partes* review, Petitioner also requested review of claims in U.S. Patent No. 7,182,958 ("the '958 patent"), Case IPR2015-00561. *Id.* We instituted trial in IPR2015-00561, and issue a final decision therein concurrently with this Final Written Decision.

B. The '975 patent (Ex. 1001)

The '975 patent discloses particulate preparations of a free drug form of a β -carboline compound having the following formula:



and pharmaceutically acceptable salts and solvates thereof. The compound

of the above formula, referred to as “compound (I)” in the ’975 patent, is alternatively known as:

- 1) tadalafil;
- 2) (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
- 3) (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)pyrazino[2',1':6.1]pyrido[3,4-b]indole-1,4-dione.

Prelim. Resp. 14–15; Ex. 1006, 3:24–25.

“The term ‘free drug’ refers to solid particles of compound (I) not intimately embedded in a polymeric coprecipitate.” Ex. 1001, 4:5–6. The free drug may be crystalline. *Id.* at 5:8.

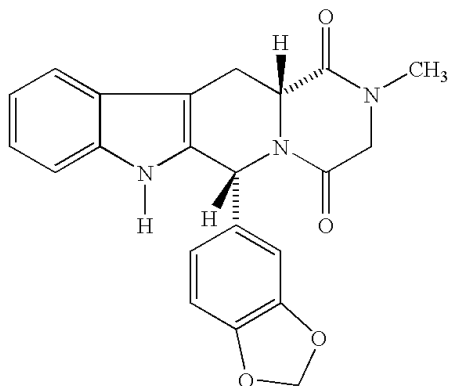
The ’975 patent discloses compound (I) as a free drug in particulate form, wherein at least 90% of the particles have a particle size of less than about 40 microns. *Id.* at 4:61–5:7. Particles less than 10 microns in size are also disclosed. *Id.* The particulate form of the free drug may be achieved using a milling process. *Id.* at 5:12–20, 10:6–17.

The ’975 patent discloses “the use of compound (I) and pharmaceutical compositions for treatment of sexual dysfunction, e.g., male erectile dysfunction and female sexual arousal disorder.” *Id.* at 2:50–53. The ’975 patent also discloses pharmaceutical compositions comprising particulate compound (I) and one or more pharmaceutically acceptable excipients, diluents, or carriers. *Id.* at 3:1–42, 7:9–55.

C. Challenged Claims

Claims 1, 6, 9, and 11 are illustrative of the challenged claims, and are reproduced below:

1. A free drug particulate form of a compound having a formula



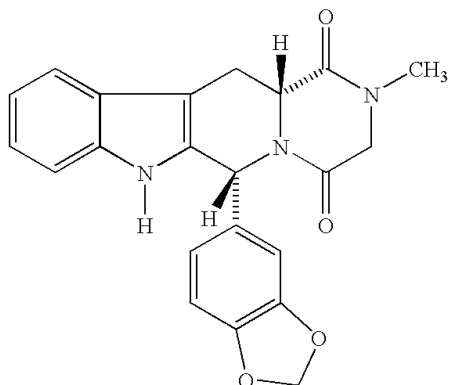
or pharmaceutically acceptable salts and solvates thereof, comprising particles of the compound wherein at least 90% of the particles have a particle size of less than about 40 microns.

6. A method of treating sexual dysfunction in a patient in need thereof, which comprises administering to the patient a therapeutically effective amount of a solid composition comprising the free drug particulate form as in any one of claims 1-4 and one or more pharmaceutically-acceptable carriers, diluents, or excipients.

9. A method of manufacturing the free drug particulate form of claim 1 comprising:

- (a) providing a solid, free form of the compound, and
- (b) comminuting the solid free form of the compound to provide particles of the compound wherein at least 90% of the particles have a particle size of less than about 40 microns.

11. A pharmaceutical solid composition prepared by admixing particles of a compound having a formula



or a pharmaceutically acceptable salt or solvate thereof, with one or more pharmaceutically acceptable carrier, diluent, or excipient, wherein the particles of the compound have a d_{90} =40 or less.

Claims 2–5 depend from claim 1, either directly or indirectly. Claims 7 and 8 depend from claim 6. Claim 10 depends from claim 9.

D. Prior Art and Supporting Evidence

Petitioner relies on the following prior art:

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

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

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

Deodatt A. Wadke, Abu T. M. Serajuddin, and Harold Jacobson, *Preformulation Testing* in PHARMACEUTICAL DOSAGE FORMS: TABLETS, VOL. 1, Chpt. 1, pp. 1-73, Marcel Decker (Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, Eds., 2nd ed., rev. and expanded 1989). Ex. 1014 (“Wadke”).

