APPENDIX

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APPENDIX A

NOTE: This disposition is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff-Appellee

v.

ELI LILLY AND COMPANY,
Defendant-Appellant

No. 2017-2603

Appeal from the United States District Court for the Eastern District of Texas in No. 2:15-cv-01202-WCB, Circuit Judge William C. Bryson.

JUDGMENT

JOHN SCOTT MCBRIDE, Bartlit Beck Herman Palenchar & Scott LLP, Chicago, IL, argued for plaintiff-appellee. Also represented by ADAM MORTARA, BENJAMIN JOHN WHITING; MEG E. FASULO, JOHN HUGHES, NOSSON KNOBLOCH, Denver, CO.

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Reston, VA, argued for defendant-appellant. Also represented by JENNIFER SWAN, Palo Alto, CA; HOWARD WARREN LEVINE, Washington, DC.

THIS CAUSE having been heard and considered, it is

ORDERED and ADJUDGED:

PER CURIAM (PROST, *Chief Judge,* MOORE and HUGHES, *Circuit Judges*).

AFFIRMED. See Fed. Cir. R. 36.

ENTERED BY ORDER OF THE COURT

Dated: October 10, 2018

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX B

UNITED STATES DISTRICT COURT EASTERN
DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff,

v.

ELI LILLY AND COMPANY,
Defendant.

Case No. 2:15-CV-1202-WCB

MEMORANDUM OPINION AND ORDER

In this patent infringement case, the plaintiff Erfindergemeinschaft UroPep GbR ("UroPep"), a German association of urology researchers and physicians, sued the defendant Eli Lilly and Company ("Lilly") for infringement of U.S. Patent No. 8,791,124 ("the '124 patent"). Claim 1 of the '124 patent is to a method of administering an effective amount of a compound known as an inhibitor of the enzyme phosphodiesterase ("PDE") V, in order to treat the condition of benign prostatic hyperplasia ("BPH"). UroPep alleged that Lilly induced infringement of claim 1 by marketing and selling the drug Cialis for the treatment of BPH. Lilly denied infringement and asserted various invalidity defenses. After a

trial, a jury found the '124 patent infringed and not invalid. The jury awarded damages in the amount of $20 million.

Pursuant to Rules 50(b) and 59, Fed. R. Civ. P., Lilly now moves for judgment as a matter of law or, in the alternative, a new trial. Dkt. No. 375. The motion is denied.

BACKGROUND

I. The Invention of '124 Patent

UroPep owns the '124 patent, entitled "Use of Phosphordiesterase [sic] Inhibitors in the Treatment of Prostatic Diseases." The disclosure was originally filed as part of a PCT application on July 9, 1997—the undisputed priority date of the '124 patent. The application under 35 U.S.C. § 371 ("the 371 application") was filed in April 2000 and later abandoned. The 371 application, in turn, gave rise to a continuation application that issued as U.S. Patent No. 8,106,061 ("the '061 patent") in January 2012. The '124 patent is a continuation of the patent application that matured into the '061 patent. '124 patent, col. 1, ll. 5-8.

The original specification filed in July 1997 begins by describing BPH, a condition in which the benign growth of the prostate gland in older males causes constriction of the neighboring urethra and results in lower urinary tract symptoms, including difficulties in urinating. *See id.*, col. 1, ll. 9-24. One prior art treatment method for BPH was surgery to reduce the size of the prostate. *Id.*, col. 1, ll. 14-15. Another prior art method was the administration of drugs, such as alpha-receptor blockers or drugs that interfere with hormonal regulation of the prostate, to induce relaxation of human prostatic muscle. *Id.*, col. 1, ll.

20-28. Those drugs, however, were not particularly effective and had significant side effects. *Id.*, col. 1, ll. 24-31; *id.*, col. 1, line 67 through col. 2, line 2.

The inventors of the '124 patent identified a new drug target: phosphodiesterase ("PDE") enzymes. '124 patent, col. 1, ll. 32-35. At that time, it was known that smooth muscle cells contain molecules called cyclic adenosine monophosphate ("cAMP") and cyclic guanosine monophosphate ("cGMP"), which promote the relaxation of smooth muscle. *Id.*, col. 1, ll. 39-42. It was also known that PDE enzymes break down cAMP and cGMP. *Id.*, col. 1, ll. 43-44. Finally, it was known that inhibitors of PDEs prevent the breakdown of cAMP and cGMP, which promotes smooth muscle relaxation. *Id.*, col. 1, ll. 44-52.

Those skilled in the art had studied PDEs and knew that PDEs come in different types (subesterases), including PDE1 through PDE5.[1] '124 patent, col. 1, ll. 53-60. Publications reported that those PDE types are distributed differently throughout the body's organs and organ systems, and that the activity of those PDE types varies depending on where they are located. *Id.*, col. 1, ll. 60-65; *see also, e.g.*, Dkt. No. 342, Trial Tr. at 307-08 (a particular PDE type may not be present in a particular tissue; or, even if the PDE type is present in that tissue, the PDE type may not be functionally relevant in that tissue because other conditions in the tissue render the activity of the PDE meaningless).

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[1] The PDE subesterases were initially identified by Roman numerals, the convention followed in the '124 patent (e.g., PDE V). It is now more common to use Arabic numerals (e.g., PDE5). For consistency, except where quoting record materials, the modern convention will be used throughout.

The prior art also identified compounds that selectively inhibit specific PDE types, i.e., compounds that suppress the activity of a specific PDE type. '124 patent, col. 1, ll. 44-52; *see also id.*, col. 1, ll. 66-67; *id.*, col. 7, ll. 35-40, 43-45. In particular, hundreds of selective inhibitors of PDE5 were known at that time, including the selective PDE5 inhibitor tadalafil, which is the active ingredient in Lilly's product Cialis. Dkt. No. 344, Trial Tr. at 1254 (Uro-Pep's expert describes the advanced state of the art regarding selective PDE5 inhibitors); Dkt. No. 343, Trial Tr. at 791-93 (Lilly's expert acknowledges that tadalafil, as well as 118 other compounds disclosed in a document published in 1995, were known PDE5 inhibitors before the priority date of the '124 patent).

The inventors of the '124 patent performed several experiments. *See* Dkt. No. 342, Trial Tr. at 316-17 (referencing experiments described in patent disclosure).

The first set of experiments revealed that PDE1, PDE4, and PDE5 were present and had significant activity in human prostatic tissue. '124 patent, col. 2, ll. 6-11. The second set of experiments showed that compounds that selectively inhibit PDE1, PDE4, and PDE5 caused the relaxation of strips of human prostatic tissue. *Id.*, col. 7, ll. 11-34. Based on those results, the inventors determined that compounds that selectively inhibit those three PDEs would treat BPH. *See id.*, col. 7, ll. 35-37; *id.*, col. 8, ll. 5-16. The disclosure identifies a number of "preferred selective inhibitors of PDE I, IV, and V," including 10 discrete chemical compounds and two classes of chemical compounds. *Id.*, col. 2, line 28 through col. 4, line 46.[2] For

[2] The disclosure also identifies, as "preferred selective inhibitors of PDE I, IV, and V," the "pharmacologically compatible salts" of

convenience, those "preferred selective inhibitors of PDE I, IV, and V" will be referred to as "the identified preferred selective inhibitors." Tadalafil is not among those identified preferred selective inhibitors.

The disclosure also describes and incorporates "known methods" to determine whether any particular compound is a "selective inhibitor" of a specific PDE type. '124 patent, col. 7, line 35 through col. 8, line 16. If a compound is a selective inhibitor of one of the identified PDE types (PDE1, PDE4, or PDE5), then that compound is "suitable for the purpose according to the invention," *id.*, col. 7, ll. 35-37—namely, for the prophylaxis and treatment of BPH and other prostatic diseases, *id.*, col. 2, ll. 17-27.

In the original Patent Cooperation Treaty ("PCT") application, the patentees claimed the "[u]se of [any of the identified preferred selective inhibitors] in the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia" and others. PCT Application, at 4 (claim 1); *see also id.* at 5 (claim 2 covers "medicaments for" the prophylaxis and treatment of BPH and other prostatic diseases using any of the identified preferred selective inhibitors); *id.* at 6 (claim 3 covers the use of the identified preferred selective inhibitors "in the preparation of medicaments for the prophylaxis and treatment of" BPH and other prostatic diseases). The '061 patent, filed in May 2003, claims "[a] method of treating" BPH or prostatism by "administering a selective inhibitor of [PDE] IV and/or [PDE] V," selected from a group of six of the identified preferred selective inhibitors. '061 patent, col. 8, ll. 4-26 (independent claim 1); *see*

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those 10 compounds and two classes of compounds. '124 patent, col. 4, line 47.

also id., col. 8, ll. 29-53 (independent claim 3 is to a method of "relaxing prostatic muscles" by administering, to someone with BPH or prostatism, a selective inhibitor of PDE4 and/or PDE5 selected from a group of nine of the identified preferred selective inhibitors).

In the 1980s and 1990s, some drug companies were investigating PDE5 inhibitors for the treatment of other conditions, such as erectile dysfunction. *See, e.g.*, Dkt. No. 342, Trial Tr. at 314-16 (Pfizer was investigating the PDE5 inhibitor sildenafil (Viagra) in the 1980s and 1990s). Lilly was one of them: Lilly developed Cialis (with tadalafil as the active ingredient) as a drug for erectile dysfunction, and Lilly sought approval of Cialis in the United States and Europe for that indication in mid-2001. *See* Dkt. No. 343, Trial Tr. at 955. Then, in December 2001, Lilly began discussing other possible indications for Cialis, including whether to develop Cialis as a treatment for BPH. *See id.*, Trial Tr. at 958, 996. Lilly decided to engage in that development and obtained FDA approval for the BPH indication in 2011. *Id.*, Trial Tr. at 1003. Lilly then began marketing and selling Cialis for the treatment of BPH.

The '061 patent was in effect at that time. The claims of the '061 patent, however, do not cover Cialis, because tadalafil is not one of the identified preferred selective inhibitors required by the claims of the '061 patent.

In December 2011, the patentees filed a continuation application that later issued as the '124 patent. During prosecution, the examiner rejected the claims on the basis of nonstatutory double-patenting over the '061 patent. *See* Dkt. No. 106-8, at 63-64. The patentees then amended

claim 1 to exclude many of the identified preferred compounds required in the claims of the '061 patent. *See* Dkt. No. 106-8, at 115.[3] Claim 1 of the issued '124 patent recites:

> A method for prophylaxis or treatment of benign prostatic hyperplasia comprising administering to a person in need thereof an effective amount of an inhibitor of phosphodiesterase (PDE) V excluding a compound selected from the group consisting of
>
> dipyridamole,
>
> 2-(N-(4-carboxypiperidine)-6-chloro-4(3,4- (methylendioxy)benzyl)amino)quinazoline,
>
> 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate.
>
> 4((3,4-(methylendioxy)benzyl)amino)-6,7,8-trimethoxy- quinazoline,
>
> 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2- ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one,
>
> 2-n-butyl-5-chloro-1-(2-chlorobenzyl)-4-methylacetate-imidazole,

[3] After that amendment, the examiner rejected the claims as anticipated by the claims of the '061 patent. The patentees entered a terminal disclaimer with respect to the '061 patent, and the examiner then allowed the claims of the '124 patent. *See* Dkt. No. 106-8, at 121-28.

> 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin- 4(5H)-one,
>
> 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chronan-4-one,
>
> and pharmacologically compatible salts thereof.

'124 patent, col. 8, ll. 18-41 (duplicate compound removed).[4] Those eight compounds excluded from claim 1 are all among the identified preferred selective inhibitors. Thus, claim 1 of the '124 patent on its face includes selective PDE5 inhibitors such as tadalafil, which is not among the identified preferred selective inhibitors.

The '124 patent issued in July 2014. In October 2014, UroPep notified Lilly by letter of potential infringement of the '124 patent. Lilly received the letter but did not respond. In July 2015, UroPep filed this action for infringement.

II. The Trial

At trial, the parties introduced evidence from several sets of competing experts, including physicians skilled in urology, medicinal chemists skilled in drug development, and economists. In addition, UroPep called one of the named inventors of the '124 patent, Dr. Stefan Ückert, to testify about the invention. Lilly called employees Dr.

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[4] Claim 1, as set forth in the '124 patent, contains a duplicate listing of 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin- 4(5H)one.

Lars Viktrup and Janelle Sabo to speak about Lilly's development of Cialis for the BPH indication.

In its Rule 50 and Rule 59 motions, Lilly has not challenged the sufficiency of the evidence of infringement. UroPep introduced ample evidence that the administration of Cialis for BPH infringed claim 1 of the '124 patent. The Court construed claim 1 of the '124 patent to require that an effective amount of a "selective PDE5 inhibitor"—i.e., a compound that is at least 20 times more selective for PDE5 than for PDE1 through PDE4—be administered to treat an individual suffering from BPH. *See* Dkt. No. 149, at 27; Dkt. No. 234, at 16. At trial, UroPep introduced the Cialis drug label approved by the U.S. Food & Drug Administration ("FDA"). That drug label expressly identifies tadalafil, the active ingredient in Cialis, as an inhibitor more than 20 times more selective for PDE5 than for PDE1, PDE2, PDE3, and PDE4. The label also states that five milligrams of Cialis is an effective amount to treat BPH, and the label directs physicians to prescribe Cialis as a treatment for individuals suffering from BPH. Dkt. No. 341, Trial Tr. at 216, 218. UroPep's expert urologist, Dr. Anthony Sliwinski, went through the Cialis label and explained how it met each of the limitations of claim 1. *Id.*, Trial Tr. at 222-23; *see also* Dkt. No. 342, Trial Tr. at 323-24, 327 (UroPep's expert medicinal chemist, Dr. Andrew Bell, did the same). Dr. Sliwinski also testified about his medical practice, in which he diagnoses patients with BPH and prescribes Cialis for the treatment of that condition. Dkt. No. 341, Trial Tr. at 216-18.[5]

[5] Lilly's only challenge to the evidence of infringement was the suggestion that doctors may prescribe Cialis to treat BPH without correctly diagnosing the patients' condition as BPH, i.e., lower urinary tract symptoms resulting from an enlarged prostate. *See* Dkt.

Second, UroPep provided evidence that Lilly had induced infringement by marketing Cialis for the treatment of BPH. For example, the Cialis label, which is addressed to physicians and patients, counsels the administration of Cialis for the treatment of BPH. *See* Dkt. No. 341, Trial Tr. at 216-19. UroPep also introduced numerous advertisements, brochures, coupons, and other marketing materials that Lilly has distributed to physicians and consumers regarding the use of Cialis as a treatment for BPH. *See* Dkt. No. 341, Trial Tr. at 223-27; *see also* Dkt. No. 342, Trial Tr. at 394-95 (evidence that Lilly spent over $100 million to run one television advertisement regarding the use of Cialis for BPH and erectile dysfunction); *id.*, Trial Tr. at 396-97 (same message regarding the administration of Cialis for BPH and erectile dysfunction on Lilly's websites). In addition, Dr. Sliwinski testified about his receipt of such materials, Cialis drug samples, and visits from Lilly pharmaceutical representatives, all of which caused him and the partners in his practice to prescribe Cialis for BPH. *See* Dkt. No. 341, Trial Tr. at 206-07, 220, 223-27.

Lilly presented four primary invalidity defenses: lack of written description under 35 U.S.C. § 112, ¶ 1; lack of enablement under that same provision; anticipation under 35 U.S.C. § 102; and obviousness under 35 U.S.C. § 103. Although the jury rejected each defense, Lilly argues that

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No. 346, Trial Tr. at 1482 (Lilly's closing argument on noninfringement: "Did they prove an enlarged prostate? I'll leave that to you."). Dr. Sliwinski, however, explained how he appropriately diagnoses BPH before prescribing Cialis. *See, e.g.*, Dkt. No. 341, Trial Tr. at 218-19 (explaining that, before prescribing Cialis for BPH, he rules out all other possible causes of the patient's symptoms to conclude that the patient in fact suffers from BPH). In the absence of contrary evidence, the jury could reasonably infer that his experience was representative.

each is a ground for judgment as a matter of law or, in the alternative, a new trial. Lilly also contends that the Court improperly rejected Lilly's argument that claim 1 of the '124 patent is indefinite and that the Court's claim constructions are erroneous, requiring judgment as a matter of law or a new trial. Finally, according to Lilly, the Court gave several erroneous jury instructions and made several erroneous evidentiary rulings, each of which requires a new trial.

DISCUSSION

Lilly asserts that the Court should enter judgment in Lilly's favor pursuant to Rule 50(b) based on (1) any one of Lilly's invalidity defenses asserted at trial, (2) indefiniteness of the claim term "inhibitor of phosphodiesterase (PDE) V," and (3) any of the rejected claim constructions. Lilly also argues that it is entitled to a new trial pursuant to Rule 59 on any of those grounds, or based on (4) the Court's jury instruction on enablement, (5) the Court's failure to give an instruction based on 35 U.S.C. § 101, (6) the exclusion of certain evidence based on untimely disclosures, or (7) the assertedly improper impeachment of one of Lilly's experts.

I. Legal Standard

Fifth Circuit law determines what legal standards apply to a motion for judgment as a matter of law under Rule 50(b) and a motion for a new trial under Rule 59. *Wi-Lan, Inc. v. Apple, Inc.*, 811 F.3d 455, 461 (Fed. Cir. 2016). A motion for judgment as a matter of law "is a challenge to the legal sufficiency of the evidence supporting the jury's verdict." *Dresser-Rand Co. v. Virtual Automation Inc.*, 361 F.3d 831, 838 (5th Cir. 2004); *see also Vadie v. Miss.*

State Univ., 218 F.3d 365, 372 (5th Cir. 2000) ("A jury verdict must be upheld unless 'there is no legally sufficient evidentiary basis for a reasonable jury to find' as it did.") (quoting Fed. R. Civ. P. 50). The court must "draw[] all reasonable inferences and resolv[e] all credibility determinations in the light most favorable to the non-moving party." *Dresser-Rand*, 361 F.3d at 838. The court "grants great deference to a jury's verdict and will reverse only if, when viewing the evidence in the light most favorable to the verdict, the evidence points so strongly and overwhelmingly in favor of one party that the court believes that reasonable jurors could not arrive at any contrary conclusion." *Id.*; *accord Wi-Lan*, 811 F.3d at 461 (applying Fifth Circuit law).

As for the alternative motion for a new trial, Lilly must show that "it is reasonably clear that prejudicial error has crept into the record or that substantial justice has not been done." *Laxton v. Gap Inc.*, 333 F.3d 572, 586 (5th Cir. 2008) (internal quotation marks omitted). In making that determination, the "court weighs all of the evidence," but the court "need not view [the evidence] in the light most favorable to the nonmoving party." *Id.* The court, however, may not grant a new trial "unless the verdict is against the great weight of the evidence." *Dresser-Rand*, 361 F.3d at 838; *accord Wi-Lan*, 811 F.3d at 461 (applying Fifth Circuit law); *see also Laxton*, 333 F.3d at 586 ("A new trial is warranted if the evidence is against the great, and not merely the greater, weight of the evidence.").

II. Written Description

The written description requirement of 35 U.S.C. § 112, ¶ 1 provides, in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112 ¶ 1 (2006). For purposes of written description, that clause has been interpreted to require that the specification "describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1345 (Fed. Cir. 2010) (en banc).

Both parties offered expert testimony and numerous exhibits addressed to the written description issue. The primary point of contention was whether the disclosure supports the claim term "an inhibitor of phosphodiesterase (PDE) V," construed as "a selective inhibitor of PDE5, which is at least 20 times more effective in inhibiting PDE5 as compared to PDE1 through PDE4." *See* Dkt. No. 346, Trial Tr. at 1412-13. Lilly's theory at trial was that the disclosure is inadequate to describe the genus encompassed by that claim term as construed. In response, UroPep presented evidence that the disclosure described both a sufficient number of representative species within the scope of that genus and structural features common to the members of the genus. *See Ariad*, 598 F.3d at 1351.

Over UroPep's objection, the Court adopted Lilly's proposed instruction regarding the written description requirement. *Compare* Dkt. No. 344, Trial Tr. at 1357 (Lilly "suggest[s] 'a sufficient number of representative

compounds'") *with* Dkt. No. 346, Trial Tr. at 1427 (Court instructs jury that written description must include "a sufficient number of representative compounds or a common structural feature so that a person of ordinary skill in the art would understand, from reading the patent, that the inventor invented the full scope of the claimed method."); *see also* Dkt. No. 346, Trial Tr. at 1397-98 (Court rejects UroPep's proposed reference to "one or more representative compounds"). Under Lilly's proposed instruction, the jury found that Lilly had failed to prove invalidity by clear and convincing evidence.

A. Written Description Support for the Claim Limitation of a Selective Inhibitor of PDE5

In its post-trial motion, Lilly argues that the evidence introduced at trial shows that Lilly is entitled to a judgment of invalidity for lack of an adequate written description of a selective inhibitor of PDE5, or a new trial. The Court disagrees.

According to Lilly, the claim term describes a genus using functional language—that is, "a selective inhibitor of PDE5" is defined by its function as a compound that selectively inhibits PDE5. Lilly contends that no reasonable jury could find that the disclosures contained within the "four corners" of the specification describe a sufficient number of representative species within the scope of the genus, or structural features common to the members of the genus. *See* Dkt. No. 375, at 15 (quoting *Ariad*, 598 F.3d at 1351); *see also* Dkt. No. 393, at 6-7 (Lilly argues that UroPep is restricted to the "four corners" of the patent and cannot rely upon "that which is undescribed but allegedly obvious from the art.").

Lilly proceeds from the wrong premise. As the Federal Circuit explained in *Ariad*, the possession inquiry is not limited to what is expressly described within the "four corners" of the specification. Instead, the possession inquiry is an objective one that is viewed from the perspective of a person of ordinary skill in the art:

> The term "possession" . . . has never been very enlightening. It implies that as long as one can produce records documenting a written description of a claimed invention, one can show possession. But the hallmark of written description is disclosure. Thus, "possession as shown in the disclosure" is a more complete formulation. Yet whatever the specific articulation, the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.

598 F.3d at 1351.

Because "the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before . . . it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention . . . ." *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). The level of detail required to satisfy the written description requirement therefore "varies depending on the nature

and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad*, 598 F.3d at 1351; *see also Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) (what is required "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence").

Under the proper legal standard, Lilly cannot establish that it is entitled to the requested relief. As the Federal Circuit has emphasized, in written description cases, "[t]he primary consideration is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000); *see also ScriptPro, LLC v. Innovation Assocs., Inc.*, 762 F.3d 1355, 1359 (Fed. Cir. 2014) (sufficiency of the written description is a question of fact). There was sufficient evidence for the jury to find that Lilly did not prove by clear and convincing evidence that the '124 patent failed to disclose "either a representative number of species falling within the scope of the genus or structural features common to members of the genus so that one of skill in the art [could] 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350.

1. Representative Number of Selective PDE5 Inhibitors

A reasonable jury could have found that Lilly failed to show that the disclosure lacked a sufficient number of representative compounds falling within the scope of the genus of selective PDE5 inhibitors. The specification describes a number of "preferred selective inhibitors of PDE I, IV, and V." '124 patent, col. 2, line 28. Those "preferred selective inhibitors" include 10 discrete compounds

(a) through (j), and two classes of compounds (k) and (l). *Id.*, col. 2, line 29 through col. 4, line 47. The patent identifies those compounds and classes of compounds by chemical name and, in most cases, structural drawings. *Id.*

The evidence at trial showed that many of the compounds identified in the '124 patent as "preferred selective inhibitors of PDE I, IV, and V" were known to be selective PDE5 inhibitors in July 1997. Based on his expert knowledge and pointing to printed publications, UroPep's expert Dr. Andrew Bell testified that the compounds identified as (a), (c), (d), and (g) in the '124 patent were publicly known as selective PDE5 inhibitors before July 1997. *See* Dkt. No. 342, Trial Tr. at 314-15 (sildenafil, MY5445, and zaprinast—compounds (a), (c), and (g) in the specification—were known selective PDE5 inhibitors); Dkt. No. 344, Trial Tr. at 1260-61, 1265-66 (compound E4021—compound (d) in the specification—was a known selective PDE5 inhibitor). Experts called by Lilly also testified as to the known PDE5 activity of those compounds in July 1997. Dr. Nicholas Terrett noted that the scientific literature showed that a number of quinazoline compounds—within the class of compounds (k) in the specification—were known to inhibit PDE5. Dkt. No. 343, Trial Tr. at 710-11. Lilly's expert Dr. David Rotella explained that sildenafil (compound (g)) is a pyrazolopyrimidone and within the class of compounds (l) in the specification. *Id.*, Trial Tr. at 740; *see also id.*, Trial Tr. at 723 (Dr. Rotella admits sildenafil was a known selective PDE5 inhibitor in July 1997).

In addition to the compounds expressly disclosed in the '124 patent, the jury heard undisputed evidence that hundreds of PDE5 inhibitors were known by July 1997.

Dr. Bell testified about the advanced state of the art regarding selective PDE5 inhibitors in July 1997: "There were hundreds of known inhibitors, selective inhibitors of PDE5 known at that time. This was a pretty mature area." Dkt. No. 342, Trial Tr. at 318; *see also* Dkt. No. 344, Trial Tr. at 1254 (explaining that hundreds of selective PDE5 inhibitors were known by July 1997); *id.*, Trial Tr. at 1267-68 (explaining that skilled artisans were aware of hundreds of other selective PDE5 inhibitors beyond those expressly named in a 1995 review article). Lilly's expert Dr. Rotella admitted that tadalafil, as well as 118 other compounds in one sample paper published in 1995, were known PDE5 inhibitors before July 1997. Dkt. No. 343, Trial Tr. at 792-93. There was also evidence that at least two selective PDE5 inhibitors—in particular, sildenafil and zaprinast—had been subjected to human clinical testing long before July 1997, albeit for conditions other than BPH. Dkt. No. 344, Trial Tr. at 1293-94; *see also* Dkt. No. 342, Trial Tr. at 315-18 (Dr. Bell describes Viagra clinical trials in 1980s and 1990s).

Given the evidence of the knowledge of a person of skill in July 1997 regarding PDE5 inhibitors, including tadalafil, a reasonable jury could have found that the specification disclosed a sufficient number of representative species of selective PDE5 inhibitors. Written description is a question of fact, and "[f]or generic claims, [there are] a number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Ariad*, 598 F.3d at 1351 (quoting *Capon v. Eshhar*, 418 F.3d at 1359). UroPep presented evidence as to all of those factors, much of which Lilly

failed to rebut. The jury was entitled to credit UroPep's evidence and find that Lilly failed to meet its burden.

Lilly nevertheless contends that the disclosure of several species of selective PDE5 inhibitors in the '124 patent is insufficient, because Lilly's evidence showed that the genus of selective PDE5 inhibitors is large. For example, one witness put on by Lilly testified that the chemical class of quinazolines—identified as preferred in the '124 patent—contains "billions of compounds." Dkt. No. 341, Trial Tr. at 182-83. Although far fewer compounds within that class of quinazolines are selective PDE5 inhibitors such that they would fall within the claimed genus, Dkt. No. 342, Trial Tr. at 342, it was generally undisputed that the claimed genus is nonetheless very large. UroPep's expert testified that hundreds of PDE5 inhibitors, including tadalafil, were known in 1997, and that at least tens of thousands have been developed since then. *See* Dkt. No. 342, at 332, 341-42.

That evidence, however, is not dispositive. There is no "bright-line rule governing the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each such invention, and it changes with progress in a field." *Ariad*, 598 F.3d at 1351; *see also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) ("where . . . accessible literature sources clearly provided, as of the relevant date, [the species falling within the claimed genus], satisfaction of the written description requirement does not require either the recitation of or incorporation by reference of such [species].") (parentheticals omitted). The specification of the '124 patent alone discloses at least four discrete compounds that were known to be selective PDE5 inhibitors,

as well as two compound classes that were known to contain selective PDE5 inhibitors. That express disclosure was in the context of a mature field in which skilled artisans knew what PDE5 inhibitors were and had already discovered hundreds of them. Those representative species would indicate to a skilled artisan at the time of the invention that selective PDE5 inhibitors such as tadalafil, well known in the mature field in 1997, would work in the claimed invention.

The Federal Circuit has rejected a rule that at least one representative compound is always needed to satisfy the written description requirement. *See Capon v. Eshhar*, 418 F.3d 1349, 1356-1358 (Fed. Cir. 2005) (rejecting the interpretation of "controlling precedent" from the Federal Circuit as "requir[ing] inclusion in the specification of the complete nucleotide sequence of 'at least one' chimeric gene"—i.e., one representative species—because the prior art may supply that understanding); *cf. Eli Lilly*, 119 F.3d at 1569 ("'Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. But where no explicit description of a generic invention is to be found in the specification[,] . . . mention of representative compounds may provide an implicit description upon which to base generic claim language.'") (quoting *In re Robins*, 429 F.2d 452, 456-57 (C.C.P.A. 1970)). The identification of a large number of representative compounds is one way to meet the written description requirement, but not the only way. *See, e.g.*, *In re Herschler*, 591 F.2d 692, 701 (C.C.P.A. 1979) (specification's disclosure of a single example species was sufficient because numerous species were known to skilled artisans); *In re Fuetterer*, 319 F.2d 259, 265 (C.C.P.A. 1963) (Rich, J.) (disclosure of four species was sufficient even for huge genus that was

not fully known at the time of the invention); *see also In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) (patentees "are not required to disclose *every* species encompassed by their claims even in an unpredictable art") (quoted in *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997)).

For example, in *Capon*, the claimed chimeric genes were "prepared from known DNA sequences of known function." 418 F.3d at 1358. Both parties "explain[ed] that th[e] invention does not concern the discovery of gene function or structure." *Id.* Both parties also "explain[ed] that the[] invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result." *Id.* The Federal Circuit ruled that the Board of Patent Appeals and Interferences "erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes." *Id.*; *see also Unocal*, 208 F.3d at 997 (written description requirement was satisfied because evidence at trial showed that skilled artisans were aware of the properties of raw petroleum sources and knew, upon reading the disclosure, how to vary those sources in combination to achieve a final product with desired characteristics; given the background knowledge of persons of skill in the art, the patentees were not required to "describe the exact chemical component of each combination that falls within the range claims of the" patent).

As in *Capon*, it was undisputed at trial that hundreds of selective PDE5 inhibitors, as well as their function, were known in the art at the time of the invention. *See*

'124 patent, col. 1, ll. 36-65. It was also clear that selective PDE5 inhibitors were not themselves the invention. '124 patent, col. 2, ll. 17-20 (describing the invention as the use of selective inhibitors of PDE1, PDE4, and PDE5 in the prophylaxis and treatment of prostatic diseases, including BPH); *see also* Dkt. No. 341, Trial Tr. at 174-78 (Lilly's counsel clarifying that the inventor did not claim the discovery of PDEs, PDE inhibitors, alpha-blockers, or the mechanism of action of cAMP and cGMP in relaxing prostatic muscle); Dkt. No. 344, Trial Tr. at 1295 (Dr. Bell: a person of skill does not "need to discover brand-new PDE5 inhibitors to use the '124 patent invention"); *id.* at 1283 (Dr. Bell confirming that the UroPep inventors did not "discover PDE5 inhibitors"). The disclosure does not describe the "novel result" of inhibiting PDE5. *Ariad*, 598 F.3d at 1349. Such compounds were already well known and the effect of inhibiting PDE5 already achieved; instead, the invention was to use a group of compounds well known in the art, including tadalafil, in a novel method of treating BPH.

It is often the case that a patent claiming the invention of a new genus, or the use of a new genus, must provide more detail regarding that genus, such as disclosing a number of representative species or a structural feature by which to recognize the new genus. *See, e.g., Ariad*, 598 F.3d 1336, 1357-58 (claiming methods of using new "molecules potentially capable of reducing NF-κB activity," where no such molecules had been completely synthesized but were merely "prophesized"); *Rochester*, 358 F.3d 916, 923 (claiming use of new COX-2 inhibitors that were merely "hypothesized"); *Eli Lilly*, 119 F.3d 1559, 1567 (claiming cDNA for human insulin that had never been characterized); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (claim to DNA that was of unknown structure);

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) (claims directed to unknown gene encoding human erythropoietin, where gene was not adequately characterized); *see also Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364-65 (Fed. Cir. 2011) (claiming use of new "macrocyclic lactone analogs of rapamycin" where none were disclosed, only a small number were known in the prior art, very little was known about their function, and no guidance was provided to determine which, if any, would work in the invention). As in *Ariad*, when one purports to have "invented a genus," the written description should "disclose a variety of species that accomplish the result," because "'[t]he description requirement of the patent statute requires a description of the invention, not an indication of a result that one might achieve if one made the invention.'" 598 F.3d at 1350 (quoting *Eli Lilly*, 119 F.3d at 1568). Otherwise, a person of skill in the art would not be aware of what makes up the new genus, and the claimed invention would not be sufficiently described.

On the other hand, when a genus is well understood in the art and not itself the invention but is instead a component of the claim, background knowledge may provide the necessary support for the claim. For example, in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1319 (Fed. Cir. 2003), the invention was the production of recombinant erythropoietin (a hormone). The method claims included the use of vertebrate or mammalian host cells to produce the recombinant erythropoietin. *Id.* at 1322. In response to a written description challenge based on the generic terms "mammalian cell" and "vertebrate cell," the Federal Circuit ruled that the disclosure did not need to identify specific representative species or common structural characteristics of the genera of vertebrate

and mammalian cells, "because the claim terms at issue here ["vertebrate cells" and "mammalian cells"] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Id.* at 1332 (distinguishing *Eli Lilly*, 119 F.3d 1559, and *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002)).

As another example, the Court of Claims and Patent Appeals determined that an application disclosing one example of a physiologically active steroidal agent provided sufficient written description to support claims directed to a novel method of using dimethyl sulfoxide in combination with such steroidal agents for delivery of those agents through topical administration. *In re Herschler*, 591 F.2d at 701. In that case, numerous steroidal agents were known in the art at the time of the invention. *Id.* As the court noted, "[w]ere th[e] application drawn to novel 'steroidal agents,' a different question would be posed." *Id.*; *see also Rochester*, 358 F.3d at 928 (discussing *Herschler*).

That principle applies equally to the chemical arts, despite Lilly's suggestion to the contrary. *See* Dkt. No. 393, at 9 (Lilly states that "decided cases have long recognized [that the field of pharmaceutical chemistry and drug development] is highly unpredictable."). *Rochester*, which Lilly cites in support, in fact states that such distinctions are "irrelevant; the statute applies to all types of inventions." 358 F.3d 916, 925; *see also Ariad*, 598 F.3d at 1352 (noting that the principles underlying the written description requirement "ha[ve] not just been applied to chemical and biological inventions.") (citing *LizardTech*, 424 F.3d at 1343-47). Although certain aspects of the chemical arts may be unpredictable, that does not mean that the chem-

ical arts always require the identification of representative species to support a claimed genus, even when there is substantial knowledge in the field regarding the genus.

In a hypothetical case involving the chemical arts, for example, a claim might be directed to the novel use of a particular salt, where the salt must be dissolved in a "solubilizing agent." The broad genus of "solubilizing agents" would not require representative species if persons of skill knew of many solvents that could dissolve the salt, and thereby serve as a "solubilizing agent" in that invention. Patents in the chemical field may often involve claims that include well-understood genera. *See, e.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1371-72 (Fed. Cir. 2001) (independent claims to methods for treating patients with taxol-sensitive tumors by administering taxol within a fixed range along "with a medicament that reduces or eliminates hypersensitivity reactions," and dependent claims specifying that such "medicaments" are chosen from the broad genera of "steroids, antihistamines, H2 receptor antagonists, and combinations thereof.").

