United States Court of Appeals for the Federal Circuit

LOS ANGELES BIOMEDICAL RESEARCH INSTITUTE AT HARBOR-UCLA MEDICAL CENTER,
Appellant

v.

ELI LILLY AND COMPANY,
Appellee

2016-1518

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, in No. IPR2014-00752.

Decided: February 28, 2017

EWA M. DAVISON, Fenwick & West LLP, Seattle, WA, argued for appellant. Also represented by DAVID KEITH TELLEKSON, ELIZABETH B. HAGAN; VIRGINIA KAY DEMARCHI, AMY HAYDEN, Mountain View, CA.

MARK J. FELDSTEIN, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for appellee. Also represented by JOSHUA GOLDBERG, YIEYIE YANG; CHARLES E. LIPSEY, Reston, VA; MARK STEWART, Eli Lilly and Company, Indianapolis, IN.

Before NEWMAN, BRYSON, and MOORE, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* BRYSON.

Opinion concurring in part, dissenting from the judgment filed by *Circuit Judge* NEWMAN.

BRYSON, *Circuit Judge.*

Appellant Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center ("LAB") seeks review of a decision of the Patent Trial and Appeal Board holding all claims of U.S. Patent No. 8,133,903 ("the '903 patent") unpatentable as obvious. We vacate the Board's order and remand for further proceedings.

I

A

The '903 patent claims a method of "arresting or regressing" a condition known as penile fibrosis. The method entails the long-term, daily administration of drugs known as type 5 phosphodiesterase ("PDE5") inhibitors. The drugs function by inhibiting the enzymatic action of PDE5, which is found in the human penis. *See* '903 patent, col. 6, line 51, through col. 7, line 15.

The penis contains two cylindrical chambers called the corpora cavernosa. Those chambers fill with blood during an erection. The corpora cavernosa are surrounded by a membrane called the tunica albuginea. Penile fibrosis is characterized by the buildup of excess collagen. It includes two conditions: penile tunical fibrosis, which results from the buildup of excess collagen in the tunica albuginea, and corporal tissue fibrosis, which results from a buildup of excess collagen in the corpora cavernosa. *See* '903 patent, col. 68, ll. 22-32, 37-39; *see also id.*, col. 9, ll. 45-46.

The two fibrotic conditions can cause erectile dysfunction, although they do not always do so. Tunical fibrosis can manifest itself as Peyronie's disease, a condition that "usually leads to penile deformation (curved penis during erection), pain, and quite frequently erectile dysfunction." '903 patent, col. 1, ll. 33-34. Corporal tissue fibrosis, which results from the death of smooth muscle cells in the corpora cavernosa and a corresponding buildup of collagen, can cause dysfunction of the mechanism that retains blood in the corpora cavernosa during an erection. In a healthy male, the relaxation of the smooth muscle cells in the penis increases the flow of blood to the corpora cavernosa. The flow of blood into the corpora cavernosa in turn compresses the veins of the penis against the tunica albuginea to block the flow of blood from the penis. The compression of those veins is known as the veno-occlusive mechanism. Disruption of that mechanism, known as corporal veno-occlusive disorder ("CVOD"), can lead to erectile dysfunction. *Id.*, col. 2, ll. 23-31.

In addition to the two types of penile fibrosis, there are many other causes of erectile dysfunction. Some causes of erectile dysfunction, such as those of psychological origin, are entirely unrelated to fibrosis.

In the early 2000s, PDE5 inhibitors such as sildenafil (Viagra) and tadalafil (Cialis) were well known and commonly used for the on-demand treatment of erectile dysfunction. *See* '903 patent, col. 10, line 59, through col. 11, line 3. The use of sildenafil and tadalafil for that purpose was not restricted to cases of erectile dysfunction resulting from penile fibrosis. Individuals with erectile dysfunction of varying causes were instructed to take PDE5 inhibitors before sexual activity in order to obtain an erection at the desired time. As the '903 patent explains, that use of PDE5 inhibitors was "not addressed to the long-term cure of underlying tissue fibrosis." *Id.*, col. 10, line 67, through col. 11, line 3.

At that time, according to the patent, there was a need for adequate non-surgical treatments for Peyronie's disease and other fibrotic conditions. '903 patent, col. 2, ll. 2-7 (noting that surgery was "the only option" available in most cases of Peyronie's disease). Erectile dysfunction resulting from those conditions could be treated symptomatically with on-demand PDE5 inhibitors, but there was "[n]o effective method of treatment . . . directed towards the molecular pathways underlying excessive collagen deposition" to address penile fibrosis. *Id.*, col. 2, ll. 44-46.

The '903 patent, owned by LAB, claims such a treatment. Claim 1, the only independent claim, recites:

> 1. A method comprising:
>
> a) administering a cyclic guanosine 3', 5'-monophosphate (cGMP) type 5 phosphodiesterase (PDE5) 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
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> b) arresting or regressing the at least one of the penile tunical 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.

'903 patent, col. 68, ll. 23-32.

The remaining four claims depend from claim 1 and concern the type of drug (claim 2), the type of fibrotic condition (claim 3), the mode of administration (claim 4),

and the duration of treatment (claim 5). *Id.*, col. 68, ll. 33-45.[1]

B

In 2013, LAB filed an infringement action in the United States District Court for the Central District of California against Eli Lilly & Company ("Lilly"), alleging that Lilly's marketing of the drug Cialis induced infringement of the '903 patent. *Los Angeles Biomed. Research Inst. v. Eli Lilly & Co.*, No. 2:13-cv-08567-JAK-JCG (C.D. Cal. filed Nov. 20, 2013). Lilly subsequently filed multiple petitions requesting that the Patent Trial and Appeal Board conduct *inter partes* review of the '903 patent. The Board instituted *inter partes* review on the petition in which Lilly contended that all the claims of the '903 patent were unpatentable as obvious in light of three references. The cited references were: Francesco Montorsi et al., *The Ageing Male and Erectile Dysfunction*, 20 World J. Urology 28-53 (2002) ("Montorsi"); International Patent Application No. WO 01/80860 (published Nov. 1, 2001) (John S. Whitaker et al., applicants) ("Whitaker"); and Hartmut Porst et al., *Daily IC351 Treatment of ED*, 12 Int'l J. Impotence Research (Supp. 3) S76, B13 (2000) ("Porst").[2]

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[1] LAB has not presented separate arguments for the patentability of any of the dependent claims.

[2] The Board also instituted *inter partes* review on the petition in which Lilly argued that all the claims of the '903 patent were unpatentable as anticipated by Whitaker. The Board conducted that *inter partes* review in a separate proceeding, No. IPR2014-00693. At the conclusion of that proceeding, the Board ruled that the claims were not anticipated. That decision, which Lilly appealed, is addressed in the related case, *Eli Lilly & Company v. Los Angeles Biomedical Research Institute at*

The '903 patent claims priority from Provisional Application No. 60/420,281, which was filed on October 22, 2002. '903 patent, col. 1, ll. 12-15. The Board rejected LAB's argument for the earlier priority date and determined that the specification of the provisional application did not disclose the dosage limitation of "up to 1.5 mg/kg/day," i.e., a dosage of up to 1.5 milligrams of PDE5 inhibitor per kilogram of the patient's body weight each day.

The Board also construed several claim limitations that are now at issue on appeal. First, the Board construed the phrase "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" to mean an "individual hav[ing] symptoms that may be associated with penile fibrosis, such as [erectile dysfunction], but not that the patient be specifically diagnosed as having penile tunical fibrosis or corporal tissue fibrosis."

