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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELI LILLY AND COMPANY.,
Petitioner,

v.

LOS ANGELES BIOMEDICAL RESEARCH INSTITUTE
AT HARBOR-UCLA MEDICAL CENTER,
Patent Owner.

Case IPR2014-00752
Patent 8,133,903 B2

Before LORA M. GREEN, FRANCISCO C. PRATS, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

Petitioner, Eli Lilly and Company ("Eli Lilly" or "Petitioner"), filed a Petition requesting *inter partes* review of claims 1–5 ("the challenged claims") of U.S. Patent No. 8,133,903 B2 ("the '903 patent"). Paper 1

("Pet."). Patent Owner, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center ("LA Biomed" or "Patent Owner"), filed a Patent Owner Preliminary Response. Paper 11 (Prelim. Resp.). We determined that the information presented in the Petition and the Preliminary Response demonstrated that there was a reasonable likelihood that Petitioner would prevail in challenging claims 1–5 as unpatentable under 35 U.S.C. § 103(a). Pursuant to 35 U.S.C. § 314, the Board instituted trial on October 23, 2014, as to the challenged claims of the '903 patent. Paper 13 ("Institution Decision" or "Dec. Inst.").

Patent Owner filed a Response (Paper 20, "PO Resp."), but did not file a motion to amend. Petitioner subsequently filed a Reply. Paper 25 ("Reply"). An oral hearing was held on June 16, 2015. The transcript of the hearing has been entered into the record. Paper 43. Patent Owner also filed a Motion for Observation on certain cross-examination testimony of Petitioner's declarant, Dr. Irwin Goldstein (Paper 32), as well as a Motion to Exclude (Paper 29).

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. Based on the record before us, we conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1–5 of the '903 patent are unpatentable.

B. Related Proceedings

According to the parties, the '903 patent is involved in the following copending case: *Los Angeles Biomedical Research Inst. v. Eli Lilly & Co.*, No. 2:13-cv-08567-JAK-JCG (C.D. Cal.). Paper 5, Pet. 52.

In addition, Eli Lilly filed, concurrently with the instant Petition, an additional petition for *inter partes* review of claims 1–5 of U.S. Patent No. 8,133,903 B2 on different grounds, IPR2014-00693. A final decision is being entered in that case concurrently with the final decision in the instant case.

C. The '903 Patent (Ex. 1001)

The '903 patent issued on March 13, 2011, with Nestor F. Gonzalez-Cadavid and Jacob Rajfer the listed co-inventors. Ex. 1001. The '903 patent relates to methods of treating fibrotic conditions, such as Peyronie's disease ("PD"), with phosphodiesterase ("PDE") inhibitors, (*e.g.* sildenafil). *Id.* at 1:20–27. PD affects the tunica albuginea, which is the specialized lining of the corpora cavernosa of the penis, and clinically leads to penile deformation, pain, and erectile dysfunction ("ED"). *Id.* at 1:29–34. A PDE5 inhibitor, which selectively inhibits an isoform of PDE, is administered at a dosage up to 1.5 mg/kg/day, wherein the upper dosage is roughly equivalent to the dose ingested by men with an on-demand single 100 mg tablet. *Id.* at 2:62–2:3, 45:7–12.

The '903 patent teaches further that fibrotic disease is not limited to the reproductive organs, but can affect other tissues, such as cardiovascular tissues, noting that "[b]oth erectile dysfunction . . . and cardiovascular disease, particularly hypertension, are prevalent in the aging male." *Id.* at 2:8–12. An underlying cause of hypertension is arteriosclerosis due to an acquired fibrosis of the media of the arterial wall. *Id.* at 2:13–15. Thus, according to the '903 patent, "[a] need exists for effective methods to treat and/or ameliorate the symptoms of a variety of fibrotic disease, such as PD, ED and arteriosclerosis. No effective method of treatment currently exists

that is directed towards the molecular pathways underlying excessive collagen deposition." *Id.* at 2:42–46.

According to the '903 patent:

> A distinction exists between long-term (weeks, months, years) continuous treatment with, for example, a PDE5 inhibitor such as sildenafil to maintain a constant level of these agents in order to arrest or regress a fibrotic condition, versus on demand (prior to the sexual act) single pill, short-term treatment with sildenafil or other PDE5 inhibitors to obtain smooth muscle vasodilation in the penis (male penile erection) or vagina/clitoris (female sexual arousal) upon sexual stimulation. Current studies with sildenafil are symptomatic to treat defects in vaginal/clitoral or penile vasodilation exclusively during a sexual act and are not addressed to the long-term cure of underlying tissue fibrosis.

Id. at 10:59–11:3.

The '903 patent teaches also that there is an increase in collagen fibers, and thus an intensification, of fibrosis in the aging man. *Id.* at 46:5–43 (Example 16, "Intensification of Aging-Related Fibrosis in the Arterial Media by iNOS Inhibition"). According to the '903 patent,

> the prevalence of ED and hypertension in man seems to parallel each other as a function of age, and many disorders that damage one of these vascular tissues also seem to impact the other e.g. diabetes, chronic renal failure, etc. In all these disorders, vascular oxidative stress and fibrosis, leading to arteriosclerosis, are common denominators at the histological and molecular and levels.

Id. at 48:47–54 (references removed).

D. Illustrative Claim

Petitioner challenges claims 1–5 of the '903 patent. Claim 1 is illustrative, and is reproduced below.