None of the cases cited by Lilly support Lilly's argument that a disclosure must include some absolute number of species to support any patent claim to a genus. Those cases instead show that patent claims may be invalidated based on the failure to disclose any, or more than one, species in a nascent area where knowledge of the art has nothing to add to the disclosure. *E.g.*, *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 918, 923 (Fed. Cir. 2004) (patent claims directed to COX-2 inhibitors were invalidated for lack of adequate written description because the existence of such inhibitors was merely "hypothesized"; no such inhibitors were yet known and none were

described in the patent); *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-01 (Fed. Cir. 2014) (affirming verdict of invalidity for lack of written description because the patent disclosed only one very limited subgenus within a diverse claimed genus); *Ariad*, 598 F.3d 1336, 1355, 1357-58 (holding invalid claims directed to "molecules potentially capable of reducing NF-κB activity," where the disclosure contained "no working or even prophetic examples of methods that reduce NF-κB activity, and no completed synthesis of any of the molecules prophesized to be capable of reducing NF-κB activity," and where the prior art "was primitive and uncertain" and had not identified even a single example inhibitor).

Boston Scientific Corp. v. Johnson & Johnson, 647 F.3d 1353 (Fed. Cir. 2011), on which Lilly relies, also does not support Lilly's position. There, the Federal Circuit affirmed the grant of summary judgment of invalidity "[g]iven the absence of information regarding structural characteristics of [the claimed] macrocylic lactone analogs or examples of macrocylic lactone analogs in the specification, the unpredictability of the art and the nascent state of using drug- eluting stents to inhibit restenosis." 647 F.3d at 1366-67. Although the patentee argued that the mechanism of action was known in the art and supplied the necessary description, the court noted that the specification expressly "refutes any conclusion that the structural elements of rapamycin and its mechanism of action and biological activity was known." *Id.* at 1366. For that reason, although "a patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement," the patentee in *Boston Scientific* could not rely on such information to overcome the express disclosures of the patent. 647 F.3d at 1366;

see also id. ("when the four corners of the specification directly contradict information that the patentee alleges is 'well-known' to a person of skill at the effective filing date, no reasonable jury could conclude that the patentee possessed the invention.").

Where representative compounds are necessary to satisfy the written description requirement, the number of such compounds that must be disclosed depends on the context, including the knowledge already available in the art. Unlike the patent at issue in *Boston Scientific*, the '124 patent expressly provides that the field of PDE5 inhibitors and their mechanism of action was well known before July 1997. '124 patent, col. 1, ll. 36-65; *see also id.* , col. 7, ll. 35-45. UroPep also provided substantial extrinsic evidence corroborating that proposition, such as testimony and documents showing that hundreds of selective PDE5 inhibitors, including tadalafil, were known at the time of the invention. The patentees were not required to include those hundreds of compounds in the disclosure, and in fact the law makes it clear that it is preferable that they not do so. *See Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) ("As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification."). Lilly does not say what number of compounds would be sufficient; even if the Court assumes that Lilly's position is that the number required must be at least one more than the number of compounds disclosed in the '124 patent, Lilly has not demonstrated that Lilly is entitled to relief under governing law in light of the evidence at trial.

Lilly highlights other evidence, but none of that evidence warrants judgment as a matter of law or a new trial on the written description issue.

1. According to Lilly, it is unclear which of all possible compounds within the genus will selectively inhibit PDE5 and effectively treat BPH. Dkt. No. 375, at 16. Lilly's argument ignores the claim construction and incorrectly assumes that the genus includes all PDE5 inhibitors, whereas the genus in claim 1 includes only selective PDE5 inhibitors. *Id.* at 17 (citing Dr. Terrett's testimony that it is "impossible to say" whether all PDE5 inhibitors—as opposed to all selective PDE5 inhibitors—would treat BPH). Lilly has not pointed to any evidence, much less clear and convincing evidence, that an effective amount of a selective PDE5 inhibitor would not treat BPH. *Compare* Dkt. No. 342, Trial Tr. at 338-39 (Dr. Bell testifies that he does not know whether a 10 milligram (relatively small) dose of the selective PDE5 inhibitor zaprinast would effectively treat BPH) *with* Dkt. No. 375, at 17 (Lilly suggests that Dr. Bell testified that he does not know whether zaprinast is capable of effectively treating BPH).[6]

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[6] Lilly contends that UroPep's experts "condemn[]" the potency and selectivity of zaprinast, a selective PDE5 inhibitor noted in the '124 patent. Dkt. No. 393, at 9. For support, however, Lilly highlights in its motion portions of trial exhibits regarding zaprinast that were not presented to the jury during trial. *Compare id.* at 8 (relying on reported results regarding zaprinast in plaintiff's exhibits 183 and 239) *with* Dkt. No. 344, Trial Tr. at 1250-51 (UroPep used plaintiff's exhibit 183 to show Dr. Bell's work on sildenafil, not zaprinast) *and id.* , Trial Tr. at 1266-67 (UroPep used plaintiff's exhibit 183 to show prior art knowledge of the potency of E4021). Lilly failed to make those points to the jury at trial, and those points cannot be used to show that the jury acted unreasonably in finding against Lilly. In any event, the results (and error margins) reported in those exhibits are

2. Lilly argues that the evidence shows that a person of skill would not know definitively, simply by looking at the structure of any particular compound, whether that compound would selectively inhibit PDE5 and effectively treat BPH. Dkt. No. 375, at 16-17. Such a high standard has never been required for written description. If Lilly's standard were required for written description, there would be no need to consider, in the context of enablement, whether any experimentation was undue or merely routine. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art."); *see also* Dkt. No. 375, at 31 (Lilly argues that the '124 patent is not enabled because "[t]he quantity of experimentation just to . . . identif[y] selective PDE V inhibitors is exceedingly high, considering that the specification of the '124 patent fails to describe any specific compound as a selective PDE V inhibitor and fails to disclose a representative number of claimed species . . . ."). Furthermore, the *Ariad* standard may be satisfied by either a representative number of species or a common structural feature. It is the latter, not the former, that requires recognition of the compound as a member of the genus upon looking at the compound's chemical structure.

It is also important to note that tadalafil was a known selective PDE5 inhibitor by July 1997. Therefore, to the

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insufficient to prove Lilly's invalidity case, particularly given the substantial evidence that persons of skill understood, and other publications reported, that zaprinast is a selective PDE5 inhibitor.

extent that preferred selective PDE5 inhibitors were disclosed and understood by skilled artisans to work in the claimed invention due to their activity, tadalafil would be known by skilled artisans and understood to work in the claimed invention because it was known to have the same activity.

In any event, UroPep introduced testimony by Dr. Bell discussing how tadalafil shares a core chemical structure with compound E4021 (compound (d) in the specification). Dkt. No. 344, Trial Tr. at 1259-63. Lilly's expert Dr. Rotella gave a general opinion that the chemical structure of tadalafil is "distinct from the other chemical classes and compounds that were presented" in the '124 patent. Dkt. No. 343, at 760; *see also id.* at 758 (stating that "[t]adalafil is miles away from these structures [compounds (a)-(j) in the '124 patent] . . . in a structural sense."). The jury was entitled to credit Dr. Bell's testimony. Furthermore, Dr. Bell's testimony was more specific than—and, in that regard, undisputed by—Dr. Rotella's testimony. Lilly introduced expert testimony that PDE5 inhibitors in general have diverse structures, but Lilly did not produce evidence distinguishing between tadalafil and E4021.[7]

3. Lilly contends that eight of the preferred compounds in the specification cannot serve as representative species because those eight compounds are excluded from

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[7] Lilly's reference to a portion of Defendant's Trial Exhibit 1347 (a 2007 review by Dr. Rotella) to show that a PDE4 inhibitor shares that core structure is not evidence on that point. The portion of the exhibit that Lilly cites was not discussed at trial. Rather, the exhibit was used for an entirely different purpose. *See* Dkt. No. 343, Trial Tr. at 807-10 (showing that Dr. Rotella referenced Dr. Ückert's 2001 publication to support a statement that PDE5 inhibitors may be used to treat BPH); *see also id.* at 863.

claim 1 of the '124 patent. Lilly cites no support for that proposition, and the Court sees no merit to it. Patentees may choose to exclude from the claims some embodiments supported by the disclosure. *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1355 (Fed. Cir. 2015) ("It is for the inventor to decide what bounds of protection he will seek."). In fact, a patentee may choose to exclude some embodiments in order to avoid double patenting problems, as happened in this case. *See, e.g.*, *In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977) (written description was adequate where two specific compounds were omitted from a claim "to avoid having [the claim] read on a lost interference count"). But the compounds' exclusion from the claims does not mean that those individual compounds are no longer representative of other, non-excluded compounds covered by claim 1.

Even if it were the case that those eight compounds could not serve as representative species, Lilly would not be entitled to relief. For one thing, zaprinast and MY5445—compounds (a) and (c) in the specification—are not excluded from claim 1, and both were identified by sufficient evidence at trial as selective PDE5 inhibitors. The jury was entitled to find that Lilly failed to show that MY5445 and zaprinast are not representative species that fall within the genus, and the great weight of the evidence does not support Lilly's position on that point.

2. Common Structural Features

A reasonable jury also could have found that Lilly failed to prove by clear and convincing evidence that the written description did not disclose "structural features common to the members of the genus." *Ariad*, 598 F.3d 1336, 1351. While the disclosure does not expressly discuss the common structural features of PDE5 inhibitors,

UroPep presented evidence at trial that persons of skill in the art would recognize such shared features. The jury was entitled to credit that evidence and find that the knowledge of persons of skill in the art satisfied the written description requirement.

UroPep's expert Dr. Bell gave a lengthy description of the core chemical structure found in a number of selective PDE5 inhibitors, including tadalafil and compound E4021 (compound (d) in the '124 patent), as well as a number of other prior art compounds. Dkt. No. 344, Trial Tr. at 1262-63; see generally *id.*, Trial Tr. at 1259-68. The patent's disclosure of E4021 is therefore the disclosure of a species with a chemical structure shared by tadalafil. The jury was entitled to credit that testimony over the contrary testimony of Lilly's expert. Dkt. No. 343, Trial Tr. at 758-60.

Lilly contends that Ariad requires the disclosure of a structural feature common to all members of the genus. The Court disagrees. A patent's specification might identify three different structural features each found in one of three subgenera (or the same structural features may already be known in the art). The patent may claim an invention that includes a limitation to a genus made up of those three subgenera. Under those circumstances, a person of skill in the art would be able to "'visualize or recognize' the members of the genus" by looking for any one of those three structural features. *Ariad*, 598 F.3d 1336, 1350.

In any event, UroPep presented unrebutted evidence that PDE5 inhibitors all share a common structural feature. According to Dr. Bell, PDE5 inhibitors may not all share a common "chemical" structure like the core chemical structure found in tadalafil and E4021, but all PDE5

inhibitors share a common "physical" structure. Dkt. No. 344, Trial Tr. at 1280-81. In three dimensions, that physical structure resembles an envelope: it contains a flat section, typically made up of two or more fused rings, and an attached section directed upwards. *Id.* at 1280. That physical structure fits into the active site of the PDE5 enzyme, inhibiting the enzyme's activity. *Id.* at 1281. UroPep's evidence indicated that skilled artisans may then add to that core physical structure to increase the PDE5 inhibitor's potency and selectivity. *See id.* at 1264.

As Lilly points out, that testimony regarding PDE5 inhibitors does not establish whether those common physical structures "will cause such an interaction [with PDE5] to occur either potently or selectively." Dkt. No. 393, at 5. UroPep, however, presented sufficient evidence that a skilled artisan would be aware of a common physical structure shared by the members of that genus, and that a skilled artisan could make modifications to increase potency and selectivity. The jury was entitled to rely on that evidence, particularly in light of the fact that Lilly failed to rebut it in any meaningful way. Lilly therefore failed to meet its burden to prove invalidity on that ground by clear and convincing evidence.

B. Permissible Breadth of the Disclosure

Lilly also notes that the disclosure describes the use of selective inhibitors of PDE1, PDE4, and PDE5 for the treatment or prophylaxis of BPH and a number of other conditions related to the prostate. Lilly argues in its motion, for the first time, that the disclosure is too broad to support the narrow scope of claim 1 of the '124 patent—i.e., the use of selective PDE5 inhibitors for the treatment or prophylaxis of BPH.

1. Lilly has waived that argument. The Court will not grant a Rule 50(b) motion based on a theory that Lilly neither gave notice of in the pretrial order nor presented at trial.[8] *See* Dkt. No. 251 (pretrial order mentioned only the general written description defense); Dkt. Nos. 341-44, 346 (at no time during trial did Lilly raise such an argument in support of its written description defense). Lilly's silence deprived UroPep at trial of any opportunity to respond to that theory and develop a record in support. *See Fujifilm Corp. v. Motorola Mobility LLC,* 182 F. Supp. 3d 1014, 1038 (N.D. Cal. 2016) (denying motion for judgment of invalidity as matter of law and motion for a new trial based on an obviousness theory purportedly supported by the evidence because the defendant waived that theory by not presenting it at trial); *see also Fractus, S.A. v. Samsung Elecs. Co.*, 876 F. Supp. 2d 802, 838 (E.D. Tex. 2012) (defendant waived affirmative defense in post-trial motion by not explicitly presenting that defense at trial, "depriv[ing] [plaintiff] of any opportunity to substantively respond with its own testimony or evidence"); *Allergan v. Barr Labs., Inc.*, 808 F. Supp. 2d 715, 735 (D. Del. 2011) (because "defendants clearly present a different theory of obviousness post-trial than was presented at trial," that new argument was waived; defendants could not "switc[h] horses by combining pieces of testimony . . . into new obviousness theories," thereby depriving plaintiff of the opportunity "to mount a defense at trial to the [new obviousness] theories"). Lilly has waived that argument as a basis for the current motion, and as a basis for appeal. *See Interactive Gift Exp., Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1346-47 (Fed. Cir. 2001) ("[A] party's argument should not be a moving target" but "should be consistent,

[8] Nor did Lilly make that argument in its earlier motion for summary judgment based on lack of written description. *See* Dkt No. 120.

thereby ensuring a clear presentation of the issue to be resolved, an adequate opportunity for response and evidentiary development by the opposing party, and a record reviewable by the appellate court that is properly crystallized around and responsive to the asserted argument.").

Lilly complains that its failure to raise that defense was due to the Court's having urged Lilly to make its oral Rule 50(a) arguments "in bite-size form." Dkt. No. 346, Trial Tr. at 1391. The Court, however, did not cut counsel off nor prevent Lilly from raising its new theory. *Cf. Blackboard, Inc. v. Desire2Learn, Inc.*, 574 F.3d 1371, 1380 (Fed. Cir. 2009) (noting that the defendant's Rule 50(a) motions were cursory and the court quickly took them under advisement, but that the defendant preserved the arguments because "it [was] clear from the context that neither the court nor [the plaintiff's] attorneys needed any more enlightenment about [the defendant's] position on those issues."). Even though Lilly had given no indication at trial that it was relying on any theory of invalidity based on an overbroad disclosure, Lilly nonetheless chose to move on its written description defense based solely on the statement: "The Rule 50 motion would be also on written description, that the evidence meets the clear and convincing evidentiary standard to show that the inventors did not possess the full scope of the claim." Dkt. No. 346, Trial Tr. at 1392. Although Rule 50(b) is construed liberally, such a general statement is not sufficient to provide notice to UroPep of Lilly's entirely new theory. *See Navigant Consulting, Inc. v. Wilkinson*, 508 F.3d 277, 288 (5th Cir. 2007) (court "may excuse 'technical noncompliance' when the purposes of [Rule 50(a)] are satisfied," which are "to enable the trial court to re-examine the question of evidentiary insufficiency as a matter of law if the jury returns a verdict contrary to the movant, and

to alert the opposing party to the insufficiency before the case is submitted to the jury."); *see also Blackboard*, 574 F.3d at 1379-80 (purpose of Rule 50(a) is "to alert the court to the party's legal position and to put the opposing party on notice of the moving party's position as to the insufficiency of the evidence.") (citing *Navigant*, 508 F.3d at 288-89). Lilly therefore waived its post-trial argument that the disclosure is too broad to support claim 1.

2. Setting aside the waiver issue, Lilly's argument fails on the merits. According to Lilly, the patentees did not appreciate the utility of using selective PDE5 inhibitors to treat BPH in July of 1997; therefore, the patentees failed to adequately disclose that narrowed invention, which is the subject of claim 1 of the '124 patent. Specifically, Lilly complains that the disclosure does not differentiate among the utility of inhibiting PDE1, PDE4, or PDE5 for any of the listed conditions, including BPH. *See* Dkt. No. 393, at 13. Lilly is wrong.

The original disclosure—shared by the PCT application, the '061 patent, and the '124 patent—describes the invention as the use of selective inhibitors of PDE1, PDE4, or PDE5 for treating BPH and other prostatic diseases. The first two paragraphs describe the condition of BPH and prior art methods of treatment. '124 patent, col. 1, ll. 9-31. The next two paragraphs set forth the biological mechanism of inducing smooth muscle relaxation in the prostate, which prior art methods had unsuccessfully targeted. *Id.*, col. 1, ll. 32-52. The disclosure then explains how PDEs work in the body generally, and posits that targeting PDEs may prove successful if such PDEs are present and functional in the prostate. *Id.*, col. 1, line 53 through col. 2, line 5. Finally, the subsequent two paragraphs discuss the inventors' work in discovering that

PDE1, PDE4, and PDE5 are present and functional in the prostate; that selective inhibitors of those PDEs would allow for relaxation of prostatic tissue; and therefore that selective inhibitors of those PDEs would be effective for the prophylaxis and treatment of BPH and other prostatic diseases. *Id.*, col. 2, ll. 6-28; *see also id.*, col. 7, ll. 11-34 (describing experiments showing the effectiveness of the use of selective inhibitors of PDE1, PDE4, and PDE5).

Lilly points to a later portion of the specification, where the patentees lay out multiple embodiments of the invention:

> Surprisingly, it has now been found that [PDE1], [PDE4] and [PDE5] are of particular importance in human prostatic muscles . . . . A well-aimed inhibition of those [PDE1, PDE4, and PDE5] isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, in particular vessels, being observed. Therefore, [those PDE] isoenzymes have an excellent efficiency in the treatment of prostatic diseases.
>
> Therefore, the subject matter of the invention is the use of specific inhibitors of [PDE1], [PDE4] and [PDE5] in the prophylaxis and treatment of prostatic diseases, in particular benign prostatic hyperplasia [BPH], the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of

> urine), prostatism, instabilities of the bladder muscles, [and] impotence.

'124 patent, col. 2, ll. 11-24. Lilly complains that the written description requirement is not satisfied because the original disclosure does not "provide sufficient detail to identify and describe the invention later claimed"—i.e., the use of selective PDE5 inhibitors (versus selective PDE1 or PDE4 inhibitors) for the treatment of BPH (versus other prostatic diseases). Dkt. No. 375, at 12. Thus, Lilly contends, the disclosure does not provide sufficient "blaze marks" directing the choice of PDE5 inhibitors to treat BPH. *See Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367 (Fed. Cir. 2011) ("[I]n the absence of blaze marks 'as to what compounds other than those disclosed as preferred, might be of special interest[,] . . . simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-gen[era].") (internal quotation marks omitted).

It is enough that the disclosure specifically identifies, among other various options, the use of selective PDE5 inhibitors for the prophylaxis or treatment of BPH.[9] For that reason, the disclosure in this case is unlike the disclosures in any of the cases cited by Lilly. *See Novozymes A/S v. DuPont Nutrition Bioscis. APS*, 723 F.3d 1336, 1348 (Fed. Cir. 2013) (specification "contained no disclosure of any variant that actually satisfies the claims, nor is there anything to suggest that [the patentee] actually

[9] The disclosure goes much farther than that. The specification singles out BPH by extensively describing that condition and explaining how specific PDE inhibitors, in particular, may be used to effectively treat BPH by relaxing the prostatic muscles. *See* '124 patent, col. 1, line 9 to col. 2, line 16.

possessed such a variant at the time of filing."); *Boston Sci. Corp.*, 647 F.3d 1353, 1367-69 (disclosure did not support claims to subgenus of "macrocyclic triene analogs of rapamycin," because the disclosure identified only the larger genus of "analogs of rapamycin," did not mention or provide any guidance toward the subgenus, and the knowledge of skilled artisans did not fill in the gaps, as no such analogs were known in the art); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570-71 (Fed. Cir. 1996) (claim to a subgenus was not adequately supported by the disclosure of a larger genus, without mention of or guidance toward the subgenus); *In re Ruschig*, 379 F.2d 990, 994 (Fed. Cir. 1967) (disclosure encompassed over half a million compounds but never identified, nor provided guidance toward, the one particular compound specifically named in a later-added claim).

It is common for patentees to disclose a range of possible embodiments, as the '124 patent's disclosure does. Contrary to Lilly's contention, a patentee need not indicate that one embodiment is "of special interest" in order to claim it. Dkt. No. 375, at 14; *see also* Dkt. No. 393, at 11 (Lilly complains that disclosure does not establish "primacy" of PDE5). Indeed, UroPep might have added other claims directed to the use of selective PDE1 inhibitors for the treatment of BPH, or to the use of selective PDE4 inhibitors for the treatment of another prostatic disease. A patentee is free to selectively claim one particular embodiment without running afoul of the written description requirement.

Lilly makes much of the fact that the disclosure does not expressly identify a selective inhibitor of PDE5 (an inhibitor 20 times more selective for PDE5 than for PDE1 through PDE4), and the fact that "the disclosure does not

describe actually using any such selective [PDE5] inhibitors to effectively treat BPH specifically." Dkt. No. 393, at 11. Neither fact is fatal, however, because the disclosure describes both selective PDE5 inhibitors and their effect in relaxing prostatic tissue to treat BPH.

The specification lists "[p]referred selective inhibitors" of PDE1, PDE4, and PDE5, and the undisputed evidence at trial demonstrated that at least four compounds in that list were known before July 1997 to be selective PDE5 inhibitors. Dkt. No. 342, Trial Tr. at 314-15 (sildenafil, MY5445, and zaprinast—compounds (a), (c), and (g) in the specification—were known selective PDE5 inhibitors); Dkt. No. 344, Trial Tr. at 1260-61, 1265-66 (compound E4021—compound (d) in the specification—was a known selective PDE5 inhibitor); *see also* Dkt. No. 343, Trial Tr. at 710-11 (a number of quinazoline compounds—within the class of compounds (k) in the specification—were known to inhibit PDE5); Dkt. No. 343, Trial Tr. at 723, 740 (sildenafil was a known selective PDE5 inhibitor and is a pyrazolopyrimidone that falls within the class of compounds (l) in the in the specification). It was also undisputed that a person of skill in the art at the time of the invention would know of hundreds of selective PDE5 inhibitors, and that several PDE5 inhibitors were already in human clinical trials, *see* Dkt. No. 342, Trial Tr. at 315-318; Dkt. No. 343, Trial Tr. at 792-93; Dkt. No. 344, Trial Tr. at 1254, 1293-94.

The specification also discusses experiments that showed that selective inhibitors of PDE1, PDE4, and PDE5 in fact relaxed prostatic tissue. '124 patent, col. 7, ll. 11-34 (describing experiments and conclusions); *see also id.*, col. 7, ll. 35-37 & col. 8, ll. 5-16 (explaining that an

inhibitor must be 20 times as selective for the PDE of interest—e.g., PDE5—to be "suitable for the purpose according to the invention."). Those experiments therefore demonstrated that selective inhibitors of PDE1, PDE4, and PDE5 could be used to effectively treat BPH. *See id.*, col. 1, ll. 20-24 (noting that prior art showed that BPH can be treated by inducing relaxation of prostatic muscle cells); *id.*, col. 2, ll. 11-16 ("A well-aimed inhibition of these isoenzymes [PDE1, PDE4, and PDE5] will result in relaxation of the prostatic muscles"; "therefore, [those selective inhibitors] have an excellent efficiency in the treatment of prostatic diseases" such as BPH.).

Lilly does not explain why the specification must describe the use of a PDE5 inhibitor for the treatment of BPH in a human clinical trial in order to satisfy the written description requirement, and the Court sees no reason to hold that it must. The evidence at trial indicates otherwise. *See* Dkt. No. 342, Trial Tr. at 527-38 (in the context of enablement, Lilly's expert admits that "[h]uman studies would not be necessary" for a person of skill to practice the full scope of the invention); Dkt. No. 344, Trial Tr. at 1295 (UroPep's expert says the same); *see also id.* at 1297-98 (human clinical data was available in 1997 for the selective PDE5 inhibitors sildenafil and zaprinast, although not for the treatment of BPH). More importantly, in addition to the lack of evidence presented by Lilly on that score, there was sufficient evidence that a person of skill, upon reading the disclosure, would understand that the administration of selective PDE5 inhibitors could be used to treat BPH by relaxing the prostatic muscle tissue. *See* '124 patent, col. 1, ll. 20-24; *id.*, col. 2, ll. 11-16; *id.*, col. 7, ll. 11-37; *id.*, col. 8, ll. 5-16; *see also* Dkt. No. 341, Trial Tr. at 166-68 (describing tissue bath experiments showing prostate tissue relaxation reported in the '124 patent).

Even if the jury had been presented with Lilly's waived argument, the jury could reasonably have determined that Lilly failed to meet the high standard of clear and convincing evidence for finding claim 1 of the '124 patent invalid based on the lack of an adequate written description of the invention.

C. Exclusion of Eight Compounds from Claim 1

Lilly next argues that the patent is invalid because the disclosure does not explain why particular compounds were expressly excluded from claim 1, while other compounds were not. According to Lilly, the disclosure must explain any negative limitation in a claim, and a failure to do so renders the patent invalid for lack of an adequate written description.[10] That is not the law.

As discussed previously, patentees are free to claim certain embodiments while excluding others. *Inphi*, 805 F.3d at 1355 ("It is for the inventor to decide what bounds of protection he will seek."). One reason a patentee may choose to exclude particular compounds is to avoid a double patenting rejection, and the patentee is not required to explain that reason in the disclosure. *E.g.*, *In re Johnson*, 558 F.2d at 1019 (excluding two compounds from the claim to avoid reading on a lost interference count, without explaining as much in the patent); *see also Inphi*, 805 F.3d at 1355 (a disclosure does not need to explain the reason; it is enough that the specification "properly describ[e] alternative features of the patented invention" to indicate that the patentees "are merely excising the inventions of another, to which they are not entitled."). As

[10] The Court has already addressed that argument in detail in a post-trial memorandum opinion. *See* Dkt. No. 359, at 10-13.

the prosecution history makes clear, the patentees expressly excluded eight compounds from claim 1 of the '124 patent in order to avoid a double-patenting rejection based on the inventors' earlier '061 patent. *See* Dkt. No. 106-8, at 63-64.

Lilly next contends that avoidance of a double-patenting rejection cannot be the reason for the negative limitation in claim 1 of the '124 patent, because claim 3 of the '061 patent includes zaprinast, which is not excluded from claim 1 of the '124 patent.[11] Lilly complains that "there is no explanation for why zaprinast was not excluded." Dkt. No. 375, at 26. According to Lilly, the failure to exclude zaprinast shows that claim 1 is an "arbitrary dissection of a unitary invention [that] the written description requirement prohibits." *Id.* at 27.

The written description requirement contains no such prohibition. *See Inphi*, 805 F.3d at 1355; *see also, e.g.*, Santarus, 694 F.3d at 1351 ("Th[e] exclusion narrowed the claims, as the patentee is entitled to do.") (citing MPEP § 2173.05(i)); *In re Johnson*, 558 F.2d at 1019. What is prohibited is a negative limitation that is contrary to the thrust of the invention. For example, in *In re Bimeda Research & Development Ltd.*, 724 F.3d 1320, 1323 (Fed Cir. 2013), the invention was a "non-antibiotic approach"—no use of anti-infectives—to preventing mastitis, or udder inflammation, in cows. Claim 32 specifically excluded the

[11] The prosecution history clearly disproves Lilly's theory. After the examiner's rejection, the patentees responded that the double-patenting "rejection is overcome by the instant amendment, which excludes from the present claims [of the application issued as the '124 patent] every compound (i.e., PDE inhibitor) recited in the patented claims [of the '061 patent] for 'treating . . . benign prostatic hyperplasia.'" Dkt. No. 106-8, at 115.

anti-infective agent acroflavine, suggesting that other similar anti-infectives could be used instead of acroflavine. That suggestion made no sense, since the invention was to avoid the use of anti-infectives. *See id.* (disclosure was "generally inconsistent with a formulation which, like claim 32, excludes acriflavine but could include antibiotics," i.e., other anti-infectives).

By contrast, the exclusion of the eight compounds in claim 1 of the '124 patent suggests that other PDE5 inhibitors could be used. That is consistent with the disclosure and exactly what the patentees intended. Moreover, Uro-Pep presented expert testimony that a person of skill would not be confused by those specific exclusions. *See* Dkt. No. 344, Trial Tr. at 1283-84.

The point is that a patentee can choose to claim any particular embodiments identified in the specification and exclude others, without explanation, as long as the claim does not indicate to persons of skill that it covers embodiments inconsistent with, and therefore unsupported by, the disclosure. As stated by the court in *In re Johnson*, 558 F.2d at 1019:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.

For those reasons, the negative limitation in claim 1 does not entitle Lilly to judgment as a matter of law or the grant of a new trial.

III. Enablement

The enablement requirement of 35 U.S.C. § 112, ¶ 1 derives from the same provision as the written description requirement:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112 ¶ 1 (2006). For purposes of enablement, that clause has been interpreted to require that a person of skill in the art, upon reading the disclosure, be able to practice the full scope of the claim without undue experimentation. *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1359-60 (Fed. Cir. 1998); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Like the written description requirement, the enablement requirement is viewed from the perspective of one of ordinary skill in the art. *See Johns Hopkins*, 152 F.3d at 1360 ("[I]t is imperative when attempting to prove lack of enablement to show that *one of ordinary skill in the art* would be unable to make the claimed invention without undue experimentation."). "'Furthermore, the test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides

a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.'" *Id.* (quoting *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996)) (alteration in original). "Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim[]." *In re Wands*, 858 F.2d 737.

Whether a disclosure fails to satisfy the enablement requirement is a question of law based on underlying factual findings. *Alcon Research*, 745 F.3d at 1188. It is the challenger's burden to prove lack of enablement by clear and convincing evidence. *Id.*

In its motion, Lilly essentially reargues the disputed case that was tried to the jury. Lilly's primary contention is that the jury should not have credited UroPep's expert's testimony regarding the routine nature of the experimentation referred to in the patent that would be required to determine whether a compound is 20 times more selective for PDE5 as compared to PDE1 through PDE4, and whether that compound could be administered to an individual to treat BPH. But Dr. Bell's testimony was detailed, credible, and supported by published research. His testimony was also supported by personal experience: Dr. Bell worked at Pfizer and discovered the selective PDE5 inhibitor sildenafil in the 1980s. *See* Dkt. 342, Trial Tr. at

293. The jury was entitled to credit his opinion over that of Lilly's expert.

For example, in determining whether a group of promising compounds were selective PDE5 inhibitors, Dr. Bell testified that it took a few weeks to screen half a million compounds. Dkt. 344, Trial Tr. at 1282-83. He also explained that drug companies, including Pfizer, would "routinely" screen their massive collections for such purposes. *Id.*; *see also* Dkt. No. 343, Trial Tr. at 729 (Lilly's expert, Dr. Rotella, identified the same screening he did at Bristol-Myers Squibb). Furthermore, Dr. Bell testified that the field was mature, and that a skilled artisan would not necessarily need to conduct any screening but could "use their own [PDE5 inhibitor] if they've got one already." Dkt. No. 344, Trial Tr. at 1295; *see also id.*, Trial Tr. at 1283 (stating that Pfizer did not need to screen its collection of compounds in 1997 "because we already had sildenafil").

Dr. Bell also discussed the methods expressly incorporated in the '124 patent to separate PDE isoenzymes and discern inhibitor selectivity. He testified that Pfizer used those methods of determining selectivity, termed "fractionation methods," when working on sildenafil. Dkt. No. 344, Trial Tr. at 1284-85 (referring to the Galwan and Nicholson articles in the '124 patent, col. 7, ll. 38-39). In addition, Dr. Bell pointed to other publications using those fractionation methods. *See, e.g.*, Dkt. No. 344, Trial Tr. at 1285. He stated that "[i]t was the standard method that was being used particularly in the [pharmaceutical] industry at the time." *Id.*

Lilly argues that those selective PDE5 inhibitors may not be sufficiently potent or otherwise effective to treat BPH (for example, by being insufficiently bioavailable).

Dkt. No. 375, at 32, 34-35. But Dr. Bell testified that the methods described in the '124 patent to identify potent and selective PDE5 inhibitors "are very common and are commonly used throughout the industry." Dkt. No. 344, Trial Tr. at 1284 (referring to the '124 patent, col. 7, line 11 through col. 8, line 16); *see also* Dkt. No. 344, Trial Tr. at 1274 (explaining that the standard industry practice to determine potency was to measure the so-called IC50 values, the same values referred to in the '124 patent, col. 8, ll. 5-7).

Beyond selectivity and potency, Lilly contends that the claim limitation regarding an effective amount of a PDE5 inhibitor to treat BPH is not enabled. But Dr. Bell clarified that skilled artisans would "simply have to do what we call routine dose ranging" in order "to determine what effective amount of a PDE5 inhibitor was needed to treat BPH." Dkt. No. 344, Trial Tr. at 1294; *see also Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 923 (Fed. Cir. 2011) ("Enablement is not negated if a reasonable amount of experimentation is required to establish dosages and formulation of an active ingredient."). Meanwhile, Lilly presented no competing evidence at trial that "any potent PDE5 inhibitor [was] dose-range studied and [did] not effectively treat[] BPH." Dkt. No. 344, Trial Tr. at 1298; *see also Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x at 922 (no enablement problem where "[t]here was no evidence that known procedures for determination of dosages and formulation did not apply," and distinguishing *ALZA Corp. v. Andrx Pharmaceuticals LLC*, 603 F.3d 935 (Fed. Cir. 2010), where "the field of ascending release dosage forms [w]as 'not mature' and 'a breakaway' from the prior art") (quoting *ALZA Corp.*, 603 F.3d at 941).

Finally, Lilly points to testimony from its experts, Drs. Rotella and Roehrborn, that the patent's working examples of oral formulations and injections "are confused, nonsensical and almost certainly non-workable to demonstrate enablement of an effective amount of a selective [PDE5] inhibitor to treat BPH." Dkt. No. 375, at 35. The jury, however, was entitled to accept Dr. Bell's testimony over that of Lilly's experts. *See* Dkt. No. 344, Trial Tr. at 1297 (Dr. Bell: In general, oral formulation in drug development was routine and "probably one of the most easy formulations to achieve"; in particular, skilled artisans would already know of available oral formulations of PDE5 inhibitors and published data, as some inhibitors were already in clinical trials.).[12]

In attacking the '124 patent's disclosure, Dr. Bell's testimony, and UroPep's other evidence, Lilly makes several fundamental errors regarding the enablement requirement. Lilly argues that undue experimentation would be required for one artisan to synthesize all members of the genus of selective PDE5 inhibitors. Dkt. No. 375, at 31-32. That is not the correct inquiry. A patent must enable a skilled artisan to practice the full scope of the invention; it does not need to ensure that a skilled artisan can practice the entire scope of the invention within a short period of time. *See In re Wands*, 858 F.2d 731, 739 (noting that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics," among

[12] Indeed, Lilly's expert Dr. Roehrborn published articles about the efficacy of PDE5 inhibitors to treat BPH, relying on the work of one of the inventors, Dr. Ückert. *See* Dkt. No. 342, Trial Tr. at 609 (Dr. Roehrborn's article cites Dr. Ückert's 2001 article, which reports results from the tissue strip experiments referenced in the '124 patent).

other process steps, and that the patentee's success in developing candidates through this procedure "indicates that . . . the amount of effort needed to obtain such antibodies is not excessive"). Such a rule would invalidate all broad claims for lack of enablement.