Second, the Board construed the phrase "arresting or regressing the at least one of the penile tunical fibrosis and corporal tissue fibrosis" as having no limiting role, but merely stating the intended result of administering a PDE5 inhibitor at a dosage of up to 1.5 mg/kg/day for at least 45 days.

Third, in the Decision on Institution, the Board construed the term "continuous long-term regimen" to mean "the administration of drug over a certain period of time without intermission such that the treatment is therapeutically effective." In its final decision, the Board concluded that the claim limitation requiring the delivery of a dosage of up to 1.5 mg/kg/day for at least 45 days "would meet the claim requirement of a continuous, long-term regimen."

Harbor-UCLA Medical Center, No. 2016-1547, decided together with this case but in a separate opinion.

The Board then addressed the three prior art references: Montorsi, Whitaker, and Porst.

Montorsi is a review article that addresses the treatment of erectile dysfunction in the aging male population. Montorsi states that male erectile dysfunction is associated with aging; that atherosclerosis (the buildup of plaque in the arteries) is common in the elderly; and that atherosclerosis is associated with CVOD and corporal fibrosis, which can cause erectile dysfunction. Montorsi at 28, 30-31. Montorsi concludes that "it seems reasonable to hypothesise that the [erectile dysfunction] from ageing is the result of atherosclerosis-induced cavernosal ischaemia leading to cavernosal fibrosis and [CVOD]." *Id.* at 31.

Montorsi discusses several relevant studies of erectile dysfunction. It begins by reviewing a group of studies on sildenafil as a treatment for erectile dysfunction in elderly patients. The patients in that study were instructed to take up to 100 mg of sildenafil on demand (one hour before sexual activity) but no more than once daily over a 12 week to 6 month period. Those studies showed that sildenafil was well tolerated and that it ameliorated the treated condition. Montorsi at 32-33. Another study reported that administering a 100 mg dose of sildenafil at bedtime to male patients between 40 and 68 years old with erectile dysfunction produced an increase in nocturnal erections. *Id.* at 31 (citing Francesco Montorsi et al., *Sildenafil Taken at Bedtime Significantly Increases Nocturnal Erections: Results of a Placebo-Controlled Study*, 56 Urology 906, 907 (2000)). Montorsi concludes that this study "opened the door to further study investigating the possible dosage of sildenafil to be administered daily at bedtime to prevent or treat [erectile dysfunction] in the elderly patient." Montorsi at 31.

Whitaker is an abandoned patent application that claims the chronic use of low-dose PDE5 inhibitors to treat erectile dysfunction. Whitaker defines "chronic" as

"the regular administration of the [PDE5 inhibitor] in intervals unrelated to the onset of sexual activity," and states that "chronic administration generally refers to regular administration for an extended period, preferably daily for three or more days, and still more preferably daily for as long as the patient suffers from erectile dysfunction (in the absence of therapy)." Whitaker at 7. Whitaker defines "daily" as "administration of the [PDE5 inhibitor] one or more times, generally one to three times, still more preferably one time, per about 24-hour period." *Id.*

Example 6 of Whitaker combines data from five clinical studies to show that chronic administration of low doses (5 mg or 10 mg) of tadalafil improved erectile function in a population of patients with male erectile dysfunction. Whitaker at 34. The study population included four subgroups, in which tadalafil was taken (1) less than 30% of the time, (2) 30-50% of the time, (3) 50-70% of the time, and (4) more than 70% of the time. *Id.* Example 6 states that tadalafil "was administered 'daily' to [these] patients." *Id.*; *accord id.* at 35 ("The Study Drug was administered in 5 mg and 10 mg doses, 'daily' and not more than once every 24 hours."). Whitaker notes "a trend toward better response with increased frequency of dose." *Id.* at 36 (referring to results showing better erectile function in subgroups 3 and 4 than in subgroups 1 and 2). In Example 7, tadalafil was administered daily for three weeks to men 21-72 years old with erectile dysfunction, in subgroups receiving either a placebo or one of four dosages (10, 25, 50, and 100 mg). The results showed that "[a]dverse events [side effects] were dose-related, and attenuated with continued daily treatment." *Id.* at 38.

Whitaker states that "[t]he enhanced efficacy demonstrated by low daily dosing of a PDE5 inhibitor in treating erectile dysfunction . . . results from improved vascular responsiveness when the PDE5 inhibitor is present con-

tinuously, or essentially continuously, in plasma." Whitaker at 12. Whitaker terms that effect "vascular conditioning," an effect that had not been reported or observed in treatments with PDE inhibitors generally, nor more specifically in the case of on-demand dosing of PDE5 inhibitors. *Id.* Whitaker concludes that "[i]t is expected that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, for example, after about three daily doses of up to 10 mg, preferably after five days of daily dosing, and more preferably after seven days of daily dosing. In addition, after about three days of daily dosing, intermittently missing one chronic dose may lead to a reduction in vascular conditioning, but not a complete loss of conditioning." *Id.* at 13. Whitaker then posits: "It is theorized, but not relied upon herein, that vascular conditioning is caused by 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.

Porst is a published abstract of a study showing that 100 mg of tadalafil administered daily for three weeks to men with erectile dysfunction having a mean age of 52.4 years was safe and well tolerated, and that it improved erectile function.

The Board found that Montorsi and Whitaker taught administering a PDE5 inhibitor to an individual with erectile dysfunction, as required by its construction of "an individual with at least one of a penile tunical fibrosis and corporal tissue fibrosis." The Board also found that Montorsi taught that erectile dysfunction in the aging male is associated with atherosclerosis, which in turn is associated with the development of corporal fibrosis, and that Whitaker taught that long-term treatment with a PDE5 inhibitor can cause reversal of circulatory dysfunctions caused by diabetes, atherosclerosis, smoking, hypertension, or a combination of such factors.

The Board further found that the three references together taught daily dosing of up to 1.5 mg/kg/day for at least 45 days, and therefore met the "continuous long-term regimen" limitation of the '903 patent. In particular, the Board found that Montorsi taught dosing of up to 100 mg of sildenafil per day. According to the '903 patent, col. 45, ll. 7-12, a dosage of 100 mg per day is roughly equivalent to 1.5 mg/kg for an average weight adult male. Although the Board acknowledged that Whitaker's Example 6 did not specifically disclose dosing every day, it noted that Whitaker taught that better results are obtained with increased frequency of dosing, that adverse effects are attenuated with daily administration, and that treatment should continue for as long as the erectile dysfunction persists. Finally, the Board found that Porst taught that a dosage of 100 mg of tadalafil per day is safe and well tolerated.

In response to Lilly's arguments based on the prior art references, LAB argued that its treatment method produced unexpected results, because at the time of the invention the scientific community believed that PDE5 inhibitors would exacerbate fibrosis, not treat it. That belief, according to LAB, was based on the understanding that the enzyme inductible nitric oxide synthase ("iNOS") and its product, nitric oxide, which have a mechanism of action similar to that of PDE5 inhibitors, were profibrotic. The Board rejected that argument on the ground that the claims of the '903 patent do not require a particular mechanism of action and that any antifibrotic effect resulting from the administration of PDE5 inhibitors, whether expected or not, is inherent.

The Board ultimately concluded that the combination of references satisfies each of the limitations of the '903 patent, as construed, and that the combination provides a reasonable expectation of success in treating erectile dysfunction.