II. ANALYSIS

A. Claim Interpretation

We interpret claims using the “broadest reasonable construction in light of the specification of the patent in which [they] appear[.]” 37 C.F.R. § 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, No. 15–446, 2016 WL 3369425, at *12 (U.S. June 20, 2016) (upholding the use of the broadest reasonable interpretation standard). Under the “broadest reasonable construction” standard, claim terms are given their “ordinary and customary meaning,” as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). “Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition.” *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004) (citation omitted). “Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Based upon the facts presented, we determine that the explicit construction of any specific claim term is unnecessary to reach our decision in this case. *See, e.g., Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (“[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Obviousness of Claims 1–11 over the Combination of Daugan, Butler, Seth, and Wadke

1. Scope and Content of the Prior Art

a. Summary of Daugan (Ex. 1006)

Daugan discloses a class of β -carboline compounds defined by the structural formula (I). Ex. 1006, 2. Daugan specifically identifies tadalafil as a compound of the invention, disclosed as (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)pyrazino[2',1':6.1]pyrido[3,4-b]indole-1,4-dione. *Id.* at 3:24–25; Prelim. Resp. 14–15.

Daugan discloses that the compounds of the invention may be used for treating male or female sexual dysfunction. *Id.* at 4:25–28. Daugan also discloses formulating the compounds together with excipients or a pharmaceutically acceptable diluent or carrier. *Id.* at 5:15–21, 32–36.

b. Summary of Butler (Ex. 1008)

Butler “relates to the field of solid dispersions of poorly water soluble drugs, to processes for their preparation and their use in pharmaceutical compositions,” and identifies co-precipitation as “a recognised technique for increasing the dissolution of poorly water soluble drugs.” Ex. 1008, 1:3–5, 15–16.

Butler formulates tadalafil (referred to as “Compound A”) as a polymeric co-precipitate. *Id.* at 4:15–21, 5:1–29, 14:13–15:16, 16:1–17:4. Butler discloses tadalafil as a poorly water soluble drug. *Id.* at 5:4–7.

c. Summary of Seth (Ex. 1011)

Seth discloses pharmaceutical compositions of hydrophobic drugs adsorbed onto carriers such as starch and/or microcrystalline cellulose.

Ex. 1011, Abstract. Seth describes the problem to be solved as follows:

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 slow. However, if such drugs are to be administered in oral dosage forms and to be used for clinical indications where a rapid onset of therapeutic activity is desirable, the slow rate of dissolution and slow rate of absorption can put very great limitations on their therapeutic utility.

A frequently used method to overcome such problems is to finely grind or ‘micronise’ drug substances so as to reduce their particle size. For example high speed running pin mills or air-jet mills are used to reduce the particle-size to a range of 5-10 microns. A major disadvantage of such grinding methods is the resulting tendency of the milled particles to agglomerate and the formation of an electrostatic charge on their surfaces which leads to poor flow and wetting of the particles. These disadvantages may even negate the very purpose of obtaining a faster rate of dissolution by the particle-size reduction.

Id. at 1:66–2:20. Seth further discloses the following:

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 (emphasis added).

Seth discloses that “[t]he drug particles have a mean size of less than 10 microns the size distribution of particles being such that at least 95% of particles are smaller than 15 microns.” *Id.* at Abstract. Seth further discloses that “high speed running pin mills or air-jet mills are used to reduce the particle-size to a range of 5-10 microns.” *Id.* 2:9–13; Ex. 1002 ¶¶ 34, 47 and 53.

Seth discloses that the particle size distribution is preferably “at least 95% of the particles are less than 9 microns.” *Id.* at 6:21–22. The compositions may be compressed into tablets for oral administration. *Id.* at 8:17–18; Ex. 1002 ¶ 35.

d. Summary of Wadke (Ex. 1014)

Wadke provides a summary of preformulation testing in the rational development of dosage forms of a drug substance. Ex. 1014. Wadke discloses the following:

It is now 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. Very fine materials are difficult to handle; but many difficulties can be overcome by creating solid solution of a material of interest in a carrier, such as a water-soluble polymer.

Id. at 7 (internal citation omitted).

Wadke discloses that grinding poorly water-soluble materials increases dissolution rate and that “[g]rinding should reduce coarse material to, preferably, the 10- to 40- μm range.” *Id.* at 7–8; Ex. 1002 ¶¶ 34, 87-97.

2. 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 ¶ 46–47). 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, 8–11, 23).

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, 7. 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.