Lilly also fails to appreciate the distinction between what is required to practice the invention and what is required for FDA approval of a selective PDE5 inhibitor as a drug to treat BPH. *See Kemin Foods, L.C. v. Pigmentos Vegetales Del Centro S.A. de C.V.*, 464 F.3d 1339, 1350 (Fed. Cir. 2006) (rejecting the argument that the claim term "'no traces of toxic chemicals' should be interpreted as limiting the claim to products in which the levels of all chemicals are below the toxic thresholds set by the [FDA]," because "[n]either the patent nor our claim construction . . . makes any reference to toxicity thresholds, whether promulgated by the FDA or otherwise."); *see also Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 435 F. App'x 927, 934-35 (Fed. Cir. 2011) (refusing to limit a claim covering a pharmaceutical composition "to those compositions that are 'safe, effective, and reliable for use in humans'" because "[t]he specification does not require this restrictive construction, nor is this property necessary for patentability."); *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) ("human trials are not required for a therapeutic invention to be patentable"). In its motion, Lilly repeatedly refers to the work that Lilly did to develop Cialis and obtain FDA approval. But that amount of experimentation, whether "undue" or not, is far beyond the amount of experimentation required to practice the scope of claim 1 of the '124 patent. *See* Dkt. No. 344, Trial Tr. at 1295 (Dr. Bell's opinion that claim 1 does not require the amount of experimentation necessary to satisfy FDA approval standards).

More generally, Lilly argues that the '124 patent does not include a variety of other tests and data showing that the invention works. *See* Dkt. No. 375, at 33-36. But the standard for enablement does not require a particular kind of confirmatory evidence or, depending on the facts of the case, any confirmatory evidence at all. *See Alcon Research*, 745 F.3d at 1189-90 ("[W]e have rejected enablement challenges based on the theory that there can be no guarantee that the prophetic examples actually work"; "it is irrelevant here, as a legal matter, whether the. . . patents contain data proving that PECOs enhance the chemical stability of prostaglandins."). The patentees do not need to disclose data showing that any particular selective PDE5 inhibitor treats BPH; rather, the patentees merely need to enable a skilled artisan to practice the invention of using a PDE5 inhibitor to treat BPH. And while Lilly complains that its experts testified that BPH "is indisputably 'complex,' 'poorly defined,' 'highly variable,' and 'complicated,'" Dkt. No. 393, at 16, the jury was not required to credit that testimony. The '124 patent's disclosure specifies the mechanism by which PDE inhibitors work, how those inhibitors may be used to relax smooth muscle tissue, and how relaxation of prostatic smooth muscle tissue to treat BPH was known in the prior art. '124 patent, col. 1, line 9 through col. 2, line 5. Given that evidence, a reasonable jury could have found that claim 1 was sufficiently enabled regarding the use of PDE5 inhibitors to treat BPH.

UroPep points out in its response that there was evidence at trial supporting each of the factors identified in *In re Wands*, 858 F.2d at 728, that bears on enablement. UroPep's evidence showed that the quantity of experimentation necessary was routine; that the specification provided direction and guidance in light of the description,

incorporated references, and the knowledge of persons of skill in the art; that the specification provides working examples; that the nature of the invention was the administration through traditional means of well-understood compounds as a novel method of treatment; that the state of the prior art was well developed and far out of its infancy; that the level of skill of those in the art was high; that the art showed that the mechanism of PDEs was known, that the research field regarding selective PDE5 inhibitors was mature, and that the relaxation of prostatic tissue would predictably treat BPH; and that claim 1 of the '124 patent, although broad, was nonetheless narrowed to a particular embodiment. *See* Dkt. No. 385, at 26-36.

Lilly makes the additional argument that this case is controlled by *Wyeth v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013), in which the Federal Circuit held certain claims invalid for lack of enablement. But Lilly's comparison of the facts in this case to the facts in *Wyeth* is faulty, as Lilly assumes facts that the jury was not required to find. For one, Lilly states that PDE5 inhibitor research was "an unpredictable and poorly understood field." *Wyeth*, 720 F.3d at 1386. UroPep presented ample evidence to the contrary. Lilly then states that the '124 patent provides no guidance as how to treat BPH and evaluate that treatment. Dkt. No. 375, at 30-31. UroPep, however, introduced evidence that such guidance was found both in the patent and in the prior art, and that procedures for such measurements were both incorporated in the patent and well understood—indeed, routine—in the art. Finally, Lilly argues that running the assays for a single compound would take weeks and thus constituted "undue experimentation" under the court's decision in *Wyeth*. 720 F.3d at 1386. In that regard, Lilly notes that it spent

10 years to obtain FDA approval for Cialis. But, once again, FDA approval is not required to enable a patent claim to a medicinal compound or a method of treatment. And, as the court in Wyeth observed, "[u]ndue experimentation is a matter of degree. Even a considerable amount of experimentation is permissible as long as it is merely routine or the specification provides a reasonable amount of guidance regarding the direction of experimentation." *Id.* at 1385-86 (internal citations and quotation marks omitted). In the context of a disclosure and a field that provides no guidance, aimless plodding through systematic experimentation of a single compound that would take weeks may be undue. *See id.* at 1386. By contrast, the '124 patent guides a practitioner to preferred selective PDE5 inhibitors and routine methods of evaluating and developing other inhibitors, in the already well-developed field of PDE5 inhibitor research.

Lilly has not shown it is entitled to judgment as a matter of law, nor has it shown that the "great weight of the evidence" is in its favor on the issue of enablement such as to justify the grant of a new trial.

IV. Obviousness

Lilly contends (in some tension with its position on the written description requirement and enablement) that everything of substance that was disclosed in the '124 patent was known in the prior art, and that claim 1 of the patent must be held invalid for obviousness as a matter of law. In particular, Lilly notes that it was known before the '124 patent that relaxing smooth muscle tissue in the prostate can help ameliorate urination difficulties and that PDE inhibitors can relax smooth muscle tissue by re-

ducing the digestion of cAMP and cGMP by PDE enzymes. According to Lilly, it would have been obvious to a person of skill in the art, knowing what was known in the prior art at the time of the invention, to conclude that a PDE5 inhibitor would be useful in the treatment or prophylaxis of BPH.

In light of the burden on Lilly to show obviousness by clear and convincing evidence, the jury was entitled to find from the evidence at trial that claim 1 of the '124 patent would not have been obvious. Dr. Ückert testified (and Lilly does not dispute) that the inventors discovered PDE1, PDE4, and PDE5 in the prostate. After conducting experiments designed to identify the functional relevance of PDE enzymes in the prostate, the inventors determined that PDE5 inhibition relaxes prostatic smooth muscle tissue, and that PDE5 inhibitors could treat the signs and symptoms of BPH. Dkt. No. 341, Trial Tr. at 162-70; *see also* Dkt. No. 342, Trial Tr. at 309.

In addition to Dr. Ückert's testimony, Dr. Bell testified that it was impossible to predict in advance which PDEs would be present in which organ, or what role, if any, a particular PDE would play in that organ. Dkt. No. 344, Trial Tr. at 1285. The jury also heard objective evidence of non-obviousness relating to the commercial success that flowed from the use of PDE5 inhibitors to treat BPH.

In its argument to the contrary, Lilly contends that in view of the state of the art at the time of the invention, a reasonable jury would have been compelled to find the invention invalid for obviousness. That is particularly so, according to Lilly, because the '124 specification discloses that the prior art had discovered the mechanism of PDEs

in smooth muscle, the role of PDE inhibitors, and the fact that relaxing smooth muscle would treat BPH.

The problem with that argument is that Lilly has failed to show that it was obvious to use a selective inhibitor of PDE5 to treat BPH. At the time of the invention, it was not known that PDE5 was even present in the prostate. *See* Dkt. No. 341, Trial Tr. at 161-62. Furthermore, other research showed that PDE5 was not particularly relevant in the bladder, which, like the prostate, is part of the urogenital tract. *See id.*, Trial Tr. at 161. It was the inventors of the '124 patent who performed experiments and discovered that PDE5 was present and functionally relevant in prostatic tissue. Based on that discovery, they used the knowledge in the prior art to come up with a novel method of treating BPH.

Given what was known in the prior art, Lilly did not show that it would have been obvious to consider using PDE inhibitors to relax prostatic tissue, and that it would have been obvious to use selective inhibitors of PDE5 to treat BPH. Moreover, the prior art reference on which Lilly principally relies for its obviousness argument, a 1995 article by Arthur L. Burnett, DX 1245, did not describe the use of a selective PDE5 inhibitor to treat BPH, that PDE5 was found in the prostate, or even that PDE5 should be investigated. *See* Dkt. No. 342, Trial Tr. at 507. In fact, Dr. Bell testified at trial that the Burnett article taught away from the presence and role of PDE5 in the prostate. Dkt. No. 344, Trial Tr. at 1290-92. Dr. Bell explained that the analysis in the article pointed to PDE3 inhibition, rather than PDE5 inhibition, as being potentially relevant in the prostate.

Lilly invokes the Federal Circuit's decision in *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007), in support of its obviousness argument, but that case is quite different from this one. In PharmaStem, the prior art references had inferred that the concentration of stem cells in umbilical cord blood was much greater than in adult blood. The court therefore rejected the patent holder's argument that the inventors had discovered that stem cells are present in high concentrations in cord blood. The inventors merely provided experimental confirmation of what the prior art references had inferred. The court held that to be insufficient to avoid a finding of obviousness. 491 F.3d at 1362-63. In this case, there was no equivalent finding or suggestion in the prior art that PDE5 was found in the prostate or what functional role PDE5 would play in the prostate. Given the state of the evidence as to what was taught and what was not taught in the prior art, the Court concludes that substantial evidence supports the jury's conclusion that Lilly failed to prove by clear and convincing evidence that the claimed invention would have been obvious to a person of skill in the art as of the priority date of the '124 patent.

V. Anticipation

Continuing its march through each of the defenses recognized by title 35, Lilly next argues that the jury improperly rejected its defense that claim 1 of the '124 patent was anticipated by a prior art reference that was introduced at trial. In making that argument, Lilly again faces an exacting standard: It must show that a rational jury could not have found that Lilly failed to prove the factual defense of anticipation by clear and convincing evidence. *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d

967, 975 (Fed. Cir. 2010). The evidence Lilly points to does not come close to satisfying that standard.

The putatively anticipating reference is a monograph by Dr. C.S. Cheung, a practitioner of traditional Chinese medicine. Brian LaForgia, one of Dr. Cheung's associates, testified at trial that Dr. Cheung made his monographs available to interested persons through a catalog that was mailed to acupuncturists and other persons interested in Dr. Cheung's work. Dkt. No. 343, Trial Tr. 885-87. Lilly made no showing that Mr. LaForgia, or acupuncturists in general (absent other training or experience), qualify as persons of skill in the art for purposes of the '124 patent. *Id.*, Trial Tr. at 898.

The reference Lilly highlighted at trial was a self-published 107-page monograph entitled "TCM Management Benign Prostate Hyperplasia Long Bi (Prostatism)," which pertained to the treatment of BPH. Dkt. No. 343, Trial Tr. at 882-85. Mr. LaForgia testified that the monograph was listed in Dr. Cheung's catalogs from 1995 and 1996, and that in late 1994 or early 1995 he saw the monograph in the library of an organization known as the American College of Traditional Chinese Medicine in San Francisco. Mr. LaForgia said that the American College of Traditional Chinese Medicine had been formed by Dr. Cheung and two other doctors. *Id.*, Trial Tr. at 886-91. Mr. LaForgia admitted that he had no idea how books were cataloged in that library. *Id.*, Trial Tr. at 900-01. In fact, there was no evidence at trial that the books were cataloged at all.

Lilly's theory of anticipation was based on the portion of 35 U.S.C. § 102(b) that relates to an anticipating printed publication. *See* 35 U.S.C. § 102(b) (2006). That portion of the statute reads as follows: "A person shall be entitled

to a patent unless—the invention was patented or described in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States."[13] The Court allowed the anticipation defense to go to the jury, but the jury found that the Cheung monograph did not anticipate claim 1 of the '124 patent.

In order to satisfy the requirements of section 102(b), a party challenging a patent on "printed publication" grounds must show that the allegedly invalidating publication contains "each and every element of [the] claimed invention." *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987); *see generally PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1243 (Fed. Cir. 2002). In addition, the printed publication must have been in the public domain more than a year before the priority date of the application, which in this case means before July 9, 1996. *See SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008). The Court concludes that it was reasonable for the jury to reject Lilly's anticipation defense in this case, based on findings either (1) that the evidence did not establish that the Cheung reference contained all the limitations of claim 1 of the '124 patent, or (2) that the Cheung reference was not in the public domain before July 9, 1996.

A. Anticipation by Cheung

The Cheung monograph contains a brief report of a study (not conducted by Dr. Cheung) in which 34 subjects

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[13] In 2011, section 102(b) was amended and recodified as part of the Leahy-Smith America Invents Act ("AIA"). Because the application that matured into the '124 patent was filed prior to March 16, 2013, the pre-AIA version of section 102(b) applies to this case. *See* AIA, 125 Stat. 284, 293 (2011).

were administered a "basic formula" containing a variety of herbs, including Horny Goat Weed. Horny Goat Weed, also known as epimedii, is an herb that contains a small amount of icariin, a known PDE5 inhibitor. Lilly contends that the Cheung reference described all 34 subjects as having been given Horny Goat Weed and that the study proved that the Horny Goat Weed ingested by the subjects was responsible for an improvement in BPH symptoms in most of the subjects. The Cheung reference, however, is not at all clear on that point, for several reasons.

First, in the reported study the subjects were given a variety of herbs. It was therefore unclear that icariin was the component that was responsible for the improvement in symptoms reported by most of the subjects. Lilly's expert, Dr. Claus Roehrborn, conceded that "it is possible that there are some compounds in the other herbs having an effect on the prostate or the symptoms." Dkt. No. 342, Trial Tr. at 573.

Second, the description of the composition given to the subjects did not make it clear that all of the subjects received icariin, since it appears from the Cheung reference that Horny Goat Weed was an optional, not a mandatory, ingredient in the formulation given to the subjects. Dr. Roehrborn testified that the fact that Horny Goat Weed was listed as an ingredient in one of the two formulations that were administered to subjects in the study reported by Cheung indicates that at least some of the subjects received a formulation containing Horny Goat Weed. While that may be true, Dr. Roehrborn did not testify, and the evidence did not clearly establish, that Horny Goat Weed was found in the formulation that was given to *any* of the subjects who reported favorable results; so far as the evidence shows, Horny Goat Weed (and thus icariin) could

have been contained only in the formulations given to the subjects who did not report an improvement in their symptoms.

Finally, evidence offered by UroPep at trial showed that icariin is a far less potent PDE5 inhibitor than tadalafil. *See* Dkt. No. 344, Trial Tr. at 1249 (5 milligrams of tadalafil is equivalent to 8120 milligrams of icariin). In addition, the evidence showed that Horny Goat Weed contains, by generous estimate, only 0.5% icariin. *Id.* at 1247. Based on that evidence, UroPep's witness, Dr. Bell, testified that a patient would have to eat approximately 1.6 kilograms (3.5 pounds) of Horny Goat Weed to get the same effect as a 5 milligram dose of Cialis. *Id.* at 1250. Yet the Cheung study indicated that the amount of Horny Goat Weed ingested by the subjects of that study was only 15 grams. *See* DX 1551, at 80 (listing 15 grams of "Hb. Epimedii" as part of one of the two basic formulations used in the reported study). Based on that evidence, the jury could have concluded that the small amount of icariin in the Horny Goat Weed administered to some of the subjects in the reported study would not have been enough to have a measurable effect on the subjects' BPH symptoms, and thus would not have satisfied the "effective amount" limitation of the '124 patent.

In support of its anticipation argument, Lilly cites *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318 (Fed. Cir. 2005), which Lilly characterizes as "a case remarkably similar to this one." Dkt. No. 393, at 22. In fact, *Rasmusson* is not at all like this case. In *Rasmusson*, the prior art reference at issue taught the same method for administering the same drug that was claimed in the patent in dispute. The appellee argued that the prior art reference did not anticipate because it presented data

showing that the method did not have anti-tumor effects, while the patent contained data showing the opposite. 413 F.3d at 1326. The court held that for anticipation it was enough that the prior art reference disclosed the invention, even though the reference may not have recognized the effectiveness of the invention for the purpose later identified in the patent. This case presents a very different scenario. Based on the evidence before it, the jury could readily have found that the administration of Horny Goat Weed discussed in the Cheung monograph differed materially from the administration of PDE5 inhibitors claimed in the '124 patent in a way that prevented the Cheung composition from satisfying the limitation requiring the administration of an "effective amount" of a PDE5 inhibitor.

In light of the evidence at trial summarized above, a reasonable jury could readily have concluded that Lilly failed to prove anticipation because the Cheung reference did not entail the ingestion of enough Horny Goat Weed to have a therapeutic effect on patients' BPH. In that event, the Cheung reference would not satisfy the "effective amount" limitation of claim 1 of the '124 patent.

B. Printed Publication

As a second ground for rejecting Lilly's anticipation defense, the jury could have found that the evidence failed to show that the Cheung reference qualified as a "printed publication." To satisfy that element of section 102(b), a reference must have been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Kyocera Wireless*

Corp. v. Int'l Trade Comm'n, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

The jury could readily have found that the Cheung reference was not made available to the public by July 1996 in a manner that would have made it accessible to persons of skill in the art. Mr. LaForgia's testimony—the only evidence regarding the distribution of the Cheung monograph—did not establish that the publication was distributed or cataloged in a way that would have made it reasonably available to a person of skill in the pertinent art. Instead, his testimony indicated only that a catalog containing an advertisement of the publication—not the publication itself—was sent to persons who had expressed an interest in Dr. Cheung's work, not persons of skill in the art, and that Mr. LaForgia found the monograph in the library of Dr. Cheung's organization, the American College of Traditional Chinese Medicine. Mr. LaForgia did not know whether, or how, the publication was cataloged in that library; there was no evidence that the publication could be found in any other locations or obtained from any source except directly from Dr. Cheung; and there was no evidence that persons of skill in the relevant art frequented, or even were aware of the American College of Traditional Chinese Medicine.[14] In light of the infirmities in the "printed publication" evidence offered through Mr. LaForgia, a reasonable jury could readily have concluded that Lilly failed to prove that element of the defense of anticipation by clear and convincing evidence. *See Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998). Accordingly, Lilly's motion

[14] Prior to trial, Lilly represented that it was prepared to introduce evidence that the Cheung publication could be found in other libraries. *See* Dkt. No. 200, at 13. No such evidence was offered at trial, however.

for JMOL on anticipation must be denied. In addition, the "great weight of the evidence" does not support Lilly on anticipation, so Lilly's Rule 59 motion on that ground is denied as well.

VI. Indefiniteness

Lilly next asserts that the evidence at trial establishes that claim 1 of the '124 patent is invalid for indefiniteness. Prior to trial, Lilly argued that the Court's construction of claim 1 as requiring the "inhibitor of phosphodiesterase (PDE) V" to be at least 20 times more selective for PDE5 than for PDE1 through PDE4 rendered claim 1 indefinite. The Court treated the question of indefiniteness as a legal issue related to claim construction and rejected Lilly's indefiniteness argument. Dkt. No. 234, at 28-47; Dkt. No. 294, at 5-8.

Pointing to the trial testimony of its expert, Dr. Joseph A. Beavo, Lilly contends that the Court must revisit its pretrial ruling on indefiniteness. Contrary to Lilly's submission, however, nothing in Dr. Beavo's testimony affects the Court's determination that the "inhibitor of phosphodiesterase (PDE) V" limitation, as construed, does not render claim 1 of the '124 patent fatally indefinite.

To begin with, there is nothing "indefinite" about a requirement that a particular inhibitor be 20 times more selective for one PDE than for another. The '124 patent describes the potency of a PDE inhibitor by reference to its "IC_{50} value," which is the concentration of the PDE inhibitor necessary to inhibit 50 percent of the PDE enzyme's hydrolysis of the target substrate molecules (cAMP or cGMP). '124 patent, col. 8, ll. 5-9. The specification of the '124 patent asserts that there are "known methods" for

determining whether a compound is a PDE5 inhibitor, such as those described in two cited articles from 1989 and 1990. In addition, the patent provides, as an example, a description of the procedure used to determining the level of enzyme activity by a method known as the peak fractionation method; that description is based on a 1995 paper by Michael C. Truss et al. *Id.*, col. 7, line 38, through col. 8, line 16; *see also* Dkt. No. 343, Trial Tr. at 664-65.

It does not matter whether it was difficult, using the testing protocols that were described in the patent (and that were available as of the patent's priority date), to determine exactly the levels of activity of a particular compound vis-à-vis different PDEs. The "20 times" requirement is clear on its face. For that reason, even though Dr. Beavo was critical of the testing protocols described in the patent, Dkt. No. 343, Trial Tr. at 671-91, nothing in Dr. Beavo's testimony suggests that the "20 times" requirement is indefinite. In particular, he does not suggest that there is no way to determine whether a particular compound is 20 times as selective for one PDE than for another or that available testing methods are so unreliable that the claim 1 of the '124 patent "fail[s] to inform, with reasonable certainly, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). Thus, even if the patent had contained no description of any particular testing protocol, the "20 times" requirement would not have been invalid for indefiniteness.

Beyond that, while Dr. Beavo was critical of the protocol described in the Truss article, which discussed the use of the peak fractionation method to determine the presence of PDEs in a pig's bladder, he did not suggest that the fractionation method itself could not be used to obtain

reliable data regarding the relative effectiveness of PDE5 inhibitors. Rather, he was critical of the particular application of that method in the three articles cited in the patent. His quarrel with the Truss article was that the methodology used did not adequately separate PDE5 from other PDEs, and his quarrel with the other two articles was that they did not test for PDE5, but instead tested for other PDEs. *See* Dkt. No. 343, Trial Tr. at 691. On cross-examination, Dr. Beavo acknowledged that the peak fractionation method had been used to identify the presence of PDE5 in tissues other than a pig's bladder. *Id.*, Trial Tr. at 700-03. Whatever the validity of Dr. Beavo's criticism of the testing protocol used in the Truss paper and in the other two cited articles, Dr. Beavo's testimony does not undermine the use of peak fractionation as a method of determining the presence of PDE5, and thus as a means of determining the IC50 values of various PDE5 inhibitors.

The peak fractionation testing methodology disclosed in the three articles cited in the '124 patent may have produced different results depending on "experimental conditions," as testified by Dr. Beavo. Dr. Beavo's testimony, however, did not establish that the fractionation method described in the articles was so unreliable as to provide no guidance in determining the selectivity of particular compounds for various PDEs. To the contrary, Dr. Bell testified that the methods for testing potency and selectivity referred to in the '124 patent "are very common and are commonly used throughout the industry." Dkt. No. 344, Trial Tr. at 1284. He added that the fractionation method described in the articles cited in the '124 patent "was the standard method that was being used particularly in industry at the time" of the patent. *Id.*, Trial Tr. at 1284-85.

For that reason as well, the Court rejects Lilly's argument that Dr. Beavo's testimony established that the requirement that the PDE5 inhibitor claimed in the '124 patent had to be at least 20 times as selective for PDE5 than for PDE1 through PDE4 rendered the claims invalid for indefiniteness.

VII. Claim Constructions

In the next portion of its brief, Lilly casts the widest possible net, asserting, without specificity, that it is entitled to JMOL "based on the claim constructions given by the Court to the jury, including those constructions given over Lilly's objections." Dkt. No. 375, at 51. In addition, Lilly asserts, without supporting argument, that the Court's constructions of the terms "prophylaxis," "a person in need thereof," "effective amount," and "inhibitor of phosphodiesterase (PDE) V" were all erroneous. *Id.* at 52. Because Lilly has made no new arguments in its JMOL motion with respect to its assertions based on claim construction, the Court will not rehearse at length each of the claim construction rulings made earlier in the case.

As for the last of the claim constructions that Lilly contests, "inhibitor of phosphodiesterase V," the Court addressed Lilly's argument at length in an order filed on March 3, 2017. Dkt. No. 234, at 3-12. That discussion will not be repeated here. As for the claim terms "a person in need thereof" and "effective amount," the Court notes that Lilly offered no competing constructions for the terms; rather, Lilly simply argued that those terms were indefinite. *See* Dkt. No. 106, at 18, 22. As for the construction of the term "prophylaxis," Lilly has no ground for ar-

guing that the Court's construction was erroneous, inasmuch as the Court essentially adopted Lilly's proposed construction of that term, and Lilly agreed to the Court's construction. *Compare* Dkt. No. 115, at 5-6 (Court stating at the claim construction hearing that "Defendants have suggested that 'prophylaxis' should be construed to mean 'prevention of a disease or a process that can lead to disease.' . . . [I]f it comes to giving a jury an instruction, I think it would be very helpful to have a definition of 'prophylaxis.' So I would be inclined to give such a definition, and that seems to me as good a definition as any.") *with* Dkt. No. 346, Trial Tr. at 1412 (instructing the jury that "[t]he term 'prophylaxis' means 'prevention of the progression or development of the disease.'"); *see also* Dkt. No. 115, at 16 (Lilly's counsel arguing at the claim construction hearing that the term "prophylaxis has to include prevention," and agreeing that prevention was "clear enough" in the Court's construction of "prophylaxis"). A party "cannot be allowed to create a new claim construction dispute following the close of the jury trial," *Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 694 (Fed. Cir. 2017), particularly when the party challenges a construction that the party itself endorsed.

VIII. New Trial

In addition to arguing generally that it is entitled to a new trial on each of the grounds asserted in its JMOL motion (including some as to which the sole logical consequence of Lilly's prevailing would be the entry of judgment in Lilly's favor, not a new trial), Lilly makes a separate argument for a new trial on four different grounds.

A. The Jury Instruction on Enablement

Claim 1 of the '124 patent recites, in part, a "method for prophylaxis or treatment of benign prostatic hyperplasia." At the charge conference, Lilly requested an instruction that the '124 specification must enable a person of ordinary skill in the art to practice both the "treatment" and "prophylaxis" of BPH, and that it would not be sufficient for the patent to enable treatment alone. Dkt. No. 325, at 5-6. The Court declined to give such an instruction. Dkt. No. 346, Trial Tr. at 1396. Both at that time and in a later written order, *see* Dkt. No. 359, at 7-10, the Court explained that it denied the requested instruction on three grounds: (1) that the evidence at trial focused almost entirely on treatment; (2) that treatment and prophylaxis, as those terms were used in the patent, were largely overlapping; and (3) that a specific instruction requiring enablement of both treatment and prophylaxis could be confusing to the jury.

First, as the Court noted in its order addressing Lilly's requested instruction, there was very little discussion of the issue of prophylaxis during the course of the trial; the focus of the evidence, including the evidence supporting Lilly's invalidity defense, was on treatment. To the extent that prophylaxis was discussed at all, it was discussed in the context of treatment (such as testimony from Lilly's expert that prophylaxis included preventing a patient's BPH symptoms from becoming worse).

In support of its proposed instruction, Lilly points out in its brief, Dkt. No. 375, at 53, that Dr. Roehrborn testified that a person of ordinary skill in the art would not be able to determine the amount of a PDE5 inhibitor that would be required for the effective treatment of BPH.

Dkt. No. 342, Trial Tr. at 545. Dr. Roehrborn was then asked, "Did the ['124] patent provide any information that you can determine or a person of ordinary skill in the art can regarding the effective amount that would be given to have prophylaxis of BPH?" He responded, "No it does not." *Id.* In response to another question, Dr. Roehrborn stated: "So, prophylaxis, meaning to prevent either the disease or prevent it from getting worse, would be probably the toughest assignment because it's so variable, would take such a long time to study it, and it would take a lot of people to study it." *Id.*, Trial Tr. at 528.

Lilly points to no other evidence beyond those two conclusory statements regarding the enablement or written description issues as they pertain to prophylaxis. Instead, throughout the trial, including in other portions of Dr. Roehrborn's testimony, prophylaxis and treatment were treated together as a single process. *See* Dkt. No. 342, Trial Tr. at 546-47 (Dr. Roehrborn: "And when it comes to looking at the issue of prevention or progression, it is even more complicated because it is highly unpredictable of a thousand men, how many of them will progress and how many will the symptoms get worse. . . . So, if you want to show an effect on preventing or progression, it would take a long, long time."); *id.* , Trial Tr. at 547 (Dr. Roehrborn: "it is very difficult to define an effective amount given that the claim involves prevention, prophylaxis, and treatment").

Second, and relatedly, the terms "treatment" and "prophylaxis," as used in the '124 patent, do not describe distinct processes. In its initial claim construction order in this case, the Court acknowledged that, as UroPep's expert explained, there was "no clear distinction [drawn] between prophylaxis and treatment for BPH." Dkt. No. 131,

at 9. The Court stated that "a course of medication designed to deal with the condition could be regarded as either prophylaxis or treatment, depending on the physician's judgment as to whether the patient has BPH or merely has risk factors for BPH or has at least one of the symptoms of BPH." *Id.* The Court noted that the uncertainty as to whether therapy should be considered treatment or prophylaxis might create a categorical difficulty, but "because the patent claims at issue in this case cover both prophylaxis and treatment, the overlapping nature of the two terms is not problematical." *Id.* at 9-10.

Similarly, Dr. Roehrborn defined prophylaxis as "meaning to prevent either the disease or prevent it from getting worse." Dkt. No. 342, Trial Tr. at 527; *see also id.*, Trial Tr. at 546-47 (referring to "prevention or progression"). Given that the terms "prophylaxis" and "treatment" are largely overlapping and that Lilly made no effort at trial to suggest that they required significantly different analysis under the written description or enablement requirements, there was no need to instruct the jury that it needed to conduct a separate invalidity analysis for each term. Any such instruction would simply have been confusing to the jury in light of the manner in which the case was tried.

Finally, the instruction that Lilly sought was directed to the principle that section 112, paragraph 1, requires that the specification enable the full scope of the claim, not just a single embodiment or group of embodiments. *See Liebel-Flarsheim*, 481 F.3d 1378-79. The Court in fact gave such an instruction, directing the jury that "[t]o be valid, a patent must contain a description of the manner of making and using the invention that would enable a persons of skill in the art to make and use the full scope of the

invention without undue experimentation. Lilly contends that claim 1 of the '124 patent is invalid because the patent does not contain a sufficiently full and clear description of how to make and use the full scope of the invention. In order to invalidate the '124 patent for lack of enablement, Lilly must prove by clear and convincing evidence that the '124 patent would not have enabled such a person to make or use the full scope of the invention." Dkt. No. 346, Trial Tr. 1428; *see also id.*, Trial Tr. 1429.[15] The principle to which Lilly's proposed instruction was directed was thus already incorporated in the Court's charge, although not with the specificity that Lilly requested. Thus, nothing barred Lilly from making a specific argument to the jury as to non-enablement of prophylaxis in its closing argument, but Lilly chose not to do so.

The Court therefore denies the motion for a new trial based on the failure to instruct as to the separate enablement of prophylaxis.

B. The Court's Failure to Instruct on Laws of Nature

Lilly contends that the Court should have instructed the jury that laws of nature are not patentable. The Court declined to give such an instruction because Lilly did not

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[15] At Lilly's request, the Court gave a similar instruction with regard to the written description requirement: "The written description requirement is satisfied if a person of ordinary skill reading the patent would have recognized that it describes the full scope of the invention that is claimed in the patent and that the inventor actually possessed the full scope of the invention as of the filing date of the patent." Dkt. No. 346, Trial Tr. at 1426; *see also id.*, Trial Tr. at 1427; Dkt. No. 344, Trial Tr. at 1365 (Lilly's counsel argued that, as to written description, "whenever we talk about the invention, we need to talk about the full scope of the invention.").

challenge the '124 patent on grounds of unpatentability under 35 U.S.C. § 101. Lilly concedes that it did not raise a section 101 challenge to the patent, but it contends that it was entitled to such an instruction anyway, and that the failure to give that instruction was prejudicial error.

Prior to trial, Lilly submitted a proposed instruction that a person who discovered that fires require oxygen would not be entitled to a patent on the process of making a fire by lighting a flame in the presence of oxygen. Dkt. No. 250-2, at 19-20; Dkt. No. 317-1, at 14. That instruction, however, was part of Lilly's requested instruction on anticipation; it related to the role of inherency in the law of anticipation, not to the principle that a natural phenomenon cannot be patented.[16] The Court declined to include the "fire and oxygen" example in its instruction on anticipation. In its proposed instructions, Lilly did not request an instruction on a section 101 defense or to the effect that laws of nature are not patentable.

During the charge conference at trial, Lilly requested that the Court instruct the jury that "the simple discovery that PDE5 is in the prostate or that PDE5 plays a functional role in the prostate is not . . . part of the analysis for this claim." Dkt. No. 353, Trial Tr. at 1361. In a brief filed in support of its request that the Court give such an instruction, Lilly asked the Court to instruct the jury that "the discovery of a phenomenon of nature cannot be the basis for patent protection." *See* Dkt. No. 325, at 4. As legal authority in support of that request, Lilly cited 35

[16] Lilly's proposed instruction was taken directly from an opinion dealing with the law of inherent anticipation, *EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1351 (Fed. Cir. 2001). The Court is unaware of that language ever having been used outside of that context.

U.S.C. § 101 and two cases applying section 101, *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013), and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012). The Court declined to give that instruction, noting that Lilly had not raised section 101 as a defense in this case. Dkt. No. 346, Trial Tr. at 1397.

For the Court to in effect introduce a section 101 defense into the case for the first time at the instruction stage would have been entirely unwarranted. Lilly did not plead section 101 as a defense in its answer, and nothing in the pretrial proceedings or the presentation of the case to the jury laid the basis for a section 101 defense. An instruction essentially directed to such a defense would have been confusing to the jury and unfairly prejudicial to UroPep.

Moreover, the instruction requested by Lilly in its brief on the jury instructions following the charge conference, Dkt. No. 353, would have been misleading. While it is true that a patent cannot be obtained on a natural law or phenomenon, it would be incorrect to instruct the jury that "the discovery of a phenomenon of nature cannot be the basis for patent protection," as Lilly requested. The discovery of a natural law or a phenomenon of nature can indeed serve as the "basis" for patent protection, as long as the phenomenon of nature is applied to achieve a useful result. As the Supreme Court has explained, "a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm. It is now commonplace that an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diamond v. Diehr*, 450 U.S.

175, 187 (1981) (quoting *Parker v. Flook*, 437 U.S. 584, 590 (1978)).

The language proposed by Lilly at the charge conference would have been even worse. Lilly requested that the Court instruct the jury that "the simple discovery that PDE5 is in the prostate or that PDE5 plays a functional role in the prostate is not part of the analysis for this claim." Dkt. No. 344 Trial Tr. at 1361. Such an instruction would have been clearly wrong. It is perfectly legitimate for the discovery of the functional role of PDE5 to be "part of the analysis" of patentability, particularly when that discovery is applied to the administration of a PDE5 inhibitor in an effective amount to treat BPH—a prostatic disease. Diehr and other section 101 cases stand for the proposition that, in addition to reciting a law of nature, a patent must apply that law of nature to a problem in a way that reflects that the inventor has "invent[ed] or discover[ed]" a "new and useful process." 35 U.S.C. § 101; *see Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. at 72; *Bilski v. Kappos*, 561 U.S. 593, 611 (2010). Lilly did not propose an instruction that would have made clear to the jury the distinction drawn by the Supreme Court in Diehr, so it would have been legal error for the Court to instruct the jury in the manner Lilly suggested. Accordingly, it was not legal error for the Court to decline to instruct the jury in accordance with Lilly's proposed language on the subject of the unpatentability of laws of nature.[17]

[17] The Court also addressed Lilly's section 101 argument in detail in a post-trial memorandum opinion. Dkt. No. 359, at 13-14.

C. The Exclusion of the Bunnage References

Prior to trial, UroPep moved to strike a reference that Lilly had proposed to use in support of its invalidity defense. UroPep's motion was based on its contention that the reference had not been timely disclosed. Dkt. No. 253. The reference consisted of two applications filed on behalf of Pfizer Inc. by Mark Edward Bunnage—a Patent Cooperation Treaty application, WO 98/49166 ("the Bunnage PCT Application"), Dkt. No. 253-2, and an earlier application filed in the United Kingdom, to which the PCT application claims partial priority ("the Bunnage UK Application"), Dkt. No. 256-1.

Lilly disclosed the Bunnage PCT Application to UroPep early in the proceedings, listing it as "additional relevant art" in Lilly's initial invalidity contentions, without further elaboration. Dkt. No. 256-3, at 1. Lilly did not disclose the earlier Bunnage UK Application at that time; the Bunnage UK Application was not disclosed until the time of Dr. Bell's deposition in January 2017, long after the date had passed for disclosing prior art references in the defendant's invalidity contentions.