On appeal, LAB argues that the Board erred (1) in denying LAB's claim of priority to the October 2002 filing date of the inventors' provisional application, (2) in construing the three disputed claim terms, (3) in deciding that claim 1 of the '903 patent would have been obvious based on incorrect claim constructions, and (4) by failing to adequately consider the prevailing beliefs in the field and the unexpected results achieved by the inventors.

II

A

In order for a patent to be entitled to priority based on an earlier application or chain of applications, each previous application in the chain must comply with the written description requirement of 35 U.S.C. § 112(a). *Bradford Co. v. Conteyor N. Am., Inc.*, 603 F.3d 1262, 1269 (Fed. Cir. 2010). To satisfy the written description requirement, the disclosure in each application must "reasonably convey[]" to those skilled in the art that as of the claimed priority date the inventor was in possession of the later claimed subject matter. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). A disclosure in a parent application is not sufficient if it "merely renders the later-claimed invention obvious . . . ; the disclosure must describe the claimed invention with all its limitations." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998).

In this case, the inventors filed a provisional application in October 2002 to which the '903 patent claims priority. Lilly argues on appeal that the three prior art references were published before the provisional application was filed and are thus prior art under 35 U.S.C. § 102(a) even with the priority date of October 2002. LAB responds that Lilly asserted Whitaker and Montorsi as prior art only under 35 U.S.C. § 102(b) before the Board and that Whitaker and Montorsi do not qualify as prior art under that provision. We decline to address the

question of Lilly's waiver, as we conclude on the merits that the '903 patent is not entitled to the priority date of the provisional application because of a lack of adequate written description.

The provisional application does not explicitly disclose a dosage of "up to 1.5 mg/kg/day." LAB, however, contends that the dosage level is disclosed by a rat study described in the provisional application. In that study, rats were provided with 100 mg/L (milligrams per liter) of sildenafil in drinking water. LAB argues that a person of skill in the art would be able to calculate the corresponding human dosage according to a conversion method devised by E. J. Freireich, and that the result of that computation would be a dosage of approximately 1.5 mg/kg/day. *See* Emil J. Freireich, *Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man*, 50 Cancer Chemotherapy Reports 219-44 (1966).

LAB's argument depends on several assumptions regarding the knowledge of a person of skill in the art. Such a person would have to know the average daily water intake of the rat model used in the '903 patent, the average weight of the rat model used in the '903 patent, the average weight of an adult human male, and the average height of an adult human male. Moreover, that person would need to know of the Freireich method for calculating the rat-to-human interspecies dosage conversion and have a reason to apply it. The Board held that the first four variables were not knowable from the disclosure in the application, but would at best require persons of skill to look to the prior art and make assumptions. That is not enough to establish priority. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("It is not sufficient for purposes of the written description requirement of § 112 that the disclosure, when combined with knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned,

but failed to disclose."). Moreover, the underlying assumptions for LAB's expert's derivation were themselves faulty. For example, LAB's expert assumed an adult male weight of 86.1 kg to calculate the 1.5 mg/kg/day human dosage from the rat study. He relied on an uncited, non-prior art reference for that data. Lilly's expert showed that the dosage would have been approximately 1.7 mg/kg/day if 67 kg—the weight disclosed in the '903 patent—had been used instead.[3]

As for the fifth assumption, LAB presented no evidence as to why a person of skill would choose to rely on the Freireich method to calculate a human dosage for therapeutic treatment of fibrosis with PDE5 inhibitors. That reference was not disclosed in the provisional application, is nearly half a century old, and was based on measurements of toxicity of anticancer agents. More importantly, LAB cannot rely on standalone references that it failed to incorporate in the provisional application in order to make out its priority claim. "[I]t is the disclosures of the [provisional] application[] that count," not those of uncited references. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (holding that it was error to rely on a clinical protocol to show earlier possession because the protocol was not disclosed in the specifications of the asserted patents).

Because proof of priority requires written description disclosure in the parent application, not simply information and inferences drawn from uncited references, the Board correctly held that LAB's expert's calculation did not satisfy the requirements for priority and that the '903

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[3] The patent states that "1.5 mg/kg . . . is about the dose ingested by men with an on demand single 100 mg tablet." '903 patent, col. 45, ll. 7-12. That passage assumes that an adult man weighs approximately 67 kg.

patent was therefore not entitled to the October 2002 priority date of the provisional application.

B

In an *inter partes* review proceeding, the Board gives claims their broadest reasonable interpretation consistent with the specification. *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1276, 1279 (Fed. Cir. 2015), *aff'd*, 136 S. Ct. 2131, 2142 (2016). We review the Board's claim construction de novo except for subsidiary fact findings, which we review for substantial evidence. *Id.* at 1280.

1. The broadest reasonable interpretation of the phrase "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" is its plain meaning: an individual with penile tunical fibrosis and/or corporal tissue fibrosis.[4] The Board's construction ("an individual hav[ing] symptoms that may be associated with penile fibrosis, such as [erectile dysfunction], but not that the patient be specifically diagnosed as having penile tunical fibrosis or corporal tissue fibrosis") reads that limitation out of the claim. That is because erectile dysfunction can have causes other than penile fibrosis, and because penile fibrosis does not necessarily result in erectile dysfunction. Because erectile dysfunction is merely a symptom that

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[4] Although Lilly claims that any "plain meaning" argument was waived below, LAB adequately preserved that argument when it stated in its Response to the Petition for Institution that "a person of ordinary skill in the art would understand the claims of the '903 patent to concern treatment of fibrosis, a disease." *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc) ("[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.").

may be, but is not necessarily, associated with penile fibrosis, erectile dysfunction cannot be equated with tunical fibrosis and corporal tissue fibrosis.

The patent makes clear that penile fibrosis and erectile dysfunction are not the same thing and do not necessarily accompany one another. The specification makes clear that penile fibrosis may result in erectile dysfunction, but it may not. *E.g.*, '903 patent, col. 1, ll. 29-34, 43-44 ("Peyronie's disease is a fibromatosis of the tunica albuginea" that "[c]linically . . . quite frequently leads to erectile dysfunction" but "is not always associated with erectile dysfunction"). Conversely, the specification acknowledges that erectile dysfunction has alternative causes and may present without underlying penile fibrosis. *See, e.g.*, *id.*, col. 2, ll. 23-26 ("aging associated [erectile dysfunction] . . . is mostly related to the loss of [smooth muscle cells] in the penile corpora cavernosa by apoptosis [cell death], with a corresponding increase in collagen fibers"); *id.*, col. 2, ll. 28-31 ("clinical result of this aging process in the penis is defective cavernosal [smooth muscle cell] relaxation leading to [CVOD], the most common cause of [erectile dysfunction]" in aging males).

The patented invention targets the treatment of fibrosis, whether or not the fibrosis causes erectile dysfunction in a particular case. For example, the invention treats Peyronie's disease even in a patient with no symptoms of erectile dysfunction. The point is that the claimed treatment method is intended to decrease the level of fibrotic tissue, without regard to whether the patient's fibrosis is accompanied by erectile dysfunction.

The Board relied on a statement in the Background section of the patent that notes that "[a] need exists for effective methods to treat and/or ameliorate the symptoms of a variety of fibrotic disease, such as [Peyronie's disease], [erectile dysfunction] and arteriosclerosis." '903 patent, col. 2, ll. 42-44. But that statement plainly refers

to instances of erectile dysfunction that arise from fibrosis (a "symptom[] of . . . fibrotic disease"), not to all cases of erectile dysfunction. The next sentence in the specification clarifies that the focus of the treatment method is fibrosis, not the possible symptoms of fibrosis, such as erectile dysfunction. That sentence states: "No effective method of treatment currently exists that is directed towards the molecular pathways underlying excessive collagen deposition [fibrosis]." *Id.*, col. 2, ll. 44-46.