3. Discussion

a. *Daugan, Butler, Seth, and Wadke disclose every limitation of the challenged claims*

Petitioner contends that Daugan, Butler, Seth, and Wadke disclose every limitation of the challenged claims. Pet. 30–42; Dec. 10–21. In particular, Petitioner contends that tadalafil is a known drug (*id.*, citing Ex. 1006) characterized by poor solubility (*id.*, citing Ex. 1008). Petitioner contends that “Seth teaches micronization of a hydrophobic poorly soluble drug to improve its dissolution and bioavailability.” *Id.* at 31 (citing 4:44–52). Petitioner further relies on Wadke to establish that “[m]icronization is often utilized in scale-up during the preformulation testing stage—particularly when as here the drug was found to be poorly soluble.” Pet. 7 (citing 1014, 7–8). In combining the teachings of Daugan, Butler, Seth, and Wadke, Petitioner reasons that “it would have been routine to grind the drug particles to the 10 to 40 micron range specified in the ’975 patent.” *Id.* at 27 (citing Ex. 1014); *see also* Ex. 1002 ¶ 81 (“[T]he best formulation will be the one that yields fine (i.e., very small) particles of ‘free drug’ in the dissolution medium.”).

- b. *Whether the general knowledge of tadalafil as a poorly water soluble substance was sufficient to motivate a person of ordinary skill in the art to micronize free tadalafil in order to improve its in vivo absorption with a reasonable expectation of success*

Petitioner's central argument for combining Daugan, Butler, Seth, and Wadke is that it would have been obvious to micronize a free drug having a low solubility in order to improve *in vivo* absorption. Pet. 16, 20–21, 31–33. More specifically, Petitioner argues that, “[s]ince tadalafil’s poor aqueous solubility was known, it would have been obvious to apply micronization to Daugan’s inventions” in order to improve the dissolution rate of tadalafil and optimize its absorption characteristics. *Id.*; Reply 12; *see also* Pet. 7 (“[T]he only significant difference between the instant patent claims and the tadalafil prior art . . . represents the routine application of a common scale-up practice well-known in the art.”); Ex. 1002 ¶ 82 (“It is an established tenet in pharmaceuticals that one method which can be used to improve the dissolution rate of a relatively insoluble substance is to reduce the particle size of its component particles.”).

Patent Owner disagrees and argues that, without a preformulation analysis or knowledge of tadalafil’s properties, it would be “impossible to rationally design a formulation and impossible to reasonably predict whether micronization would be useful.” PO Resp. 34; Ex. 2075 ¶¶ 27–29. Patent Owner notes that, in addition to dissolution, absorption of a drug may be influenced by solubility or permeability of the substance and that micronization does not improve either solubility or permeability. PO Resp. 33–36; Ex. 2075 ¶¶ 133–137 (“Without more information on tadalafil’s properties, a person of ordinary skill could have had no reasonable

expectation that micronization could be used to develop a successful tadalafil formulation.”).

In this regard, the evidence of record reflects that “[a]t the time of the invention, it was known that tadalafil was poorly water soluble, but its exact solubility had not been reported.” Ex. 2075 ¶ 135. The evidence of record further suggests that the permeability of tadalafil also was not reported at the time of the invention. Ex. 2075 ¶ 143 (“The permeability of tadalafil was also apparently unreported at the time of the invention.”); Ex. 2077,¹ 14; Ex. 2041;² Ex. 2070;³ Ex. 1044;⁴ Ex. 1037,⁵ 9; Ex. 1038,⁶ 26. Thus, the question before us is whether the general knowledge of tadalafil as a poorly water soluble substance was sufficient to motivate a person of ordinary skill in the art to micronize free tadalafil in order to improve its *in vivo* absorption with a reasonable expectation of success. PO Resp. 18–44. Based on the

¹ Hanna et al., US Patent No. 8,586,687, “Crystalline Molecular Complex of Tadalafil and Methylparaben,” issued Nov. 19, 2013. Ex. 2077.

² Hancock, et al., “What Is the True Solubility Advantage for Amorphous Pharmaceuticals?” *PHARM. RESEARCH* 17(4): 397-404 (2000).

³ Zakowiecki, et al., WO 2012/095151, “Solid Pharmaceutical Dosage Forms Comprising Tadalafil and Methods of Preparation Thereof,” published Jul. 19, 2012. Ex. 2070.

⁴ Mehanna et al., Tadalafil Inclusion in Microporous Silica as Effective Dissolution Enhancer: Optimization of Loading Procedure and Molecular State Characterization, *J. PHARM. SCI.*, Vol. 100, No. 5, pp. 1805–1818 (May 2011). Ex. 1044.

⁵ Center for Drug Evaluation and Research, Application No.: 21-368, Chemistry Review. Ex. 1037.

⁶ Excerpt from Tadalafil Clinical Biopharmaceutics Review, Application No.: 21-368. Ex. 1038.

evidence of record, we conclude that it was.