> 1. A method comprising:
> a) administering a cyclic guanosine 3′, 5′-monophosphate (cGMP) type 5 phosphodiesterase (PDE 5) inhibitor according to a continuous long-term regimen to an individual with at least one of a penile tunical fibrosis and corporal tissue fibrosis; and
> b) arresting or regressing the at least one of the penile tissue fibrosis and corporal tissue fibrosis, wherein the PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg/day for not less than 45 days.

E. Instituted Challenge

Claims	**Basis**	**References**
1–5	§ 103(a)	Montorsi,[1] Whitaker,[2] and Porst[3]

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1276–79 (Fed. Cir. 2015); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012).. Claim terms also are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249,

[1] Francesco Montorsi et al. ("Montorsi"), *The Ageing Male and Erectile Dysfunction*, 20 WORLD J. UROL 28–35 (2002) (Ex. 1051).
[2] Whitaker et al. ("Whitaker"), Pub. No. WO 01/80860 A2, published Nov. 1, 2001 (Ex. 1086).
[3] Hartmut Porst et al. ("Porst"), *Daily IC351 Treatment of ED*, 20 INT'L J. IMPOT. RES. (SUPPL. 3) S76, Abstract B13 (2000) (Ex. 1096).

1257 (Fed. Cir. 2007). "[A] claim construction analysis must begin and remain centered on the claim language itself, for that is the language the patentee has chosen to 'particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention.'" *Innova/Pure Water, Inc. v. Safari Water Filtration Sys,, Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004); *see also Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) ("The starting point for any claim construction must be the claims themselves."). Only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

1. "continuous long-term regimen"

> In the Decision on Institution, we interpreted this claim phrase as:
>
> the administration of drug over a certain period of time without intermission such that the treatment is therapeutically effective. With regard to claims of the '903 patent, the time period is not less than 45 days, as recited in claim 1.

Dec. Inst. 10.

Patent Owner argues that the term "should be construed to mean 'a regimen of sufficient duration and frequency to establish and maintain a constant level of the administered PDE-5 inhibitor.'" PO Resp. 18 (emphasis removed). In particular, Patent Owner notes that the Specification contrasts on demand dosing with continuous treatment, which maintains a constant level of the agents. *Id.* at 18–19 (citing Ex. 1001, 10:59–67).

Patent Owner contends further that the ordinary artisan would understand "constant level" to "refer to the average plasma concentration of that drug upon reaching steady state." *Id.* at 19. Patent Owner argues:

> Whether a constant level of a PDE-5 inhibitor is established through daily administration depends on the pharmacokinetics of the particular compound administered. For a PDE-5 inhibitor such as tadalafil having a half-life of 17.5 hours, steady-state plasma concentration is achieved within five days of once-daily dosing. Ex. 2099 at 4–5. But for a PDE-5 inhibitor such as sildenafil having a half-life of only about four hours, the establishment and maintenance of a constant level requires substantially more frequent dosing. Ex. 2023 ¶ 93.

Id. at 21.

Petitioner responds that "daily administration of a tadalafil according to *Whitaker* will necessarily result in a steady state concentration, as Patent Owner has asserted." Reply. 11.

As set forth in the Decision on Institution (Dec. Inst. 8–10), the Specification does not define the term "continuous," and we decline to read it as narrowly as Patent Owner suggests. In addition, the language of the claim itself requires that a dosage up to 1.5 mg/kg/day of a PDE5 inhibitor be administered for at least 45 days, and, thus, that step as required by the claim meets the limitation of a continuous, long-term regimen. Stated differently, delivering a PDE5 inhibitor at a dosage up to 1.5 mg/kg/day for at least 45 days would meet the claim requirement of a continuous, long-term regimen.

2. "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis"

Patent Owner contends that the term "should be construed to mean 'an individual with fibrosis of either the tunica albuginea or corpora cavernosa

of the penis, in which the fibrosis is clinically significant.'" PO Resp. 22 (emphasis removed). In particular, Patent Owner contends that "a person of ordinary skill in the art would understand the claims of the '903 patent to concern treatment of penile fibrosis, a disease." *Id.* According to Patent Owner, Petitioner's proposed interpretation of a patient having any degree of fibrosis "risks encompassing not only men with subclinical penile fibrosis, but men with no penile fibrosis at all." *Id.* at 22–23.

Petitioner responds that the term "clinically significant" "is largely subjective—what is clinically significant to one patient or doctor may not be clinically significant to another." Reply 11.

The '903 patent teaches that there is a need "to treat and/or ameliorate the symptoms of a variety of fibrotic disease, such as PD, ED and arteriosclerosis." Ex. 1001, 2:42–46. Thus, although the claim requires the patient to have penile tunical fibrosis or corporal tissue fibrosis, we conclude that the broadest reasonable interpretation of "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis," in view of the Specification of the '903 patent, requires that the individual have symptoms that may be associated with penile fibrosis, such as ED, but not that the patient be specifically diagnosed as having penile tunical fibrosis or corporal tissue fibrosis.

3. "arresting or regressing the at least one of the penile tunical fibrosis and corporal tissue fibrosis"

Patent owner contends that the term should be interpreted as "stopping or reversing the progression of a clinically significant fibrosis of either the tunica albuginea or corpora cavernosa of the penis." PO Resp. 23 (emphasis removed). We agree with Petitioner (Reply 10), however, that it is the

intended result of administering a PDE5 inhibitor at a dosage up to 1.5 mg/kg/day for at least 45 days.

4. "penile corporal veno-occlusive dysfunction"

Patent Owner offers a construction of this term (PO Resp. 25–27), arguing that "Petitioner's argument that claim 3 is anticipated relies on the meaning its expert gives this term." *Id.* at 25. As an anticipation challenge is not at issue in this proceeding, and as the construction of this term is not at issue in the obviousness challenge, we need not interpret this term for purposes of this decision.