This court's decision in *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), is closely analogous to this case. There, the appellant argued that the claim term "treatment of sleep apneas" encompassed treatment of the symptoms associated with sleep apnea. *Id.* at 1059. This court disagreed, noting that the plain meaning of the term sleep apnea and the specification made clear that the patent was directed to treatment of the underlying sleep apnea condition, even though the written description noted that the claimed "treatment [also] alleviates the sleep apnea-related symptoms of anxiety, depression, fatigue, malaise, irritability, anger and hostility." *Id.* (citing patent application).

In this case, similarly, the '903 specification mentions various fibrotic conditions and their possible symptoms. *See, e.g.*, '903 patent, col. 2, ll. 13-22 (arteriosclerosis, or fibrosis of the media of the arterial wall, is one of the underlying causes of hypertension). But the claims are narrower and are clearly aimed at penile fibrosis—not other types of fibrosis, and not at symptoms such as erectile dysfunction. *See Rapoport*, 254 F.3d at 1059 ("[t]he plain language . . . unambiguously refers to 'treatment of sleep apneas' narrowly defined, and does not also include by its plain terms 'treatment of symptoms associated with sleep apneas.'"). The specification's references to erectile dysfunction as a possible symptom of penile fibrosis do not broaden the phrase "an individual with at least one of penile tunical fibrosis and corporal tissue

fibrosis" beyond its ordinary meaning. As in *Rapoport*, the ordinary meaning "narrowly refers to . . . the underlying disorder itself." *Id.*

The Board's construction would make the patent claims applicable to individuals with erectile dysfunction not caused by penile fibrosis. Yet for patients suffering from erectile dysfunction without penile fibrosis, the claimed method would have no effect on the treatment of penile fibrosis. The Board's construction is therefore not the broadest reasonable interpretation of the disputed claim language; rather, it is overly broad. Given the relationship between erectile dysfunction and penile fibrosis, it is unreasonable to use the symptom of erectile dysfunction as a proxy for penile fibrosis.

On the other hand, there is no support in the patent or the prosecution history for LAB's contention that the phrase "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" requires an individual to have "clinically significant" penile tunical or corporal tissue fibrosis. Both parties' experts agreed that some physicians would treat fibrosis even if it was not deemed "clinically significant." We see no reason to import such a limitation here, and we conclude that "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" includes an individual with one or both of those conditions, even if the condition is not deemed "clinically significant."

2. The limitation "arresting or regressing the at least one of the penile tunical fibrosis and corporal tissue fibrosis" requires halting the progression of, or reversing, penile fibrosis. Lilly contends that the phrase "arresting or regressing the [penile fibrosis]" has no patentable weight. We conclude, however, that the phrase is more than a statement of the intended result of administering the PDE5 inhibitor within the dosage limits, with the

frequency, and for at least the minimum period prescribed in the patent.

The full text of the limitation in which the "arresting or regressing" language appears reads: "arresting or regressing the [penile] fibrosis, wherein the PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg/day for not less than 45 days." '903 patent, col. 68, ll. 29-32. While not dispositive, it is significant that the phrase "arresting or regressing the [penile] fibrosis" is drafted as part of a separate step of the method, not as the preamble or introduction to a process carried out by the administration of the drug. The structure of the '903 patent claim 1 is therefore not comparable to the structure of patent claims in which statements of general purpose in the preambles of method claims have been held to carry no patentable weight. *E.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001) (preamble phrase "for reducing hematologic toxicity" was "non-limiting, and merely expressing a purpose"); *see also In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (expressing "skeptic[ism]" that the phrase "for the treatment or prevention of stroke" in a claim preamble was more than an expression of purpose for the claimed method).

Other intrinsic evidence shows that the "arresting or regressing" limitation does not merely duplicate the wherein clause that follows. "Arresting or regressing" demands efficacy; the wherein clause does not. As explained in the specification, "arresting" means "halt[ing] the progression" or "prevent[ing] the further development" of the fibrotic condition, and "regressing" means "reduc[ing] in size" or "reversing" the fibrotic condition. '903 patent, col. 3, ll. 8-13; *id.*, col. 9, ll. 13-15; *see also id.*, col. 2, ll. 53-61. In Example 3 of the specification, the inventors demonstrated the arrest or regression of fibrosis when administering a PDE5 inhibitor to rats daily for 45 days at a dosage equivalent to 1.5 mg/kg/day for an adult

human male. '903 patent, col. 36, line 25, through col. 37, line 5 (Example 3); *id.*, col. 45, ll. 7-12.

The wherein clause sets forth the minimum duration supported by the disclosure (45 days) for the arrest or regression of fibrosis at a high dosage of the PDE-5 inhibitor. But the reference to a minimum duration period of 45 days says nothing about the efficacy of the method if a lower dosage of PDE5 inhibitor is administered. As the inventors explained during prosecution, "it is likely that if the dose [administered to the rats in Example 3] is reduced to 1/2 of the current dose to adapt it to the clinic and minimize side effects, the duration of the antifibrotic treatment may take 2 to 6 months or longer."[5]

Because the '903 patent claims specify only a maximum dosage level and a minimum treatment period, it is different from cases in which the claims contain express dosage amounts as material claim limitations, and in which efficacy is "inherent in carrying out the claim steps." *Dawson v. Dawson*, 710 F.3d 1347, 1355 (Fed. Cir. 2013) (citing *Bristol-Myers Squibb*, 246 F.3d at 1375, and *In re Montgomery*, 677 F.3d at 1381). We therefore conclude that "arresting or regressing" the fibrosis adds an efficacy requirement that is not otherwise found in the claim language.

Nor do LAB's infringement contentions in the ongoing district court case render the "arresting or regressing"

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[5] The inventors also stated during prosecution that, "like in the aging rat model [Example 3], it takes at least 45 days of treatment with sildenafil to ameliorate the CVOD and underlying corporal fibrosis," which "was done with daily doses equivalent to 2.5 fold the doses currently applied in the clinic to elicit an erection."

limitation irrelevant.[6] LAB alleged that the "[l]ong-term administration of Cialis on a once daily basis for the treatment of [erectile dysfunction] results in the arrest or regression of penile tunical fibrosis (i.e., [Peyronie's disease]) and corporal tissue fibrosis (i.e., [CVOD])." [LAB]'s Disclosure of Asserted Claims and Preliminary Infringement Contentions, Ex. A at 5, *Los Angeles Biomed. Research Inst. v. Eli Lilly & Co.*, No. 2:13-cv-08567-JAK-JCG (C.D. Cal. filed May 19, 2014). But LAB did not define "long-term" in that context. In order to prove infringement, LAB may need to show, for example, that Lilly induces the administration of 2.5 mg or 5 mg of Cialis daily by patients with penile tunical or corporal tissue fibrosis for a period of time that is long enough, given the dosage levels, to result in the arrest or regression of fibrosis. In any event, LAB does not contend that the Cialis label induces infringement by instructing the daily administration of 2.5 mg or 5 mg of Cialis, regardless of the duration of the treatment.

3. Claim 1 of the '903 patent contains a limitation providing for a "continuous long-term regimen" in addition to the limitation providing for administering a PDE5 inhibitor in an amount "up to 1.5 mg/kg/day for not less than 45 days." The 45-day requirement makes clear that the "continuous long-term regimen" must be at least 45 days in length.