At oral hearing, the parties each referenced the *in vivo* absorption model disclosed by Yu,⁷ which may be summarized as follows:

the absorption [of a drug] can be limited by dissolution rate and permeation rate, where permeation rate refers to the flux of drug across the intestinal membrane. The supply rate of dissolution and the uptake rate of permeation determine the concentration of drug in the GI tract. However, the concentration in the GI tract is also limited by the solubility of drug. When the supply rate is far more than the uptake rate, the drug concentration in the gastrointestinal fluid approaches its solubility limit.

Ex. 2071, 2; Tr. 28, 30–31, 66–67. Yu thus teaches that the factors affecting absorption are dissolution, solubility and/or permeability. Table 2 of Yu states that permeability-limited absorption occurs for highly soluble drugs.

Ex. 2071, 3; Paper 48, 37; Tr. 28, 30–31, 66–67.

Table 2. Absorption Limiting Steps and their Corresponding Conditions

Absorption limiting steps	Conditions	Comments
Dissolution limiting	$T_{\text{diss}} > 199 \text{ min}^a$ $P_{\text{eff}} > 2 \times 10^{-4} \text{ cm/sec}$ $D_{\text{abs}} \gg \text{Dose}$	Solubility also contributes to poor dissolution. But, the dissolution here mainly refers to particle size. The absolute amount of drug absorbed increases with increasing dose.
Permeability limiting	$T_{\text{diss}} < 50 \text{ min}^b$ $P_{\text{eff}} < 2 \times 10^{-4} \text{ cm/sec}$ $D_{\text{abs}} \gg \text{Dose}$	Permeability-limited absorption occurs for highly soluble drugs or drugs dosed in solutions; assume no precipitation occurs. The absolute amount of drug absorbed increases with increasing dose.
Solubility limiting	$T_{\text{diss}} < 50 \text{ min}^b$ $P_{\text{eff}} > 2 \times 10^{-4} \text{ cm/sec}$ $D_{\text{abs}} < \text{Dose}$	Solubility-limited absorption occurs mainly when a high dose saturates part of the gut. The absolute amount of drug absorbed does not increase with increasing dose.

^a For un-micronized drugs.

^b For micronized drugs.

Table 2 of Yu states that dissolution is a function of particle size, and solubility of the drug is a factor in limiting the dose of the drug. Ex. 2071, 3.

⁷ Yu, “An Integrated Model for Determining Causes of Poor Oral Drug Absorption,” *PHARM. RESEARCH* 16(12):1883-1887 (1999). Ex. 2071 (“Yu”).

Yu further suggests that “poor dissolution can be caused either by particle size . . . or solubility.” *Id.* at 2.

The information disclosed in Yu is consistent with Wadke. Wadke also provides a discussion of parameters affecting absorption. Ex. 1014, 26–36. In particular, Wadke states:

As pointed out earlier for relatively insoluble compounds, the rate-determining step in the overall absorption process is generally the rate of dissolution. On the other hand, for relatively soluble compounds, the rate of permeation across biological membranes is the rate-determining step.

Id. at 26; *see also* Ex. 2060, 6 (“Increasing the surface area for water-soluble drugs . . . appears to be of little value.”).

The teachings of Yu and Wadke are also consistent with the disclosure in Seth that:

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 slow. However, if such drugs are to be administered in oral dosage forms and to be used for clinical indications where a rapid onset of therapeutic activity is desirable, the slow rate of dissolution and slow rate of absorption can put very great limitations on their therapeutic utility.

A frequently used method to overcome such problems is to finely grind or ‘micronise’ drug substances so as to reduce their particle size.

Ex. 1011, 1:66–2:11.

In view of the above, we do not find the evidence to support Patent Owner’s argument that “it would have been impossible to rationally design a

formulation and impossible to reasonably predict whether micronization would be useful.” PO Resp. 34 (citing Ex. 2017; Ex. 2018; Ex. 2031; Ex. 1033, 166:8–167:21, 121:16–23, 140:11–16, 126:21–127:8, 159:17–160:22; Ex. 2075 ¶¶ 133-138). The knowledge of tadalafil as a poorly soluble drug would have informed a person of ordinary skill in the art as to whether tadalafil’s absorption would be limited by dissolution, solubility and/or permeability. For example, we are not persuaded that a person of ordinary skill in the art would have expected tadalafil, a poorly water soluble substance, to be permeability-limited. Tadalafil’s poor water solubility would have suggested dissolution issues, which would have been addressed by either improving solubility and/or dissolution (particle size). *See* Ex. 2071, 2 (defining the dissolution/solubility-limited case as solubility-limited and dissolution/particle size-limited case as dissolution-limited absorption).