5. "at a dosage up to 1.5 mg/kg/day for not less than 45 days"

Neither party has offered an express construction for this claim limitation, but instead address the claim limitation "a continuous long-term regimen," which we have addressed above. The plain language of that limitation of claim 1, however, requires that a dosage up to 1.5 mg/kg/day be administered for at least 45 days. Also, administering a dosage up to 1.5 mg/kg/day for at least 45 days would, according to the language of the claim, meet the limitation of a "continuous, long-term regimen," as well as result in "arresting or regressing the at least one of the penile tunical fibrosis and corporal tissue fibrosis," as recited by claim 1.

We need not construe any other claim terms for purposes of this Decision.

B. The '903 Patent Priority Claim

"[T]he test to determine if an application is to receive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application." *Noelle v.*

Lederman, 355 F.3d 1343, 1348 (Fed. Cir. 2004); *see* 35 U.S.C. § 120. "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Nonetheless, the disclosure must convey with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. *Id.* "Put another way, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Id.* However, "the question [of adequate written description] is not whether a claimed invention is an obvious variant of that which is disclosed in the specification." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see also Tronzo v. Biomet Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998) ("A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations.").

The '903 patent claims benefit to Provisional Application No. 60/420,281, filed on October 22, 2002, as well as PCT Application No. US03/33400, filed on October 21, 2003. Ex. 1001, 1:12–15. Patent Owner contends that the '903 patent is entitled to the filing date of the provisional application, which was filed on October 22, 2002. PO Resp. 27–31. In the Decision on Institution, we determined that

> the dosage limitation of "up to 1.5 mg/kg/day" is not supported by the written description of the provisional application. The provisional application discloses an experiment in which sildenafil, a specific PDE-5 inhibitor, was administered orally to rats via their drinking water at a concentration of 100 mg/L for 45 days. Ex. 1003 ¶ 0138. However, there is no evidence

> on the record to support a conclusion that the rats drank a daily amount of water such that the dose they received was exactly 10 mg/kg/day. Thus, even assuming that the conversion from a rat dosage to a human dosage was well-known in the art, a person of ordinary skill in the art could not derive an upper dosage limit of 1.5 mg/kg/day, as recited in claim 1, from the disclosure of the provisional application. As such, claims 1–5 of the '903 patent are not entitled to the priority date of the provisional application. Rather, the '903 patent's claims are entitled only to the October 21, 2003 filing date.

Dec. Inst. 7. Patent Owner argues that determination is in error as "both the conversion of rat dosage to human dosage and the daily water intake of the rats used in the '903 patent were well known in the art, the omission of this information from the provisional application does not render the dosage limitation unsupported." PO Resp. 28–29.

In particular, Patent Owner argues that the rat model used in the provisional application was well known in the art before October 2002. *Id.* at 29. According to Patent Owner:

> The provisional application describes the rat TGF-β1 model and discloses that a sildenafil dosage of 100 mg/L was administered to these rats in their drinking water. Ex. 1003 at ¶¶ 119, 138. The provisional application also discloses that the rats used for the penile fibrosis model were male Fischer 344 rats aged 9–11 months. *Id.* at ¶ 119. As of October 2002, these rats were known to weigh between 390 and 450 grams, and to have an average daily water intake of 8–11 mL water per 100 grams body weight. Ex. 2023 ¶¶ 123–124. Accordingly, a person of skill in the art would have known in October 2002 that the rats used in the '903 patent consumed on average 31.2–49.5 mL of water daily, and thus 8–11 mg/kg of sildenafil daily. *Id.* ¶ 125.

Id. at 29–30. Patent Owner contends further that "[a]s of October 2002, the conversion of drug dosages between rats and humans was also well known

to a person of skill in the art, and has been for decades." *Id.* at 30 (citing Ex. 2023 ¶ 126).

In addition, Patent Owner argues that the safe and effective doses of sildenafil, vardenafil, and tadalafil were publicly available as of October 2002, and each was below the 1.5 mg/kg that would have been obtained using those well-known methods of conversion from rats to humans. *Id.* at 31. Thus, Patent Owner asserts that "one of skill in the art would have understood that the correct dosages for use in humans when practicing the claimed invention should be 'up to 1.5 mg/kg,' as this value both encompasses the dosages disclosed by the provisional application as well as the available safety and efficacy data for use of PDE-5 inhibitors in humans." *Id.*

Petitioner, in reply, notes that the provisional application only discloses one data point, and thus does not provide support for the "up to" limitation. Reply 5. Petitioner contends further that Patent Owner's calculations rely on assumptions that are not contained within the provisional application, such as male human weight and height and the weight of the rat. *Id.* at 6–8.

We agree with Petitioner that the provisional application does not support the limitation of "up to of 1.5 mg/kg/day" required by independent claim 1. The ordinary artisan, following Patent Owner's analysis, would need to look to the art for a teaching the formula for converting rat dosages to human dosages, make assumptions regarding the weight of the rat used as the model, as well as assumptions about the weight and height of an average man, as Patent Owner does not point us to where such disclosure appears in the provisional application, contending only that the information was well

known. *See* Ex. 2021; Ex. 1004 ¶ 234. And then, the ordinary artisan would also have to be aware of safe and effective doses of PDE5 inhibitors, such as sildenafil, vardenafil, and tadalafil, which Patent Owner asserts were publicly available as of October 2002. Thus, at best, Patent Owner may have made a case as to why the provisional application would have rendered obvious the limitation of a dosage of 1.5 mg/kg/day, but the ordinary artisan would not have immediately discerned that limitation from a reading of the disclosure of the provisional application. We determine, therefore, that the claims of the '903 patent are not entitled to the October 22, 2002 filing date of the provisional application.