Lilly served amended invalidity contentions a month before trial indicating that Lilly planned to use the Bunnage reference as invalidating prior art at trial. Dkt. No. 253-1. UroPep then moved to strike that reference on the ground that it was an untimely disclosure of invalidating prior art. In response, Dkt. No. 256, Lilly withdrew the designation of the Bunnage PCT Application as prior art and argued instead that the two Bunnage applications should be admissible to show "simultaneous invention," a secondary consideration that bears on the issue of obviousness. *See Geo M. Martin Co. v. Alliance Mach. Sys.*

Int'l LLC, 618 F.3d 1294, 1305 (Fed. Cir. 2010); *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000).[18]

The Court ruled that the failure to disclose the Bunnage UK Application in Lilly's invalidity contentions and the disclosure of the simultaneous invention theory, in violation of the Court's Discovery Order, barred the affirmative use of those applications at trial. The Court stated, however, that Lilly would be permitted "to make use of that evidence for impeachment to the extent UroPep opens the door by offering contrary testimony." Dkt. No. 293, at 8-9.

1. Lilly begins by reiterating its contention that the Bunnage applications should have been admissible as affirmative evidence. As the Court noted in its initial order striking the use of the Bunnage applications as affirmative evidence, Lilly did not disclose the Bunnage UK Application at any point before January 2017, long after the invalidity contentions had been served and after the parties' expert reports had been exchanged. Lilly did not disclose its intention to use either application to prove "simultaneous invention" until March 31, 2017, only about two weeks before the trial.

There is no plausible ground for arguing that the Bunnage UK Application should have been admitted, as its disclosure was long out of time. Admitting it into evidence

[18] Lilly withdrew the applications as prior art after UroPep pointed out that, as a legal matter, neither Bunnage application qualified as prior art to the '124 patent. The Bunnage PCT Application was filed in November 1998, long after the July 9, 1997, priority date of the '124 patent. Although the Bunnage UK Application was filed in April 1997, it was an unpublished foreign application and therefore did not qualify as prior art under 35 U.S.C. § 102(e).

would have been plainly prejudicial to UroPep, which would have been denied the opportunity to have its experts consider and comment on the reference. As for the Bunnage PCT Application, although it was listed in a lengthy collection of "additional prior art" in Lilly's initial invalidity contentions, it was not discussed in any of Lilly's expert's reports, and the "simultaneous invention" theory of admissibility for that application was not disclosed until shortly before trial. As the Court noted in its order on the motion to strike the Bunnage applications, Dkt. No. 293, at 7-8, the Court's Discovery Order required Lilly to disclose the legal theories and factual bases for its claims and defenses. But prior to March 31, 2017, Lilly made no mention of the "simultaneous invention" component of its obviousness defense or the proposed role of the Bunnage applications as supporting a simultaneous invention theory.

Even if the Bunnage PCT Application had not been excludable because of Lilly's failure to satisfy its obligations under the Discovery Order, Lilly would not have been allowed to offer expert testimony regarding that document (or the theory of simultaneous invention), as Lilly does not point to any place where any of its experts discussed the document (or that theory) in their reports. It is therefore unclear to the Court how Lilly would have been able to offer the Bunnage PCT Application and the simultaneous invention theory at trial. Accordingly, the Court adheres to its ruling on UroPep's motion to strike and holds that it was not error to exclude both Bunnage applications from Lilly's affirmative case.

2. The second issue that Lilly raises in the portion of its JMOL brief directed to the Bunnage applications relates to the Court's refusal to permit Lilly to use the ap-

plications during the cross-examination of Dr. Bell. Analysis of Lilly's argument on that issue requires a detailed recitation of the pertinent portions of Dr. Bell's deposition and the corresponding events at trial.

During Dr. Bell's deposition, Lilly asked Dr. Bell if he knew whether Pfizer, Dr. Bell's employer, had ever identified BPH as a target for a PDE5 inhibitor. Dkt. No. 256-2, at 65. Dr. Bell responded that it had. Asked if he knew when that had occurred, Dr. Bell referred to a patent application. When Lilly showed him the Bunnage PCT Application, Dkt. No. 253-2, which was filed in 1998, he recognized that as an application filed by Pfizer scientists. Lilly then pointed to the earliest priority date listed on that application, which was April 25, 1997. Dr. Bell agreed that the April 25, 1997, date was before the filing date of the '124 patent. Dkt. No. 256-2, at 66-67. Lilly then directed Dr. Bell's attention to a passage in the Bunnage PCT Application that recites various therapeutic uses for certain selective PDE5 inhibitors, including the treatment of BPH. *Id.* at 68. Finally, Lilly asked Dr. Bell the following questions:

> **Q.** So Pfizer scientists, at least by April of 1997, had identified PDEV inhibitors as useful to treat BPH?
>
> **A.** Since—I don't know. There are subsequent priority dates and a filing date. I don't know from this whether that initial filing included BPH.
>
> **Q.** We're going to educate you, sir.

Id. at 68-69.

Lilly then showed Dr. Bell the earlier Bunnage UK Application, Dkt. No. 256-1, and directed his attention to the page that listed the priority date for that application as April 25, 1997. Lilly then asked, "And that corresponds to the earliest priority date on [the later Bunnage PCT Application], doesn't it?" Dr. Bell responded, "I would presume so, since you—never having looked at the initial documents, that looks sensible to me." Dkt. No. 256-2, at 69. Lilly then pointed out the reference to BPH in the UK Application and asked, "So, at least as of April 1997, Pfizer scientists had found that selective and potent PDE V inhibitors would be useful to treat BPH, and put it in a patent application, right?" Dr. Bell responded, "Yes, they believed it would be." *Id.* at 70.

On direct examination at trial, UroPep asked Dr. Bell if other PDE5 inhibitors, such as sildenafil, could be used to treat BPH, and Dr. Bell responded that they could. Dkt. No. 342, Trial Tr. at 320-21. UroPep did not ask Dr. Bell if he knew whether Pfizer had ever considered patenting sildenafil. On cross-examination, Lilly asked the following question: "And are you aware that Pfizer scientists themselves have discovered the use and filed a patent claim on the use of sildenafil to treat BPH before 1997, the filing date of the UroPep patent?" *Id.*, Trial Tr. at 343. UroPep objected on the ground that the question violated the Court's previous order excluding the Bunnage applications except for impeachment purposes in the event that UroPep opened the door to impeachment with those applications.

The Court permitted Lilly to ask Dr. Bell how he knew that sildenafil can be used to treat BPH, but directed Lilly not to question Dr. Bell about the Bunnage applications. Dkt. No. 342, Trial Tr. at 346-48. When Lilly asked Dr.

Bell how he knew that sildenafil can be used to treat BPH, Dr. Bell answered that he knew it from reading a 2014 paper on the subject. *Id.*, Trial Tr. at 348. Lilly then asked Dr. Bell if he recalled "when Pfizer scientists first began looking at sildenafil to treat BPH," to which Dr. Bell responded, "I don't know the exact answer. I think—I believe it would have been after they filed the initial submission to the FDA in 1997, in September 1997." *Id.*, Trial Tr. at 349. Lilly then asked, "Do you have any information that Pfizer scientists were looking at using sildenafil to treat BPH before September of 1997?" Dr. Bell replied, "I do not." *Id.*, Trial Tr. at 349-50.

At that point, Lilly sought to impeach Dr. Bell with his deposition testimony. Lilly represented (incorrectly) that "[h]is testimony in his deposition is he recalled the date. And I can refresh his recollection." Dkt. No. 342, Trial Tr. at 350.[19] UroPep objected on the ground that Dr. Bell's trial testimony did not contradict his deposition testimony. UroPep argued that Dr. Bell's testimony at the deposition was not based on his independent knowledge, but merely consisted of his reading from the Bunnage applications that Lilly provided to him. *Id.*, Trial Tr. at 350-51. Lilly then asserted (again, incorrectly) that Dr. Bell remembered the April 1997 date in his deposition "after I

[19] Dr. Bell did not testify in his deposition that he recalled the priority date of the Bunnage UK Application. Dr. Bell learned that date only because Lilly's counsel put the Bunnage applications before him and decided to "educate" him by pointing the date out to him. Dkt. No. 256-2, at 69. Thus, use of the Bunnage applications did not refresh Dr. Bell's recollection at the deposition and would not have refreshed his independent recollection at trial; at most, the Bunnage applications would have refreshed his recollection of Lilly's having pointed out the April 1997 date to him at his deposition.

refreshed his recollection."[20] *Id.*, Trial Tr. at 351. Lilly argued that it was entitled to use the Bunnage applications to "re-refresh" Dr. Bell's recollection and to impeach him regarding his response to the question about his knowledge as to when Pfizer began looking at sildenafil to treat BPH. *Id.* Regarding the deposition, the Court asked Lilly's counsel, "What is said that suggests this is refreshment of recollection as opposed to simply recitation of something that is on the document?" *Id.*, Trial Tr. at 353. Lilly's counsel replied, "He said he didn't know, and I handed him a document, and then he learned." *Id.* The court then had the following exchange with Lilly's counsel:

> **The Court:** Well, that's different from saying it refreshes his recollection. If you handed me a copy of your graduation – college graduation diploma and said, "Do you know when I graduated from college," I would look at it, and I would say, "Well, you know, 1984" or whatever. That wouldn't refresh my recollection.
>
> **[Lilly's counsel]:** Well, that's what I would like permission to do now is refresh his recollection with the documents that refreshed his recollection in the –

[20] As noted, Dr. Bell's recollection was not refreshed as to that date at his deposition; he was simply directed to the date and accepted it as true. *See* Dkt. No. 256-2, at 69 ("Q. And this is identified as a priority document. If you go to the third page of Exhibit 5, do you see the stamp April 25, 1997 with the number 0708406.5? A. I do. Q. And that corresponds to the earliest priority date on Exhibit 4, doesn't it? A. I would presume so, since you – never having looked at the initial documents, that looks sensible to me.").

> **The Court:** Well, if it didn't refresh his recollection and all he did is recite what is on the documents, then that gets into just introducing the documents with no valid reason other than to get the documents in because we are not refreshing recollection. And that's not inconsistent with his testimony in the deposition.

Id., Trial Tr. at 354. The Court then ruled that there had been no showing that Dr. Bell "has an independent recollection that's been refreshed by the showing of the document." *Id.*, Trial Tr. at 355.

Lilly argues that it was entitled to question Dr. Bell about the Bunnage applications either to refresh his recollection or to impeach him. Both theories are flawed, however.

As for refreshing Dr. Bell's recollection, it appears that Dr. Bell may have seen the Bunnage PCT Application in the course of his work on this case. *See* Dkt. No. 256-2, at 66; Dkt. No. 342, Trial Tr. at 356-57. But there is no indication that he had seen, or knew of, the earlier Bunnage UK Application, or that he was aware of the reference to the April 1997 priority date listed in the Bunnage PCT Application. Lilly's counsel simply pointed that date out to him at Dr. Bell's deposition. That does not constitute refreshing recollection. At trial, likewise, the use of the Bunnage applications would not have refreshed Dr. Bell's independent recollection as to the April 25, 1997 priority date. Simply showing Dr. Bell the April 25, 1997, date did not have the effect of "refreshing" his recollection; Lilly sought to use the Bunnage applications not to refresh Dr. Bell's independent recollection of the April 25,

1997, priority date, but to elicit the fact that he had agreed that the 1997 date was found in the Bunnage applications after having been shown the date during his deposition. That use of the Bunnage applications would have been a distortion of the refreshing recollection procedure set forth in Rule 612 of the Federal Rules of Evidence.

It is well established that Rule 612 allows a writing to be used to refresh a witness's recollection only if the writing actually refreshes the witness's memory. *See United States v. Carey*, 589 F.3d 187, 190 (5th Cir. 2009); *Thompson v. United States*, 342 F.2d 137, 139-40 (5th Cir. 1965). The document must be used for purposes of refreshing, "and not for purposes of putting words in the mouth of the witness." *Esperti v. United States*, 406 F.2d 148,150 (5th Cir. 1969). The court "has the discretion to withhold any writing from a witness where the judge believes that the document will be the source of direct testimony rather than the key to refreshing the witness's independent recollection." *United States v. Weller*, 238 F.3d 1215, 1221 (10th Cir. 2001).

The policies underlying Rule 612 require that a court guard against the risk that a witness will testify from "false memory" by simply repeating the contents of the writing he has been shown. *See* 4 Marc S. Brodin et al., *Weinstein's Federal Evidence* § 612.02[2] (2d ed. 2017) ("Rule 612 is intended to curb the false memory that might occur when a witness who purports to testify based on a refreshed recollection merely parrots the contents of the writing."); 28 Charles Alan Wright & Victor S. Gold, *Federal Practice & Procedure* § 6184, at 511-12 (2d ed. 2012) (same); *United States v. Faulkner*, 538 F.2d 724, 727 (6th Cir. 1976) ("[C]aution must be exercised to insure that the document is not used to put words into the mouth

of the witness."). In this case, it is evident to the Court that the Bunnage applications were not being used to refresh Dr. Bell's independent recollection, but to attempt to get the priority date of April 25, 1997, before the jury by having Dr. Bell recite that date that had been shown to him at his deposition. The use of the Rule 612 procedure for that purpose would violate Rule 103(d) of the Federal Rules of Evidence, which provides that, "[t]o the extent practicable, the court must conduct a jury trial so that inadmissible evidence is not suggested to the jury by any means." *See Rush v. Ill. Cent. R.R. Co.*, 399 F.3d 705, 717 (6th Cir. 2005) ("[T]he trial court may abuse its discretion when otherwise inadmissible evidence is introduced to the jury through the guise of refreshing a witness's recollection.").

As for impeachment, a similar problem is presented. At Dr. Bell's deposition, Lilly showed Dr. Bell the priority dates listed in the Bunnage PCT Application and showed him the Bunnage UK Application, which he had not seen before. As Lilly stated during the deposition, it showed the Bunnage applications to Dr. Bell in order to "educate" him as to their contents. Lilly then got Dr. Bell to agree that the priority date of April 25, 1997 was listed on those documents. At trial, Lilly asked Dr. Bell a question that was designed either to elicit an answer regarding the contents of the Bunnage applications, based on what Lilly showed him at the deposition, or to lead to Lilly's use of the applications for impeachment if he did not testify at trial that as of April 1997, Pfizer scientists had found that PDE5 inhibitors "would be useful to treat BPH and put it in a patent application." Dkt. No. 342, Trial Tr. at 354.

When Dr. Bell testified that he believed Pfizer scientists began looking at sildenafil to treat BPH in September of 1997, Lilly sought to impeach him by questioning him about the contents of the Bunnage applications. That is an improper use of impeachment, as it would enable a party to avoid limitations on the use of a document by permitting the party to question a witness about the document at a deposition and then either exploit his newly obtained knowledge of the document at trial or impeach him if he did not testify at trial consistently with the contents of the document.

Courts have frequently warned against the improper use of impeachment evidence, advising, for example, that it is improper to use evidence for impeachment that is inadmissible as substantive evidence when the purpose of its use is not to impeach the witness but to put inadmissible evidence before the jury. *See United States v. Gomez-Gallardo*, 915 F.2d 553, 555 (9th Cir. 1990) ("[T]he government must not knowingly elicit testimony from a witness in order to impeach him with otherwise inadmissible evidence."); *United States v. Hogan*, 763 F.2d 697, 702 (5th Cir. 1985); *United States v. Webster*, 734 F.2d 1191, 1192 (7th Cir. 1984); *United States v. Miller*, 664 F.2d 94, 97 (5th Cir. 1981); *United States v. DeLillo*, 620 F.2d 939, 946 (2d Cir. 1980); *United States v. Pantone*, 609 F.2d 675, 683 (3d Cir. 1979); *United States v. Morlang*, 531 F.2d 183, 190 (4th Cir. 1975) ("impeachment by prior inconsistent statement may not be permitted where employed as a mere subterfuge to get before the jury evidence not otherwise admissible"). Impeachment is not a mechanism for getting substantive evidence before the jury that is not otherwise admissible; as one court put it, "the maximum legitimate effect of the impeaching testimony can never be more than the cancellation of the adverse answer by which

the party is surprised." *United States v. Crouch*, 731 F.2d 621, 623 (9th Cir. 1984).

That principle applies here. Lilly cannot be permitted to get the contents of an otherwise inadmissible document before the jury by showing the document to a witness at his deposition and then using it for impeachment purposes if the witness testifies at trial in a manner that is arguably inconsistent with the text of the document the witness was shown in his deposition.

The impeachment of Dr. Bell would have been improper for a second reason as well: the lack of a conflict between Dr. Bell's testimony in his deposition and his testimony at trial. Lilly's argument is based on a single statement in the two Bunnage applications that "the compounds [certain PDE5 inhibitors] are of value in the treatment of male erectile dysfunction (MED) and female sexual dysfunction (FSD), but clearly will be useful also for treating other medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated. Such conditions include [a list of various maladies, including BPH]." Dkt. Nos. 253-2 and 256-1. At trial, Dr. Bell was asked, "Today, do you recall when Pfizer scientists first began looking at sildenafil to treat BPH?" to which he answered, "I believe it would have been after they filed the initial submission to the FDA in 1997, in September 1997." Dkt. No. 342, Trial Tr. at 349. He was also asked, "Do you have any information that Pfizer scientists were looking at using sildenafil to treat BPH before September of 1997," to which he answered, "I do not." *Id.*, Trial Tr. at 349-50.

Because the questions referred to when Pfizer scientists began "looking at using sildenafil to treat BPH," Dr. Bell's answers were not inconsistent with his deposition

testimony in which he acknowledged that the Bunnage applications had recognized that PDE5 inhibitors could be of value in the treatment of a variety of medical conditions. It would have been reasonable for Dr. Bell to interpret the question about when Pfizer began "looking at using sildenafil" to treat a particular condition as entailing a more active interest in treating BPH than merely recognizing the possibility that sildenafil could be effective against that disease. Thus, the evidence Lilly sought to use for impeachment would not have contradicted Dr. Bell's testimony.

Finally, whatever limited value the Bunnage applications would have had in impeaching Dr. Bell's credibility would have been swamped by the unfair prejudice to UroPep from the use of those materials at trial. Lilly acknowledged that the Bunnage applications were not prior art, but the introduction of the contents of those materials at trial would have carried a substantial risk that the jury would conclude that the '124 patent was invalid because it was predated by the Bunnage UK Application. It is by no means clear that a limiting instruction would have cured the prejudicial effect of allowing the Bunnage applications into the case in that manner. To be sure, if UroPep had opened the door to the use of those applications for impeachment purposes, it would have had to live with the risk that a limiting jury instruction would not have been effective. But UroPep did not open that door.

In sum, Lilly's invocation of the rules governing impeachment and refreshing recollection is not suited to the facts of this case, where Lilly attempted to create the basis for the admission of otherwise inadmissible evidence and then attempted to get the evidence in through cross-examination. This is not a case of UroPep's having opened

the door, but rather a case of Lilly having encountered a wall, kicked a hole in the wall, and then insisted on the right to walk through it.

The Court discerns no error in the disposition of the issues at trial relating to the Bunnage applications.

D. Allowing Cross-examination of Dr. Rotella Regarding His Patent

At trial, UroPep cross-examined Lilly's expert, Dr. Rotella, regarding a patent on which Dr. Rotella was a named inventor. The cross-examination was designed to challenge Dr. Rotella's opinions on the infirmities of the '124 patent by showing similarities between the '124 patent and Dr. Rotella's patent. Lilly contends that the cross-examination of Dr. Rotella regarding his patent was improper and was sufficiently prejudicial to require the grant of a new trial.

At the outset of the trial, the parties agreed that Lilly would not raise a "scope" objection to the cross-examination of Dr. Rotella with respect to matters on which he was examined at his deposition and with respect to any opinions he had given in the case. Dkt. No. 342, Trial Tr. at 265-66; *see also Dkt.* No. 343, Trial Tr. at 785-86. In his expert report, Dr. Rotella offered opinions on a number of subjects, including obviousness, and he was questioned about those opinions during his deposition. Accordingly, under the parties' agreement, Dr. Rotella was subject to cross-examination on the issue of obviousness, even though his trial testimony was limited to the issues of written description and enablement, and did not include an expert opinion on obviousness.

Dr. Rotella's patent, U.S. Patent No. 6,087,368 ("the '368 patent") is entitled "Quinazolinone Inhibitors of cGMP Phosphodiesterase." It claims priority to a provisional application filed on June 8, 1998. The '368 patent discloses "[n]ovel quinazolinone compounds, methods of using such compounds in the treatment of cGMP-associated conditions such as erectile dysfunction, and pharmaceutical compositions containing such compounds." Dr. Rotella is one of five named inventors on the '368 patent. Dkt. No. 252-1, at 2.

UroPep did not seek to have the '368 patent admitted into evidence, and it was not admitted. Instead, UroPep used it to cross-examine Dr. Rotella with regard to his opinions as to the invalidity of UroPep's '124 patent. Lilly counters that UroPep should not have been permitted to use the '368 patent in that manner because nothing in the patent is inconsistent with or contradicts Dr. Rotella's testimony.

The Court disagrees. First, the '368 patent, with a priority date of 1998, lists a large number and variety of conditions that are amenable to treatment with PDE5 inhibitors, but it does not list BPH among those conditions. Dkt. No. 252-1 ('368 patent, col. 16, line 66, through col. 17, line 15). The point of UroPep's questioning was that it is reasonable to infer from the omission of any reference to BPH in the Rotella patent that as of 1998, the inventors of the '368 patent, including Dr. Rotella, did not regard BPH as a potential treatment target of PDE5 inhibitors. For that reason, the omission of any reference to BPH in the '368 patent arguably contradicts Dr. Rotella's conclusion in his expert report that it would have been obvious to persons of skill in the art to use PDE5 inhibitors to treat BPH in 1997. As for written description and enablement, Dr.

Rotella based his invalidity opinions in part on the absence of quantitative clinical data in the '124 patent. *See* Dkt. No. 177-8, at 74; Dkt. No. 252-7, at 147. But, as Dr. Rotella acknowledged on cross-examination at trial, the '368 patent also does not disclose quantitative clinical data. *See* Dkt. No. 343, Trial Tr. at 844-47. The absence of such data arguably contradicts Dr. Rotella's opinion that clinical data is required in this setting for persons of skill in the art to describe what the invention is (written description) and show them how to make and use it (enablement).

With regard to obviousness, Lilly argues that the list of targeted conditions in the '368 patent did not purport to be exhaustive, and that the patent's failure to mention BPH as a target disease for PDE5 inhibitors was therefore insignificant. With regard to written description and enablement, Lilly contends that the '368 patent is otherwise distinguishable from the '124 patent; for example, the '368 patent contains a much more detailed disclosure and narrower claims than the '124 patent. While it is arguable that the differences between the '124 and '368 patents provide at least a possible answer to UroPep's assertions of inconsistency between the '368 patent and Dr. Rotella's invalidity opinions, that point was properly left to Lilly to make through redirect examination and argument to the jury.

Lilly further contends that any infirmities or omissions in Dr. Rotella's '368 patent are irrelevant, because the '124 patent has to stand on its own merits, without regard to whether the '368 patent is valid. While it is true that the validity of the '124 patent does not turn on whether the'368 patent is valid, that was not the point of UroPep's cross-examination. Rather, it was proper for

UroPep to point out the similarities between the two patents, as the jury might reasonably have concluded that the parallels between Dr. Rotella's patent and the '124 patent bore on the credibility of Dr. Rotella's critique of the '124 patent.

Finally, Lilly suggests that it did not have enough time in the course of the five-day trial "to teach the jurors the needed principles of advanced medicinal chemistry or patent law to understand the defects in UroPep's facile arguments," Dkt. No. 375, at 60, and that the cross-examination of Dr. Rotella raised complex issues that Lilly did not have an opportunity to address in the time allotted. Prior to trial, however, the parties agreed that the trial could be conducted in five days. Dkt. No. 251, at 18. Lilly sought 14 hours of trial time during that five-day period, but the Court advised the parties that it would be difficult to fit 14 hours of testimony from each side into a five-day trial. The Court then offered to give each side 12 hours to present its case, and neither party objected that it could not reasonably present its case in that period. *See* Dkt. No. 320, at 289. Lilly had the opportunity, on Dr. Rotella's redirect examination, to correct any misapprehensions it felt may have been created by the cross-examination, and it took full advantage of that opportunity. The Court sees no merit in Lilly's late-blooming claim that it did not have sufficient time to respond to the issues raised by UroPep's cross-examination of Dr. Rotella. In fact, the Court notes that Lilly was able to fit into its case four affirmative defenses, lengthy testimony on damages, and background on Lilly's development of Cialis. Lilly's claim that it did not have enough time rings hollow. Lilly is not entitled to a new trial on that ground.

For the foregoing reasons, Lilly's motion for judgment as a matter of law and a new trial is denied. The Clerk is directed to close the case.

IT IS SO ORDERED.

Dated: August 25, 2017

/s/ William C. Bryson
William C. Bryson
United States Circuit Judge

APPENDIX C

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff,

v.

ELI LILLY AND COMPANY,
Defendant.

Case No. 2:15-CV-1202-WCB

MEMORANDUM OPINION AND ORDER

Before the Court is Plaintiff UroPep's Motion to Preclude Lilly's Experts from Presenting Testimony that Contradicts the Court's Summary Judgment Ruling ("Motion to Preclude"), Dkt. No. 257. The motion is GRANTED IN PART and DENIED IN PART.

UroPep's motion is directed to barring some or all of the testimony corresponding to seven expert reports submitted by Lilly. UroPep explains that its motion is directed to three categories of what it considers impermissible opinion testimony.

First, UroPep objects to any testimony from Lilly's experts on indefiniteness and non-infringement issues

that contradict this Court's claim constructions and its March 3, 2017, summary judgment order, Dkt. No. 234. Relatedly, UroPep objects to any expert testimony to the effect that tadalafil is not 20 times more selective for PDE5 than for PDE11. UroPep argues that any such testimony would be inconsistent with this Court's March 3 order, in which the Court held that the '124 patent only requires selectivity for PDE5 as compared to PDE1 through PDE4.

Second, UroPep objects to testimony from one of Lilly's experts, Dr. Joseph A. Beavo, regarding three prior art compounds that Lilly claims are PDE5 inhibitors. UroPep argues that the three compounds are not selective inhibitors, within the meaning of the Court's definition of that term for purposes of UroPep's U.S. Patent No. 8,791,124 ("the '124 patent"). For that reason, UroPep argues, evidence regarding those compounds is irrelevant and should be excluded.

Lilly responds that it has no intention of introducing evidence that would contradict the Court's claim construction. In particular, Lilly represents that it will not offer expert testimony or opinion that Lilly does not infringe the '124 patent because tadalafil treats only the signs and symptoms of BPH and does not treat enlargement of the prostate. Defendant Eli Lilly & Company's Opposition to Plaintiff Erfindergemeinschaft UroPep GbR's Motion to Strike Experts ("Lilly's Response"), Dkt. No. 263, at 1-2.

In addition, Lilly represents that it will not offer any expert testimony or opinion that Lilly does not infringe the '124 patent because Cialis is not 20 times as selective for PDE5 as it is for PDE6 through PDE11. However, Lilly states that it intends to offer expert testimony going to the issues of written description and enablement, as set

forth in portions of Lilly's experts' reports that UroPep is seeking to exclude. Lilly's Response, Dkt. No. 263, at 2-3. The parties have therefore joined issue in that regard.

With respect to the three compounds as to which Dr. Beavo intends to offer expert testimony corresponding to the contents of his second report, Lilly argues that Dr. Beavo's testimony regarding those compounds is relevant and does not controvert anything in the Court's March 3, 2017, order.

Finally, in its opposition and in the Joint Proposed Pre-trial Order, Dkt. No. 251, Lilly has requested direction from the Court as to the status of the Court's indefiniteness ruling in the March 3, 2017, summary judgment order, so that the parties will understand what the Court's intentions are with regard to the indefiniteness issue.

I. Expert Testimony That Would Contradict the Court's March 3 Order

Because Lilly has made clear that it does not intend to elicit expert testimony that would contradict any of the Court's claim constructions, the only remaining question raised by UroPep's first and second objections is whether Lilly's expert testimony will conflict with anything in the portion of the Court's March 3, 2017, order dealing with indefiniteness. To resolve that issue, it is necessary to address both the Court's role in deciding the indefiniteness issue and Lilly's constitutional right to a jury trial on other issues that may be related to the matters resolved by the Court in the course of its indefiniteness discussion.

Lilly intends to have its experts testify that the '124 patent gives inadequate guidance as to whether a particular compound is a PDE5 inhibitor. On the assumption

that the indefiniteness issue has been resolved by the Court or, in any event, is an issue of law for the Court and not for the jury, Lilly proposes to offer that evidence not on the issue of indefiniteness, but instead in support of Lilly's written description and enablement defenses. UroPep has two responses: first, that some of the testimony in question was expressly directed to the issue of indefiniteness and cannot be repurposed as relevant evidence going to written description and enablement; and second, that much of the expert testimony that is expressly directed to written description and enablement conflicts with the Court's March 3, 2017, indefiniteness ruling and thus should be barred at trial.

The first issue raised by the parties' briefs relates to the status of the indefiniteness issue in this case. The Court held a claim construction hearing on June 23, 2016. The docket control order that was in effect at that time, like each of the subsequent docket control orders issued in this case, advised that "the parties are directed to include any arguments related to the issue of indefiniteness in their *Markman* briefing."

In its initial claim construction briefing, Lilly argued that the claim term "inhibitor of phosphodiesterase (PDE) V" should be construed as a "means plus function" term under 35 U.S.C. § 112, ¶ 6. If viewed in that manner, Lilly argued, the claims of the '124 patent would be limited to two compounds, zaprinast and MY5445. In the alternative, Lilly argued that the term "inhibitor of phosphodiesterase (PDE) V" should be construed broadly to mean "any compound able to inhibit PDE V." At that time, Lilly reserved the right to call expert witnesses regarding claim construction, *see* Dkt. No. 84, at 6, but Lilly

did not call any witnesses at the claim construction hearing, which was held on June 23, 2016.

On August 11, 2016, the Court entered its claim construction order. Dkt. No. 131. In that order, the Court construed several of the terms in dispute. However, the Court postponed construing the phrase "inhibitor of phosphodiesterase (PDE) V" pending the Court's ruling on Lilly's motions for summary judgment of noninfringement, Dkt. No. 119, and invalidity, Dkt. No. 120. Lilly's invalidity motion was based on the alleged failure of the '124 patent to satisfy the written description requirement of 35 U.S.C. § 112, ¶ 1. On October 21, 2016, the Court entered an order that denied Lilly's motions for summary judgment. In that order, the Court construed the term "inhibitor of phosphodiesterase (PDE) V." Dkt. No. 149. The Court rejected Lilly's argument that the term should be construed as a means-plus-function limitation, and the Court construed the term to mean "a compound that selectively inhibits PDE V." *Id.* at 27.

Lilly subsequently filed a motion for summary judgment on indefiniteness. In the course of the briefing of that and other related motions, it became clear that the parties disagreed about the meaning of the Court's claim construction. Accordingly, in an order entered on March 3, 2017, the Court clarified its claim construction, construing the term "selectively inhibits" in its earlier claim construction to mean a compound that is at least 20 times more effective in inhibiting PDE5 compared to PDE1 through PDE5. Dkt. No. 234. The Court then turned to Lilly's motion for summary judgment of indefiniteness. The Court first noted that indefiniteness is a question of law for the Court and that the general principles of claim construction apply to the question of indefiniteness. Dkt.

No. 234, at 28-29. The Court then ruled that in light of the manner in which the claim construction issue had been litigated, Lilly had not waived its indefiniteness argument by not raising it earlier in the proceedings. *Id.* at 30-33. The Court also rejected UroPep's argument that Lilly had waived its indefiniteness argument by submitting much of its evidence on that issue belatedly, through a responsive report of its expert, Dr. David Rotella.

On the merits of the indefiniteness issue, the Court held that Lilly had failed to show that the '124 patent claims were invalid for indefiniteness. Dkt. No. 234, at 34-47. After reviewing all of the argument and evidence presented by the parties on the indefiniteness issue, the Court stated that "the asserted claims are . . . sufficiently definite to satisfy the requirements of section 112, paragraph 2, of the Patent Act," *id.* at 44, and that "[t]he Court holds that the claims of the '124 patent are not invalid for indefiniteness," *id.* at 47.

In its response to UroPep's Motion to Preclude, Dkt. No. 263, and also in the Proposed Joint Pretrial Order, Dkt. No. 251, Lilly ought the Court's guidance as to whether the indefiniteness issue is still in this case, given that the Court's March 3, 2017, order had been issued in response to Lilly's motion styled as a motion for summary judgment.

The Court now advises the parties that the issue of indefiniteness has been resolved. The Court's March 3, 2017, order held that the claim language, as construed by the Court, is "sufficiently definite to satisfy the requirements of section 112, paragraph 2, of the Patent Act," and that "the claims of the '124 patent are not invalid for indefiniteness." Even though Lilly addressed the issue of indefiniteness in a paper denominated as a motion for

summary judgment, the indefiniteness issue was before the Court as a part of the Court's claim construction, and it was properly addressed and finally resolved in conjunction with the claim construction process. That conclusion follows from the principles the Federal Circuit has announced regarding the role of the indefiniteness inquiry in infringement litigation.

First, the Federal Circuit has made clear that indefiniteness is a question of law for the court. *Ethicon Endo-Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1317 (Fed. Cir. 2015); *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1328 (Fed. Cir. 2005); *Intellectual Prop. Dev., Inc. v. UA-Columbia Cablevision of Westchester, Inc.*, 336 F.3d 1308, 1318 (Fed. Cir. 2003). Moreover, the general principles of claim construction apply to the question of indefiniteness. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1370 (Fed. Cir. 2017); *Eon Corp. IP Holdings LLC v. AT&T Mobility LLC*, 785 F.3d 616, 620 (Fed. Cir. 2015); *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377-78 (Fed. Cir. 2015); *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008) ("Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determine whether allegedly indefinite language is subject to construction."). In fact, as the Federal Circuit has explained, indefiniteness presents a question of law that is "inextricably intertwined with claim construction," *Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224, 1232 (Fed. Cir. 2016) (quoting *Atmel Corp. v. Info Storage Devices, Inc.*, 198 F.3d 1374, 1379 (Fed. Cir. 1999)); *see also Personalized Media Commc'ns, LLC v. Int'l Trade Comm'n*, 161 F.3d 696, 705 (Fed. Cir. 1998) (indefiniteness "is a legal conclusion that is drawn from the court's performance of its duty as the construer of patent

claims"); *ePlus, Inc. v. Lawson Software, Inc.*, 700 F.3d 509, 517 (Fed. Cir. 2012) (same). As such, the issue of indefiniteness does not ordinarily turn on an underlying factual dispute that is not amenable to decision on summary judgment. *See Exxon Res. & Eng'g Co v. United States*, 265 F.3d 1371, 1376 (Fed. Cir. 2001), and cases cited therein. As in the case of claim construction, factual issues relating to indefiniteness determinations can arise; when factual findings are required to be made, however, those findings are made by the court and reviewed for clear error. *See Media Rights Techs, Inc. v. Capital One Fin. Corp.*, 800 F.3d 1366, 1371 (Fed. Cir. 2015); *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-42 (Fed. Cir. 2015).

Lilly expresses uncertainty about whether this Court has finally ruled on the issue of indefiniteness. Citing *Meadwestvaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258 (Fed. Cir. 2013), and *Lisle Corp. v. A.J. Mfg. Co.*, 398 F.3d 1306, 1317 (Fed. Cir. 2005), Lilly explains that it wants to take whatever measures are necessary to ensure that it not be found to have waived its indefiniteness argument for purposes of appeal, even though it will not be offering evidence on that issue to the jury at trial. In the Court's view, Lilly has plainly not waived its right to appeal the Court's determination on indefiniteness. To be clear, Lilly is not required to offer evidence going to indefiniteness at trial, and will not be allowed to do so. Lilly asks whether this Court in its March 3, 2017, order finally ruled on the indefiniteness issue, as opposed to simply having denied Lilly's motion for summary judgment on that issue. In fact, the Court did both. As the Court stated in its March 3, 2017, order, the Court not only denied summary judgment to Lilly, but also held that

the claims of the '124 patent "are not invalid for indefiniteness."