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[6] We deny LAB's motion to strike Lilly's references to those filings. We can properly take judicial notice of the records of related court proceedings. *See Function Media, L.L.C. v. Google, Inc.*, 708 F.3d 1310, 1316 n.4 (Fed. Cir. 2013). Because we take judicial notice of those records, we do not reach Lilly's conditional objection to LAB's reliance on the Final Written Decision in the related IPR proceeding on anticipation. *See* note 2 *supra*.

LAB argues that the term "continuous long-term regimen" adds a requirement that the drug concentration in the patient's body attain a "constant level," i.e., maintain a "steady state" plasma concentration. The patent, however, never mentions the "steady state" of a drug or other agent. As for "constant level," LAB points to a single sentence buried in the middle of the 68-column disclosure that states:

> 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.

'903 patent, col. 10, ll. 59-67. In that passage, the term "constant level" is not presented as a definition of "continuous long-term regimen," or its equivalent. Rather, the passage simply confirms that long-term continuous PDE5 inhibitor treatment excludes an "on demand . . . single pill, short-term treatment"; the passage does not exclude any treatment that fails to maintain an unvarying level of the drug within the patient's body.

Nor is "a constant level" required by anything else in the specification. If an applicant intends to ascribe a meaning to a claim term different from its ordinary meaning, he must "set out the different meaning in the specification in a manner sufficient to give one of ordinary skill in the art notice of the change from ordinary meaning." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1117 (Fed. Cir. 2004). Because the patentees in this case have not "demonstrated a clear intention to limit the claim scope," *id.*, in a manner incon-

sistent with the ordinary meaning of the term "continuous," it would be improper to construe the claim language in the manner that LAB suggests.

Although LAB argues that the term "continuous long-term regimen" should be construed to require a "constant level of the administered PDE-5 inhibitor," the position LAB took before the Board and takes in its briefs before this court makes clear that LAB is not using the word "constant" in its conventional sense. In its opening brief, LAB argues that a "constant level" of a PDE5 inhibitor refers to "the average plasma concentration of that drug upon reaching steady state," even though the actual concentration "peaks and then declines." LAB Opening Br. 36. In its reply brief, LAB departs even farther from the ordinary meaning of "constant" and argues that "a meaningful steady state ('constant level') requires a dose interval that allows drug concentration to stay within its therapeutic range." LAB Reply Br. 16.

LAB cites its expert's report and a pharmacology text to support its argument that frequent dosages of a drug with a short half-life are required to maintain a high, if varying, level of plasma drug concentration. However, LAB points to nothing in the patent that supports the construction of the term "continuous long-term regimen" to require dosing frequency sufficient to maintain the level of drug concentration within what LAB refers to as "its therapeutic range."

The prosecution history also undercuts LAB's argument. In the provisional application, claim 16 required both a "continuous long term regimen" and "maintaining a constant level." It provided: "The method of claim 1, wherein said administering comprises long term continuous treatment for weeks, months or years to maintain a constant level of the inhibitor." But in the 2004 application that matured into the '903 patent, the claims did not include the language "maintaining a constant level." The

separate use of those terms in the provisional application gives rise to the inference that "maintaining a constant level" is not implicit in the term "continuous long-term regimen." And the omission of the reference to "maintaining a constant level" from the non-provisional application strongly suggests that the claims in the patent were not meant to require that a constant level of the PDE5 inhibitor be maintained.

LAB points out that during prosecution the inventors distinguished "continuous long-term" treatment from on-demand treatment. While that is true, the inventors drew that distinction based on the duration of the treatment regimen, not on the plasma level of the drug. For example, in addressing the prior art, the inventors "predict[ed] that 21 days of even a daily or twice a day treatment with a PDE5 inhibitor would be totally insufficient . . . to prevent or ameliorate CVOD, since in our unpublished study on the time course of CVOD in the rat after cavernosal nerve damage, . . . once CVOD is established, . . . it takes at least 45 days of treatment with sildenafil to ameliorate CVOD and underlying corporal fibrosis." There is no suggestion in the prosecution history that a "constant level" of the drug is required for patentability or efficacy.

Finally, LAB argues that the Board's construction impermissibly renders the term "continuous long-term regimen" superfluous in light of the limitation requiring administration of the PDE5 inhibitor "at a dosage up to 1.5 mg/kg/day for not less than 45 days." While the two limitations clearly overlap, the more general reference to a "continuous long-term regimen" limitation serves to emphasize that the treatment is continuous and not sporadic. The fact that the limitations overlap is not fatal, nor does it compel us to adopt an otherwise unsupported construction of the claims. *See SimpleAir, Inc. v. Sony Ericsson Mobile Commc'ns AB*, 820 F.3d 419, 429 (Fed. Cir. 2016) (Although "interpretations that render

some portion of the claim language superfluous are disfavored," that "preference for giving meaning to all terms . . . is not an inflexible rule that supersedes all other principles of claim construction."). The overlap in the limitations that results from giving them their plain meaning does not justify importing a "constant level" or "steady state" limitation into the claims where such a limitation has no support in the specification or the prosecution history.

C

Determining whether an invention would have been obvious requires consideration of the scope and content of the prior art, differences between the prior art and the patent claims, the level of ordinary skill in the art, and any secondary considerations. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). In the case of a combination of references that together disclose all the limitations of the claimed invention, the adjudicator must determine whether there was an "apparent reason to combine the known elements in the fashion claimed by the patent at issue," *id.* at 418, and whether a person of skill in the art at the time of the invention would have had a "reasonable expectation of success" in pursuing that combination, *see Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1373 (Fed. Cir. 2016).

LAB contends that the Board's findings are insufficient to establish obviousness under the correct constructions of "an individual with at least one of a penile tunical fibrosis and corporal tissue fibrosis" and "arresting or regressing the at least one of a penile tunical fibrosis and corporal tissue fibrosis." We agree. The Board concluded that the references on which it relied rendered obvious the treatment of erectile dysfunction via the claimed method, but it did not determine whether those references showed that it would have been obvious to use long-term continuous treatment with a PDE5 inhibitor to treat

individuals with penile fibrosis and to achieve the arrest or regression of that condition.

1. The Board found that Montorsi and Whitaker taught the treatment of erectile dysfunction, a symptom sometimes associated with penile fibrosis, and that the combination of Montorsi, Whitaker, and Porst gave rise to a reasonable expectation of success in treating erectile dysfunction. What the Board did not do, however, was to find that those references taught treating a patient with penile tunical fibrosis or corporal tissue fibrosis. Nor did the Board find that those references provided the basis for a reasonable expectation of success in treating those conditions. *See Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) ("Importantly, without a sound explanation for doing otherwise, . . . the expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worthwhile pursuit."). As indicated above, the correct construction of the pertinent claim language requires more than simply treating erectile dysfunction.[7]

To be sure, Montorsi teaches that corporal fibrosis is associated with erectile dysfunction in atherosclerotic or aging patient populations. Montorsi, however, is directed

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[7] The dissent states that the Board found that the method of claim 1 was used in the prior art. The Board's findings, however, rest on its erroneous claim constructions, including equating erectile dysfunction with penile fibrosis. The Board found in the prior art the method of long-term administration (i) to an individual with *erectile dysfunction* (ii) to symptomatically treat the erectile dysfunction. It did not find in the prior art the method of claim 1: long-term administration (i) to an individual with penile fibrosis (ii) in an effective amount to arrest or regress the fibrosis.

to on-demand dosing of PDE5 inhibitors; it does not teach long-term daily treatment. The only statement in Montorsi relating in any way to long-term treatment appears in Montorsi's discussion of a study showing that a one-time administration of sildenafil at bedtime increased nocturnal erections in men between 40 and 68 years of age with erectile dysfunction. Montorsi comments that the study "opened the door to further study investigating the possible dosage of sildenafil to be administered daily at bedtime." Montorsi at 31. The study discussed by Montorsi, however, was not limited to a population of patients suffering from erectile dysfunction caused by an underlying fibrotic condition (or even aging or atherosclerotic patients who have a higher likelihood of an underlying fibrosis).