In this regard, the evidence demonstrates that improving solubility and dissolution are not mutually exclusive. Rather, solubility and dissolution are related in such a manner that each may be addressed at varying degrees to produce the desired clinical outcome. *See* Ex. 2071, 4–5 (“At the high dose, absorption is largely limited by solubility, while at the low dose, dissolution also limits the absorption. Therefore, particle size reduction has a much stronger effect on the low dose than the high dose.”); Ex. 1046 ¶ 24. That is, particle size may be varied, which ultimately influences the ultimate dose amount used in a formulation.

Yu demonstrates this relationship using the drug griseofulvin as an example, which is explained in the following excerpt from Petitioner’s Reply:

Yu (Ex. 2071) demonstrated that micronization improves absorption, despite griseofulvin being “solubility limited” at high doses. *Id.*, pp. 4-5. The curves Dr. Byrn refers to are in Ex. 2071, p. 4, Fig. 4. These show Yu’s modeling prediction that the percent of griseofulvin dose absorbed increased as the diameter of micronized particles decreased. *Id.*, 4-5. Yu also cited literature reporting that at a dose of 250 mg “about twice as much micronized griseofulvin is absorbed as regular size griseofulvin.” *Id.* at 5; Ex. 1046 ¶ 24. But even if the Board credited all Dr. Byrn’s testimony, Ex. 2071 (Yu) demonstrates that micronization would still have been expected to double the absorption of even a so-called solubility-limited drug at doses above the theoretical absorbable dose. Ex. 1046 ¶ 24.

Reply 20; *see also* Ex. 2071, 5 (“about twice as much micronized griseofulvin is absorbed as regular size griseofulvin”).

In view of the above, we find that particle size is a result-effective variable that affects absorption of relatively insoluble substances. Pet. 48 (citing Ex. 1002 ¶ 54). As such, persons of ordinary skill in the art would have been motivated to micronize free tadalafil in order to improve absorption. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (“[T]he discovery of an optimum value of a variable in a known process is usually obvious.”); *id.* (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)) (“The rationale for determining the optimal parameters for prior art result effective variables flows from the ‘normal desire of scientists or artisans to improve upon what is already generally known.’”); Pet. 7–8. A person of ordinary skill in the art would also have reasonably expected micronization to increase drug particle surface area, and reasonably expected that the increase in surface area would result in improved dissolution and absorption. Ex. 1002 ¶ 47.

c. Whether Daugan, Butler, Seth, and Wadke teach away from micronization

Patent Owner contends that Daugan, Butler, Seth, and Wadke teach away from micronization of drugs and toward alternative methods of drug formulation. PO Resp. 15–16 (“Petitioner’s references, as well as the art as a whole, would have discouraged one skilled in the art from micronizing tadalafil free drug particles”) (citing Ex. 2075 ¶¶ 87–92, 113–230); *id.* at 24–33. We are not persuaded and address Petitioner’s contentions with regard to each reference below.

(1) Seth and Wadke

With regard to Seth, Patent Owner contends that it discloses precipitating dissolved drug from solution directly onto a carrier, a solvent deposition method, and argues that “Seth presents a textbook example of ‘teaching away’ as it expressly criticizes micronization and instead suggests a ‘drug plus’ formulation for a poorly water soluble drug.” *Id.* at 24–30; Ex. 2075 ¶¶ 112–119. To support its teaching away argument, Patent Owner directs our attention to the following passage from Seth:

A frequently used method to overcome [slow rate of dissolution and slow rate of absorption] is to finely grind or ‘micronize’ drug substances so as to reduce their particle size A major disadvantage of such grinding methods is the resulting tendency of the milled particles to agglomerate and the formation of an electrostatic charge on their surfaces which leads to poor flow and wetting of particles. These disadvantages may even negative the very purpose of obtaining a faster rate of dissolution by the particle-size reduction. [Micronization] often leads to agglomerate formation of the milled product due to its poor wetting properties and is not helpful in increasing dissolution.

Ex. 1011, 2:9–2:23, 3:65–4:2.

With regard to Wadke, Patent Owner argues that

Wadke expressly teaches that (1) particle size reduction does not improve drug absorption when the absorption is solubility or permeability limited but not dissolution-rate-limited, (2) coprecipitation is a recommended approach to substantially improve drug solubility and is superior to micronization in improving dissolution rate, and (3) micronization has multiple disadvantages that can be overcome by coprecipitation.

PO Resp. 33. Specifically, Patent Owner argues that Petitioner's analysis emphasizes Wadke's disclosure that "finely subdivided" particles may improve bioavailability, but ignores "that Wadke limits this to poorly soluble drugs that 'show a dissolution rate-limiting step in the absorption process.'"