C. Patentability

To prevail on its challenges to the patentability of claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

1. Obviousness of Claim 1 Under 35 U.S.C. § 103(a) over Montorsi, Whitaker, and Porst

Petitioner contends that the combination of Montorsi, Whitaker, and Porst renders obvious independent claim 1. Pet. 19–40. Petitioner sets forth claim charts demonstrating where each element of the claim is taught by the references (*id.* at 26–32), and relies, initially, on the Declarations of Dr. Goldstein (Ex. 1002, 1089). Patent Owner disagrees with Petitioner's assertions (PO Resp. 32–60), and relies on the Declaration of Trinity J. Bivalacqua, M.D. Ph.D. (Ex. 2023) as evidence that the Whitaker does not anticipate the challenged claims. Petitioner then relies on an additional Declaration of Dr. Goldstein (Ex. 1121) in its Reply.

a. Montorsi (Ex. 1051)

Montorsi teaches that ED is common in the aging male, and that the pathophysiology in that patient group "mainly includes chronic ischemia, which triggers the deterioration of cavernous smooth muscle and the development of corporeal fibrosis." Ex. 1051, Abstract.

According to Montorsi, numerous studies have shown that atherosclerosis, and subsequent tissue ischemia, significantly affect both arterial inflow, as well as the veno-occlusive mechanism of the corpora cavernosa. *Id.* at 30. Montorsi teaches:

> The reduction in the smooth muscle content of the corpus cavernosum is associated with the impairment of cavernosal expandability and subsequent veno-occlusive dysfunction. These animal studies have, thus, identified the association between veno-occlusive dysfunction of the corpora cavernosa and corporeal fibrosis.

Id. (references removed). Montorsi teaches, therefore, "[a]s the ED from ageing appears to be a slowly progressive disorder, it appears wise for the patient to seek medical intervention earlier rather than later, so as to minimise the development of veno-occlusive dysfunction." *Id.* at 31.

Therapy includes oral drug therapy, which Montorsi teaches "has been necessary and useful." *Id.* at 32. Montorsi specifically teaches the use of sildenafil, a PDE5 inhibitor, which is taught to be "an effective and well-tolerated oral agent for treating ED in the general population of adult men with ED of broad-spectrum aetiology." *Id.* Montorsi discusses a study devoted to assessing the efficacy of treating ED in elderly men, wherein sildenafil was taken as required, but no more than once daily, over a 12 week to 6 month period. *Id.* Patients were instructed to take the sildenafil one hour before sexual activity, but no more than once daily, and received

25 mg, 50 mg, or 100 mg of sildenafil, either in a fixed dose or flexible dose. *Id.* at 32–33.

Montorsi teaches:

> The results of this combined analysis show that sildenafil is an effective treatment for ED in elderly men with ED of various aetiologies and with concomitant illnesses. More than two-thirds of the men in the broad spectrum ED subgroup and one-half of the men in the ED and diabetes subgroup reported improved erections with sildenafil treatment.

Id. at 33.

b. Whitaker (Ex. 1086)

Whitaker, which is titled "Daily Treatment for Erectile Dysfunction Using a PDE5 Inhibitor," discusses problems with treatment using sildenafil, which is marketed under the trademark VIAGRA®. Ex. 1086, 2:25–27. Specifically, Whitaker teaches:

> While sildenafil has obtained significant commercial success, problems in the treatment of erectile dysfunction (ED) still exist. First, ED therapy using sildenafil is based on an on-demand or PRN therapy. "On demand" dosing is defined as an acute administration of a drug for treating erectile dysfunction prior to expected sexual activity. The user therefore must plan ahead, and, as presently labeled, ingest a relatively large oral dose (i.e., at least 25 mg) of sildenafil at least one hour prior to engaging in sexual activity. The onset of beneficial effects may be delayed when sildenafil is administered with a meal.
>
> Second; the relatively large on-demand dose of sildenafil results in significant adverse side effects, including facial flushing (10% incidence rate). Thus, even with the availability of sildenafil, there remains a need to identify improved pharmaceutical products that are useful and more convenient in treating sexual dysfunction.

Id. at 2:25–3:11.

Whitaker, therefore, discloses methods of treating male erectile dysfunction involving the chronic administration of a PDE5 inhibitor at a dose of 1 mg/day to 10 mg/day. *Id.* at 4:13–18. The method also "provides a method of improving the relaxant response in corpus cavernosum smooth muscle tissue." *Id.* at 4:19–21. In particular, Whitaker suggests that the method may result in a "partial or complete reversal of circulatory dysfunctions in penile circulation arising from conditions such as diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors." *Id.* at 13:11–16.

Whitaker teaches further that tadalafil ((6R- trans)-6-(1,3-benzodioxol-5-yl)-2 ,3, 6, 7, 12, 12a-hexahydro-2-methylpyrazino[l ',2' :1, 6]pyrido [3,4-b] indole -1,4-dione, alternatively named (6R, 12aR) -2, 3, 6, 7, 12, 12a-hexahydro-2-methyl-6- (3, 4-methylene-dioxyphenyl) pyrazino [2', l' :6,l]pyrido[3,4-b]indole 1,4-dione;active agent in CIALIS®), sildenafil and vardenafil may be used for chronic administration, wherein sildenafil and vardenafil may be used at a dosage from about 1 to about 25 mg/day. *Id.* at 16:3–17:32.