The Board found that Whitaker taught the chronic administration of PDE5 inhibitors to individuals with erectile dysfunction and, in particular, that it taught treating individuals with erectile dysfunction that is associated with atherosclerosis. The first of those findings is supported by substantial evidence, but the second is not.

Whitaker mentions atherosclerosis only once in its 39-page disclosure. It does so when addressing an effect that Whitaker refers to as "vascular conditioning," which was not previously seen in patients treated with PDE5 inhibitors. Whitaker at 12-13. Upon observing that effect in the case of chronic treatment of patients with erectile dysfunction, Whitaker states that "[i]t is expected that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, for example, after about three daily doses of up to 10 mg, preferably after five days of daily dosing, and more preferably after seven days of daily dosing." *Id.* at 13. Whitaker then states that "[i]t is theorized, but not relied upon herein that vascular conditioning is caused by 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," conditions that "result in thickening of the arterial wall, decreased arterial compliance, and decreased responsiveness to endogenous vasodilators, such as nitric oxide." *Id.*

Whitaker, however, provides no data to support this "vascular conditioning" causation theory. None of the studies reported in Examples 5, 6, and 7 of Whitaker were expressly limited to atherosclerotic, or even aging, patient populations. *E.g.*, Whitaker at 34 (PDE5 inhibitor in Example 6 was administered to "patients with male erectile dysfunction"). Nor can the presence of an underlying fibrotic condition be inferred, because the Board pointed to no findings regarding the rate of incidence of atherosclerosis in males with erectile dysfunction. In sum, Whitaker provides no information about whether the vascular conditioning effect was observed in erectile dysfunction patients with atherosclerosis and associated corporal fibrosis.

Indeed, Whitaker makes clear that the observation about "vascular conditioning" and its cause is speculative. Whitaker states that the "vascular conditioning" effect was not previously observed, and notes that its relationship to circulatory dysfunctions such as atherosclerosis is merely "theorized." Whitaker at 12-13. As such, Whitaker's observation cannot serve as an express or implicit teaching. *See, e.g.*, *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375-76 (Fed. Cir. 2011) (prior art's "speculative and tentative disclosure of what 'might' or 'may' [explain the cause of a desired effect] does not sufficiently direct or instruct one of skill in this art"); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) ("[L]egal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture.").

Following its analysis of Whitaker, the Board found that persons of skill in the art would have had a reasonable expectation of success in treating erectile dysfunction in fibrotic patients, as in Montorsi, and doing so through long-term treatment, as in Whitaker. In so finding, however, the Board summarily dismissed LAB's counter-argument that those references would not have given rise to a reasonable expectation of success in treating erectile dysfunction in the subpopulation suffering from penile fibrosis.

According to LAB's expert, it was widely believed at the time of the invention that the enzyme iNOS and its product nitric oxide were profibrotic, i.e., they exacerbated fibrotic conditions and the accompanying symptom of erectile dysfunction. It was known that nitric oxide activates guanylate cyclase, which increases intracellular cyclic guanosine monophosphate ("cGMP"). It was also known that PDE5 inhibitors operate similarly: They inhibit the enzyme PDE5, which breaks down cGMP, so inhibiting PDE5 also leads to an increase in intracellular cGMP. LAB contends that the prevailing view in the field at the time of the invention was that PDE5 inhibitors would also be profibrotic. Therefore, according to LAB, persons of skill in the art would not have prescribed a PDE5 inhibitor on a long-term basis to treat erectile dysfunction in patients with penile fibrosis.

The Board dismissed LAB's argument as addressed only to the mechanism of action inherent in the claimed method, which it found was taught by the combination of Montorsi and Whitaker. That answer, however, does not address LAB's point that even if the combination of Montorsi and Whitaker teach long-term treatment with a PDE5 inhibitor of individuals with some forms of erectile dysfunction, a person of skill in the art would not have been motivated to combine those references to treat individuals with fibrosis-related erectile dysfunction because, according to LAB, the results would have been

expected to be detrimental. *See Institut Pasteur*, 738 F.3d at 1346 (error to disregard prior art evidence of toxicity, which was relevant to question of whether skilled artisan would have a reasonable expectation of success in achieving the claimed invention).

To be sure, LAB's evidence is not undisputed. At the time of the invention, according to Lilly, the biochemical pathway was under study by those in the field as a way of addressing CVOD. And Whitaker, in discussing the possibility of such a treatment, does not single out atherosclerotic individuals (or others with an underlying penile fibrosis) and specifically warn against the profibrotic effects of long-term treatment with a PDE5 inhibitor.

The question remains whether a person of skill in the art would have had a reason to combine Montorsi, Whitaker, and Porst to treat penile fibrosis with a long-term regimen of a daily dosage of a PDE5 inhibitor, and would have had a reasonable expectation of success from doing so. Because the Board's obviousness analysis was based on an erroneous construction of the claim language and an overly broad interpretation of Whitaker, and because the Board did not address the record evidence summarized above, we remand for the Board to make new findings as to whether there was an apparent reason to combine the prior art references and whether that combination would have rendered obvious the long-term administration of PDE5 inhibitors to treat penile fibrosis.[8]

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[8] LAB contends (LAB Opening Br. 60-62) that the Board failed to consider the evidence of unexpected results as objective evidence of nonobviousness. As indicated above, the issue of unexpected results (and the related question of a reasonable expectation of success) is tied to the proper construction of the claim language. We there-

2. The Board also made no findings as to whether any reference or combination of references rendered obvious the claim limitation "arresting or regressing the at least one of a penile tunical fibrosis and corporal tissue fibrosis," because the Board erroneously concluded that arresting or regressing fibrosis is an inherent effect of any regimen exceeding 45 days regardless of the dosage. The Board did not consider, for example, whether the chronic low dose of tadalafil (5 mg or 10 mg administered "daily" for 8 or 12 weeks) in Whitaker's Example 6 would arrest or regress penile fibrosis, including the relevant inventor statements during prosecution that administration for 45 days of an extremely high dose of sildenafil was required to achieve the arrest or regression of penile fibrosis, *see supra* note 5. On remand, the Board should make the findings necessary to determine whether the references render the "arresting or regressing" limitation obvious.

3. LAB also challenges the Board's findings regarding the limitation "at a dosage up to 1.5 mg/kg/day for not less than 45 days." But the Board's findings on that issue are well founded. Porst discloses that taking up to 1.5 mg/kg/day of a PDE5 inhibitor for three weeks is safe, well-tolerated, and effective as a treatment for erectile dysfunction. Whitaker teaches chronic dosing of PDE5 inhibitor for at least 45 days. Whitaker does not explicitly disclose that dosing must occur every day, but it suggests as much, noting that a "better response" was obtained "with increased frequency of dose." Whitaker at 36 (better results reported with closer to daily compliance, in the context of comparing the subgroups in Example 6); *see also id.* at 38 ("Adverse events were . . . attenuated with continued daily treatment."). And those remarks are supported by Montorsi's observation that the study re-

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fore leave it to the Board on remand to address that issue in the first instance.

viewed by Montorsi "opened the door to further study investigating the possible dosage of sildenafil to be administered daily at bedtime to prevent or treat [erectile dysfunction] in the elderly patient." Montorsi at 31.