PO Resp. 30. Patent Owner further argues that Wadke "recommends coprecipitation as the optimal solubility-enhancing approach and the 'ultimate in particle size reduction,' superior to micronization." *Id.* at 32 (citing Ex. 1014, 7, 19–20; Ex. 2075 ¶¶ 124-145).

We are not persuaded. Seth discloses that "a conventional method for increasing the rate of dissolution of solids is by reduction of their particle size by micronisation or similar dry grinding methods." Ex. 1011, 3:64–67. Despite the difficulties and disadvantages associated with finely grinding drug substances disclosed in Seth and Wadke, Seth discloses that grinding or milling is "[a] frequently used method to overcome" a slow rate of dissolution and slow rate of absorption. Ex. 1011, 2:1–13.

Wadke discloses that "[i]t is now 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, 5.

Thus, both Seth and Wadke guide to reduced particle size for poorly

soluble drugs, and disclose micronization as a conventional method. The conventional method has known disadvantages, but such problems can be addressed by other means. For example, the issue of agglomeration is addressed with the addition of surfactants. Reply 15 (citing Ex. 1034; Ex. 1035; Ex. 1046 ¶¶ 34–38; Ex. 1033, 45:18–46:5, 46:21–22, 47:11–19).

We are therefore not persuaded that the discussion in Seth and Wadke regarding the disadvantages of micronization amount to a teaching away. Seth, for example, may guide the person of ordinary skill in the art to alternative methods that do not share those same disadvantages. However, we are unable to conclude that the disclosure of such preferred non-conventional methods renders the use of conventional methods disclosed in Seth and Wadke non-obvious.

Patent Owner further argues as follows:

Petitioner emphasizes that Wadke states that “[i]t is now generally recognized” that drug bioavailability may be improved by particle size reduction, but ignores in its analysis that Wadke limits this to poorly soluble drugs that “show a dissolution rate-limiting step in the absorption process.” IPR-561, Paper 1 at 19 (emphasis added); IPR-562, Paper 1 at 27. Yet not even Petitioner’s declarant asserts that either of the two tadalafil specific references (Daugan and Butler) show that tadalafil has a dissolution rate-limiting step in the absorption process, nor do they so teach. Ex. 2075 at ¶ 122.

PO Resp. 30. Similarly, Patent Owner argues that “Wadke expressly teaches the importance of measuring permeability during preformulation to avoid the ‘mistaken efforts’ of improving drug dissolution rate if the absorption is permeability-limited.” PO Resp. 31 (citing Ex. 1014, 26–27; Ex. 2075 ¶¶ 53, 123, 132); *see also* Ex. 2075 ¶ 132 (“Wadke teaches that . . . improving

the dissolution rate would be a ‘mistaken effort’ if drug absorption is solubility- or permeability-limited.”).

When read as a whole, and in view of Yu, we are not persuaded that Wadke guides toward measuring permeability for poorly soluble drugs. Rather, we read the phrases such as “show a dissolution rate-limiting step in the absorption process” set forth in Wadke to distinguish between substances having high and low solubility. For example, in light of the teaching in Wadke that the rate-determining step for relatively insoluble compounds in the overall absorption process is generally the rate of dissolution, it may be a “mistaken effort” to improve dissolution of a relatively soluble substance. Ex. 2014, 26–27. A poorly soluble drug would have been expected to display dissolution-limited, where “poor dissolution can be caused either by particle size . . . or solubility.” Ex. 2071, 2.

Thus, we agree with Petitioner that “a [person of ordinary skill in the art] would have reasonably expected based on Wadke that the rate-determining step in drug absorption is the rate of dissolution – not permeation.” Reply 5–6 (Ex. 1046 ¶¶ 23–25); *see also* Ex. 1014, 20–21 (“Since dissolution precedes absorption in the overall scheme, any change in the process of dissolution would influence the absorption.”). Here, we credit the testimony of Dr. Brittain that “the person of ordinary skill in the art would . . . conclude that the absorption of tadalafil would be improved by micronizing the drug substance prior to its formulation.” Ex. 1046 ¶¶ 23–25 (citing Ex. 2071, 4–5, Table 3).