In the *Meadwestvaco* case, the district court did not make clear whether it was merely denying summary judgment or ruling on the merits of the indefiniteness issue. Under those circumstances, the Federal Circuit found that there had been a waiver because the defendant had not raised the indefiniteness issue at the subsequent bench trial. In this case, Lilly has made its intentions clear—that it has no intention of abandoning its indefiniteness claim—and the Court views that as fully sufficient to preserve that issue for appeal. Moreover, in this case, unlike in *Meadwestvaco*, this Court has sought to make its intentions clear—that the Court's ruling on the summary judgment motion was "the last word on the matter until appeal." *ePlus, Inc.*, 700 F.3d at 517-18.[1]

While the Court's ruling on the indefiniteness issue is final, that does not resolve the question of whether the Court's ruling—and the Court's component findings made in the course of its analysis of the indefiniteness issue—should be accorded binding effect for other purposes at trial, as UroPep argues. The problem is this: To the extent the Court's findings are given preclusive effect when similar factual questions arise in connection with other legal issues at trial, any such preclusion could have the effect of restricting Lilly's Seventh Amendment right to have the jury decide the factual issues in the case without

[1] UroPep has objected to several of Lilly's proposed trial exhibits on the ground that the exhibits were offered in support of Lilly's indefiniteness case, an issue that the Court has already decided. *See* Dkt. No. 268, at 5-6, 14 (objecting to Lilly trial exhibits 1259, 1600, 1601, 1602, 1603, 1604). UroPep's objection is SUSTAINED.

the constraint of a Court's order resolving factual issues that the jury would otherwise be charged with deciding.

This issue is closely akin to the issue addressed by the Supreme Court in two seminal Seventh Amendment cases, *Dairy Queen v. Wood*, 369 U.S. 489 (1962), and *Beacon Theatres, Inc. v. Westover*, 359 U.S. 500 (1959). Those cases stand for the proposition that a district court's decision on an issue cannot, consistent with the Seventh Amendment, be binding on a jury on an issue that is triable to the jury. *See Shum v. Intel Corp.*, 499 F.3d 1272, 1277 (Fed. Cir. 2007); *Gardco Mfg., Inc. v. Herst Lighting Co.*, 820 F.2d 1209, 1212-13 (Fed. Cir. 1987). In this case, the course that UroPep invites the Court to follow would potentially have the effect of precluding the jury from deciding the issues of written description and enablement free from the fetters of the Court's pronouncements made in the course of its earlier decision on the indefiniteness defense.

The Court must therefore determine whether the factual findings underlying its indefiniteness ruling are intertwined with factual issues Lilly wishes to present in support of its enablement and written description defenses. In the Court's indefiniteness ruling, the key factual findings were (1) that the '124 patent "points to" a detailed testing protocol for determining whether a particular compound qualifies as a PDE5 inhibitor; (2) that any uncertainty in determining whether zaprinast satisfies the 20-fold selectivity test does not, by itself, support the inference that testing of many or all other inhibitors would generate similar uncertainty; and (3) that zaprinast is specifically identified in the patent as a PDE5 inhibitor. Dkt. No. 234, at 35.

UroPep argues that large portions of several of Lilly's expert reports are contrary to those findings and thus should be precluded from use at trial. That argument fails to recognize, however, that "there is a fundamental difference between *evidence* and *issues*." *Gardco Mfg., Inc. v. Herst Lighting Co.*, 820 F.2d at 1213. The fact that particular evidence may have been submitted in support of a failed indefiniteness argument does not disable the evidence from being used to mount, for example, a successful enablement defense.

The relevant question is whether Lilly now wishes to relitigate, in support of its written description and enablement defenses, the factual findings that the Court decided in its indefiniteness ruling. Based on Lilly's representations, that may not be the case, but the Court has not yet seen the full contours of Lilly's defenses.

It is difficult to discern in the abstract whether the indefiniteness findings will overlap with the factual issues underlying Lilly's enablement and written description defenses. But in any event the Court's earlier factual findings would not necessarily preclude Lilly from offering evidence at trial that is relevant to those defenses, even if the same evidence was previously offered in support of Lilly's unsuccessful indefiniteness defense.

At this point, the Court is not aware of any facts that Lilly seeks to establish in support of its written description and enablement defenses that contradict one of the Court's indefiniteness findings. But it is possible that the problem could surface at trial, giving rise to the Seventh Amendment issue discussed above. There are several ways of resolving that conundrum, but the one that seems both most efficient and fully protective of Lilly's Seventh Amendment rights is for the Court to treat the factual

analysis conducted in the course of the Court's indefiniteness order as non-binding on Lilly for purposes of Lilly's presentation of its written description and enablement defenses to the jury at trial. *See Dairy Queen*, 369 U.S. at 479 (if legal claims involve factual issues "common with those upon which [the] claim to equitable relief is based, the legal claims involved in the action must be determined prior to any final court determination of [the] equitable claims."); accord *Shum*, 499 F.3d at 1277. That resolution will preserve Lilly's Seventh Amendment right to present its defenses without the constraints imposed by the Court's previous rulings made in connection with the indefiniteness ruling. At the same time, that procedure will respect the Court's authority to decide the indefiniteness issue as a legal matter in conjunction with the claim construction process. And it will not have the effect of making the finality of the resolution of the indefiniteness issue turn on whether a party later wishes to raise an issue at trial that overlaps with some determination made in the course of the indefiniteness proceedings.[2]

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[2] There are other ways the Court could achieve the same objective, and the Federal Circuit has recognized that district courts enjoy some flexibility in the way that they implement the policies underlying the *Dairy Queen* and *Beacon Theatres* cases. *See In re Glaxo, Inc.*, 69 F.3d 553, 1995 WL 616605(Fed. Cir. Oct. 6, 1995) (table). For example, the Court could vacate its indefiniteness ruling, subject to reissuing it following the trial, if necessary. That procedure would avoid the preclusive effect of the indefiniteness ruling, but without conferring any benefit beyond that conferred by the process adopted by the Court in this case. Alternatively, and more generally, courts could postpone ruling on indefiniteness challenges until after trial. But that procedure could be cumbersome and would deny the parties the benefits of early resolution of an important and potentially dispositive issue. The Court is satisfied that the procedure to be employed here is the most efficient, at least in the specific context of this case.

Accordingly, the Court will DENY UroPep's Motion to Preclude insofar as it seeks to bar testimony from Lilly's experts that is inconsistent with some aspect of the Court's indefiniteness analysis set forth in the Court's March 3, 2017, order. As indicated above, of course, Lilly will not be permitted to introduce evidence that is contrary to the Court's claim construction. To that extent only, the Court will GRANT UroPep's Motion to Preclude.

II. Testimony from Dr. Beavo Concerning Three Prior Art Compounds

In their respective briefs, the parties touch on the question whether Dr. Beavo should be permitted to testify in accordance with his second report, which concerns compounds known as flavoxate, MFCA, and Permixion, three compounds that are alleged to be PDE5 inhibitors. Those compounds are not alleged to be invalidating prior art, but Lilly seeks to introduce evidence regarding those compounds as relevant to written description, enablement, and damages. The relevance of the evidence to damages, according to Lilly, is that it shows the existence and availability of noninfringing, PDE5-inhibiting alternatives to tadalafil.

Based on the limited presentation made by the parties in their motions and at the pretrial conference, the Court is not persuaded that Dr. Beavo should be barred from testifying about the three compounds at trial. UroPep's motion to preclude his testimony on that subject is therefore DENIED.

IT IS SO ORDERED.

Dated: April 13, 2017

/s/ William C. Bryson
William C. Bryson
United States Circuit Judge

APPENDIX D

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff,

v.

ELI LILLY AND COMPANY,
Defendant.

Case No. 2:15-CV-1202-WCB

MEMORANDUM OPINION AND ORDER

Before the Court are the following motions: (1) Defendant Eli Lilly & Company's Motion for Summary Judgment That the Claims of the '124 Patent Are Anticipated ("Lilly's Anticipation Motion"), Dkt. No. 172; (2) Defendant Eli Lilly & Company's Motion for Summary Judgment of Indefiniteness ("Lilly's Indefiniteness Motion"), Dkt. No. 173; (3) Defendant Eli Lilly & Company's Motion for Summary Judgment of Noninfringement and No Willful Infringement ("Lilly's Noninfringement Motion"), Dkt. No. 174; and (4) Plaintiff UroPep's Motion for Confirmation of the Court's Claim Construction Order and Partial Summary Judgment of Infringement ("UroPep's Infringement Motion"), Dkt. No. 176.

Also before the Court is Defendant Eli Lilly and Company's Motion to Supplement Evidence in Support of Its Motion for Summary Judgment That the Claims of the '124 Patent Are Anticipated ("Lilly's Motion to Supplement Evidence"), Dkt. No. 213. The Court heard argument on the motions on February 21, 2017. Following the hearing, Eli Lilly & Company filed Defendant Eli Lilly & Company's Motion to Supplement the Record on Its Motion for Summary Judgment of Indefiniteness ("Lilly's Second Motion to Supplement Evidence"), Dkt. No. 232.

The Court DENIES each of the motions for summary judgment. To the extent that UroPep's motion for "confirmation of the Court's claim construction order" is a request for clarification of the Court's claim construction, the Court GRANTS that request and clarifies its claim construction order as indicated below. In all other respects, the Court DENIES the motions for summary judgment. The Court also GRANTS Lilly's Motion to Supplement Evidence and Lilly's Second Motion to Supplement Evidence.

BACKGROUND

The plaintiff, Erfindergemeinschaft UroPep GbR ("UroPep"), has filed this patent infringement action against the defendant, Eli Lilly & Company ("Lilly"). The action charges Lilly with direct and/or induced infringement of UroPep's U.S. Patent No. 8,791,124 ("the '124 patent") by marketing Cialis (the commercial name of Lilly's product in which tadalafil is the active ingredient) for the treatment of benign prostatic hyperplasia ("BPH," or an enlarged prostate). Asserted claim 1 of the '124 patent recites a method "for prophylaxis or treatment of benign

prostatic hyperplasia comprising administering to a person in need thereof an effective amount of an inhibitor of phosphodiesterase (PDE) V," excluding certain specified compounds.

Following a *Markman* hearing, the Court entered a claim construction order. Dkt. No. 131. At the claim construction hearing and in a subsequent telephonic conference, the Court suggested that the parties file papers addressing a validity question that arose during the claim construction hearing. Dkt. Nos. 115, 126. The parties briefed that issue, and the Court subsequently entered an order, Dkt. No. 149, denying Lilly's motion for summary judgment of noninfringement, and Lilly's motion for partial summary judgment that claims 1 and 3 of the '124 patent are invalid for failure to meet the written description requirement of 35 U.S.C. § 112, ¶ 1 (under the America Invents Act, that provision is now codified as 35 U.S.C. § 112(a); the America Invents Act, however, does not apply to this case, which arose from a patent application filed before that Act became effective).

The parties' summary judgment motions now before the Court direct the Court's attention to several issues that either would be case dispositive (in the case of Lilly's motions for summary judgment of anticipation, indefiniteness, and noninfringement) or would dispose of a significant part of the case (in the case of UroPep's motion for partial summary judgment of infringement).

DISCUSSION

I. The Cross-Motions for Summary Judgment Regarding Infringement

A. Claim Construction: Selective Inhibitors of PDE5

1. Clarification of the definition of selective inhibitors

In its opening claim construction brief, UroPep argued that the reference in claim 1 of the '124 patent to "an inhibitor of phosphodiesterase (PDE) V" should be construed to mean a "selective" inhibitor of PDE V.[1] UroPep made that argument based on the specification of the '124 patent and the prosecution history of its parent patent, U.S. Patent No. 8,106,061 ("the '061 patent"). *See* Plaintiff UroPep's Corrected Opening Claim Construction Brief, Dkt. No. 105, at 23-25; *see also* Plaintiff UroPep's Reply Claim Construction Brief, Dkt. No. 109, at 2 & n.2 ("[T]he inventors of UroPep's patent-in-suit sought to claim the use of selective PDE V inhibitor compounds to achieve

[1] As the Court has noted previously, the nomenclature for specific phosphodiesterases has changed over time. As of the priority date of the '124 patent, in July 1997, the specific phosphodiesterases were identified by Roman numerals, as in PDE I through PDE V. More recently, it has become conventional to identify the specific phosphodiesterases by Arabic numerals, as in PDE1 through PDE5. Although the Court has previously used the prior convention employed in the patent, it appears that the use of Arabic numerals has become universal, so henceforth the Court will use that more modern form except when quoting or discussing language from the '124 patent or its prosecution history.

previously unimagined therapeutic benefits.").[2] UroPep described a "selective" inhibitor as one that is "relatively selective for PDE V." Dkt. No. 105, at 25. In support of that characterization, UroPep cited prosecution history indicating that the patentees had distinguished their invention over the prior art by emphasizing the selective nature of their PDE V inhibitors. *Id.* at 23-24. UroPep also discussed a portion of the specification of the '124 patent that addressed what UroPep's expert described as an assay to identify compounds that are particularly potent inhibitors of specific phosphodiesterases, including PDE V. *Id.* at 25. UroPep's expert explained that a compound that is able to inhibit one specific PDE enzyme when the compound is present in low concentrations, without similarly inhibiting other PDEs, is generally considered to be a "selective" inhibitor. *See* Corrected Declaration of Nicholas K. Terrett, Ph.D. Regarding Claim Construction of U.S. Patent No. 8,791,124, Dkt. No. 105-1, at ¶ 42. As support for his view, the expert cited U.S. Patent No. 6,492,371, which defined "selective PDE5 inhibitors" as "those that inhibit PDE5, but do not significantly inhibit other PDE enzymes." *Id.* at ¶ 43.

In an October 21, 2016, order, the Court had occasion to address that claim construction issue in the context of ruling on Lilly's previous motions for summary judgment

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[2] Lilly asserts that UroPep did not argue in favor of a selectivity requirement during claim construction. Defendant Eli Lilly & Co.'s [Corrected] Opposition to Plaintiff Erfindergemeinschaft UroPep's Motion for Partial Summary Judgment of Induced Infringement, Dkt. No. 194, at 1 n.1. In fact, UroPep clearly made that argument in both its opening claim construction brief and in its reply claim construction brief. However, while UroPep argued in favor of a selectivity requirement, it did not urge the Court to adopt the "20-fold" selectivity test that the Court ultimately adopted.

of noninfringement, Dkt. No. 119, and invalidity, Dkt. No. 120. The Court agreed with UroPep and construed the term "an inhibitor of phosphodiesterase (PDE) V" to mean "a compound that selectively inhibits PDE V." With respect to how great the differential inhibitory effect must be in order for a PDE inhibitor to be regarded as "selective," the Court looked to the specification of the '124 patent, which states that "[a] substance is considered an inhibitor of an sPDE if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase (sPDE)."[3] '124 patent, col. 8, ll. 5-9. Based on that passage in the specification, the Court concluded that "a selective inhibitor of a specific PDE is at least 20 times more effective in inhibiting that specific PDE as compared to all other specific PDEs." The Court then construed the term "an inhibitor of phosphodiesterase (PDE) V" to mean "a compound that selectively inhibits PDE V." Memorandum Opinion and Order (Oct. 21, 2016), Dkt. No. 149, at 27.

In Lilly's Noninfringement Motion, Lilly argues that the Court's construction of the term "an inhibitor of phosphodiesterase (PDE) V" requires that the Court grant summary judgment of noninfringement because tadalafil is not at least 20 times as potent in inhibiting PDE5 as in inhibiting PDE11A1, a specific PDE that was not identi-

[3] More generally, the IC50 value represents the concentration of an inhibitor that is required for 50% inhibition of the function of its target, in this case a PDE enzyme. The potency of the inhibitor with respect to a specific PDE can be quantified by using the IC50 value for a specific PDE. The relative selectivity of an inhibitor with respect to two different PDEs can be expressed as the ratio of the IC50 values for those two PDEs, or the IC50 ratio.

fied in the '124 patent. In particular, Lilly argues that although the evidence shows that tadalafil is vastly more potent as an inhibitor of PDE5 than as an inhibitor of PDEs 1-4 and 6-10, tadalafil's inhibiting effect on PDE5 is only about 14 times as great as its inhibiting effect on PDE11A1. For that reason, according to Lilly, tadalafil cannot be regarded as a "selective" PDE5 inhibitor within the meaning of the Court's construction of that term.

UroPep has responded to Lilly's motion for summary judgment of noninfringement and has filed its own separate motion seeking partial summary judgment of infringement. UroPep's Infringement Motion, Dkt. No. 176. Lilly's motion has spawned a response from UroPep, Dkt. No. 189; a reply from Lilly, Dkt. No. 200; and a surreply from UroPep, Dkt. No. 217. UroPep's motion has given rise to a response from Lilly, Dkt. No. 194; a reply from UroPep, Dkt. No. 202; and a surreply from Lilly, Dkt. No. 215.

The multiplicity of briefs addressed to the issue of infringement has led to considerable overlap in the briefing on the issue of the proper meaning of "selective inhibitor of PDE5." The essence of the dispute at this point, however, is simply stated: Lilly argues that the Court's interpretation of "selective PDE5 inhibitor" requires a comparison between the potency of a particular compound in inhibiting PDE5 and the potency of that compound in inhibiting any other currently known PDE, including PDE 6 and PDE11A1. UroPep, on the other hand, argues that the Court's interpretation of "selective PDE5 inhibitor" requires a comparison between the potency of a particular compound in inhibiting PDE5 and the potency of that compound in inhibiting other specific PDEs from among the group consisting of PDE1 through PDE4.

Quoting the Court's statement in its October 21, 2016, order, that "a selective inhibitor of a specific PDE is at least 20 times more effective in inhibiting that specific PDE as compared to all other specific PDEs," Dkt. No. 149, at 27, Lilly argues that the Court has already answered that question and has held that a selective PDE5 inhibitor must be at least 20 times as effective in inhibiting PDE5 compared to all other currently known PDEs, not just PDE1 through PDE4, the only PDEs discussed in the '061 and '124 patents.

The Court disagrees with Lilly's characterization of the Court's earlier order. Contrary to Lilly's contention, the Court's October 21, 2016, order did not advert to the issue of which other PDEs were to be considered when assessing the comparative potency of a particular compound to inhibit PDE5, as that issue was not the one in dispute at that time.

The issues before the Court at the time of the Court's October 21, 2016, order were (1) whether the '124 patent requires that the recited PDE5 inhibitor be selective and (2) if so, how much more potent must the inhibitor be with regard to PDE5 in order to be deemed selective within the meaning of the '124 patent. Those questions were not focused on the identity of the other specific PDEs with which the selectivity of the PDE5 inhibitor was to be compared. For that reason, the Court did not specifically address that issue in its October 10, 2016, order. From the parties' current arguments and the very different interpretations the parties have assigned to the Court's previous order regarding the "selective" requirement, it is clear that further claim construction by the Court is required. In order to determine whether the PDE5 inhibitor claimed in the '124 patent must be selective as to all

specific PDEs or only as to some of them, it is necessary to return to the source of the Court's conclusion that the PDE5 inhibitors claimed in the '124 patent had to be selective at all.

In the course of the prosecution of the parent '061 patent, as the Court previously explained, the UroPep inventors distinguished the pending claims of the application from a prior art reference cited by the examiner on the ground that the "compounds of the currently pending claims are selective inhibitors of PDE IV and/or PDE V." Amendment (Mar. 7, 2010), at 10 ('061 File History), Dkt. No. 176-22; *see also* Amendment (Oct. 27, 2009), at 10. By contrast, the inventors stated that the compounds of the prior art reference that were shown to have PDE V inhibitory activity "do not predictably possess selective inhibitory PDE V and/or PDE IV activity, as required by the currently pending claims," because the prior art compounds that possess PDE V inhibitory activity "also possess PDE I and/or PDE II inhibitory activity." *Id.* at 10-11. For that reason, the inventors stated, the prior art reference did not exhibit the selective inhibition of PDE IV and/or PDE V that the inventors characterized as highly valuable in the treatment of prostatic disorders such as BPH.

The discussion of the nonselective prior art reference in the prosecution history of the parent '061 patent establishes that the PDE V inhibitors claimed in that patent had to be selective for PDE5 at least as compared to PDE I and PDE II. It did not, however, establish a broader principle of selectivity applicable to all types of PDEs, known and unknown. That is, the prosecution history contained no general statement that the claimed PDE IV and PDE V inhibitors have to be selective vis- -vis all possible

specific PDEs. The prosecution history of the parent '061 patent therefore does not support Lilly's proposed claim construction.

A second source of guidance as to how to measure the selectivity of a PDE5 inhibitor for purposes of the '124 patent can be found in the specification of the '124 patent. The specification cites three articles that discuss the mechanism of action of PDEs. '124 patent, col. 1, ll. 47-52. The specification then states that "from those publications as well as two other references, there is further known the distinction of a number of subesterases of PDE, the specific phosphodiesterases (sPDE)." *Id.*, col 1, ll. 53-59. The specification then adds, "There is distinguished between five different sPDEs which are differently distributed in the individual organs and organ systems." *Id.*, col. 1, ll. 60-65.

While the language of that passage is clumsy, the message is clear: that the sPDEs under discussion were the original five sPDEs, PDE1 through PDE5. We know that for several reasons. First, each of the five references cited in the specification discusses PDE1 through PDE5, not the other specific phosphodiesterases to which Lilly refers.[4] Second, the patent uses the abbreviation "sPDE" to refer to those five specific phosphodiesterases, a further indication that for purposes of the patent, those five PDEs were the only specific phosphodiesterases of concern. '124

[4] The only allusion to any other specific PDEs in the five cited references is in a table in one of the articles that refers to PDE VI, VII, and VIII with the notation "to be characterized." C.D. Nicholson & M. Shahid, *Inhibitors of Cyclic Nucleotide Phosphodiesterase Isoenzymes— their Potential Utility in the Therapy of Asthma*, 7 Pulmonary Pharmacology 1, 4 (Table 1) (1994). The rest of that article, like the other articles and the book cited in that portion of the '124 specification, focuses on PDE1 through PDE5.

patent, col. 1, line 59. Third, in the context of the discussion of selective PDE5 inhibition, the specification explicitly refers to the "five different sPDEs which are differently distributed in the individual organs and organ systems and exhibit different levels of effectiveness according to their distribution." *Id.*, col. 1, ll. 60-63. That passage indicates that for purposes of the '124 patent, the class of phosphodiesterases identified as "sPDEs" refers to the five phosphodiesterases, PDE1 through PDE5, that were discussed in the five cited references. Accordingly, the context of the discussion of the selective PDE inhibitors in the '124 specification supports UroPep's argument that the group of PDE inhibitors that the specification was addressing were inhibitors of PDE1 through PDE5.

A third important consideration in determining the proper interpretation of the term "selective inhibitor," as used in the '124 specification, is the effect that adopting Lilly's interpretation would have on any attempt to make sense of either the '124 patent or the parent '061 patent. The two patents (which have essentially identical specifications) list a number of "[p]referred selective inhibitors" of PDE1, PDE4, and PDE5. The problem with Lilly's interpretation of the phrase "selective PDE5 inhibitor" is that many, if not all, of the exemplary "preferred" inhibitor compounds set forth in the common specification of the '061 and '124 patents and expressly referred to as "[p]referred selective inhibitors," '124 patent, col. 2, line 28, would fail to qualify as selective inhibitors of PDE5 under Lilly's proposed standard.

As the Federal Circuit has frequently stated, a claim construction that has the effect of excluding a preferred embodiment is disfavored. *Clare v. Chrysler Grp. LLC*,

819 F.3d 1323, 1331 (Fed. Cir. 2016); *PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 747, 755 (Fed. Cir. 2016); *Adams Respiratory Therapeutics v. Perrigo Co.*, 616 F.3d 1283, 1290 (Fed. Cir. 2010); *On-Line Techs. v. Bodenseewerk Perkin-Elmer*, 386 F.3d 1133, 1138 (Fed. Cir. 2004) (citing cases); *Hoeschst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1581 (Fed. Cir. 1996) ("[I]t is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment or that persons of skill in this field would read the specification in such a way."). In this case, it is not clear that any of the "preferred selective inhibitors" set forth in the '124 specification would qualify as selective inhibitors of PDE5 under the "20-fold" test. And a construction that would have the effect of excluding all of the embodiments of an invention is even more disfavored; such a construction, the Federal Circuit has held, is "rarely, if ever, correct." *Nellcor Puritan Bennett, Inc. v. Masimo Corp.*, 402 F.3d 1364, 1368 (Fed. Cir. 2005); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) (holding that a construction excluding all of the embodiments of a claim "would require highly persuasive evidentiary support").

An examination of the '061 patent in light of Lilly's definition of selectivity is particularly instructive, because Lilly's definition clashes with the text of the '061 patent. Claim 1 of that patent is drawn to a method of treating a prostatic disease "comprising administering a selective inhibitor" of PDE4 or PDE5, wherein said inhibitor is selected from the group consisting of" six identified compounds.[5] The problem is that under Lilly's definition, none

[5] The six compounds set forth in claim 1 of the '061 patent are all discussed in the common specification of the '061 and '124 patents,

of those six compounds would qualify as "selective" PDE4 or PDE5 inhibitors.

Lilly notes that as of 1997, the filing date of the application from which the '061 and '124 patents claim priority, two other specific PDEs were known, PDE6 and PDE7. However, the evidence proffered by the parties shows that by 1997, PDE7 had not been identified as present in any human tissue, so the differential inhibition of PDE7 was not pertinent to the issue addressed in the original specification. Validity Expert Report of Dr. Andrew Bell, Dkt. No. 193-3, at ¶ 68. As for PDE6, UroPep points to evidence that as of July 1997 "it was believed that all PDE5 inhibitors would also inhibit PDE6, as there had not yet been a report of an inhibitor that was highly selective for PDE5 over PDE6." *Id.* at ¶ 21 (citing Edmund Sybertz & Michael Czarnieki, Inhibitors of PDE1 and PDE5 cGMP Phosphodiesterases: Patents and Therapeutic Potential, 7(6) Expert Opinion on Therapeutic Patents 631, Dkt. No. 202-3, at 633.).[6] In light of that evidence, which the Court credits, Lilly's construction of the term "selective" would mean that none of the compounds listed in claim 1 of the '061 patent would qualify as "selective inhibitors of PDE V."

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although one of the listed compounds (sildenafil) is described with a different nomenclature in the specification than in the claim.

[6] Lilly's expert, Dr. David Rotella, provided evidence that is consistent with UroPep's in this regard. He offered data with respect to three of the six compounds listed in claim 1 of the '061 patent—zaprinast, E4021, and sildenafil—and none of them qualified as selective inhibitors of PDE4 and/or PDE5 when PDE6 was taken into account. Dr. Rotella provided no data for the IC50 values of the other three compounds listed in claim 1 of the '061 patent. Expert Report of David Rotella, Ph.D., Dkt. No. 177-8, at ¶ 125.

Yet claim 1 of the '061 patent states that the "selective inhibitor" used in the claimed method must be "selected from the group" consisting of the six identified compounds. Thus, Lilly's test cannot be right; not only would it result in claim 1 of the '061 patent having no scope, but it would also be squarely contrary to the language of claim 1 that effectively defines each of the six identified compounds as selective inhibitors.

2. The effect of the claim construction issue on tadalafil

Even if the specific PDEs that are referenced in the '124 patent are regarded as including PDE6 and PDE7 on the ground that those compounds were known by the priority date of the '124 patent in 1997, the infringement analysis in this case would not be affected. That is because the parties agree that tadalafil is more than 20 times as selective for PDE5 as for any of the other sPDEs from PDE1 through PDE7.

In fact, Lilly acknowledges that tadalafil is more than 20 times as effective in inhibiting PDE5 as compared to any of the other PDEs except for PDE11A1. Yet PDE11A1 was unknown as of the priority date of the '124 patent. Accordingly, although Lilly argues that later-discovered PDEs should be considered in determining the coverage of the '124 patent claims, the proper analysis of the meaning of terms used in the claims is based on the state of the art as of the priority date of the patent, which in this case is 1997, before PDE11A1 was discovered. *See Kopykake Enters., Inc. v. Lucks Co.*, 264 F.3d 1377, 1383 (Fed. Cir. 2001) ("[W]hen a claim term understood to have a narrow meaning when the application is filed later acquires a broader definition, the literal scope of the term is limited to what it was understood to mean at the time of

filing."); *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1352-54 (Fed. Cir. 2000); *see generally Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 968 (Fed. Cir. 1995) (en banc) ("[T]he focus in construing disputed terms in claim language is what one of ordinary skill in the art at the time of the invention would have understood the term to mean."), *aff'd*, 517 U.S. 370 (1996). Accordingly, it is clear that tadalafil satisfies the requirement of being 20 times as potent in inhibiting PDE5 than it is in inhibiting any other PDE known as of the priority date of the '124 patent. For that reason, the Court would reject Lilly's noninfringement argument even if it accepted the portion of Lilly's argument urging that the selective inhibitory potency of particular compounds for PDE5 be compared to PDE1 through PDE7, rather than to PDE1 through PDE4.

3. Lilly's other noninfringement arguments

Lilly makes other arguments in support of its motion for summary judgment of noninfringement, none of which is persuasive. First, Lilly points out that UroPep's expert has not performed the assay described in the patent to determine whether tadalafil is a "selective" inhibitor of PDE5 with an IC50 ratio of 20:1, which Lilly refers to as the "peak fraction" test. '124 patent, col. 7, line 35 through col. 8, line16. Because UroPep has not performed the selectivity assay described in the patent, Lilly argues that UroPep has not shown that tadalafil "meets the Court's 20-fold threshold as to other PDEs under a peak fraction method as stated in the '124 patent and as relied upon by the Court." Lilly's Noninfringement Motion, at 4. Lilly's argument on that point, however, depends on its argument that the "other PDEs" to be compared to PDE5 are all of the other currently known PDEs, including

PDE11A1. While it is true that UroPep's expert did not perform the specific assay described in the patent, there is ample evidence in the summary judgment record that tadalafil is more than 20 times as selective for PDE5 than for PDE1 through PDE4 under any known test.

In his infringement report, UroPep's expert, Dr. Andrew Bell, pointed to a 2003 reference that determined the IC_{50} ratios for tadalafil with respect to PDE5 as compared to PDE1 through PDE5. That data showed that tadalafil was in excess of 2000 times as potent in inhibiting PDE5 as compared to PDE1 through PDE4. Infringement Expert Report of Dr. Andrew Bell, Dkt. No. 177-11, at ¶ 16, citing Alan Daugan et al., The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor, 46 J. of Med. Chemistry 4533 (2003). In addition, Dr. Bell relied on the Cialis label, which states that tadalafil is more than 10,000-fold more potent in inhibiting PDE5 than in inhibiting PDE1 through PDE4. Dkt. No. 177-34, at 11.

Lilly's expert, Dr. Rotella, stated that tadalafil does not satisfy the "20-fold" test, but he reached that conclusion only because he included PDE11A1 in the set of PDEs to consider in looking at the inhibitory effect of tadalafil. Expert Report of David Rotella, Ph.D., Dkt. No. 177-8. Pointing to the Cialis label, which states that tadalafil is "14-fold more potent for PDE5 than for PDE11A1," Dr. Rotella concluded that tadalafil did not satisfy the Court's "20-fold" definition. Because Dr. Rotella relied on the measurements reported in the Cialis label as proof that tadalafil does not satisfy the selectivity requirement of the '124 patent, it is apparent that Dr. Rotella regarded the measurements reported in the Cialis label as a reliable measure of the relative potency of tadalafil with respect to PDE5 as compared to other PDEs. *Id.* at ¶ 135. Yet

the Cialis label states that tadalafil is more than 10,000-fold more potent for PDE5 than for PDE1 through PDE4. *Id.* Because a finder of fact could rely, as Dr. Rotella did, on the Cialis label as a reasonable basis for assessing the selectivity of tadalafil, it is clear that the evidence is sufficient to allow a finder of fact to conclude that tadalafil satisfies the "20-fold" test.

Based on the patent's description of an assay to determine selectivity, *see* '124 patent, col. 7, line 35, through col. 8, line 16, Lilly next argues that this assay would have disclosed the presence of other PDEs in the tissue being studied even if those PDEs were not known as of the priority date of the '124 patent. Therefore, according to Lilly, the use of this assay on prostatic tissue, as discussed in the common '061 and '124 specification, would have disclosed that tadalafil is not more than 20 times as potent in inhibiting PDE5 than in inhibiting an unknown PDE that would later be identified as PDE11A1. On this point, Lilly argues that "[i]f a person of ordinary skill in the art performed the peak fraction test [the patent's selectivity assay] for a given compound on tissue from the prostate in 1997, PDE11 would likely be represented in a peak fraction—without knowing its identity—and may have been evaluated against other peak fractions, including PDE5's peak fraction, to determine relative selectivity among peak fractions."

The evidence Lilly cites in support of that argument is speculative. Lilly relies on the *Responsive Expert Report of Joseph A. Beavo, Ph.D.*, Dkt. No.177-7, in which Dr. Beavo stated that even though PDE11 was not known in 1997, a person of skill in the art "might still be able to use a peak fraction method with prostatic tissue to determine an inhibitor's selectivity between various fractions, one of

which would likely contain PDE11. The peak fraction assays, therefore, could have picked up PDE11 activity if abundant enough in that tissue." *Id.* at ¶ 28. Even apart from the fact that Dr. Beavo referred to PDE11 in general, and not PDE11A1 in particular, the several qualifications attached to that statement are such that the statement does not support the conclusion that Lilly wishes the Court to draw from it. The cited portion of Dr. Beavo's responsive expert report does not establish to the Court's satisfaction that a person of skill in the art performing the selectivity assay described in the patent would necessarily have noticed that the potency of tadalafil in inhibiting PDE5 was not much greater than its potency in inhibiting another PDE that was later determined to be PDE11A1. Dr. Beavo states that a person of skill "could have picked up PDE11," but only "if abundant enough in that [prostatic] tissue." Lilly has presented no evidence showing that PDE11A1 is abundant enough in prostatic tissue to be picked up in the assay described, nor that a person of skill in the art would necessarily have used prostatic tissue in evaluating tadalafil's selectivity. *See, e.g.*, Michael C. Truss et al., *Porcine Detrusor Cyclic Nucleotide Phosphodiesterase Isoenzymes: Characterization and Functional Effects of Various Phosphodiesterase Inhibitors in Vitro*, 45(5) Urology 893 (1995) (using porcine bladder tissue) (cited in '124 patent, col. 7, ll. 43-45), Dkt. No. 190-4. For those reasons, Dr. Beavo's report does not establish that the reference to PDEs in the '124 specification must necessarily be understood to include all PDEs, known and unknown as of 1997, not just PDE1 through PDE5.

The parties disagree about whether PDE11A1 is found in the prostate, as opposed to a different member of the PDE11 family, PDE11A4. Lilly cites a 2000 article that reported finding PDE11A1 in the prostate. *See*

Lindsay Fawcett et al., *Molecular Cloning and Characterization of a Distinct Human Phosphodiesterase Gene Family: PDE11A*, 97 PNAS 3702 (2000), Dkt. No. 191-17. UroPep, on the other hand, cites a later article, sponsored by a joint venture between Lilly and Icos Corporation, that reported finding PDE11A4 in the prostate, but not PDE11A1, despite additional testing for the presence of PDE11A1. *See* K. Loughney et al., *3',5'-Cyclic Nucleotide Phosphodiesterase 11A: Localization in Human Tissues*, 17 Int'l J. of Impotence Research 320 (2005), Dkt. No. 189-22, at 323-24. The Court does not find it necessary to resolve that factual issue in order to conduct a proper claim construction. That is because the Court rejects Lilly's argument that, if PDE11A1 is located in the prostate, it would necessarily have been discovered by a person performing the described selectivity assay on prostatic tissue. Dr. Beavo's testimony on that point is too speculative to support that conclusion. The Court therefore rejects Lilly's argument that the patent's described selectivity assay supports Lilly's contention that the use of the term "selective inhibitor" necessarily refers to selectivity over all currently known PDEs, including PDE11A1.