Whitaker defines chronic as follows:

> The term "chronic or chronically" refers to the regular administration of the product in intervals unrelated to the onset of sexual activity. To receive the full benefit of the present invention, chronic administration generally refers to regular administration for an extended period, preferably daily for three or more days, and still more preferably daily as long as the patient suffers from erectile dysfunction (in the absence of therapy). The term "chronic" administration encompasses other regimens in addition to daily dosing. For example, chronic administration encompasses administration of a sustained release formulation that provides sufficient PDE5 inhibiter on a regular basis and unrelated to the onset of sexual activity.

> Contrary to acute or on-demand administration, chronic administration does not link the administration of the PDE5 inhibitor to the onset of sexual activity (e.g., one hour prior to intercourse).

Id. at 7:10–29. Whitaker teaches specifically that daily dosing is preferred, and that the enhanced efficacy of low daily dosing "results from improved vascular responsiveness when the PDE5 inhibitor is present continuously, or essentially continuously, in plasma." *Id.* at 12:6, 21–27.

Whitaker Example 6 discloses the results of five clinical studies assessing the efficacy of daily oral dosing of a PDE5 inhibitor in males with erectile dysfunction. *Id.* at 34–37. According to Whitaker:

> One study was of eight weeks duration, and the other four studies were of twelve weeks duration. The Study Drug was administered "daily" to patients with male erectile dysfunction. "Erectile dysfunction (ED)" is defined as the persistent inability to attain and/or maintain an erection adequate to permit satisfactory sexual performance.

Id. at 34:17–24. There were four subgroups in the study, with the first subgroup taking the study drug less than 30% of the time during the study, the second subgroup taking the study drug 30% to 50% of the time during the study, the third subgroup taking the study drug 50% to 70% of the time during the study, and the fourth subgroup taking the study drug greater than 70% of the time during the study. *Id.* at 34:25–31. Whitaker teaches that the "Study Drug was administered in 5 mg and 10 mg doses, 'daily' and not more than once every 24 hours." *Id.* at 35:3–4. As taught by Whitaker, a better response was obtained with an increased frequency of dose. *Id.* at 36:1–4.

Whitaker Example 7 assessed the safety and efficacy of a PDE5 inhibitor in men 21–72 years of age, experiencing mild-to-moderate ED. *Id.*

at 37:18–22. The participants received a placebo, 10 mg, 25 mg, 50 mg, or 100 mg of the study drug daily for three weeks. *Id.* at 37:24–27. Whitaker found that the study drug significantly improved ED, with adverse events being attenuated by daily use. *Id.* at 38:6–21.

c. Porst (Ex. 1096)

Porst is a printed abstract. Porst assessed the efficacy and safety of the daily administration of the PDE5 inhibitor IC351, *i.e.*, tadalafil, in men with mild to moderate ED. Ex. 1096. Patients were randomized, wherein some patients received up to 100 mg of IC351 daily for three weeks. *Id.* The authors concluded that "IC351 administered up to 100 mg was safe and generally well tolerated and improved patient's erectile functions and sexual satisfaction." *Id.*

d. Analysis

Claims 1–5 encompass a method of administering a PDE5 inhibitor, at a dosage up to 1.5 mg/kg/day for not less than 45 days, to an individual with a corporal tissue fibrosis, e.g., corporal veno-occlussive dysfunction ("CVOD"), such that the fibrosis is arrested or regresses. As noted above in the section discussing claim construction, arresting or regressing the fibrosis is the intended result of administering a PDE5 inhibitor, at a dosage up to 1.5 mg/kg/day for not less than 45 days. In addition, the claim does not require a diagnosis of penile tunical fibrosis or corporal tissue fibrosis, but encompasses treatment of a patient presenting with symptoms that may be associated with fibrosis, such as ED in certain patient populations, as discussed below.

Petitioner relies on Montorsi for teaching that administering sildenafil daily at bedtime to treat or prevent erectile dysfunction in the elderly patent

minimizes the development of COVD. Pet. 20 (citing Ex. 1051, 31). Whitaker, Petitioner contends, "provides motivation and specific guidance on . . . long-term, continuous use of a daily PDE5 inhibitor at up to 1.5 mg/kg/day for at least 45 days." *Id.* (citing Ex. 1089 ¶ 43).

Specifically, in addition to teaching the use of sildenafil, Whitaker teaches that "tadalafil is 'especially preferred.'" *Id.* (citing Ex. 1086, 16:3; Ex. 1089 ¶ 44). Whitaker teaches also administration of PDE5 inhibitors for eight to twelve weeks. *Id.* at 21 (citing Ex. 1089 ¶ 45). Petitioner notes further that Whitaker teaches that the treatment should last as long as the patient suffers from ED, which, Petitioner asserts, the experts agree would be at least months. Reply 19 (citing Ex. 1122, 298:20–300:8). Petitioner cites multiple references as evidence that the ordinary artisan would have understood that conditions such as diabetes, atherosclerosis, smoking, and hypertension lead to penile fibrosis, and in particular CVOD. Pet. 21, *see also id.* n.17 (quoting from multiple cited references that purportedly establish a link between the above conditions and CVOD). Moreover, Petitioner argues, Whitaker teaches daily administration of a PDE5 inhibitor not only to treat ED, but also to improve vascular conditioning and the relaxant response of cavernosal smooth muscle tissue. *Id.* (citing Ex. 1086, 4:19–23; Ex. 1089 ¶ 45).