(2) Daugan

With regard to Daugan, Patent Owner argues that Daugan “suggest[s]

that tadalafil's biological absorption is likely to be solubility-limited and also potentially permeability-limited—problems that cannot be resolved by micronization.” *Id.* at 18–19 (citing Ex. 1006, 11:7; Ex. 2057, 5–6;⁸ Ex. 1033, 178:25–180:16; Ex. 2075 ¶¶ 94–101). To support this argument, Patent Owner notes that Daugan teaches that crystalline free drug tadalafil has a high melting point of 302–303°C, and directs us to Dr. Byrn's testimony that “[i]f [] the melting point is greater than 300°C . . . , it is certainly a major determinant of low aqueous solubility.” *Id.* at 19 (citing Ex. 1006, 11:7; Ex. 2075 ¶ 96). Patent Owner further notes that Daugan's disclosure that 50 mg of tadalafil forms a suspension in 1 ml of Labrafil further suggested general solubility problems. *Id.* (citing Ex. 1006, 16:4–8; Ex. 2075 ¶¶ 98, 135). Patent Owner contends this is significant because, “[i]f solubility was thought to be a limiting factor, it would be predicted that the full dose simply could not be dissolved, regardless of the initial dissolution rate, in the relatively small gastrointestinal volume because the fluid would become saturated almost immediately.” *Id.* at 20; *see also id.* at 31 (“there was no indication that tadalafil's dissolution was ‘considered to be slow.’”) (citing Ex. 2075 ¶ 72, n.19).

We are not persuaded. As discussed above, the evidence of record does not support a finding that a person of ordinary skill in the art would have expected tadalafil to be permeability-limited. While a person of ordinary skill in the art would have expected tadalafil to have solubility issues, this would not have precluded pursuing an approach that sought to

⁸ Yalkowsky, “Overview and Strategy for Solubilization,” in *Solubility and Solubilization in Aqueous Media* (ed. Yalkowsky 1999). Ex. 2057.

reduce particle size of the drug. Ex. 2071, 4–5.

(3) Butler

With regard to Butler, Patent Owner contends that Butler uses a coprecipitation method to increase the solubility of tadalafil, and thus “teaches away from micronizing—which, unlike a coprecipitate process, does not increase solubility.” PO Resp. 21 (citing Ex. 1008 3–5; Ex. 2075 ¶ 103). Patent Owner contends that “[a]fter the Butler patent application was filed, it appeared that there was no remaining problem with tadalafil solubility,” and moreover, that “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.” PO Resp. 21–24.

We are not persuaded. As discussed above, we find that dose and particle size are result-effective variables that affect absorption of relatively insoluble substances. While Butler discloses a formulation that appears to solely attempt to improve the solubility of tadalafil—thus affecting the total dose that may be absorbed—the disclosure in Butler does not amount to a disclosure that directs a person of ordinary skill in the art away from micronized free tadalafil in order to improve overall absorption via increased dissolution rate. As discussed above, we do not find the evidence of record to support a finding that a person of ordinary skill in the art would have been confined to improve dissolution to the exclusion of improving solubility. Ex. 2071, 4–5.

d. Patent Owner's reliance on tadalafil's properties reported post-filing

Patent Owner further argues that, “[f]or tadalafil, a person of ordinary skill would have expected that micronization would not have been suitable.” PO Resp. 37. Here, Patent Owner relies on post-filing references reporting the aqueous solubility of tadalafil to be 2 µg/ml. *Id.* (citing Ex. 2065, 5:11–13;⁹ Ex. 2075 ¶¶ 140, 141). Similar arguments are made with regard to what a person of ordinary skill in the art would have determined with regard to the permeability of tadalafil if a preformulation investigation been conducted. *Id.* at 38–40.

Petitioner responds, citing peer-reviewed literature, that the aqueous solubility of tadalafil at 37°C is 0.02 mg/ml or 20 µg/ml, and argues that Dr. Byrn made assumptions on the incorrect tadalafil solubility (i.e., 2 µg/mL) at the incorrect temperature of 25°C to arrive at an incorrect conclusion. Reply 7–9 (citing Ex. 1046 ¶¶ 16–20; Ex. 1036, 4 (Table 2);¹⁰ Ex. 2075 ¶¶ 139, 152).

The parties thus dispute certain facts about the drug, such as aqueous solubility, and dispute the conclusions drawn based on assumptions and calculations that rely on such facts. These arguments from the parties, however, are supported by data points disclosed in post-filing references. We do not find persuasive the arguments that rely on post-filing knowledge

⁹ Anderson, et al., U.S. Patent No. 6,841,167, “β-Carboline Pharmaceutical Compositions,” issued Jan. 11, 2005. Ex. 2065.