In sum, Whitaker teaches long-term chronic treatment for more than 45 days, Montorsi and Whitaker suggest daily administration, and Porst and Montorsi teach a dosage of up to 1.5 mg/kg/day. The Board's findings regarding the dosage and treatment period limitation are therefore supported by substantial evidence.

4. Because we agree with the Board that the "continuous long-term regimen" limitation is satisfied by the administration of a PDE5 inhibitor "up to 1.5 mg/kg/day for not less than 45 days," we conclude that the same references teach "continuous long-term regimen." The Board's findings regarding that limitation are therefore supported by substantial evidence as well.

III

Because the Board's obviousness determination was predicated on an erroneous claim construction of two of the limitations of claim 1, and because the Board did not make factual findings as to whether there was an apparent reason to combine the prior art references to treat penile fibrosis and whether a person of skill in the art would have had a reasonable expectation of success from such a combination, we remand this case to the Board. We also remand for the Board to make findings bearing on the obviousness of the "arresting or regressing" limitation.[9] The Board's order is vacated, and the case is re-

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[9] Although the dissent urges that we should resolve the obviousness question without a remand, it would be improper for us to do so in the absence of the necessary factual findings by the Board. *Personal Web Techs., LLC v. Apple, Inc.*, No. 2016-1174, at 8-9 (Fed. Cir. Feb. 14,

manded for further proceedings consistent with this opinion.

VACATED AND REMANDED

2017) (discussing the "basic principle[] of administrative law" that an agency must provide a full and reasoned explanation for its decision, which is necessary to both enable judicial review and "prevent judicial intrusion on agency authority"); *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015) ("[W]e must not ourselves make factual and discretionary findings that are for the agency to make.") (citing *SEC v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947)); *see also, e.g.*, *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1126 (Fed. Cir. 2004) ("vacat[ing] the Board's decision with respect to the written description requirement and remand[ing] for reconsideration under the proper test" because the court's "resolution of the [written description] question" previously decided by the Board under an incorrect legal standard would "require[] fact findings this court is not permitted to make.").

United States Court of Appeals for the Federal Circuit

LOS ANGELES BIOMEDICAL RESEARCH INSTITUTE AT HARBOR-UCLA MEDICAL CENTER,
Appellant

v.

ELI LILLY AND COMPANY,
Appellee

2016-1518

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, in No. IPR2014-00752.

NEWMAN, *Circuit Judge*, concurring in part, dissenting from the judgment.

I agree generally with the court's discussion of the '903 patent and the prior art. However, I conclude that the Patent Trial and Appeal Board correctly held the claim invalid on grounds of obviousness and inherency. No dispositive error of law, no absence of support of dispositive findings by substantial evidence, has been shown. I would affirm the Board's decision, and thus I respectfully dissent from the ruling of vacatur and remand.

DISCUSSION

The subject claim of the '903 patent is:

> 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 tunical 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.

'903 Patent, col. 68, lines 23–32. The references cited by the PTAB show the subject cGMP products for treatment of erectile dysfunction, and discuss the mode of action in erectile dysfunction. The cited references are in the same field of endeavor, and include a review article. I outline some relevant PTAB findings:

> • the prior art shows that the cGMP products of claim 1 were known PDE-5 inhibitors, and known to relieve erectile dysfunction;
>
> • the prior art shows use of these cGMP products in the claimed dosages and over extended time periods.
>
> • the prior art shows that penile fibrosis was known to be a cause of erectile dysfunction.

The PTAB held trial, with evidence and expert witnesses from both sides. The Board concluded that the subject matter of claim 1 would have been obvious in view of the cited references. Reversible error in this conclusion has not been shown, and the Board's findings on which its

conclusion was based are supported by substantial evidence.

The court's extensive opinion sets forth the relevant facts, which I repeat only as needed to explain why I conclude that our proper action is to affirm the decision of the PTAB.

PDE-5 inhibitors were known to treat erectile dysfunction, which was known to be caused by penile fibrosis.

That penile fibrosis is a cause of erectile dysfunction, and that erectile dysfunction is relieved by treatment with these PDE-5 inhibitors, was known before the filing of the '903 application. LABio stresses that erectile dysfunction was known to have other causes, such as diabetes, atherosclerosis, and psychological problems. However, on the prior art and expert testimony that when penile fibrosis was present it was affected by the PDE-5 inhibitors, the Board found that this effect was inherent in the use of these products to treat erectile dysfunction.

There was no claim that the '903 inventors discovered that penile fibrosis is a cause of erectile dysfunction. Their work is described as relating to understanding the production of nitric oxide, and other scientific aspects of the mechanism of erectile dysfunction and how PDE-5 inhibitors work. I do not diminish the scientific value of their investigations. However, this does not diminish the evidence and the Board's findings that PDE-5 inhibitors were known and used by others under the conditions set forth in claim 1.

Claim 1 is directed to use of the cGMP PDE-5 inhibitors in dosages and for periods shown in the prior art; and the Board found that this use existed in the prior art, with the effect on penile fibrosis inherent in this use. This finding is supported by substantial evidence. In *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed.

Cir. 1999), the court explained that "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art."

We are reminded of the truism that "that which infringes if later anticipates if earlier." *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1573 (Fed. Cir. 1986) (quoting *Peters v. Active Mfg. Co.*, 129 U.S. 530, 537 (1889)). Both parties have advised that LABio has charged Lilly with "willfully inducing infringement of the '903 patent by marketing Cialis®, whose active ingredient is the PDE-5 inhibitor tadalafil, to erectile dysfunction patients for daily use, knowing and intending that it would be used to treat the penile fibrosis of those erectile dysfunction patients suffering from that underling condition." LABio Br. 12.[1] I agree with the court that this representation is relevant to the issues of obviousness and inherency, for the prior art shows such daily use and at the claimed dosages.

The cited references lead to the PTAB's ruling of obviousness

The Montorsi reference is a review article published in April 2002, entitled "The Ageing Male and Erectile Dysfunction." The Whitaker reference is an international application published November 1, 2001, entitled "Daily Treatment for Erectile Dysfunction Using a PDE5 Inhibitor." The Porst reference is an article entitled "Daily IC351 [tadalafil] Treatment of ED," published in September 2000.[2]

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[1] The district court action has been stayed pending resolution of the PTAB proceedings.

[2] LABio appeals the PTAB's denial of priority to LABio's provisional application, filed on October 22, 2002.

At the PTAB trial, witnesses discussed the mechanism whereby penile fibrosis is related to erectile dysfunction, and the mechanism of these cGMP compounds in PDE-5 inhibition. The PTAB found that "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." PTAB Op. at 22. Substantial evidence supports this finding.

The PTAB cited Montorsi, which is a review of the causes of erectile dysfunction, an ailment that had been extensively studied over the years. Montorsi reports on the use of cGMP compounds as PDE-5 inhibitors, and compiles information from many scientific publications. Montorsi describes studies investigating the causes of erectile dysfunction in aging men, summarizing that "it seems reasonable to hypothesize that the ED from ageing is the result of atherosclerosis-induced cavernosal ischaemia leading to cavernosal fibrosis and veno-occlusive dysfunction." Montorsi at 31.