Porst, Petitioner contends, provides a further reason to treat a patient with up to 1.5 mg/kg/day of PDE5 inhibitor for at least 45 days, as it teaches that 100 mg per day, which corresponds to 1.43 mg/kg/day, is safe, well, tolerated, and improves erectile function. *Id.* at 22–23 (citing Ex. 1089 ¶ 47, 49).

Petitioner asserts that the ordinary artisan would have combined the references not only for the purpose of treating ED, but also for the purpose of treating the underlying pathophysiology. *Id.* at 24 (citing Ex. 1089 ¶ 51). Specifically, Petitioner notes that Montorsi teaches that atherosclerosis affects the veno-occlusive mechanism of the corpora cavernosa, teaching the daily use of a PDE5 inhibitor, and Whitaker teaches that daily administration of a PDE5 inhibitor improves the relaxant response in corpus cavernosum smooth muscle tissue. *Id.* Moreover, Petitioner contends, both Montorsi and Whitaker each address ED induced by atherosclerosis. *Id.* at 24–25. The ordinary artisan would also have had a reasonable expectation of success of achieving the claimed invention, Petitioner asserts, as Montorsi teaches early intervention, Whitaker teaches daily administration, and Porst teaches that the administration of 100 mg per day was safe and generally well tolerated. *Id.* at 25.

We conclude that Petitioner has demonstrated, by a preponderance of the evidence, that the combination of Montorsi, Whitaker, and Porst renders obvious claim 1 of the ’903 patent. Montorsi teaches that ED in the aging male is associated with the development of corporal fibrosis. Ex. 1051, Abstract. Montorsi discusses a study devoted to assessing the efficacy of treating ED in elderly men, wherein sildenafil was taken as required, but no more than once daily, over a 12 week to 6 month period, concluding that sildenafil is an effective treatment for ED in elderly men. *Id.* at 32–33.

Whitaker, which is entitled “Daily Treatment for Erectile Dysfunction Using a PDE5 Inhibitor,” teaches daily administration with a PDE5 inhibitor “for as long as the erectile dysfunction continues.” Ex. 1086, 7:17–19. Dr. Bivalacqua, Patent Owner’s expert, notes that it can take months to resolve

ED based on factors like diet modification, exercising, and reducing other risk factors. Ex. 1122, 300:1–8. And although the fourth subgroup in Example 6 of Whitaker took the study drug in 5 mg and 10 mg doses only greater than 70% of the time during the study, Whitaker does suggest administering the study drug eight to twelve weeks. Ex. 1086, 34:17–19, 25–31. Whitaker also notes that a better response was obtained with an increased frequency of dose, with adverse effects being attenuated with daily use. *Id.* at 36:1–4, 38:19–21. Whitaker teaches reversal of circulatory dysfunctions in diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors. Ex. 1086, 13:11–16. Porst provides evidence that daily dosing of tadalafil administered up to 100 mg was safe and generally well tolerated and improved patient's erectile functions and sexual satisfaction. Ex. 1096.

Thus, each of Montorsi, Whitaker, and Porst teaches a dosage of a PDE5 inhibitor of no more than 1.5 mg/kg/day. While Montorsi teaches more of an on-demand dosing, Montorsi teaches that the PDE5 inhibitor, sildenafil was administered no more than once daily to elderly patients suffering from ED from a 12 week to 6 month period. Whitaker expressly teaches once daily dosing, teaches that treatment should last as long as the erectile dysfunction continues, and expressly teaches time periods of eight to twelve weeks. Whitaker also teaches a better response was obtained with an increased frequency of dose, with adverse effects being attenuated with daily use. Porst teaches that daily dosing with of tadalafil administered up to 100 mg was safe and improved patient's erectile functions. Thus, the combination of Montorsi, Whitaker, and Porst suggests daily dosing for at least 45 days.

As to the limitation that individual has at least one of a penile tunical fibrosis or corporal tissue fibrosis, as construed above, that limitation does not require that the patient be specifically diagnosed as having penile tunical fibrosis or corporal tissue fibrosis, but has symptoms associated with penile fibrosis, such as ED. Montorsi specifically teaches treatment of ED in elderly patients, which Montorsi teaches is associated with the development of corporal fibrosis. Whitaker teaches treatment of ED in patent populations with diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors. Montorsi ties atherosclerosis to the veno-occlusive mechanism of the corpora cavernosa. Thus, treatment of ED in elderly patients or patients with atherosclerosis, as suggested by both Montorsi and Whitaker, would result in treatment of patients with the fibrosis, as Montorsi teaches that corporal fibrosis is associated with ED in those patient populations. Patent Owner's arguments and evidence to the contrary have been carefully considered, but do not persuade us otherwise.

Patent Owner contends that that the claimed invention was "not just unexpected—it ***contradicted*** the scientific community's belief regarding the role of iNOS in fibrosis." PO Resp. 33.

Patent Owner is arguing the mechanism of action underlying penile fibrosis. The claim requires administering up 1.5 mg/kg/day of PDE5 inhibitor for at least 45 days to a patient presenting with symptoms that may be associated with fibrosis, such as ED in the elderly male, or patients suffering from atherosclerosis. The claim does not require any impact on iNOS or cGMP levels, and any impact that would result from the administration of PDE5 inhibitors would be inherent in the method of claim 1. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed.

Cir. 2012) (explaining in an obviousness context that "[e]ven if no prior art of record explicitly discusses the [limitation,] the [patent applicant's] application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in the [claimed invention]."); *see also Atlas Powder Co. v. Irene, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."). As discussed above, the combination of Montorsi, Whitaker, and Porst renders obvious the claimed method.