In sum, the Court concludes that the '124 patent requires the accused compound to be selective for PDE5 as compared to all of the other PDEs addressed in the '124 specification, i.e., PDE1 through PDE4.

B. Treatment of BPH

A second issue raised in the motions for summary judgment is also in large part a new claim construction issue. Lilly argues that the phrase "treatment of benign

prostatic hyperplasia" in claim 1 of the '124 patent is limited to shrinking or slowing the growth of the prostate, as opposed to ameliorating the signs and symptoms of BPH. Because Lilly contends that tadalafil does not shrink or retard the growth of the prostate, but instead ameliorates the signs and symptoms of BPH, Lilly argues that summary judgment of noninfringement should be granted.

The problem with that theory is that it is contrary to the specification of the '124 patent. The '124 patent does not define "treatment," but it describes the effect of the claimed PDE5 inhibitor as follows: "A well-aimed inhibition of these isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, in particular vessels, being observed. Therefore, they have an excellent efficiency in the treatment of prostatic diseases." '124 patent, col. 2, ll. 11-16.

That passage makes clear that the '124 patent regards the relaxation of prostatic muscles as leading to the treatment of BPH. Because the relaxation of prostatic muscles addresses the symptoms of BPH, but does not shrink or retard the growth of the prostate, it is clear that ameliorating the symptoms of BPH constitutes the "treatment" referenced in the claims. For that reason, the Court rejects Lilly's argument that tadalafil cannot be regarded as "treating" BPH because it does not shrink or retard the growth of the prostate.

Although the Court rejects Lilly's argument that the "treatment" of BPH does not encompass the treatment of the signs and symptoms of BPH, Lilly makes a separate and more persuasive point. Lilly argues that in order to satisfy the requirement that the claimed method result in the "treatment" of BPH, the patient must be suffering

from BPH in the first place.[7] As noted, the patent makes clear that the "treatment" of BPH requires that the patient suffer from BPH, even though the treatment may only ameliorate the signs and symptoms of BPH and not shrink or retard the growth of the prostate. On that point, the Court concludes that Lilly is correct. BPH is often associated with lower urinary tract symptoms, and it is fair to characterize the treatment of those symptoms, when they are associated with BPH, as the treatment of BPH. However, lower urinary tract symptoms can occur even in the absence of an enlarged prostate. And when such symptoms occur in the absence of an enlarged prostate, the treatment of those symptoms does not constitute the treatment of BPH. Thus, in order to prove infringement (and in order to determine the amount of any infringement-based damages), UroPep will be required to prove that Lilly has directly or indirectly caused the treatment of BPH (or symptoms traceable to BPH); it will not be enough to show that tadalafil is frequently prescribed to address lower urinary tract symptoms regardless of whether those symptoms are caused by BPH. Where those symptoms are not associated with BPH, the act of prescribing tadalafil to address those symptoms does not infringe.

UroPep has not offered the Court any firm basis in the summary judgment record for determining how frequently Cialis is prescribed for non-BPH-based lower urinary tract symptoms. For that reason, while it may be true that there is infringement in cases in which Cialis is prescribed for the lower urinary tract symptoms that are

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[7] The claims of the '124 patent are not limited to the "treatment" of BPH, but also include the "prophylaxis" of BPH. The discussion in the text relates only to the "treatment" objective of the claims.

caused by BPH, the scope of any such infringement remains undetermined. Accordingly, the Court DENIES *UroPep's Infringement Motion.*

C. Summary Judgment of No Willfulness

Lilly next argues that the Court should grant summary judgment that it is not liable for willful infringement.

Determining willfulness is a highly fact-based endeavor. In this case, it is undisputed that by October 2014 Lilly was aware of the '124 patent and UroPep's assertion that the patent read on tadalafil. Lilly argues that it had good faith reasons to believe that the patent did not read on tadalafil and that the patent was invalid. The Court recognizes that the arguments Lilly has made in its summary judgment motions of noninfringement and invalidity provide some support for its contention that it was at least not clear that the patent was both valid and infringed. The Supreme Court has made clear, however, that the issue of willfulness turns not on the objective reasonableness of the defendant's conduct, but on the defendant's subjective beliefs. *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1933 (2016) ("The subjective willfulness of a patent infringer, intentional or knowing, may warrant enhanced damages, without regard to whether his infringement was objectively reckless.").

A jury might well conclude from the objective evidence regarding the disputed claim construction and invalidity issues that Lilly did not subjectively believe it was infringing a valid patent. *See WesternGeco L.L.C. v. Ion Geophysical Corp.*, 837 F.3d 1358, 1363 (Fed. Cir. 2016) (even after *Halo*, the objective reasonableness of the accused infringer's positions can still be relevant to the section 284

issue). But Lilly has offered no other summary judgment evidence going to the subjective beliefs of its decisionmakers. Given the state of the evidence presented on summary judgment, the Court cannot conclude at this juncture that it would be unreasonable for a jury to find that Lilly knew the '124 patent was both valid and infringed. The Court therefore DENIES Lilly's motion for summary judgment of no willfulness.

With that said, the Court is mindful of the Supreme Court's admonition that case law has channeled the courts' discretion in granting enhanced damages under section 284 of the Patent Act, limiting the award of such damages "to egregious cases of misconduct beyond typical infringement." *Halo*, 136 S. Ct. at 1935. The Court will therefore closely monitor the evidence at trial to determine whether UroPep has demonstrated that level of willfulness necessary to trigger the enhanced damages provision of section 284.[8]

For the foregoing reasons, the Court DENIES the requests for summary judgment in both Lilly's Noninfringement Motion and UroPep's Infringement Motion.

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[8] UroPep argues that its showing of willfulness is buttressed by various acts that it characterizes as "litigation misconduct" on Lilly's part. Those acts include Lilly's characterization in a brief of a point made by its expert, Dr. Beavo; Lilly's position on a claim construction issue regarding whether claim 1 of the '124 patent is functional in nature; and Lilly's failure to call a particular journal article to the Court's attention during the summary judgment briefing. The Court does not regard any of those cited acts as constituting litigation misconduct. Lilly's claim construction argument, in particular, was made in response to an invitation from the Court to address that question. The Court will not permit UroPep to rely on those supposed acts of litigation misconduct as part of its willfulness case at trial.

II. Lilly's Motion for Summary Judgment of Anticipation

In Lilly's Anticipation Motion, Dkt. No. 172, Lilly argues that the '124 patent is anticipated by a 1994 book authored by C.S. Cheung and K. Deaton entitled "TCM Management Benign Prostate Hyperplasia-Long Bi (Prostatism)." That book, according to Lilly, discloses the use of compositions containing *Herba Epimedii* (also known as "Horny Goat Weed") to treat the symptoms of BPH (which the reference also characterizes as "prostatism" or "Long Bi").

According to Lilly's experts, the compound icariin is a major constituent of *Herba Epimedii* and is more than 20 times as potent as an inhibitor of PDE5 than as an inhibitor of PDE1 through PDE4. Lilly argues that the 1994 Cheung publication qualifies as a "printed publication" within the meaning of 35 U.S.C. § 102(b) (2006) (35 U.S.C. § 102(a)(1) of the America Invents Act, which does not apply to this case) and that it therefore constitutes anticipating prior art for purposes of the anticipation statute, section 102 of the Patent Act. For that reason, Lilly argues, it is clear that the 1994 Cheung publication anticipates the claims of the '124 patent and that summary judgment of anticipation should be granted.[9]

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[9] Lilly relies on 35 U.S.C. § 102(b), which provides, in pertinent part, that a claim is anticipated if the invention was "described in a printed publication . . . more than one year prior to the date of the application for patent in the United States." Lilly does not rely on 35 U.S.C. § 102(a), which provides that a claim is anticipated if the invention was "described in a printed publication . . . before the invention thereof by the applicant for patent." Accordingly, in order to anticipate, the Cheung reference must have qualified as a "printed publication" before the critical date for the '124 patent, or July 9, 1996, not the priority date for the patent, July 9, 1997.

UroPep has several responses. First, UroPep contends that the Cheung publication, a self-published book, is not widely accessible. In fact, UroPep was able to find that the Cheung book is currently available in only three libraries worldwide. UroPep argues that under Federal Circuit precedents, the limited accessibility of the Cheung publication prevents the book from qualifying as a "printed publication," as provided in section 102(b) of the Patent Act. Second, UroPep argues that the Cheung publication is "junk science" and is not a reliable source of medical information. UroPep points to problems with the study reported in Cheung; in particular, UroPep argues that it is not even clear that the formulation ingested by the subjects of the Cheung study actually included Horny Goat Weed. Finally, UroPep argues that the Cheung reference does not disclose the administration of "an effective amount" of a PDE5 inhibitor.

A. Whether Cheung Is a "Printed Publication"

There is a considerable volume of case law dealing with whether a particular writing qualifies as a "printed publication" for purposes of section 102. Much of the case law turns on whether a very small number of copies of a writing are sufficient to qualify the writing as a "printed publication." That issue calls for a legal determination based on underlying facts, *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009). The Federal Circuit has emphasized that the inquiry is heavily dependent on the particular circumstances of each case. *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194-95 (Fed. Cir. 2008) ("The decision whether a particular reference is a printed publication 'must be approached on a case-by-case basis.'") (quoting *In re Cronyn*, 890 F.2d 1158, 1161 (Fed.

Cir. 1989)). The circumstances on which the "printed publication" issue turns include factors such as how widely circulated the reference was, whether the reference was indexed in a manner that would have made it accessible to interested persons with a reasonable degree of effort, and whether the reference was distributed with a pledge or understanding that the contents would remain confidential.

The principle underlying the "printed publication" rule is that "once an invention is in the public domain, it is no longer patentable by anyone." *In re Hall*, 781 F.2d 897, 898 (Fed. Cir. 1986). To satisfy the requirement that the printed publication be considered "in the public domain," it must have been "sufficiently accessible to the public interested in the art." *In re Cronyn*, 890 F.2d at 1160. And to be considered publicly accessible, the reference must have been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008).

Based on the summary judgment record, the Court finds that there is a genuine dispute as to the underlying facts regarding whether persons of ordinary skill in the treatment of BPH, exercising reasonable diligence, would have been able to locate the Cheung reference. The record reveals the following: The copyright date of the Cheung book is November 1994, and the name of the organization associated with the publication is the Harmonious Sunshine Cultural Center of San Francisco, Dkt. No. 177-21. The book is 107 pages long, is not peer-reviewed, and deals with traditional Chinese herbal medicine approaches to various maladies including benign

prostatic hyperplasia. It is offered for sale on the website of the Harmonious Sunshine Cultural Center. UroPep has placed evidence in the record that the website of that organization did not exist in 1997, and Lilly has not offered evidence to the contrary.

UroPep has placed in the record evidence that the Cheung book was self-published and is not available on Amazon.com, Dkt. No. 187-12. According to WorldCat, the world's largest network of library content, it is currently listed in only three library catalogues in the world: the Pacific College of Oriental Medicine in San Diego, Touro College in New York, and the Hong Kong Baptist University in Hong Kong, Dkt. Nos. 187-10, 187-11. Lilly has offered evidence that the Cheung book is available and catalogued at a fourth library, the library of the American College of Traditional Chinese Medicine in San Francisco ("ACTCM"), founded by Dr. Cheung, Dkt. No. 201-6 & Exh. A, although WorldCat apparently contains no entry for the book at that library.

In a motion to supplement the record, filed on the day before sur-reply briefs on the summary judgment motions were due, Lilly moved to supplement the record with a declaration from an associate of Dr. Cheung. The declaration stated that Dr. Cheung regularly made his publications available for sale to persons on a mailing list and that it was his practice to immediately provide his publications to the library of the ACTCM. Dkt. No. 227-2.[10]

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[10] UroPep has objected on timeliness grounds to *Lilly's Motion to Supplement Evidence*. Lilly responds that the untimely submission of the new evidence is excused because UroPep did not raise the "printed publication" issue until it filed its opposition to *Lilly's Anticipation Motion*. It is true, as Lilly contends, that UroPep did not point out specific infirmities in the Cheung references, such as the failure to satisfy the "printed publication" requirement before filing

What is left unresolved by the parties' submissions is whether the Cheung book was lodged in any, some, or all of the four identified libraries as of July 1996; whether the book was indexed and catalogued as of that date; and, depending on the answers to those questions, whether a person of skill in the art pertinent to the '124 patent invention, exercising reasonable diligence, would have discovered the book at that time. Those open questions go to whether the Cheung book constitutes a "printed publication" within the meaning of section 102(b). In light of the burden on Lilly to show by clear and convincing evidence that the anticipating reference was publicly accessible as of the priority date of the '124 patent, the open factual questions bearing on whether the Cheung reference qualifies as a

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its opposition to *Lilly's Anticipation Motion*. While the parties dispute whether the fault lies with Lilly for not being specific enough regarding the portion of the Cheung reference on which it intended to rely or with UroPep for not calling out the "printed publication" requirement prior to its opposition to the summary judgment motion, the fact of the matter is that the printed publication issue arose late in the process, at which point Lilly had a relatively short period within which to gather evidence to support its motion on that issue. Without making a finding as to where fault lies in this matter, the Court believes it was not unreasonable for Lilly to have submitted a modest amount of supplemental evidence when it did. That evidence consists of one new item—a five-page affidavit from a practitioner of traditional Chinese medicine who states that Dr. Cheung maintained a catalogue of his publications for sale to mailing list subscribers and that it was Dr. Cheung's practice to make a copy of his monographs available to ACTCM. The Court therefore GRANTS Lilly's motion to file the supplemental evidence. However, the Court has determined that the new material does not affect the Court's ruling that summary judgment of anticipation should be denied. The evidence adds little more than support for the inference that the Cheung book has been in the ACTCM library since shortly after its publication in November 1994, although it does not establish that the book was catalogued at that time.

"printed publication" foreclose the grant of summary judgment on the issue of anticipation.

B. Whether Cheung Represents Reliable Science

With the support of its experts, UroPep argues that the Cheung reference is flawed in several respects: (1) it contains scientifically unreliable statements regarding the causes and treatment of BPH; (2) its clinical reports would not be trusted by a person of skill in the art because they were not peer-reviewed or placebo-controlled and because they produced no verifiable clinical results; and (3) established guidelines of the American Urological Association state that Horny Goat Weed is not an effective treatment for BPH, which casts into doubt whether Cheung's reported clinical results are sufficient to overcome that accepted scientific conclusion. The problems with the reliability of the Cheung reference, according to UroPep, foreclose any grant of summary judgment of anticipation based on that reference.

Lilly responds that UroPep's arguments are simply the expressions of a bias in favor of western medical conventions and do not undermine the basic point that the Cheung reference reports clinical results that disclose that icariin, a known PDE5 inhibitor, can be effective in treating BPH. In addition, Lilly points out that the Patent and Trademark Office has previously invalidated a patent directed to the treatment of erectile dysfunction with PDE5 inhibitors based on the use of Horny Goat Weed in Chinese traditional medicine (although that decision was not based on the Cheung reference).

While it is true that in format and content the Cheung reference has few of the trappings of a rigorous scientific study as judged by conventional standards, that is not

enough to disqualify it from serving as an anticipatory reference. Nonetheless, the departures in Cheung from conventional scientific norms for clinical trials give rise to some doubt as to the credibility of the Cheung findings. Moreover, as UroPep points out, there are specific aspects of Cheung, beyond its unconventional format, that undermine its reliability. Those include Cheung's reporting that in some cases his treatment resulted in reduction in the size of the prostate, even though Lilly's expert, Dr. Roehrborn, has represented that a PDE5 inhibitor such as Cialis does not reduce the size of the prostate. *See* Rebuttal Expert Report of Clause Roehrborn, M.D., Dkt. No. 187-4, at 12. In addition, some of the symptoms that the Cheung reference characterizes as symptoms of various types of BPH, such as "fatigue, shortness of breath, and backache," Dkt. No. 177-24, at 81; "acute rapid breathing, cough, dyspnea, oral dryness, restless thirst . . . red tongue with yellow dry fur, a rapid strong or slippery rapid pulse," Dkt. No. 177-23, at 44; and "low voice, pallor, poor appetite, pale tongue with white fur," *id.* at 51, are not known symptoms of BPH. Those characterizations of the symptoms addressed by Dr. Cheung's book raise doubts as to whether the reported improvements in the patients' symptomatology reflect the effects of a treatment of BPH.

The Court concludes that the reliability of Dr. Cheung's clinical tests presents a jury question. The fact that the Cheung book advocates some practices and entertains some beliefs that seem unconventional to the point of being scientifically dubious does not necessarily mean that Dr. Cheung's advocacy of the use of Horny Goat Weed (and its active component, icariin) to treat BPH is not valid. However, the issues of reliability raised by UroPep give rise to sufficient doubts as to the accuracy

of Dr. Cheung's reported success in using Horny Goat Weed to treat BPH to foreclose summary judgment.

C. Whether Cheung Discloses an "Effective Amount" of a PDE5 Inhibitor

UroPep next argues that the Cheung reference does not disclose an "effective amount" of a PDE5 inhibitor. Lilly points to Dr. Cheung's brief report of a clinical observation of 34 BPH patients who received Dr. Cheung's herbal remedies. His report on that clinical observation reads, in full, as follows: "Total effective rate: 94.12%. Seventeen cases had received ultra sound examination; 4/17 cases demonstrated a reduction of prostate. It took 3-4 weeks to show an improvement in urinary dysfunction." Dkt. No. 177-24, at 81.

There are several problems with reliance on Dr. Cheung's results. First, the herbal remedies given to Dr. Cheung's patients included many ingredients other than Horny Goat Weed, which calls into question whether it was the Horny Goat Weed, rather than some other ingredient in the formulation given to the patients, that was responsible for the favorable reported results.

Second, the clinical results for the 34 patients were reported with regard to a formulation in which Horny Goat Weed was not a necessary component, but only an optional one. There is no information in the Cheung book that suggests which, if any, of the patients were given the formulation containing Horny Goat Weed as opposed to the alternative component.[11]

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[11] Lilly responds that at another point in the Cheung reference a formulation is set forth in which Horny Goat Weed is a necessary ingredient. *Defendant Eli Lilly & Company's Consolidated Reply in*

Finally, UroPep points out that Horny Goat Weed contains only a very small amount of icariin (less than 0.5%, according to UroPep's expert, *see* [Corrected] Declaration of Dr. Andrew Bell in Support of UroPep's Combined Opposition to Defendants' Motions for Summary Judgment, Dkt. No. 187-16, at ¶ 76). Given the low concentration of icariin in Horny Goat Weed, UroPep's expert estimated that a patient would have to consume approximately 3.5 pounds of Horny Goat Weed per day to achieve the same PDE5 inhibiting effect as the standard 5 milligram dose of tadalafil that is prescribed for BPH. *Id.* Yet the patients who were the subjects of Dr. Cheung's clinical observation received only 15 grams of Horny Goat Weed per day. UroPep argues that such a small dose of icariin could not be expected to successfully treat BPH. Moreover, because it is questionable whether patients would consent to consuming 3.5 pounds of an herb each day, UroPep argues that to the extent the Cheung reference is read to direct the ingestion of enough icariin to have the same effect on BPH that is observed with tadalafil, there is substantial doubt whether Cheung establishes that treatment with Horny Goat Weed (and the icariin contained therein) can serve as a practical method of administering a PDE5 inhibitor in any amount that is effective to treat BPH.

Support of Its Motions for Summary Judgment of Indefiniteness, Noninfringement, Anticipation, and Willfulness, Dkt. No. 200, at 16 (citing Cheung, Dkt. No. 177-24, at 81). As UroPep notes, however, that formulation is not identified as the one that was the subject of the clinical test involving the 34 patients, so it does not support the conclusion that the clinical results for the 34 patients were necessarily attributable to Horny Goat Weed.

The Court is persuaded that UroPep's challenges to the Cheung book as an anticipating reference present factual questions that cannot be resolved in Lilly's favor on the summary judgment record. The Court agrees with UroPep that there are genuine disputes of material fact surrounding Lilly's reliance on Cheung as an anticipating reference. The Court therefore DENIES Lilly's motion for summary judgment of anticipation.

III. Lilly's Motion for Summary Judgment of Indefiniteness

Lilly next urges the Court to hold that the claims of the '124 patent are invalid for indefiniteness as a matter of law, under 35 U.S.C. § 112, ¶ 2 (2006) (35 U.S.C. § 112(b) of the America Invents Act). The applicable legal standard for assessing indefiniteness was set forth in the Supreme Court's decision in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014). There, the Court held that the mandate of definiteness requires "that a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Id.* at 2129. "The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable." *Id.* The Court added that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." *Id.* (quoting *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270 (1916)).

Indefiniteness is a question of law for the court. *Ethicon Endo-Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1317 (Fed. Cir. 2015); *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1328 (Fed. Cir. 2005*); Intellectual Prop. Dev., Inc.*

v. UA-Columbia Cablevision of Westchester, Inc., 336 F.3d 1308, 1318 (Fed. Cir. 2003). The general principles of claim construction apply to the question of indefiniteness. *Eli Lilly & Co. v. Teva Parenteral Meds.*, Inc., 845 F.3d 1357, 1370 (Fed. Cir. 2017*); Eon Corp. IP Holdings LLC v. AT&T Mobility LLC*, 785 F.3d 616, 620 (Fed. Cir. 2015); *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377-78 (Fed. Cir. 2015); *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008) ("Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determine whether allegedly indefinite language is subject to construction."). Accordingly, when the court needs to consult extrinsic evidence to decide the issue of indefiniteness, it may be required to make factual findings bearing on the indefiniteness issue. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-42 (Fed. Cir. 2015). The facts giving rise to a finding of indefiniteness must be proved by clear and convincing evidence. *Warsaw Orthopedic, Inc., v. NuVasive, Inc.*, 776 F.3d 1365, 1371 (Fed. Cir. 2015), *vacated on other grounds*, 136 S. Ct. 893 (2016); *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 783 (Fed. Cir. 2010); *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005). That is, overcoming the presumption of patent validity "demands clear and convincing evidence that a skilled artisan could not discern the boundaries of the claim." *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008).

Lilly's indefiniteness argument is based on the Court's claim construction, in which it held that the '124 patent requires that the PDE5 inhibitor be a selective inhibitor and that selectivity requires that the claimed compound be at least 20 times more potent in inhibiting PDE5 than

other PDEs. Lilly notes that the specification provides that the question whether a particular compound meets the "20-fold" test is answered by determining if the concentration of the compound "which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions." '124 patent, col. 8, ll. 5-9.

The use of IC_{50} ratios, Lilly argues, can produce widely varying results depending on the conditions under which particular assays are run. As an example, Lilly points to the compound zaprinast, which is cited in the '124 specification and claimed in unasserted claim 2 of the '124 patent. In some published studies, zaprinast has been found to have a selectivity ratio that meets the 20-fold standard, while in other studies it has not. For that reason, Lilly argues, the asserted claims of the '124 patent are fatally indefinite, since it is impossible to know, without specifying the conditions under which the particular assay is done, whether a particular compound will be found to meet the 20-fold selectivity standard as measured by the IC_{50} values derived from that assay.

UroPep offers a procedural answer and a substantive one. Its procedural answer is that Lilly has waived its indefiniteness argument by not advancing that argument at the claim construction stage of the case, as is required by the standard docket control order that was entered and is still in effect in this case. Its substantive answer is that even though the fact that the assays for determining whether the 20-fold test is met in a particular case may produce a range of values, that does not make the claims indefinite; the variation in results is merely the product of

experimental uncertainty, which affects all scientific measurements to a greater or lesser degree.

A. Waiver of the Indefiniteness Argument

1. Untimely filing of the indefiniteness challenge

UroPep points to the original docket control order in this case, which provided that "[i]n lieu of early motions for summary judgment, the parties are directed to include any arguments related to the issue of indefiniteness in the *Markman* briefing, subject to the local rules' normal page limits." Dkt. No. 65, at 4. Each docket control order issued in this case since that time has contained the same language. UroPep argues that because Lilly did not make its indefiniteness argument at the time the parties briefed the issue of claim construction, it has waived its right to argue indefiniteness now.

Lilly responds that the issue of indefiniteness did not become ripe until the Court's October 21, 2016, order in which it construed the term "inhibitor of phosphodiesterase (PDE) V" to mean a selective inhibitor that satisfied the 20-fold test. Because it did not have reason to file its indefiniteness motion any earlier than that, Lilly argues that it cannot fairly be deemed to have waived the motion.

The Court agrees with Lilly. In its original claim construction brief, Lilly presented arguments as to the indefiniteness of the '124 patent claims, but not the same arguments that it now presses. That is because at that time neither party was advocating the construction that the Court ultimately adopted. Even in the briefing leading up to the Court's October 21, 2016, order, while UroPep urged the Court to adopt a requirement of selectivity, it did not advocate the 20-fold test that the Court ultimately

adopted. For that reason, it was reasonable for Lilly not to make an indefiniteness argument at that time. Although UroPep argues that Lilly should have raised its indefiniteness argument when UroPep argued in favor of a "selectivity" construction of the claims, Lilly's indefiniteness argument is directed not just to the selectivity requirement, but also to the 20-fold test that the Court adopted. Because UroPep did not argue in favor of that test, it would have been unreasonable to expect Lilly to anticipate the Court's claim construction and argue that the construction that the Court ultimately adopted would render the claims indefinite.

UroPep argues, with some plausibility, that the indefiniteness issue was even more clearly presented by UroPep's initial argument that the claims required selective inhibition but did not require a particular degree of selectivity. For that reason, UroPep contends that Lilly cannot point to the Court's construction as an excuse for not raising the indefiniteness issue at the time the parties first briefed issues of claim construction. But even if Lilly had challenged UroPep's initial claim construction argument on indefiniteness grounds, the nature of the argument changed substantially when the Court imposed the 20-fold potency requirement, and Lilly would have been entitled to recast its indefiniteness argument at that time. That being the case, the Court discerns no waiver by Lilly in failing to raise at an earlier time an argument that would have been rendered largely moot when the Court entered its "20-fold" claim construction order.

UroPep next argues that even if Lilly is right that it should not have been expected to raise its indefiniteness argument prior to the Court's October 21, 2016, order that included the 20-fold selectivity construction, Lilly should

have raised the indefiniteness argument shortly thereafter, and its failure to do so until the summary judgment motions were filed constitutes a waiver of Lilly's indefiniteness challenge. Again, the Court disagrees with UroPep. Neither the docket control order nor any local rule or court directive provides a deadline for filing an indefiniteness motion in response to a claim construction order, where it was the Court's new claim construction that gave rise to the indefiniteness challenge. While the Court would have entertained a motion from Lilly raising the indefiniteness issue immediately after the Court's claim construction order, there was no scheduling directive that obligated Lilly to file its challenge at that time.

To be sure, it may have simplified matters if Lilly had raised the indefiniteness issue shortly after the October 21, 2016, order, since that presumably would have precipitated an earlier resolution of the claim construction issue that the parties have now raised in their infringement summary judgment motions. But the same could be said of UroPep's motion to clarify the Court's claim construction; an earlier motion for clarification would have been more efficient than having the Court address the new claim construction issue along with all of the other summary judgment motions and forcing the parties to argue their summary judgment motions without being certain how the Court would ultimately rule on the open claim construction issue. But UroPep was not legally obligated to file its motion at that time, and neither was Lilly.

Thus, the Court concludes that it was permissible for Lilly to raise the issue of indefiniteness when it filed its summary judgment motions. The Court therefore rejects UroPep's waiver argument and holds that Lilly has preserved its indefiniteness argument.

2. Untimely submission of evidence of indefiniteness

UroPep raises a second issue of waiver. It complains that much of Lilly's evidence on the indefiniteness issue was presented through the responsive report of its expert, Dr. Rotella. UroPep argues that it is improper for Lilly to present new arguments and evidence on validity in its responsive expert report on infringement.

Lilly replies to UroPep's argument about Lilly's improper reliance on Dr. Rotella's responsive report with a waiver argument of its own, arguing that UroPep should have moved to strike the report, a motion that would have been due on January 17, 2017. Beyond that, Lilly argues that Dr. Rotella discussed the variability among IC_{50} measurements and "peak fractionation" methods in his opening report, as did Lilly's expert, Dr. Beavo, in his initial report. Moreover, Lilly points out that Dr. Rotella's responsive report was responding to assertions in the report of UroPep's expert, Dr. Bell, as to selective PDE5 inhibition.

Although the manner in which the evidence regarding indefiniteness was placed in the record is less than ideal, the Court discerns no prejudice to UroPep from the sequence of reports, as both of Lilly's experts were deposed after the filing dates of their pertinent reports, and UroPep makes no argument that the timing of Dr. Rotella's responsive report deprived it of the opportunity to introduce evidence of its own or to respond meaningfully to Lilly's evidence on the issue of indefiniteness. Nor is there any prejudice to Lilly from UroPep's failure to file a motion to strike Dr. Rotella's responsive expert report on January 17, 2017, but instead waiting until January 31, 2017, to challenge the use of that report to support Lilly's

indefiniteness argument. The Court therefore denies UroPep's request that the evidence in Dr. Rotella's responsive report be disregarded, and denies Lilly's request to disregard UroPep's challenge to Dr. Rotella's opinions on the indefiniteness issue.

B. The Indefiniteness of the 20-Fold Test

Although the Court accepts Lilly's arguments on the procedural issues, the Court concludes that UroPep has the better of the argument on the ultimate question of indefiniteness.

Lilly's argument on the merits is that the '124 patent claims are indefinite because in 1997 the testing methods for obtaining IC_{50} values for PDE inhibitors often produced widely varying results, depending on differing experimental conditions. Lilly complains that the '124 specification does not contain any guidance as to which experimental conditions should be used. For that reason, Lilly argues, it is impossible to determine with reasonable certainty whether any particular compound is within the scope of the '124 patent claims as construed by this Court.

Lilly supports its argument with evidence regarding zaprinast, one of the compounds identified in the '124 patent as a selective PDE5 inhibitor. As proof of the variability of the results in testing for IC50 values as of the priority date of the '124 patent, Lilly points to the wide range in IC_{50} values obtained for zaprinast in various studies conducted between 1989 and 2003. Lilly argues that because of the lack of sufficient detail as to a particular testing protocol in the '124 specification and because IC_{50} values obtained for zaprinast during the 1990s varied widely depending on testing conditions, a person of skill in the art would not have known how to tell if a particular compound

qualified as a selective inhibitor of PDE5 under the claims of the '124 patent as construed by this Court.

There are three answers to Lilly's argument. First, contrary to Lilly's contention, the '124 patent points to a detailed testing protocol for determining whether a particular compound qualifies as a selective PDE5 inhibitor. Second, even though Lilly points to wide variations in IC_{50} values as to the potency of zaprinast as a selective PDE5 inhibitor, the lack of certainty as to whether zaprinast is covered by the claims does not render the claims indefinite for all compounds, including tadalafil. Third, zaprinast is specifically identified in the patent as a selective PDE5 inhibitor. For that reason, zaprinast is unequivocally covered by the claims, and any uncertainty as to the testing results regarding zaprinast is immaterial. Each of these points is discussed in more detail below.

1. The protocol described in the '124 patent

Lilly's expert reports make clear that assays used to obtain IC_{50} values can produce widely varying results, depending on the selected experimental conditions. Because of that, Lilly argues, it is critical that a patent using IC_{50} values as a basis for defining claim scope must set out in detail the testing protocol used to determine the IC_{50} values that define the claims. The '124 patent, according to Lilly, lacks any such detailed testing protocol.

In fact, the '124 specification provides considerably more guidance with respect to the prescribed testing protocol than Lilly suggests. The specification states that the proof of whether a compound is an inhibitor of a particular PDE "is furnished by known methods," and it refers to the methods set forth in two journal articles, M. Galvan et

al, *Actions of the Phosphodiesterase Inhibitor Zardaverine on Guinea-Pig Ventricular Muscle*, 342 Archives of Pharmacology 221 (1990), Dkt. No. 189-13, and C.D. Nicholson et al., *the Ability of Denbufylline to Inhibit Cyclic Nucleotide Phosphodiesterase and its Affinity for Adenosine Receptors and the Adenosine Re-Uptake Site*, 97 British J. of Pharmacology 889 (1989), Dkt. No. 189-14. Those articles contain detailed descriptions of methods used to ascertain potency levels for particular PDE inhibitors. '124 patent, col. 7, ll. 37-39. The specification then refers to "the following general procedure," *id.* at line 40, which is directed to the ensuing paragraph.

The paragraph that describes that "general procedure," '124 patent, col. 7, line 35, through col. 8, line 16, refers to a 1995 journal article by the named inventors and others. The specification states that the "determination of sPDEs is performed as described" in that article. The article in turn contains a detailed account of a specific protocol for isolating PDE isoforms and measuring PDE activity. The "general procedure" paragraph closes by stating that the compound to be tested "is added prior to the incubation of the enzyme mixtures according to peak fractions," followed by "renewed determination and plotting of the enzyme activity," which allows for the "identi[fication] of a substance as being an inhibitor of the specific phosphodiesterase" according to the definition given in the specification. '124 patent, col. 7, line 41, to col. 8, line 16.

Lilly complains that the '124 specification does not lay out in detail various features of the testing protocol, such as the nature of the substrate tissue used in the testing process and the concentration of the substrate. But the inventors' journal article to which the specification points

as setting out the "general procedure" to establish "whether a compound is . . . an inhibitor of sPDE I, IV or V," '124 patent, col. 7, ll. 35-37, 40, contains just such details. Although Lilly contends that the '124 specification lacks details such as the source and type of tissue used in the testing, the purity of the enzyme, the properties of the assay buffer, and the substrate concentration, the inventors' cited journal article contains all of that information. *See* Michael C. Truss et al., *Porcine Detrusor Cyclic Nucleotide Phosphodiesterase Isoenzymes: Characterization and Functional Effects of Various Phosphodiesterase Inhibitors in Vitro*, 45(5) Urology 893 (1995), Dkt. No. 190-4. The article describes in detail the source and purification of the enzyme, the properties of the assay buffer, the components and concentration of the substrate, and the method used to prepare the tissue used for the study. *Id.* at 894-97. Based on the details set forth in the specification and in the three cited journal articles—particularly the one the patent characterizes as setting forth the "general procedure" to be followed—the Court concludes that there is sufficient guidance in the specification to teach a person of skill in the art how to perform the tests necessary to determine the IC50 ratios required by the claims.[12]

2. Experimental evidence regarding zaprinast

Lilly spends a considerable portion of its indefiniteness motion pointing to studies of zaprinast between 1989

[12] UroPep points out that the Galvan and Nicholson references also contain detailed accounts of the methodology used in their assays. While their methodology differs in some respects from that employed in the Truss reference, Lilly has not offered any evidence that the IC50 ratios obtained from assays performed under the Galvan or Nicholson methodology would differ materially from the IC50 ratios obtained from assays performed under the methodology described in Truss.

and 2003. Those studies reported results from which Lilly determined that there was a wide range in the derived IC_{50} ratios measuring zaprinast's potency as an inhibitor of PDE5 compared to PDE1. As a result, Lilly contends, it would have been impossible for a person of skill in the art to know whether or not zaprinast satisfied the 20-fold test for PDE5 selectivity vis- -vis PDE1 through PDE4. By extrapolation, Lilly contends that in light of experimental uncertainties in measuring IC_{50} values, the claims of the '124 patent would be indefinite as to any compound.

Lilly's expert, Dr. Rotella, points to 15 different papers published between 1989 to 2003 that reported IC_{50} values for zaprinast. Responsive Expert Report of David P. Rotella, Ph.D., Dkt. No. 177-9, at ¶ 25. From the results reported in each of those papers, Dr. Rotella calculated the relative selectivity of zaprinast for PDE5 as compared to PDE1. He found that the measured IC_{50} ratio for zaprinast varied widely. The results of one study, according to Dr. Rotella, showed zaprinast to be 270 times more selective for PDE5 than for PDE1, while the results of another study showed zaprinast to be only 1.4 times more selective for PDE5 than for PDE1. The results of other studies produced numbers between those two extremes.