¹⁰ El-Badry et al., Solubility and Dissolution Enhancement of Tadalafil Using Self-Nanoemulsifying Drug Delivery System, *J. OLEO SCI.*, Vol. 63, No. 6, pp. 567-576 (2014)

of tadalafil, but instead focus on the knowledge of the person of ordinary skill in the art at the time of the invention. In this regard, we agree with Petitioner that a person of ordinary skill in the art would not have been “drawing on a blank canvas,” but would have had the benefit of the disclosures of Daugan and Butler with regard to what was known about tadalafil’s properties. Reply 12; see Ex. 1008 (relied on by Petitioner to demonstrate that tadalafil is characterized by poor solubility); Ex. 1002 ¶ 33.

e. Patent Owner’s evidence of unexpected results

Patent Owner contends that micronizing tadalafil surprisingly improved absorption and to a greater extent than tadalafil coprecipitates. PO Resp. 44–47. Specifically, Patent Owner argues that

the data in Example 2 of the ’975 patent demonstrate that micronized tadalafil free drug formulations achieved substantially faster (Tmax of 2.0 hours v. 3.0 hours) and greater (blood level 51 ng/ml v. 29 ng/ml after 30mins) tadalafil absorption than the tadalafil coprecipitate. Ex. 1001 at 10:33-61; Ex. 2075 at ¶¶ 232-235. This is the opposite of what would have been expected based on the teachings of Wadke and others. Ex. 2075 at ¶¶ 232-235.

Id. at 46.

Patent Owner further contends that

faster dissolution does not lead to greater absorption if the absorption is solubility-limited or permeability-limited rather than dissolution rate-limited. Ex. 2025 at 4; Ex. 2071 at 2-5; Ex. 1014 at 26-27; Ex. 2075 at ¶¶ 51, 57, 72. Therefore, Petitioner’s allegation that reducing particle size “naturally result[s] in faster [] absorption” (IPR-562, Paper 1 at 46) is fundamentally wrong.

Id. at 47.

Patent Owner further argues that Dr. Kral’s Declaration demonstrated

the surprisingly rapid onset of therapeutic effect, enhanced bioavailability, and improved stability. PO Resp. 47–49. Specifically, Patent Owner argues as follows:

Dr. Kral found that the “Daugan Example A2” tablets were extremely hard and had inherent unacceptably low and incomplete dissolution, and “Daugan Example B2” tablets were “not sufficiently robust for a further manufacturing step [] without significant breakage or erosion.” Ex. 2012, pgs. 6-7; Ex. 2075 at ¶ 237. In contrast, the micronized tadalafil formulations “provid[ed] physically robust tablets that also released the drug quickly and completely.” Ex. 2012, pgs. 7-8; Ex. 2075 at ¶ 238. As such, Dr. Kral’s declaration further confirms the nonobviousness of the claimed inventions by showing that the claimed inventions provided “a rapid onset of the therapeutic effect and enhanced bioavailability, as well as providing tablets with uniform potency and desirable stability.” Ex. 2012, pgs. 10-11; Ex. 2075 at ¶ 239.

Id. at 48–49.

We are not persuaded by Patent Owner’s arguments that persons of ordinary skill in the art would have been surprised that the finely divided drug particles were absorbed more rapidly. Rather, we find the evidence of record to support the conclusion that micronizing drug particles improves the absorption of poorly soluble drugs. Ex. 1014; Ex. 2071. Specifically, it was a well-known principle that micronization increases the drug particle surface area, and that increase in surface area would naturally result in faster dissolution and absorption. Ex. 1002 ¶ 53.

C. Patent Owner’s Motion to Exclude Evidence

Patent Owner filed a Motion to Exclude Exhibits 1036–1038 and 1043–1045, as well as Dr. Brittain’s Reply Declaration (Ex. 1046) that 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 35.

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 (Ex. 1046), that Declaration should be excluded. Paper 27, 10. We disagree. First, as explained above, we deny Patent Owner's Motion to Exclude 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.

D. Petitioner’s First Motion to Exclude Evidence

Petitioner filed a Motion to Exclude Exhibits 2041, 2051, 2062, 2063, 2065, 2066, and 2070. Paper 24. It is undisputed that none of these references qualifies as prior art. 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.

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 an 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.¹¹ 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 provide (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 test, the party must provide an affidavit explaining” all “information necessary for the Board to evaluate the test and data.” Patent Owner asserts

¹¹ 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.

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.

E. 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 determine that Exhibits 2083–2102 are admissible, but solely for impeachment purposes.¹² 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 not find Exhibits 2091 and 2092 admissible for substantive purposes. Indeed, together with its Response, Patent Owner filed Exhibits 2065 and

¹² Alternatively, because we do not rely on Exhibits 2083–2102, we dismiss Petitioner's Motion to Exclude regarding these exhibits as moot.

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 exhibit 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.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioner has demonstrated by a preponderance of the evidence that claims 1–11 are unpatentable for obviousness over the combination of Daugan, Butler, Seth, and Wadke.

This is a final written decision of the Board under 35 U.S.C. § 318(a). Parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–11 of the '975 patent are 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.

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