Patent Owner contends further that Whitaker does not teach all of the elements of the claimed method, whether taken alone, or combined with Montorsi and Porst. PO Resp. 34–35. According to Patent Owner, Whitaker "contains no express disclosure of an individual with either tunical or corporal fibrosis." *Id.* at 35. Patent Owner argues that penile fibrosis is only one cause of ED, and may not always result in ED. *Id.* (citing Ex. 2023 ¶ 182; Ex. 2103, 34:24–35:3, 42:8–11, 97:6–10, 116:10–14). That is, according to Patent Owner, there is "no inherent relationship between penile fibrosis and erectile dysfunction," as not all patients suffering from erectile dysfunction also suffer from penile tunical or corporal fibrosis. PO Resp. 46; *see also id.* at 47–51 (contending that Example 6 of Whitaker does not inherently teach an individual with tunical fibrosis and corporal tissue fibrosis). Moreover, Patent Owner asserts, the ordinary artisan would not have equated the vascular conditioning taught by Whitaker with penile fibrosis. *Id.* at 36–37. Patent Owner contends also that Whitaker does not

teach or suggesting arresting or regressing penile fibrosis, as required by claim 1. *Id.* at 37–40. Whitaker, Petitioner argues, citing the deposition testimony of Petitioner's expert, Dr. Goldstein, teaches at best slowing the progression of fibrosis. *Id.* at 38 (citing Ex. 2103, 150:3–151:20).

Patent Owner contends next that Montorsi does not remedy the deficiencies of Whitaker. PO Resp. 51–57. According to Patent Owner, the portion of Montorsi relied upon by Petitioner "at best hypothesizes that sildenafil ***might*** be useful in ***preventing*** corporal fibrosis," and that hypothesis, along with suggesting further study, does not render obvious the claim invention. *Id.* at 51–52 (citing Ex. 1051, 31). Patent Owner argues there is nothing in Montorsi that suggests arresting or regressing fibrosis, as required by challenged claim 1. *Id.* at 52, *see also id.* at 56 (arguing that there is no teaching in Montorsi that once-daily dosing of sildenafil is therapeutically effective to arrest or regress penile fibrosis). Patent Owner argues that while Montorsi refers to preventing or minimizing corporal fibrosis, "[a] person of skill in the art would understand . . . that prevention and treatment are very different, and that stopping or reversing a disease is not the same as preventing it in the first place." *Id.* at 52.

Patent Owner contends also that Porst fails also to remedy the deficiencies of Montorsi and Whitaker. *Id.* at 57–58. According to Patent Owner, the ordinary artisan would understand that Porst "focuses on using tadalafil therapy to ameliorate the ***symptoms*** of erectile dysfunction, and not to treat any underlying cause or pathophysiology of erectile dysfunction." *Id.*

Although Whitaker may not contain an express disclosure of either tunical or corporal fibrosis, it does teach a patient population comprising

patients with atherosclerosis. Ex. 1086, 13:11–16. Montorsi teaches that atherosclerosis is associated with the veno-occlusive mechanism of the corpora cavernosa. Ex. 1051, 30. Montorsi also teaches that corporal fibrosis is associated with ED in the aging male. Ex. 1051, Abstract. Montorsi suggests treating the aging male with a PDE5 inhibitor, and both Montorsi and Whitaker suggest treating patients with ED associated with atherosclerosis with a PDE5 inhibitor. As noted above in the section on claim construction, the claim term "arresting or regressing . . . penile tissue and fibrosis and corporal tissue fibrosis" would be the intended result in treating those patients with up to 1.5 mg/kg/day of PDE5 inhibitor for at least 45 days.

Patent Owner contends that the chronic administration of Whitaker is not the same as the long-term regimen required by claim 1. PO Resp. 41. Specifically, Patent Owner asserts that the chronic administration of Whitaker "merely requires administration of the drug at regular intervals, as contrasted with as-needed administration whose timing is determined solely by the opportunity to engage in sexual activity," but "does not require that such administration at regular intervals *necessarily* occur with the requisite frequency and duration to establish and maintain steady state, i.e., a constant level of the PDE5 inhibitor." *Id.* at 42 (citing Ex. 2023 ¶¶ 205–208; Ex. 2018, 23–24); *see also* PO Resp. 42–45 (noting that Whitaker allows for missing a dose, and as such, does not teach continuous administration). Patent Owner argues also that Whitaker does not teach administration for not less than 45 days as also required by claim 1. *Id.* at 45. According to Patent Owner, although the studies in Example 6 of Whitaker were ostensibly of eight or twelve weeks duration, Whitaker makes clear that the unidentified

PDE5 inhibitor was not administered to the subjects on each and every day." *Id.* at 42–43 (citing Ex. 2023 ¶ 211).

Montorsi, Patent Owner asserts, also does not teach or suggest a continuous long-term regimen for not less than 45 days, as required by claim 1. *Id*. at 54–57. In particular, Patent Owner argues that Montorsi's teaching regarding the daily administration of sildenafil is speculation based on a study that administered a single dose to study its effect on nocturnal, penile tumescence, and that the ordinary artisan "would not and could not reasonably rely on that study to support any inference about the possible effects of daily (let alone continuous and long-term) sildenafil administration." *Id.* at 55 (citing Ex. 2023 ¶ 171). Patent Owner argues further that daily administration of sildenafil would not maintain a steady state of the drug in plasma due to its short half-life, and, thus, would not meet Patent Owner's proposed construction of continuous long-term regimen of requiring constant plasma levels. *Id.* at 55–56 (citing Ex. 2023 ¶¶ 86–94). Montorsi is also silent as the duration for which sildenafil should be administered nightly, and, thus, Patent Owner argues does not teach the limitation of claim 1 that the sildenafil is administered for at least 45 days. *Id.* at 56–57.