In response, UroPep challenges Dr. Rotella's presentation regarding zaprinast. UroPep criticizes Dr. Rotella's evidence because his report (like several of the studies on which he relies) does not include margins of error for the reported data. Taking account of margins of error, UroPep argues, the calculated IC_{50} ratios studies are much less inconsistent than presented in Dr. Rotella's report. In addition, UroPep argues that several of the studies were not conducted for the purpose of obtaining accurate IC_{50} ratios. For that reason, UroPep contends,

those studies are not as reliable as the studies that were conducted with an eye to determining the correct IC_{50} ratios for zaprinast. The studies that were designed to obtain IC_{50} ratios, according to UroPep, produce values that are more consistent and well above the 20-fold test set out in the '124 specification. Finally, UroPep points out that some of the studies listed by Dr. Rotella did not use the same tissue to obtain IC_{50} values for both PDEs under investigation and therefore are less reliable than the studies that UroPep deems the most pertinent. Excluding the studies that UroPep regards as less reliable and as "outliers," UroPep offers the opinion of its expert that "the data of the best quality shows that zaprinast was 20x more selective for PDE5 than for PDE1." Validity Expert Report of Dr. Andrew Bell, Dkt. No. 193-3, at ¶ 81.

There is some force to UroPep's observations. The failure to note the error margins in Dr. Rotella's results tends to make his results appear more divergent than they really are. In addition, the failure of some of the studies to report any error margin at all not only makes those studies less useful as data points, but also supports UroPep's contention that those articles were not intended to be used to establish quantitative selectivity ratios.

Those points raised by UroPep (as well as several of UroPep's other challenges to particular references) tend to undercut Lilly's showing. However, they do not provide a complete answer to Lilly's contention that the calculated IC_{50} ratios for zaprinast vary significantly and are not consistently above the 20:1 ratio of potency for inhibition of PDE5 to PDE1 through PDE4 required by the Court's claim construction. The range of IC_{50} ratios derived from the studies identified by Dr. Rotella is quite large, and one of the derived ratios that is less than the

"20-fold standard" comes from the inventors' own study that is featured in the '124 specification. If those numbers stood alone, they would warrant doubt as to whether zaprinast falls within the scope of the '124 claims. In Lilly's view, any such doubts would give rise to indefiniteness concerns.

There are several problems with the argument Lilly makes based on its zaprinast evidence. First, simply because it is difficult to determine whether one particular compound satisfies the 20-fold test for being a selective inhibitor does not mean that the claims are indefinite. Lilly asks the Court to generalize from the data regarding zaprinast and to assume that experimental variations would produce similarly varying results for any other tested compound. But Lilly's evidence does not support such an inference. Zaprinast may indeed present a close question under the 20-fold test. But even if zaprinast does not satisfy that test or satisfies that test under some experimental conditions but not under others, that would not mean that the '124 patent is invalid. It would merely mean that there is one possible embodiment for which the issue of claim coverage is a close one.

Nor does Dr. Rotella's evidence establish that the other exemplary selective inhibitors described in the patent's specification fail the 20-fold test. Of the ten compounds listed in the '124 patent as "preferred selective inhibitors of PDE I, IV and V," '124 patent, col. 2, line 28, Dr. Rotella's calculations of the IC_{50} ratios show only one that is not a selective inhibitor of PDE1, PDE4, and PDE5—that is, only one does not meet the 20-fold test in comparison to PDE2 and PDE3. *See* Expert Report of

David Rotella, Dkt. No. 177-8, at ¶125.[13] Even zaprinast, according to Dr. Rotella's calculations, is a "selective inhibitor[] of PDE I, IV and V," as it has a potency ratio for those enzymes greater than 20:1, as compared to PDE2 and PDE3.

Dr. Rotella's calculations do indicate that several of the ten compounds (three in addition to zaprinast) do not meet the 20-fold test for potency in inhibiting PDE5 as compared to inhibiting PDE1 or PDE4.[14] But as to each of those three compounds, Dr. Rotella relied on a single reference to calculate the IC50 ratios; he did not point to multiple studies reporting differing IC_{50} ratios for those compounds' potency for PDE5 against PDE1 and PDE4. That evidence therefore does not support Lilly's indefiniteness argument.

In any event, Lilly does not present evidence that there are similar difficulties in determining whether other compounds, in general, are selective PDE5 inhibitors. In particular, Lilly presents no evidence of any studies suggesting that tadalafil is less than 20 times as potent in inhibiting PDE5 compared to PDE1 through PDE4. In fact, as noted, record evidence shows that tadalafil is many times more potent as an inhibitor of PDE5 than as

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[13] The one exception is dipyridamole, which was listed in the one study cited by Dr. Rotella as having an IC50 ratio (PDE2 to PDE5) of between 5 and 11.

[14] For at least two of the three, the IC50 ratio reported, accounting for experimental error, may satisfy the 20-fold test. *See* Takase et al., *Cyclic GMP Phosphodiesterase Inhibitors. 1. The Discovery of a Novel Potent Inhibitor, 4-((3,4-(Methylenedioxy) benzyl)amino)-6,7,8-trimethoxyquinazoline*, 36 J. Med. Chem. 3765, 3766 (1993) (dipyridamole has an IC50 ratio (PDE4 to PDE5) between 8 and 21; compound f, depicted in the '124 specification at col. 3, ll. 36-48, has an IC50 ratio (PDE1 to PDE5) between 7 and 30).

an inhibitor of PDE1 through PDE4: as much as 10,000 times as potent according to the Cialis label. Regardless of the difficulty in determining whether the IC_{50} assay results show that claim 1 of the '124 patent covers zaprinast, the available testing data clearly shows that other identified compounds satisfy the "20-fold" test for PDE5 selectivity, including tadalafil.

Second, Lilly's "zaprinast argument" ignores the fact that the '124 patent contains a detailed description of a protocol that can be used to derive data for use in calculating IC_{50} ratios. The numerous zaprinast studies assembled by Dr. Rotella did not employ a single uniform protocol. That evidence therefore says little about whether the results for zaprinast would vary widely if a single protocol were used. It says even less about whether the results for other compounds would vary widely under a single testing protocol such as the one set forth in the '124 specification.

3. The '124 patent defines zaprinast as a PDE5 inhibitor

Finally, the discussion of whether zaprinast has a potency ratio of more than 20:1 is immaterial in light of the fact that the '124 patent identifies zaprinast as a selective inhibitor within the meaning of the claims. Claim 1 of the '124 patent recites a method for prophylaxis or treatment of BPH comprising administering an effective amount of a compound that is a selective inhibitor of PDE5. Dependent claim 2 claims the method of claim 1 in which the compound at issue is zaprinast. That means that the patent conclusively identifies zaprinast as a selective inhibitor of PDE5. Therefore, whether or not a particular assay shows that zaprinast satisfies the "20-fold" test does not matter; the patent announces that zaprinast is a selective

inhibitor of PDE5, and there is therefore no indefiniteness issue regarding the status of zaprinast. For that reason, Lilly's elaborate presentation of the conflicting scientific evidence as to whether zaprinast satisfies the 20-fold test is entirely beside the point.

4. Lilly's supplemental evidence of indefiniteness

Lilly argues that, because of differing experimental conditions, the calculated IC_{50} value for a particular compound can vary. Lilly made that argument through counsel at the motions hearing, and on March 2, 2017, Lilly filed its Opposed Second Motion Supplement Evidence in which elaborated upon that argument and offered evidence in support. Through Dr. Rotella, Lilly submits that differences in factors such as the source and concentration of the enzyme, purification methods used, and the composition of the substrate can all affect the IC_{50} ratios for particular PDE inhibitors under examination.[15]

The Court accepts Lilly's submission that, in the abstract, differences in experimental conditions can affect the derived IC_{50} ratios. Lilly's evidence, however, does not indicate how significant those differences can be,

[15] Although Lilly's motion is opposed, the Court will grant the motion in light of questions asked by the Court during the hearing, which are addressed in the motion. The argument and evidence in the motion does not change the Court's ruling on indefiniteness, however, and in the interest of expediting the proceedings, the Court will issue this order without waiting for a response from UroPep. UroPep is free to file a response to Lilly's motion for the record if it chooses to do so. However, the Court will not entertain any reply or sur-reply in connection with the motion to file supplemental evidence or any further motions to submit additional argument or evidence on this issue.

other than to say that IC_{50} values derived from such experiments can vary "sometimes substantially" depending on assay conditions. Dr. Rotella points to differences in the experimental conditions such as differences in the concentration of the enzyme and substrate, the pH of the enzymatic reaction, the concentration of the substrate, and the source of the tissue used to obtain the PDEs being tested. Declaration of David P. Rotella, Ph.D., Dkt. No. 232-1.

Significantly, as noted earlier, the '124 patent provides a protocol in which many of those variables are controlled. The discussion in the specification at column 7, line 35, through column 8, line 16, and in the cited Truss article, which is described as providing the "general procedure" to be used in testing compounds for PDE5 selectivity, provides values for many of the variables discussed by Dr. Rotella as affecting the derived IC_{50} ratios. As Dr. Rotella acknowledges in his report, Dkt.No.232-1, at 9 (chart), the Truss article contains a wealth of detail as to the composition of the substrate, the pH level, the nature of the reducing agent, and the process used during the experiments. As for Dr. Rotella's point about the variations in the source and concentration of the enzyme, the Truss article provides that the source of the enzyme is porcine bladders. Thus, the source for all of the enzymes is the same, and but for individual variations from pig to pig, the concentration levels of the enzymes can be expected to be the same.

More generally, undisputed testimony from UroPep's expert, Dr. Bell, shows that it was standard practice in 1997 (and into the 2000s) to test PDE inhibitors by using PDEs isolated from tissue and to calculate selectivity ratios based on those experiments. Infringement Expert

Report of Dr. Andrew Bell, Dkt. No. 189-1, Ex. A, at ¶ 27. Thus, persons of skill in the art relied on selectivity ratios calculated from the results of experiments just like the one described in the Truss article.

The Court concludes that the testing protocol provided in the '124 patent for determining whether a particular compound falls within the scope of the claims minimizes the risk of obtaining different IC_{50} ratios depending on different experimental conditions. In any event, the burden is on Lilly to show indefiniteness by clear and convincing evidence, and the Court concludes that Lilly's factual case on indefiniteness has not met that burden. The asserted claims are thus sufficiently definite to satisfy the requirements of section 112, paragraph 2, of the Patent Act.

5. Authorities cited by Lilly

Lilly cites several cases in support of its indefiniteness argument, but none of them apply here. The difference between this case and all of the cases on which Lilly relies is that in this case the patent identifies a particular value, the IC_{50} ratio, as the measure for determining whether an unidentified compound is a selective PDE5 inhibitor, and it points to a testing protocol that would allow a person of skill in the art to calculate that ratio. In the cases on which Lilly relies, the parameters referred to in the claims had no fixed meaning, leading to the risk that a person of skill in the art would not know whether a particular product fell within the scope of the claim.

For example, in *Dow Chemical Co. v. Nova Chemicals Corp. (Canada),* 803 F.3d 620 (Fed. Cir. 2015), the claim was directed to a type of plastic having a "slope of strain hardening coefficient greater than or equal to 1.3." The

problem in that case was that the "slope of strain hardening coefficient" did not have a single accepted value, but instead had three different accepted values (and a fourth created for purposes of the case) with the value of the slope in each instance depending on which method was used to calculate it. *Id.* at 633-34. Because the method chosen to calculate the slope could affect whether or not a given product infringed, and because the patent did not specify a particular method as the one governing the slope determination in the claims, the court held the claims indefinite.

In this case, unlike in *Dow*, there is only one definition for the critical term, IC_{50} value. As the patent clearly states, '124 patent, col. 8, ll. 6-7, the IC_{50} value is the concentration of a particular inhibitor necessary for inhibiting 50% of a specific PDE's hydrolysis of a substrate compound, and it can be determined via a specified testing protocol, '124 patent, col. 7, ll. 43-45. There are not multiple different ways of expressing that number that would produce a different value.

The same analysis applies to *Teva Pharmaceuticals USA, Inc. v. Sandoz*, 789 F.3d 1335 (Fed. Cir. 2015). In that case, the claim at issue recited "molecular weight," but did not reveal which of the three common measures of the average molecular weight of a polymer sample was intended, even though each measure "is calculated in a different way and would typically yield a different result [average molecular weight] for a given polymer sample." 789 F.3d at 1341. The court held the claim indefinite on the ground that there was no reasonable certainty that the average molecular weight should be calculated using the particular measure advocated by the patentee on appeal.

In that case, as in *Dow*, the problem was that it was unclear from the claim what standard was to be used to determine infringement.

Again, in this case the standard is clear: to fall within the scope of the claim, the accused product must have a potency ratio of at least 20:1 with regard to the inhibition of PDE5 as compared to PDE1 through PDE4, as determined by the respective IC_{50} values. The fact that experimental measurements of those values may be difficult to calculate with precision in some cases does not render the claim language indefinite.

Similarly, in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), the claim language in question recited a non-naturally occurring erythropoietin ("EPO") glycoprotein product that, among other things, has glycosylation (the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins) that "differs from that of human urinary [EPO]." *Id.* at 1340. The Federal Circuit sustained the district court's conclusion that there was no single standard for determining the glycosylation of human urinary EPO, and therefore no single standard against which to measure the glycosylation of recombinant EPO. Because there was no "standard by which the appropriate comparison can be made," the court held the asserted claims invalid for indefiniteness. *Id.* at 1341-42. In this case, by contrast, there is a single "standard"—an IC_{50} ratio of 20 or more.

Finally, in *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, 117 F. Supp. 3d 632 (D. Del. 2015), the claim limitation at issue recited "an amino acid sequence having at least 95% identity to SEQ ID No: 179 or 187." *Id.* at 639.

The specification stated that the preferred methods to determine identity are "codified in publicly available computer programs." *Id.* The problem in that case was that there were at least five different equations known in the art for calculating a numerical "% identity," and the claims failed to identify which method of aligning amino acid sequences should be used to calculate that numerical value. That was important, because "different sequenced alignment programs can provide different alignments for two given sequences, affecting the calculation of % identity." *Id.* at 640. Furthermore, as the court noted, the method of measurement is in fact outcome determinative in the infringement analysis. *Id.* at 641. Accordingly, the court held the claim indefinite.

This case is different from *Butamax* because in *Butamax*, unlike in this case, the meaning of the claim limitation depended on the equation used to calculating "% identity." In addition, unlike in *Butamax*, there is no suggestion in this case that different testing protocols could produce different results with regard to whether tadalafil infringes the asserted claims.[16]

In view of the complex of arguments regarding the validity of the '124 patent, it is worth restating the Supreme Court's observation that definiteness requires only reasonable certainty in light of the subject matter. *Nautilus*,

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[16] Lilly also relies on *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003), but the issue in that case has little to do with the issue in this one. The court in *Geneva* rejected a claim construction that would have made the "synergistically effective amount" of a certain component depend on its activity against bacteria not identified in the claims; the effect would have been that a particular composition would either infringe or not infringe depending on the bacterium chosen for analysis, which would have rendered the claim indefinite. 349 F.3d at 1384.

134 S. Ct. 2120, 2129 (2014). The Court is satisfied that the claims of the '124 patent are reasonably definite in light of the uncertainties of the science as of the patent's priority date. Particularly in light of the Federal Circuit's instruction that a finding of claim indefiniteness "demands clear and convincing evidence that a skilled artisan could not discern the boundaries of the claim," *Halliburton Energy Servs., Inc.*, 514 F.3d at 1249, the Court holds that the claims of the '124 patent are not invalid for indefiniteness. The Court therefore DENIES Lilly's motion for summary judgment of indefiniteness.

IT IS SO ORDERED.

Dated: March 3, 2017 /s/ William C. Bryson
William C. Bryson
United States Circuit Judge

APPENDIX E

UNITED STATES DISTRICT COURT EASTERN
DISTRICT OF TEXAS
MARSHALL DIVISION

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff,

v.

ELI LILLY AND COMPANY, and BROOKSHIRE
BROTHERS, INC.,
Defendants.

Case No. 2:15-CV-1202-WCB

MEMORANDUM OPINION AND ORDER

In this patent case, the plaintiff, Erfindergemeinschaft UroPep GbR ("UroPep"), has alleged that the defendants, Eli Lilly and Company and Brookshire Brothers, Inc., have infringed U.S. Patent No. 8,791,124 ("the '124 patent"), owned by UroPep. Before the Court are two motions for summary judgment filed by the defendants: a motion for summary judgment of non-infringement, Dkt. No. 119, and a motion for partial summary judgment that claims 1 and 3 of the '124 patent are invalid for failure to meet the written description requirement of 35 U.S.C. § 112 ¶ 1, Dkt. No. 120.

Following a hearing on June 23, 2016, the Court entered an order construing several disputed terms of the '124 patent. Dkt. No. 131 (construing the terms "administering," "a person in need thereof," and "an effective amount"). In that order, the Court did not construe the term "an inhibitor of phosphodiesterase (PDE) V," which appears in the '124 patent, but instead postponed the construction of that term until summary judgment motions were filed. In addition, prior to issuing its claim construction order, the Court entered an amended docket control order setting forth a schedule for expedited briefing of the defendants' summary judgment motions. Dkt. No. 117. In accordance with that schedule, the defendants filed motions for summary judgment of non-infringement and for partial summary judgment of invalidity. Those motions focus on the phrase "an inhibitor of phosphodiesterase (PDE) V."

In their non-infringement motion, the defendants argue that the disputed phrase should be construed under 35 U.S.C. § 112 ¶ 6 and that the scope of the claims should therefore be limited to certain specifically disclosed PDE V inhibitors. The necessary result of such an interpretation of the phrase, according to the defendants, would be a judgment of non-infringement. In their invalidity motion, the defendants argue that if the phrase "an inhibitor of phosphodiesterase (PDE) V" were construed to include all compounds capable of inhibiting PDE V (other than those specifically excluded by the claim language), the claims would lack the written description required under 35 U.S.C. § 112 ¶ 1, and therefore would be invalid.

UroPep responds that the phrase "an inhibitor of phosphodiesterase (PDE) V" should not be construed under 35 U.S.C. § 112 ¶ 6 and that construing the phrase

without reference to 35 U.S.C. § 112 ¶ 6 does not give rise to a written description problem under 35 U.S.C. § 112 ¶ 1.

In this order, the Court construes the term "inhibitor of phosphodiesterase (PDE) V" and DENIES the defendants' two motions for summary judgment.

BACKGROUND

The '124 patent is directed to a method of treatment or prophylaxis of a person affected with benign prostatic hyperplasia ("BPH"), a condition associated with an enlarged prostate, leading to difficulty in urination and associated problems. By 1983, it was known that a significant improvement in the condition could be achieved by the administration of drugs that trigger the relaxation of the prostatic muscle cells. However, prior art treatments that relaxed those cells, such as the use of alpha-receptor blockers, were characterized by low effectiveness slow onset of action, or significant side effects. As an improvement over the prior art, the '124 patent purports to "have examined a completely different pharmacological principle of action, namely the affection of a key enzyme within the smooth muscle cells of the prostate gland, phosphodiesterase." '124 patent, col. 1, ll. 9-35.

The specification explains that the relaxation of smooth muscle cells is caused by the transmission of information through either hormones or neurotransmitters. That passage of information causes an increase in the levels of cyclic adenosine monophosphate ("cAMP") and cyclic guanosine monophosphate ("cGMP") in the muscle, which promotes the relaxation of those cells. The level of those compounds is reduced by the presence of phosphodiesterases ("PDEs"), which hydrolyze cAMP and

cGMP. '124 patent, col. 1, ll. 36-52. To promote muscle relaxation, "[i]nhibitors of the PDEs in turn reduce the digestion of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell." *Id.*, col. 1, ll. 44-47. The '124 patent states that this mechanism of action had been described by a number of publications in the early 1990s. *Id.*, col 1, ll. 48-52.

The '124 patent notes that the cited prior publications describe PDEs in the body as consisting of at least five categories of subesterases of PDE (i.e., PDE I to PDE V), and that the various PDEs are distributed differently throughout different organs and organ systems.[1] The specification asserts that the side effects and low effectiveness of the prior art prostate treatments suggests that "a well-aimed affection of the prostatic muscles by inhibiting a functionally important sPDE [specific PDE] isoenzyme appears to be superior to conventional therapy methods." '124 patent, col. 2, ll. 3-5. The specification states that PDE I, PDE IV, and PDE V have been found in prostate tissue and that a "well-aimed inhibition of these isoenzymes will result in relaxation of the [prostatic] muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips." *Id.*, col. 2, ll. 3-5. It then concludes that the "subject matter of the invention is the use of specific inhibitors of sPDE I, sPDE IV, and sPDE V in the prophylaxis and

[1] The specific PDEs were initially identified by Roman numerals, the convention followed in the '124 patent. It is now more common to use Arabic numerals to describe the specific PDEs. The current practice is to refer, for example, to PDE V as PDE5. For consistency, except where quoting record materials, the Court will use the Roman numeral convention that was commonly employed as of the July 1997 priority date of the '124 patent.

treatment of prostatic diseases, in particular [BPH] . . . ." *Id.*, col. 2, ll. 17-20.

The '124 patent has one independent claim. It reads as follows:

> 1. A method for prophylaxis or treatment of benign prostatic hyperplasia comprising administering to a person in need thereof an effective amount of an inhibitor of phosphodiesterase (PDE) V excluding a compound selected from the group consisting of
>
> dipyridamole,
>
> 2-(N-(4-carboxypiperidine)-6-chloro-4(3,4-(methylendioxy)bezyl)amino) quinazoline,
>
> 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate.
>
> 4((3,4-(methylendioxy)benzyl)amino)-6,7,8-trimethoxy-quinazoline,
>
> 1-methyl-3-propyl-6-(5-(N-(4methyl-morpholino)sulfonyl)-2ethoxy-phenyl)pyrazole[4,5]pyrimidin-4(5H)one,
>
> 2-n-butyl-5-chloro-1-(2-chlorobenzyl)-4-methylacetate-imidazole,
>
> 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d)pyrimidin-4(5H)-one,

> 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro chronan-4-one,
>
> and pharmacologically compatible salts thereof.

'124 patent, col. 8, ll. 18-41 (emphasis added and duplicate compound removed). [2] In other words, the inventors "claimed a method of treatment for BPH by administering an effective amount of a PDE5 inhibitor" that is not one of the eight listed compounds or their pharmacologically compatible salts. Pl. UroPep's Combined Sur-Reply to Defs.' Mots. for Summ. J., at 11, Dkt. No. 141. Claim 3, which depends from claim 1, reads as follows:

> 3. The method of claim 1 wherein the compound in combination with a pharmacologically acceptable excipient is administered in a unit dose form.

'124 patent, col. 8, ll. 45-48.

The structure of claim 1, which covers all inhibitors of PDE V except for certain specifically listed compounds, is not common in the Court's experience. As UroPep acknowledges "there are not a lot of claims that are drafted in this way." Claim Construction Hr'g Tr., at 62:22-25, Dkt. No. 125.

The application for the '124 patent was a continuation of the application that matured into U.S. Patent No.

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[2] Claim 1, as set forth in the '124 patent, contains a duplicate listing of 1-methyl-3- propyl-6-(5-(N-(4-methylmorpholino)sulfonyl)-2 ethoxyphenyl)pyrazole[4,5]pyrimidin- 4(5H)one, which is one of the eight excluded compounds.

8,106,061 ("the '061 patent"). The '061 patent includes claims that cover methods of treating of BPH and prostatic disease or relaxing prostatic muscles by administering a selective inhibitor of PDE IV and/or PDE V selected from a group of specific compounds. '061 patent, col. 8, ll. 4-59. The specific compounds identified in the claims of the '061 patent include most of the compounds that are specifically excluded from the claims of the '124 patent.

During the prosecution of the application that led to the '124 patent, the examiner rejected the claims on the ground of nonstatutory double patenting. The patentees then amended claim 1 to exclude from the scope of the claim most of the PDE inhibitors recited in the '061 patent. Dkt. No. 106-08, at 115. When the examiner nonetheless rejected the new claims as being anticipated by the claims of the '061 patent, *id.* at 121-23, the patentees entered a terminal disclaimer with respect to the'061 patent, *id.* at 126-28. The claims were then allowed.

DISCUSSION

The matters presently before the Court raise three issues: (1) whether the term "an inhibitor of phosphodiesterase (PDE) V" in claim 1 of the '124 patent is governed by 35 U.S.C. § 112 ¶ 6; (2) how that term should be construed if it is not governed by section 112 paragraph 6; and (3) whether the specification of the '124 patent satisfies the written description requirement of 35 U.S.C. § 112 ¶ 1.

I. The Motion for Summary Judgment of Non-Infringement

UroPep's theory of infringement is that the defendants infringe, directly or indirectly, by the administration

of the drug tadalafil (the active ingredient in Lilly's commercial product Cialis) to treat BPH. According to UroPep, tadalafil is "an inhibitor of phosphodiesterase (PDE) V" that is effective for prophylaxis or treatment of BPH, and its administration for that purpose therefore infringes UroPep's '124 patent.

The defendants' motion for summary judgment of non-infringement turns on the construction of the term "an inhibitor of phosphodiesterase (PDE) V." As noted, when the Court entered its claim construction order in this case, *see* Dkt. No. 131, it postponed construction of that term until briefing on the defendants' motions for summary judgment was complete. The Court will now construe that term.

UroPep proposes that the phrase "an inhibitor of phosphodiesterase (PDE) V" should be construed to mean a "compound able to inhibit phosphodiesterase (PDE) V." *See* Pl. UroPep's Corrected Opening Claim Constr. Br., at 21, Dkt. No. 105. In addition, UroPep asserts that the intrinsic record requires that the phrase should be understood to contain three additional limitations: the PDE V inhibitor must be "selective"; it must consist of a small molecule; and it must be therapeutically effective.[3] *See id.* at 22-25; Pl. UroPep's Reply Claim Constr. Br., at 8-10, Dkt. No. 109.

The defendants argue that the term "an inhibitor of phosphodiesterase (PDE) V" is "an element in a claim for

[3] A selective inhibitor is one that inhibits a particular compound significantly more than it does others. For example, a selective inhibitor of PDE V would inhibit PDE V significantly more than it inhibits other PDEs, such as PDE II or PDE III. The parties dispute how selective a selective inhibitor must be in order to qualify as a "selective" inhibitor.

a combination" that recites function without reciting structure and therefore is governed by 35 U.S.C. § 112 ¶ 6. *See* Defs. Eli Lilly and Company and Brookshire Brothers, Inc.'s Resp. Claim Constr. Br., at 7-8, Dkt. No. 106. For that reason, they contend, only those compounds that are specifically described in the specification and not otherwise excluded would be covered by the claims. Construed in that manner, the patent would read only on zaprinast and MY5445, the only two non-excluded compounds that are specifically identified in the '124 specification as PDE V inhibitors and are not expressly excluded from the scope of the claims.

A. Analysis of the Term "an inhibitor of phosphodiesterase (PDE) V" Under 35 U.S.C. § 112 ¶ 6

The Court first addresses the question whether the term "an inhibitor of phosphodiesterase (PDE) V" is governed by 35 U.S.C. § 112, ¶ 6, the "means- (or step-) plus-function" clause of section 112 of the Patent Act.[4] Whether that clause applies to a particular claim element is a matter of claim construction and is therefore a question of law. *Personalized Media Commc'ns, LLC v. Int'l Trade Comm'n*, 161 F.3d 696, 702 (Fed. Cir. 1998).

Section 112 paragraph 6 was first enacted as part of the 1952 Patent Act "in response to *Halliburton Oil Well Cementing Co. v. Walker*, 329 U.S. 1 (1946), which rejected claims that do not describe the invention but use

[4] Under the America Invents Act ("AIA"), section 112 paragraph 6 was recodified as 35 U.S.C. § 112(f). Although the AIA did not make any change in the substance of the provision, this opinion refers to it as section 112 paragraph 6, since the pre-AIA version of the provision governs cases involving the '124 patent.

conveniently functional language at the exact point of novelty." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 27 (1997) (quoting *Halliburton*, 329 U.S. at 8); *see also Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 371 (1938). The statute allows functional claiming subject to certain restrictions. It provides as follows:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

35 U.S.C. § 112 ¶ 6 (2006).

1. Section 112 paragraph 6 as applied to method claims

The Federal Circuit has held that for method claims, such as the claims of the '124 patent, section 112 paragraph 6 "is implicated only when steps plus function without acts are present." *Epcon Gas Sys., Inc. v. Bauer Compressors, Inc.*, 279 F.3d 1022, 1028 (Fed. Cir. 2002). As the Federal Circuit has explained, the word "means" in the statute refers to an apparatus element, which is implemented by structure or material, while the word "step" refers to a process element, which is implemented by an act. *O.I. Corp. v. Tekmar Co.*, 115 F.3d 1576, 1582-83 (Fed. Cir. 1997). In other words, "structure and material go with means, acts go with steps." *Id.* at 1583. Overall, section 112 paragraph 6 is "implicated only when means *plus function* without definite structure are present, and

that is similarly true with respect to steps, that the paragraph is implicated only when steps *plus function* without acts are present." *Id.* "The statute thus in effect provides that an element in a combination method or process claim may be recited as a step for performing a specified function without the recital of acts in support of the function." *Id.*

Based on those Federal Circuit decisions, the Court concludes that means-plus-function analysis is not applicable to the method claims at issue in this case. The statutory provision permits a description of a claim "element" by function instead of structure, material, or act. 35 U.S.C. § 112, ¶ 6; *see also Cole v. Kimberly-Clark Corp.*, 102 F.3d 524, 531 (Fed. Cir. 1996) ("[The Court] decide[s] on an element-by-element basis, based upon the patent and its prosecution history, whether § 112, ¶ 6 applies."); *In re Fuetterer*, 319 F.2d 259, 1460 n.11 (C.C.P.A. 1963) ("[Section 112, paragraph 6] in reality will give statutory sanction to combination claiming as it was understood before the Halliburton decision. All the [individual] elements of a combination now will be able to be claimed in terms of what they do as well as in terms of what they are.") (emphasis added) (quoting H.R. 3760, 82d Cong., 1st Sess., § 112 (1951) (statements of Representative Joseph R. Bryson, chairman of the subcommittee in charge of the legislation that resulted in the Patent Act of 1952)).

For method claims, the "elements" are acts; for apparatus claims, the "elements" are structures or materials. While a method element may describe the use of a structure or material, the "use" is still an act. Here, the reference to a PDE V inhibitor is not an element of the claims of the '124 patent; the element in question is the step of administering an effective amount of a PDE V inhibitor to

a patient. Thus, even if means-plus-function analysis would apply to a product claim to "an inhibitor of PDE V," it does not apply to a method claim reciting a method of administering that substance to a patient. *See O.I. Corp.*, 115 F.3d at 1583 ("[E]ven if we were to hold that the word 'passage' in the apparatus claims meets the section 112, ¶ 6, tests, we would not agree with [defendant] that the parallelism of the claims means that the method claims should be subject to the requirements of section 112, ¶ 6"; instead, "[e]ach claim must be independently reviewed in order to determine if it is subject to the requirements of section 112, ¶ 6."); *Epcon*, 279 F.3d at 1028 (same).[5]

The inventive contribution of the patent is not the discovery or invention of PDE V inhibitors, which were both numerous and well-known at the time of the invention. Instead, the invention is based on the discovery that PDE V inhibitors can be effective in treating BPH. It is thus not

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[5] Notwithstanding the decisions in *O.I. Corp.* and *Epcon*, the Federal Circuit subsequently applied means-plus-function analysis to a method claim in *On Demand Machine Corp. v. Ingram Industries, Inc.*, 442 F.3d 1331 (Fed. Cir. 2006). In that case, the claim limitation at issue recited "providing means for a customer to visually review said sales information." *Id.* at 1341. The Federal Circuit approved the district court's instruction to the jury that the "providing" limitation should be applied to the customer computer module disclosed in the specification plus its equivalents.

Although the defendants argue that the *On Demand* case shows that in appropriate cases means-plus-function analysis can be applied to method claims as well as apparatus claims, the Court disagrees. The parties in that case did not dispute that means-plus-function analysis was applicable, so the *O.I. Corp.* and *Epcon* decisions were never argued to the court. Moreover, the claims in the *On Demand* case expressly used the "means for" construction; the claims in that case could therefore be viewed as hybrid claims to which means-plus-function analysis might be applicable. No such "means for" language is present in the method claims of the '124 patent.

the point of the patent to disclose or claim particular PDE V inhibitors; the point is to disclose and claim that PDE V inhibitors can be used to treat BPH. The patent is agnostic as to what PDE V inhibitor is used. It simply recites that by using an appropriate amount of a PDE V inhibitor, a therapeutic effect on BPH can be obtained.

In this respect, the reference in the '124 patent to a PDE V inhibitor is analogous to a reference, in a patent on a novel surgical procedure, to a cutting device that is used to begin the procedure. In such a patent, it is irrelevant what particular cutting device is used; that is not the point of the invention. In that setting, the reference to a cutting device would not implicate section 112 paragraph 6, and would not require that the patent be interpreted to read only on the particular cutting device or devices that may have been referred to in the specification.

Another similar example would be a patent that claimed a novel method for treating a particular type of cardiac arrhythmia by administering a blood thinner. Although the claim could be viewed as referring to the blood thinner by its function, the claim would not invoke section 112 paragraph 6, because the invention would be directed not to a new blood thinner, but to the use of the blood thinner (of whatever type) to treat a disease in a novel way. For that reason, the patentee would not be limited to any particular type of blood thinner that may have been referred to in the specification.

The same is true in this case. The point of the patent is not the invention of compounds that inhibit PDE V, but the invention of a treatment using compounds that have that effect. Thus, the '124 patent does not contain the flaw that led to the enactment of section 112 paragraph 6, by "us[ing] conveniently functional language at the exact

point of novelty." *Warner-Jenkinson*, 520 U.S. at 27; *Halliburton*, 329 U.S. at 8; *Gen. Elec.*, 304 U.S. at 371. For that reason, the use of the term "an inhibitor of phosphodiesterase (PDE) V" does not convert the claims of the '124 patent into the sort of claims to which section 112 paragraph 6 was meant to apply.

2. Section 112 paragraph 6 as applied to an "inhibitor of phosphodiesterase (PDE) V"

Even if means-plus-function analysis can apply to method claims in some instances, the Court concludes that the method claims at issue in this case are not in means-plus-function form.

The question whether section 112 paragraph 6 applies to a particular claim element turns on whether the words of the claim element would be understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for a structure or an act. *Williamson v. Citrix Online, LLC*, 792 F.3d 1339, 1349 (Fed. Cir. 2015) (en banc). The use of the word "means" in a claim element "creates a rebuttable presumption that § 112, para. 6 applies." *Id.* at 1347. On the other hand, "[w]hen a claim term lacks the word 'means,' the presumption can be overcome and § 112, para. 6 will apply if the challenger demonstrates that the claim term fails to 'recite sufficiently definite structure' or else recites 'function without reciting sufficient structure for performing that function.'" *Id.* at 1349. When section 112 paragraph 6 applies, it limits the functional term "to only the structure, materials, or acts described in the specification as corresponding to the claimed function and equivalents thereof." *Id.* at 1347.

Because the claims of the '124 patent do not contain the words "means for" (or "step for"), there is a rebuttable presumption that section 112 paragraph 6 does not apply to the term "an inhibitor of phosphodiesterase [PDE] V." For the reasons set forth below, the Court concludes that the defendants have not overcome that presumption by presenting evidence showing that a person of ordinary skill in the art as of the 1997 priority date of the '124 patent would have regarded "an inhibitor of phosphodiesterase [PDE] V" to be a purely functional limitation.