Montorsi describes a study "wherein sildenafil was taken as required, but no more than once daily, over a 12 week to 6 month period," relied on by the PTAB to show "that sildenafil is an effective treatment of ED in elderly men." PTAB Op. at 20. The court observes that "Montorsi teaches that corporal fibrosis is associated with erectile dysfunction in atherosclerosis of aging patient populations," Maj. Op. at 25, and finds that substantial evidence

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Lilly points out, without apparent dispute, that the relevant prior art would not be eliminated by LABio's provisional application's filing date of October 22, 2002, because all the references are prior art within the meaning of 35 U.S.C. § 102(a), even if they do not qualify under § 102(b). Lilly Br. at 18.

supports "the Board[s] f[inding] that Whitaker taught the chronic administration of PDE5 inhibitors to individuals with erectile dysfunction." *Id.* at 26. I agree. Whitaker states that "[t]o 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)." Whitaker at 7. Lilly's expert testified that "it would take 'months' to resolve ED based on circulatory dysfunction due to diabetes, atherosclerosis, smoking hypertension or a combination of those factors (i.e., Whitaker's patient population)." Goldstein Decl. at 73.

The court cites Whitaker's statement that "[i]t is expected that vascular conditioning occurs after chronic administration of the PDE5 inhibitor, . . ." Maj. Op. at 26, citing Whitaker at 13. My colleagues criticize Whitaker's lack of data on vascular conditioning. *Id.* at 27. However, that does not erase Whitaker's teaching of chronic administration; and I point out that claim 1 does not mention or require vascular conditioning. The PTAB found that "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." PTAB Op. at 21. These findings are supported by substantial evidence.

On this appeal LABio argues, as it did during prosecution, that "[t]he pending claims are directed to a 'curative' effect as opposed to a 'palliative' effect . . . for a long-term result (e.g., years), not a pathophysiology (function) for a very short-term result of a vasodilation (e.g., hours, maximum 2-3 days." LABio Br. 10. However, the references show use longer than hours or 2-3 days. The Porst reference shows clinical trials in which tadalafil was administered for three weeks to "men with mild to moderate erectile dysfunction." The dosages were in the

range shown in claim 1. The PTAB considered this reference in combination with the references to Montorsi and Whitaker; no error has been shown in this combination for the treatment of erectile dysfunction.

The PTAB's decision accords with precedent

Precedent has dealt with a variety of factual situations in which a purported new use or property has been discovered for a known product, and patentability is sought on various premises. In *Bristol-Myers Squibb Co. v. Ben Venue Laboriatories, Inc.*, 246 F.3d 1368 (Fed. Cir. 2001), the court held that "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent," having observed that the claimed term "for reducing hematologic activity" "merely express[ed] a purpose" and is "non-limiting." *Id.* at 1375, 1376.

Alcon Research, Ltd. v. Apotex Inc., 687 F.3d 1362 (Fed. Cir. 2012), involved a claim to a method comprising "stabilizing conjunctival mast cells by topically administering" olopatadine in a known composition. *Id.* at 1364. The prior art described the known composition used as an antihistamine. *Id.* This court reversed the district court's finding that a person would not have used the composition to stabilize mast cells because "a person of ordinary skill in the art at the time of the invention would have been motivated to use olopatadine to treat human eye allergies as claimed for its established antihistaminic efficacy." *Id.* at 1369.

A contrary result was reached in *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013), where the proposed claim was for "reducing the number of daily topical ophthalmic doses." *Id.* at 1289. The court held that the enhanced efficacy was not taught in or suggested in the prior art or inherent in the prior dosage regimen, *Id.* at 1294, and allowed claims to the multiple daily doses. In *Alcon Research*, the court allowed claims to a

specific high concentration of a known product for treatment of allergic eye disease, finding that the prior art only taught lower concentrations, and that the higher concentration would not be obvious to try. *Id.* at 1370. And in *Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), the court upheld claims to the use of a known product to treat sleep apnea, holding that the prior use to treat anxiety "did not address treatment of the underlying sleep apnea disorder" because the sleep apnea treatment was not inherent in the prior art's anxiety treatment. *Id.* at 1060, 1062–63. While LABio states that *Allergan* and *Rapoport* support its position, each of those cases relies on facts missing here.

Precedent thus illustrates that the later discovery of a new and unobvious use of a known product may be patentable when the standards of unobviousness are met. Here, however, penile fibrosis was known in the prior art to be a mechanism of causing erectile dysfunction. A person of ordinary skill would, as the PTAB found, use the claimed compounds at the claimed doses for the claimed duration, for the purpose of treating erectile dysfunction in patients with penile fibrosis. The PTAB's findings are supported by substantial evidence, and its conclusions based thereon are in accordance with law. *See Alcon Research*, 687 F.3d at 1369 ("Given that the patent defines, and expressly claims, olopatadine concentrations that are 'therapeutically effective' to stabilize conjunctival mast cells, Kamei's disclosure of overlapping concentrations, even if for a different purpose, meets these claim limitations."). The PTAB's decision should be affirmed.

Finality and the America Invents Act

I respectfully dissent from my colleagues' judgment of vacatur and remand, for such further proceedings fail the policy and purpose of the America Invents Act, and should be invoked only when there are major defects in the PTAB

proceeding, requiring activity and redetermination that is not available on the appellate record.

The court at its footnote 9 takes issue with my position that our appellate obligation is to decide the appeal on the record on which the appeal reaches us. The court states that if an aspect is insufficiently established in the PTAB proceeding, our appellate role is to remand, despite the usual protocol that when sufficient basis has not been provided to support a necessary ruling, the side with the burden of establishing that position, loses. When, as here, the dispositive facts are not in dispute, it is not customary to authorize the deficient party to return to the trial tribunal to try again.

The America Invents Act adds rigor to this protocol, for the AIA created an expedited administrative procedure with strict time limits. Within these time limits, the parties must present their case and the PTAB must make its decision. It negates a foundation of the AIA for the appellate tribunal simply to remand for further proceedings after the statutory deadline. Our obligation is to decide the appeal as it reaches us.

According to the majority, the Board did not find that the prior art taught "long-term administration (i) to an individual with penile fibrosis (ii) in an effective amount to arrest or regress the fibrosis." Maj. Op. at 25 n.7, 31. Respectfully, the majority is incorrect, because the Board expressly found that the Whitaker reference taught long-term administration to patients with erectile dysfunction, and the Board expressly found that in some of those patients erectile dysfunction is caused by penile fibrosis. It is not necessary to return to the Board to find whether the prior art administered "an effective amount to arrest or regress the fibrosis," *id*. at 25 n.7, because LABiomed has conceded that it does; that is the basis for its litigation position.

Our obligation is to review the rulings of law and fact on the record presented. On this record, preponderant evidence is on the side of obviousness. Thus the decision in this IPR proceeding should be affirmed, not vacated and remanded.

The America Invents Act was enacted to remedy the lack of expedition and to add predictability in infringement disputes, by assigning to an expert administrative tribunal and presumed expert federal court the resolution of some major patentability issues, with tight procedural rules and deadlines. It was expected that in the normal course questions of patentability under Section 102 and 103 would be reliably and speedily resolved. Implementing this policy, when we find analytic lapses by the PTAB, it appears that the statute contemplates that we will make the determination, on the record that was made at the Board. Indeed, the depth of briefing by the parties suggests that this was their understanding, too.

I don't say that remands are never appropriate, but remands should be rare. Here the issues were fully developed, with eloquent argument all around, and an extensive Board opinion in which my colleagues find only slight gaps. Finality is available; it is our obligation to decide the merits.