As discussed above, although Montorsi teaches more of an on-demand dosing, Montorsi teaches that a PDE5 inhibitor was administered no more than once daily to elderly patients suffering from ED from a 12 week to 6 month period. Whitaker expressly teaches once daily dosing, and expressly teaches that the treatment should last as long as the erectile dysfunction continues. Although the PDE5 inhibitor was not necessarily administered daily in the eight to twelve week periods in Example 6 in of Whitaker,

Whitaker teaches that a better response was obtained with an increased frequency of dose, as well as teaching that adverse effects were attenuated with daily administration. Porst teaches that daily dosing with of tadalafil administered up to 100 mg was safe and improved patient's erectile functions. Thus, the combination of Montorsi, Whitaker, and Porst suggests daily dosing for at least 45 days, and provides a reasonable expectation of success of treating ED. As to Patent Owner's argument that daily administration of sildenafil would not maintain a steady state of the drug in plasma due to its short half-life, and, thus, would not meet Patent Owner's proposed construction of continuous long-term regimen of requiring constant plasma levels, we declined to construe the claims as requiring a steady state of the drug in plasma, noting that administering a dosage up to 1.5 mg/kg/day for at least 45 days would, according to the language of the claim, meet the limitation of a "continuous, long-term regimen."

Patent Owner contends moreover the ordinary artisan would not have been motivated to combine the teachings of Montorsi, Whitaker, and Prost to achieve the claimed method. PO Resp. 58–60. According to Patent Owner, Whitaker criticizes a higher, as needed dosage of a PDE5 inhibitor as causing adverse side effects, and thus advocates the use of smaller, 1 mg to 10 mg, doses of PDE5 inhibitor. *Id.* at 58–59. Montorsi and Porst, however, both rely on 100 mg doses, which Whitaker criticizes. *Id.* at 59. Thus, Patent Owner argues, the ordinary artisan would not have combined the references as suggested by Petitioner. *Id.*

> We decline to read Whitaker as teaching away from the combination.
>
> Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of applicant's

> invention. A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.

Syntex (USA) LLC v. Apotex, Inc., 407 F.3d 1371, 1380 (Fed. Cir. 2005). While Whitaker teaches that the relatively large dose of sildenafil may result in significant adverse side effects, such as facial flushing (Ex. 1086, 3), both Montorsi and Porst teach that the 100 mg doses are well tolerated and safe when given for an extended period of time. Ex. 1051, 33; Ex. 1096. Thus, the ordinary artisan would have understood that doses up to 1.5 mg/kg/day would be well tolerated, and that daily treatment would results in treatment of ED in which there is underlying corporeal fibrosis.

2. Claims 2–5

Patent Owner does not present separate patentability arguments as dependent claims 2–5. We have reviewed Petitioner's contentions as to these claims, as well as the claim charts (Pet. 26–32), and determine that Petitioner has demonstrated the unpatentability of dependent claims 2–5 by a preponderance of the evidence.

3. Conclusion

After considering Petitioner's and Patent Owner's positions, as well as their supporting evidence, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–5 are unpatentable under 35 U.S.C. § 103 over the combination of Montorsi, Whitaker, and Porst.

D. Patent Owner's Motion to Exclude Evidence (Paper 30)

Patent Owner seeks to exclude Petitioner's Exhibits 1103, 1106, 1107, 1115, 1116, 1118–1121, 1124, 1127, 1128–1130, 1131, 1135–1137, 1139–1140, 1142, 1144, and portions of Dr. Bivalacqua's deposition testimony (Ex. 1122). Paper 30, 1. As we did not rely on any of exhibits 1103, 1106,

1107, 1115, 1116, 1118–1121, 1124, 1127, 1128–1130, 1131, 1135–1137, 1139–1140, 1142, 1144 in this decision, Patent Owner's Motion to Exclude is dismissed as moot as to those exhibits.

Patent Owner also seeks to exclude portions of Dr. Bivalacqua's deposition (Ex. 1122) that relate to whether the '903 patent is directed to unpatentable subject matter, as well as the construction of the claim term "individual." Paper 30, 7–8. As we did not rely on those portions of the deposition testimony, Patent Owner's Motion to Exclude is dismissed as moot as to that testimony.

E. Motion for Observation (Paper 32)

Patent Owner's observations are directed to the cross-examination testimony of Irwin Goldstein, M.D. (Ex. 2108), who was cross-examined after Petitioner filed its Reply. Paper 32. As previously discussed, we did not rely on the Dr. Goldstein's Reply Declaration in this decision. Therefore, we have not considered Patent Owner's observations directed to the cross-examination testimony of Dr. Goldstein.

F. Objections to Demonstratives

Each of Petitioner (Paper 41) and Patent Owner (Paper 42) objected to the other's demonstratives. In view of the objectives, we expunge the demonstratives from the record. Thus, Petitioner's demonstratives (Paper 39) and Patent Owner's demonstratives (Paper 40) are expunged.

III. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims 1–5 are unpatentable under 35 U.S.C. § 103 over the combination of Montorsi, Whitaker, and Porst.

IV. ORDER

Accordingly, it is hereby:

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1–5 of the ’903 patent are unpatentable;

FURTHER ORDERED that Petitioner’s Motion to Exclude is *dismissed* as moot;

FURTHER ORDERED that Papers 39 and 40 are expunged; and

FURTHER ORDERED that, because this is a Final Written Decision, 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.

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