The defendants' position is that the term "an inhibitor of phosphodiesterase [PDE] V" describes the compound by what it does—i.e., it inhibits PDE V by any means—rather than by reference to a specific chemical structure. It is true that the term "inhibitor of phosphodiesterase (PDE) V" is described in part by its function. However, the fact that a thing is defined in part by its function does not necessarily compel the conclusion that a person of ordinary skill would not have a sufficiently definite idea of what that thing is. To the contrary, "[f]unctional language may [] be employed to limit the claims without using the means-plus-function format." *Microprocessor Enhancement Corp. v. Tex. Instruments Inc.*, 520 F.3d 1367, 1375 (Fed. Cir. 2008); *see also Lighting World, Inc. v. Birchwood Lighting, Inc.*, 382 F.3d 1354, 1360 (Fed. Cir.2004) ("[T]he fact that a particular mechanism . . . is defined in functional terms is not sufficient to convert a claim element containing that term into a 'means for performing a specified function' within the meaning of section 112(6)."). That is because it is not uncommon for functional language to be used to describe particular structural objects, such as a brake, a drill, a lock, a putter, or a post-hole digger. In such cases, the name of the object is not congruent

with the function suggested by the name: thus, for example, a driver is not a putter simply because a golfer decides to use his driver to putt, and a trowel is not a post-hole digger just because a gardener chooses to use the trowel to dig a post hole.

The "essential inquiry" in such cases is "whether the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for structure." *Williamson*, 792 F.3d at 1348; *see also Greenberg v. Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1583 (Fed. Cir. 1996) ("What is important is not simply that [the term in question] is defined in terms of what it does, but that the term, as the name for structure, has a reasonably well understood meaning in the art."); *Personalized Media Commc'ns*, 161 F.3d at 704 (concluding that section 112 paragraph 6 did not apply to the term "detector" because, although defined in terms of its function, it "had a well-known meaning to those of skill in the art connotative of structure."). Moreover, it is not necessary that a term "connote a precise physical structure in order to avoid the ambit of [section 112 paragraph 6]." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1370 (Fed. Cir. 2002).

Based on the evidence of record, the Court finds that the defendants have failed to rebut the presumption that the term "inhibitor," which is used in the '124 patent without the word "means," does not invoke section 112 paragraph 6. In particular, the Court finds that the term "an inhibitor of [PDE] V" is not merely the description of a function, but would convey structure to a person of skill in the art at the time of the invention.

The evidence before the Court shows that PDE V inhibitors have been "under investigation since around

1985" and "were well-understood by the time of the invention." Corrected Decl. of Nicholas K. Terrett, Ph.D., Regarding Claim Constr. of U.S. Patent No. 8,791,124 ("Terrett Decl."), at ¶ 21, Dkt. No. 105-1. By 1997, evidence of the general structure of the PDE V enzyme, as well as that of its cGMP-specific catalytic site, were reported in the literature. *E.g.*, Michael Czarniecki et al., *Inhibitors of Types I and V Phosphodiesterase: Elevation of cGMP as a Therapeutic Strategy*, 31 ANN. REPORTS IN MED. CHEM. 61, 61-62 (1996) ("Czarniecki") (Phosphodiesterase "classes [including PDE V] share several common structural features and the amino acid sequences in the putative hydrolytic sites are highly conserved"; and the cDNA of PDE V, which "binds and selectively hydrolyzes cGMP," encodes "an 875 amino acid polypeptide with a homologous catalytic segment that is conserved across PDE types."), Dkt. No. 99-34; Kate Loughney & Ken Ferguson, *1. Identification and Quantification of PDE Isoenzymes and Subtypes by Molecular Biological Methods*, in PHOSPHODIESTERASE INHIBITORS 1, 2 (Christian Schudt et al., eds., 1996) (PDEs, including PDE V, "share in common an arrangement of structural domains," including a "catalytic region [that] is localized in the carboxy-terminal portion of the protein."), Dkt. No. 99-35.

It is undisputed that, as understood in the art, "inhibitors" act by binding to the enzyme in a way that "inhibits," or suppresses, its catalytic activity. Nicholas Terrett, Ph.D., Dep., at 22:9-19 (May 26, 2016) (agreeing that "to inhibit an enzyme like PDE . . . a molecule binds to that enzyme and decreases its [catalytic] activity"), Dkt. No. 106-9; Decl. of David P. Rotella, Ph.D. in Support of Defs.' Mot. for Partial Summ. J. Regarding the Written Description of U.S. Patent No. 8,791,124 ("Rotella Decl."), at

¶ 8(e) ("[an inhibitor of PDE V] encompasses compounds that may interact with the active site of the enzyme or some other site on the enzyme to inhibit activity"), Dkt. No. 121-4; *see also* Terrett Dep. at 15:25-16:22 (to inhibit the PDE V enzyme "means that the compound, the inhibitor, would [(a)] bind to the enzyme to make specific interactions with the catalytic site of the enzyme, and, thereby, prevent the phosphodiesterase from undertaking its normal catalytic activity," or (b) "bind to another site on the protein surface, a so-called allosteric site, . . . [to] block the [catalytic] activity of the enzyme."); David P. Rotella Dep. ("Rotella Dep."), at 71:12-72:16 (Aug. 24, 2016) (acknowledging PDE V inhibitors bind to the enzyme), Dkt. No. 130-1.

By the time of the invention, artisans had developed hundreds of PDE V inhibitors that bound competitively to the enzyme's catalytic site. Corrected Decl. of Dr. Andrew Bell in Support of Corrected Pl. UroPep's Combined Opp'n to Defs.' Mots. for Summ. J. ("Bell Decl."), at ¶¶ 45-47, 49 (noting that a review article published in 1995 contains evidence of more than 100 PDE V inhibitors, a 1995 patent now owned by Lilly lists 119 PDE V inhibitors, and a 1996 patent includes 55 examples of PDE V inhibitors), Dkt. No. 137-2. Indeed, it is undisputed even today that all known PDE V inhibitors bind competitively to the catalytic site of the enzyme. Bell Decl., at ¶ 50 (stating that, to his knowledge, "all PDE5 inhibitors bind to the same catalytic site on PDE5."); Terrett Dep., at 17:7-9 ("[A]ll of the PDE V inhibitors known do bind to the catalytic site."); Rotella Dep., at 71:12-16 (admitting that "all of the approved PDE5 inhibitors bind competitively with substrate [cGMP]."); *see also* Sharron R. Francis et al., *Inhibition of Cyclic Nucleotide Phosphodiesterases by*

Methylxanthines and Related Compounds, 200 HANDBOOK OF EXP. PHARMACOL. 93, 94 (2011) ("Francis") ("All known PDE inhibitors contain one or more rings that mimic the purine in the [cyclic nucleotide] substrate and directly compete with [the cyclic nucleotide] for access to the catalytic site."), Dkt. No. 99-37.

According to UroPep's expert, Dr. Andrew Bell, a review of the large numbers of PDE V inhibitors that were known in the art reveals "the overall structural similarity that [these] inhibitors have." Bell Decl., at ¶ 50. He concluded that all of the known PDE V inhibitors "share common physical structural features which include a planar region and typically a neighboring moiety capable of donating or accepting a hydrogen bond." *Id.* This result is unsurprising for two reasons. First, persons of skill in the art used known PDE inhibitors, such as zaprinast, "as the conceptual starting point for the design of new compounds." Terrett Decl., at ¶ 21 (quoting Czarniecki, at 62). For example, defendants' expert, Dr. David P. Rotella, used that approach in developing PDE V inhibitors. David P. Rotella et al., *N-3-Substituted Imidazoquinazolinones: Potent and Selective PDE5 Inhibitors as Potential Agents for Treatment of Erectile Dysfunction*, 43 J. MED. CHEM., no. 7, 2000, at 1257 ("[u]sing the prototypical PDE5 inhibitor zaprinast . . . as a template" to screen other potential PDE5 inhibitors), Dkt. No. 121-9; *see also* Rotella Dep., at 71:12-16 (noting use of a "template upon which inhibitors are based"). Second, persons of skill in the art at the time explored inhibitors that would mimic the structure of, and therefore compete with, cGMP to occupy the catalytic site of PDE V. *E.g.*, Nicholas K. Terrett et al., *Sildenafil (Viagra™), a Potent and Selective Inhibitor of Type 5 cGMP Phosphodiesterase with Utility for the Treatment of Male Erectile Dysfunction*, 6 BIOORG.

MED. CHEM. LETT., no. 15, 1996 at 1819, 1820-21 (in synthesizing potential PDE V inhibitors, relying on "[m]odelling studies [that] suggested that the nucleus may mimic the guanosine base of cGMP, as both are of similar size, shape and have a similar dipole moment," and considering that "extending the 3-substituent might fill a space in the enzyme active site occupied by ribose, and substituents on the 5'-position of the phenyl ring could, depending on the conformation of cGMP in the enzyme active site, reproduce the role of the phosphate in binding"), Dkt. No. 121-12; *see also* Francis, at 94 (reporting that "[a]ll known PDE inhibitors contain one or more rings that mimic the purine in the [cyclic nucleotide] substrate and directly compete with [the cyclic nucleotide] for access to the catalytic site."), Dkt. No. 99-37.

This is not to say that "an inhibitor of PDE V" describes a fixed structure, or even a small subset of structures. Indeed, many authorities explain that PDE V inhibitors vary widely in structure. Terrett Decl., at ¶ 23; *see also*, *e.g.*, Czarniecki, at 62 ("Significant structural latitude is possible while retaining potent inhibition of Type V PDE," and "there appears to be a wide tolerance for substitution [at certain positions of the inhibitor molecule]"), Dkt. No. 99-34. For that reason, Dr. Terrett stated that "[n]o one could know the range of compounds that could be included in that class." Terrett Dep., at 15:9-17. And, in response to counsel's question whether a person of skill in the art would "understand or know of a common chemical structure or feature for all inhibitors of PDE V," Dr. Terrett said no, as "[t]he PDE V inhibitors . . . represent a fairly diverse collection of different chemical structures." *Id.* at 25:17-22.

Yet even though PDE V inhibitors constitute a "diverse collection of different chemical structures," the evidence shows that they fall within the class of compounds designed to compete with cGMP to occupy the enzyme's catalytic site. Bell Decl., at ¶ 50. That class is not a small one, as Dr. Bell explained, because "the active site of the PDE5 enzyme accommodates such diversity." *Id.* at ¶ 51; *see also id.* at ¶¶ 51-55 (pointing out that the catalytic sites of some enzymes, such as COX and NMT, accommodate structurally diverse inhibitors, while those of other enzymes, such as CYP51, do not); Rotella Dep., at 78:1-14 (giving several examples of other enzyme inhibitors that show structural diversity similar to that of PDE V inhibitors). But "[t]he fact that these [fundamental] physical structures can be accomplished through diverse chemical structures and that PDE5 inhibitors permit a variety of substituents does not take away from the overall structural similarity that inhibitors have, and must have, in order to bind to the catalytic site of the PDE5 enzyme." Bell Decl., at ¶ 50.

As such, "the words of the claim are understood by persons of ordinary skill in the art to have a sufficiently definite meaning as the name for structure." *Williamson*, 792 F.3d at 1349. Artisans understood that "an inhibitor" is a compound with a structure that can bind to a key site on the enzyme to inhibit its catalytic activity, and therefore developed inhibitors with structures complementary to particular portions of the enzyme's structure. In the case of PDE V, the artisans targeted the catalytic site and designed inhibitors with structures complementary to that site.

Put another way, the term "inhibitor of phosphodiesterase (PDE) V," as used in the '124 patent, is not

simply a term that refers to any substance that will inhibit the chemical activity of PDE V. It does not apply, for example, to a very strong acidic solution which, when added to a solution containing PDE V, could be expected to destroy the PDE V molecules in a way that would disable their ability to hydrolyze cGMP. *See also* Terrett Decl., at ¶ 30 (noting that one of ordinary skill would not understand the patent to encompass techniques that "reduce the levels of PDE V enzyme in the cell" or that "insert a mutation into the gene(s) encoding the PDE V enzyme" to "disrupt its structure," as that would be inconsistent with the understanding of the term "inhibitor"). Instead, as both parties' experts attest, "an inhibitor" refers to a category of compounds with certain physical structures that bind to PDE V molecules in a way that prevents them from hydrolyzing cGMP.

In construing claims in light of section 112 paragraph 6, it is important to confine that statutory provision to cases for which it was designed to apply, and not to apply it mechanically whenever any seemingly functional term appears anywhere in a claim. That provision allows drafters to describe a structure, material, or act by its function, with the understanding that the structure, material, or act will be limited by what is disclosed in the specification. Drafters should not, however, be confined by section 112 paragraph 6 when they use a term that is understood by persons of skill in the art to have a meaning that denotes structure, even though the term may also describe the function performed by the object in question. Instead, in such cases the conventional tools of claim construction should be applied to discern the scope of the term. *See Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1374-75 (Fed. Cir. 2014); *Greenberg*, 91 F.3d at 1583.

For example, in *Personalized Media Communications, LLC v. International Trade Commission*, which involved a patent claiming a receiver system that detects and manipulates digital control signals in a broadcast or cablecast transmission, the Federal Circuit rejected the Commission's argument that "detector" should be read as a means-plus-function limitation. 161 F.3d 696, 704 (Fed. Cir. 1998). The term was "not a generic structural term such as 'means,' 'element,' or 'device,'" and it "had a well-known meaning to those of skill in the electrical arts connotative of structure." *Id.* The court acknowledged "the fact that a 'detector' is defined in terms of its function" and "does not connote a precise physical structure in the minds of those of skill in the art." *Id.* at 705. But, "[e]ven though the term 'detector' does not specifically evoke a particular structure, it does convey to one knowledgeable in the art a variety of structures known as 'detectors.'" *Id.* Therefore, the term "detector" was "a sufficiently definite structural term to preclude the application of § 112, ¶ 6." *Id.*

Like the term "detector" in *Personalized Media Communications*, the term "inhibitor" in this case presents a good example of an instance in which a seemingly functional term does not play the role in the claim that section 112 paragraph 6 was directed to and therefore does not trigger the application of that provision. *See also*, *e.g.*, *CCS Fitness*, 288 F.3d at 1369 (concluding that section 112 paragraph 6 did not apply to "reciprocating member" because a person of ordinary skill in the art would understand the term to connote beam-like structures encompassing more than the "single-component, straight bar structures (and their equivalents) shown in the patents' drawings.").

The observations of the defendants' expert, Dr. Rotella, are not inconsistent with this conclusion. Dr. Rotella agreed that all known PDE V inhibitors bind to the enzyme's cGMP catalytic site. Rotella Dep., at 71:12-16;[6] *see also* Rotella Decl., at ¶¶ 101, 103 (describing the method of determining how an inhibitor binds to PDE V by combining the inhibitor with a fragment of the PDE V molecule that includes the cGMP catalytic site, rather than the whole enzyme), Dkt. No. 121-3. He then explained that inhibitors may vary in structure and have different binding interactions with PDE V. Rotella Decl., at ¶ 33; *see also*, *e.g.*, Rotella Decl., at ¶ 102 (comparing how structural features of tadalafil and sildenafil bind to various pockets within the catalytic site of PDE V). Dr. Rotella focused on minute differences in binding interactions and made the general statement that "there is no structure that would be common to all compounds able to inhibit PDE5." Rotella Decl., at ¶ 19. But he never described any particular PDE V inhibitor as lacking the fundamental structures identified by Dr. Bell that account for "the overall structural similarity that [PDE V] inhibitors have, and must have, in order to bind to the catalytic site of the PDE5 enzyme." Bell Decl., at ¶ 50. More importantly, Dr. Rotella's review of how certain inhibitor molecules may differ—for example, by including other components that bind to additional regions of the catalytic site—does not undermine the experts' agreement that all

[6] Dr. Rotella mentioned "one paper" that he "believe[d]" was "published in 2005 that illustrates that it is possible to inhibit PDE V by binding at a site distinct from the active site." Rotella Dep., at 71:18-22. But he could not remember the name of the lead author on the paper, *id.* at 72:6-16, and the defendants have submitted nothing to supplement that statement. Dr. Bell stated that he was not aware of any such paper or similar evidence. Bell Decl., at ¶ 50.

PDE V inhibitors bind to the enzyme and therefore have structures that correspond to that of PDE V.

The evidence, of course, does not show—nor does Uro-Pep attempt to argue—that simply stating that a compound is a PDE V inhibitor would resolve all the questions that might have come to the mind of a person of ordinary skill about its nature. Clearly there are issues as to additional properties of the compound that a person of ordinary skill would consider, such as its precise chemical composition, its toxicity, its selectivity, and its kinetics. Thus, a person of skill in the art would need to have additional information in order to describe a particular PDE V inhibitor in detail, just as a golfer would need additional information beyond the term "putter" to describe a particular type of putter in detail. However, the Court finds that those additional questions do not rise to a level such that a person of ordinary skill would lack a reasonably definite understanding of the structure in question.

In sum, a person of ordinary skill in the art as of the priority date of the '124 patent would have had a reasonably certain understanding of the structural features necessary for a particular compound to be an inhibitor of PDE V, as that term was used in the field. For that reason, the Court finds that the defendants have not carried their burden to overcome the presumption that 35 U.S.C. § 112 ¶ 6 does not apply to the term "an inhibitor of phosphodiesterase (PDE) V."

B. Construction of the Term "an inhibitor of phosphodiesterase (PDE) V"

The parties agree that if section 112 paragraph 6 does not apply to the term "an inhibitor of phosphodiesterase

(PDE) V," the term should be construed to mean "a compound able to inhibit PDE V." However, UroPep argues that the term should be given an even narrower construction in three respects: first, the compound must be a "small molecule" compound; second, it must be "therapeutically effective"; and third, it must be "relatively selective" as to PDE V. The defendants disagree and argue that the term is not limited in any of those three additional respects.

1. Small molecule compound

The Court agrees with the parties that "an inhibitor of phosphodiesterase (PDE) V" refers to a compound, as is clear from the claim language. The phrase "an inhibitor of phosphodiesterase (PDE) V" is followed by the limitation that it "exclud[es] a compound selected from the group" of eight listed compounds. That formulation, although unusual, is a modified form of a claim to a Markush group, which is "a listing of specified alternatives of a group in a patent claim, typically expressed as "a member selected from the group consisting of A, B, and C." *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003). Because the term "an inhibitor of phosphodiesterase (PDE) V" is defined, albeit in negative form, by reference to a group of compounds, the claim language suggests that "an inhibitor of phosphodiesterase (PDE) V" must be a compound, like the compounds that are excluded from its coverage. Moreover, as the defendants have noted, "the specification of the '124 Patent . . . uses the terms 'inhibitor,' 'compound' and 'substance' interchangeably." Defs. Eli Lilly and Company and Brookshire Brothers, Inc.'s Resp. Claim Constr. Br., at 8, Dkt. No. 106.

The dispute between the parties centers on whether the term "inhibitor" is limited to a compound of a particular size. UroPep argues that "inhibitor," as used in the '124 patent, is limited to a "small molecule compound." UroPep adopts that position based on the testimony of its expert, Dr. Terrett, who stated in his declaration that the "inhibitor of phosphodiesterase (PDE) V" referred to in the '124 patent must be a compound whose molecular weight does not exceed about 600 Daltons. He stated:

> Small molecule compounds are formed by the combination of multiple atoms in a specifically defined structural arrangement. Such compounds are referred to as small molecules if the total molecular weight does not exceed around 600 Daltons. The definition also distinguishes the compounds from larger molecules such as peptides, proteins or polymers. An individual compound has a unique chemical structure that confers the compound's pharmacological and physical properties, and no alteration of the connections between atoms is permitted as such change would redefine the identity of the compound.

Terrett Decl., at ¶ 22. While Dr. Terrett's definition of "small molecule compounds" may be consistent with the definition of a small molecule compound in the art, nothing in the record suggests that the term "inhibitor," as used in the '124 patent, is limited to a compound having a molecular weight under a particular limit, such as 600 Daltons. The Court therefore does not adopt UroPep's contention that the term "an inhibitor of phosphodiesterase

(PDE) V" is limited to "small molecule" compounds, as defined by Dr. Terrett.

2. Therapeutically effective

UroPep next argues that the term "an inhibitor of phosphodiesterase (PDE) V" requires that the inhibitor be therapeutically effective. The Court disagrees. The "inhibitor of phosphodiesterase (PDE) V" is simply a compound that inhibits PDE V. Of course, claim 1 of the '124 patent describes a "method of prophylaxis or treatment of [BPH] comprising administering . . . an effective amount of an inhibitor of phosphodiesterase (PDE) V." Therefore, the claim separately requires that the administration of the PDE V inhibitor be "effective" in the "prophylaxis or treatment of [BPH]." For that reason, a particular inhibitor of PDE V may be insufficiently potent to be effective in treating BPH, in which case a treatment using that inhibitor would not satisfy the "effective amount" limitation of the claims. But nothing in the record supports UroPep's contention that the requirement of effectiveness in treating BPH is inherent in the definition of the term "inhibitor of phosphodiesterase (PDE) V."

3. Selective inhibitor

Finally, UroPep argues that the claimed inhibitor of PDE V must be a selective inhibitor, i.e., a compound that inhibits PDE V to a significantly greater extent than other specific PDEs. UroPep's position is that "statements made during the prosecution of the '124 patent family confirm that the claims cover the use of selective inhibitors." Pl. UroPep's Corrected Opening Claim Constr. Br., at 23 (citing portions of the prosecution history of the parent application and stating that "patentees thus distinguished its invention over the prior art by emphasizing

the selective nature of the PDE V inhibitors"), Dkt. No. 105; *see also* Pl. UroPep's Reply Claim Constr. Br., at 2 n.2 (citing statements made during the prosecution of the parent application), Dkt. No. 109.

The defendants respond to UroPep's argument by pointing out that the patentees claimed "a selective inhibitor" in the patent that issued from the parent application and therefore knew how to claim that the inhibitors in the '124 patent were "selective" if that is what was intended. The failure to include the term "selective" in the claims of the '124 patent, according to the defendants, is a clear indication that the reference to "an inhibitor of phosphodiesterase (PDE) V" in that patent was not intended to be limited to "selective" inhibitors of PDE V, as was the case for the earlier patent. Defs. Eli Lilly and Company and Brookshire Brothers, Inc.'s Resp. Claim Constr. Br., at 15-16, Dkt. No. 106.

The Court finds that the term "inhibitor of phosphodiesterase (PDE) V" in the '124 patent refers to a selective inhibitor of PDE V. The specification of the '124 patent makes clear that a PDE V inhibitor is a member of the class of specific PDE inhibitors, or sPDEs. '124 patent, col. 1, line 53, through col. 2, line 16; col. 7, line 35, through col. 8, line 27. The specification further explains that a substance is considered an inhibitor of a specific PDE if the amount of that substance needed to hydrolyze the specific PDE is much less than the amount needed to hydrolyze other specific PDEs. *Id.*, col. 8, ll. 5-9.

In addition, the prosecution history supports the conclusion that the term "inhibitor of phosphodiesterase (PDE) V" refers to a selective PDE inhibitor. The application for the '124 patent was a continuation of application number 10/443,870, which matured into the '061 patent.

As noted, the '061 patent claimed many of the compounds that were expressly excluded from the claims of the '124 patent. In the prosecution of that application, the applicants distinguished the claimed compounds from the compounds disclosed in a prior art reference on the ground that the prior art reference did not teach the use of a specific PDE V inhibitor for treating prostate hypertrophy, *see* Oct. 27, 2009, Am. and Remarks, at 10, Dkt. No. 99-26. The applicants asserted that "[t]he compounds of the currently pending claims are selective inhibitors," unlike the compounds disclosed in the prior art, *see* Mar. 7, 2010, Am. and Remarks, at 10, Dkt. No. 99-27. Thus, in the course of the prosecution of the '061 patent, the applicants clearly disclaimed non-selective inhibitors (and amended the claims in accordance with that disclaimer). The question is whether the disclaimer that the applicants made during the prosecution of the '061 patent applies to the continuation application that led to the '124 patent.

In general, a prosecution disclaimer "will only apply to a subsequent patent if that patent contains the same claim limitation as its predecessor." *Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F.3d 929, 943 (Fed. Cir. 2013). Where the limitations are different, the question whether the disclaimer is to be carried forward turns on whether there is a material difference between the earlier and later claim limitations. *Id.* at 944. However, there is "an exception [to that rule] where an amendment to a related limitation in the parent application distinguishes prior art and thereby specifically disclaims a later (though differently worded) limitation in the continuation application." *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005) (citing *Elkay Mfg. Co. v. EBCO Mfg. Co.*, 192 F.3d 973, 978-79 (Fed. Cir. 1999)). Here, the patentees amended their claims during the prosecution of

the parent '061 patent to overcome a prior art rejection by arguing that its inhibitors of PDE IV and/or PDE V were "selective." Therefore, it does not matter that UroPep did not affirmatively include that limitation in the '124 patent; the limitation was included through the earlier disclaimer and amendment. Even if that were not true, it would be difficult to imagine one of ordinary skill reading the specification of the '124 patent and concluding that the reference to an inhibitor of PDE V was not meant to be limited to a selective inhibitor. *See*, *e.g.*, '124 patent, col. 2, ll. 3-4 ("a well-aimed affection of the prostatic muscles by inhibiting a functionally important sPDE isoenzyme"); col. 2, line 28 ("[p]referred selective inhibitors of PDE I, IV, and V").[7]

The parties also dispute how great the differential effect must be for a compound to be considered a "selective" inhibitor. On this issue, the specification of the'124 patent provides helpful guidance. The specification states that an inhibitor is a considered an inhibitor of a specific PDE "if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20

[7] The defendants assert that *Housey Pharms., Inc. v. Astrazeneca UK Ltd.*, 366 F.3d 1348 (Fed. Cir. 2004), stands for the proposition that the inhibitor claimed in the '124 patent cannot be selective because the claim language does not include the terms "selective" or "relatively selective." *Housey* does not stand for such a broad proposition. In determining the correct construction of the term at issue in that case, the *Housey* court considered both the prosecution history and the specification, and it concluded that they did not support the argument that the claim term in question should be given a restrictive construction. *Id.* at 1354-55. Having considered both the prosecution history and the specification in this case, the Court concludes that those sources of guidance as to the meaning of the claims indicate that the claim language must be construed to refer to a selective inhibitor of PDE V.

times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions." '124 patent, col. 8, ll. 6-9. The parties do not appear to dispute that this "20 times" standard represents the general understanding of a person of ordinary skill in the art. The Court therefore finds that a selective inhibitor of a specific PDE is at least 20 times more effective in inhibiting that specific PDE as compared to all other specific PDEs.

In summary, the Court finds that "an inhibitor of phosphodiesterase (PDE) V" is "a compound that selectively inhibits PDE V."

C. The Motion for Summary Judgment of Non-Infringement Is Denied

As noted earlier, the defendants' motion for summary judgment of non-infringement was predicated on their assertion that the claims of the '124 patent are governed by 35 U.S.C. § 112 ¶ 6. In the course of construing the term "inhibitor of phosphodiesterase (PDE) V," the Court has found otherwise. The Court therefore DENIES the motion for summary judgment of non-infringement.

II. The Motion for Summary Judgment of Invalidity

The defendants argue that if the '124 patent claims are not restricted to the specific compounds disclosed in the specification, the specification fails to satisfy the "written description" requirement of 35 U.S.C. § 112 ¶ 1, and the asserted claims are invalid.

Section 112 paragraph 1 provides, in pertinent part:

> The specification shall contain a written description of the invention, and of the manner

> and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112 ¶ 1 (2006). That provision has remained largely unchanged since the Patent Act of 1793.[8]

The written description clause has been interpreted to require that the specification "describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1345 (Fed. Cir. 2010) (en banc).[9] The level

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[8] *See* Act of Feb. 21, 1793, 1 Stat. 318, 319 (the applicant "shall deliver a written description of his invention, and of the manner of using, or process of compounding the same, in such full, clear and exact terms, as to distinguish the same from all other things before known, and to enable any person skilled in the art or science . . . which it is most nearly connected, to make, compound and use the same").

[9] As the Federal Circuit explained in *Ariad*, 598 F.3d at 1351, the possession inquiry is an objective one that is viewed from the perspective of a person of ordinary skill in the art:

> The term "possession" . . . has never been very enlightening. It implies that as long as one can produce records documenting a written description of a claimed invention, one can show possession. But the hallmark of written description is disclosure. Thus, "possession as shown in the disclosure" is a more complete formulation. Yet whatever the specific articulation, the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must de-

of detail required to satisfy the written description requirement "varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* at 1351; *see also Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) (what is required "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence"). In the case of a claim to a genus, the Federal Circuit has held that "a sufficient description of the genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350.

Whether the written description requirement is satisfied is a question of fact. *Scriptpro, LLC v. Innovation Assocs., Inc.*, 762 F.3d 1355, 1359 (Fed. Cir. 2014). The failure to satisfy the requirements of 35 U.S.C. § 112 ¶ 1 must be proved by clear and convincing evidence. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1297 (Fed. Cir. 2014).

The defendants argue that they are entitled to summary judgment on the written description issue. Summary judgment is appropriate when there are no genuine issues of material fact and when, drawing all factual inferences in favor of the nonmoving party, no "reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986); *accord Scriptpro*, 762 F.3d at 1359. Even under the clear

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scribe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.

and convincing evidence standard, the defendants contend, a reasonable jury would be compelled to find that the specification of the '124 patent provides an inadequate written description of the invention set forth in the claims.

In particular, the defendants argue that UroPep's proposed construction of the term "inhibitor" encompasses a great number of compounds, including many that are not disclosed in the patent or in the prior art, and many that have not even been discovered. UroPep's "overreaching construction," according to the defendants, "far exceeds the disclosure of the '124 patent and if adopted, renders claims 1 and 3 of the '124 patent invalid." Eli Lilly & Co.'s and Brookshire Brothers, Inc.'s Mot. for Partial Summ. J. that Claims 1 and 3 of U.S. Patent No. 8,791,124 Are Invalid for Failure to Meet the Written Description Requirement of 35 U.S.C. § 112 ¶ 1 and Mem. of Law in Support Thereof, at 10, Dkt. No. 120.

The Court concludes that there is at least a disputed issue of material fact as to whether the '124 patent specification satisfies the written description requirement. In the first place, the claims of the '124 patent are directed to the use of PDE V inhibitors to treat BPH, not to the discovery of PDE V inhibitors themselves. As UroPep explains, the "inventors did not purport to, and did not, contribute novel PDE V inhibitors" to the art. *See* Pl. UroPep's Combined Opp'n to Defs.' Mots. for Summ. J., at 22, Dkt. No. 129. Given the nature of the claims, the proper inquiry under the written description requirement is whether the disclosure in the specification shows that the inventors possessed the invention that administering an effective amount of a PDE5 inhibitor would treat BPH. Thus, given that at least some PDE V inhibitors were known and were disclosed in the '124 specification, the

written description issue does not turn on whether the patentees were in possession of the entire genus of PDE V inhibitors.

In re Herschler, 591 F.2d 692 (C.C.P.A. 1979), presented a similar issue. In that case, the court found adequate written description support for broad claims for topically administering a steroidal agent by administering the steroidal agent together with dimethyl sulfoxide. Even though the specification disclosed only a single example of a steroidal agent, the court found that the disclosure was sufficient because the claim was drawn to the method of administering the steroidal agent, and numerous active steroidal agents were known to persons of skill in the art. 591 F.2d at 701. The court noted that "[w]ere this application drawn to novel 'steroidal agents,' a different question would be posed." *Id.*; *see also Rochester*, 358 F.3d at 928 (discussing *Herschler*).

To the same effect is *In re Fuetterer*, 319 F.2d 259 (C.C.P.A.) (Rich, J.), in which the application was directed to a combination of substances used to make rubber tire tread stock, including "an inorganic salt that is capable of holding a mixture of . . . carbohydrate and protein in colloidal suspension in water." *Id.* at 261. The Patent Office Board of Appeals rejected the representative claim on the ground that it was functional and because the specification included only four examples of such salts. *Id.* at 262. The court reversed the Board. In his opinion, Judge Rich explained that the "invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties." *Id.* at 265. He continued, in words applicable here by analogy,

> We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

Id.

UroPep's evidence shows that PDE V inhibitors were not unknown as of the July 9, 1997, priority date of the '124 patent. To the contrary, there were hundreds of known PDE V inhibitors at that time. Accordingly, the written description requirement is satisfied if the specification shows that the inventors possessed the method of treating BPH by administering an inhibitor of PDE V.

Relying on language from *Rochester* and *AbbVie*, the defendants assert that the written description requirement applies "[r]egardless whether a compound is claimed per se or a method is claimed that entails the use of the compound[]." *See Rochester*, 358 F.3d at 926. That statement was made in a different context, however. The claims at issue in that case were directed to methods "for selectively inhibiting PGHS-2 activity in a human host." 358 F.3d at 918. In that context, it made sense for the court to say that the written description requirement was the same whether the claims were directed to inhibitors of PGHS-2 activity or to methods of inhibiting PGSH-2 activity, as the essence of the invention was the same in

both cases—the identification of compounds that would inhibit PGHS-2 activity.

In this case, by contrast, the invention is not a method for inhibiting PDE V, which would be analogous to the invention in the *Rochester* case. Instead, the invention is a method of treating BPH by using inhibitors of PDE V. Because the invention is not the identification of particular inhibitors, but the use of compounds having the inhibiting feature for a particular therapeutic purpose, the particular risk presented in *Rochester*—that the inventor is seeking claim coverage for a genus of compounds that perform a particular function, while only disclosing a small and unrepresentative subset of such compounds—is not directly presented here.[10]

These distinctions of the *Rochester* and *AbbVie* cases might not have much force if the specification of the '124 patent had disclosed very little information about PDE V inhibitors, or had provided no examples of such inhibitors. In that setting, it could be argued that, absent knowledge of the substances to be used in the claimed treatment, the inventors were not shown to be in possession of the invention.

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[10] The same distinction applies to the *AbbVie* case on which the defendants rely. 759 F.3d 1285. The claims in that case were drawn to isolated antibodies that would neutralize the activity of human interleukin 12, and the patent purported to teach how to make such antibodies. The examples given in the patent, however, were limited to certain species of the claimed antibodies, even though the claims were not so limited, and the specification did not disclose structural features common to the members of the claimed genus of antibodies. 759 F.3d at 1299. Under these circumstances, the Federal Circuit upheld the jury's verdict that the written description requirement was not satisfied.

Indeed, the patent in *Rochester* did "not disclose any compounds that [could] be used in its claimed methods"; the court explained that "[w]ithout such disclosure, the claimed methods cannot be said to have been described." 358 F.3d at 927. The court distinguished the case before it from other cases in which the specification also failed to cite examples but was nevertheless held sufficient because persons of skill in the art "could recognize what was being claimed" based on the prevailing knowledge. *Id.* at 928 (discussing, e.g., *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000), where "evidence was adduced . . . that artisans skilled in petroleum refining were aware of the properties of raw petroleum sources and knew how to mix streams of such sources to achieve a final product with desired characteristics."). In *Rochester*, the lack of examples and anything beyond a "vague functional description" meant that the patent was drawn to no more than "a mere wish or plan for obtaining the claimed chemical invention." *Id.* at 927.

In this case, however, the disclosures in the specification regarding PDE V inhibitors go beyond merely providing a functional description, or only a single example, of a PDE V inhibitor. As noted above, the '124 specification contains a description of the biochemistry underlying the invention. It discloses that the relaxation of smooth muscle cells in the prostate can result in a distinct improvement in the symptoms of BPH. It discloses the physiological mechanism by which information is transmitted that causes the relaxation of smooth muscle cells, explaining that hormones or neurotransmitters cause an increase in cAMP and cGMP in the smooth muscle cells, resulting in relaxation of those cells. It explains that because cAMP and cGMP are hydrolyzed by phosphodiesterases, inhibitors of PDEs reduce the digestion

of cAMP and cGMP, "resulting in an increase in these molecules within the cell and thus in a relaxation of the smooth muscle cell." '124 patent, col. 1, ll. 36-47.

The specification teaches that three specific PDEs—PDE I, PDE IV, and PDE V—"are of particular importance in human prostatic muscles." *Id.*, col. 2, ll. 6-8. The specification then concludes that a "well-aimed inhibition of these isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, particularly vessels, being observed. Therefore, they have an excellent efficiency in the treatment of prostatic diseases." *Id.*, col. 2, ll. 11-16. The specification lists 12 "preferred selective inhibitors" of PDE I, IV, and V: 10 compounds and two general names of compounds. The journal articles cited in the specification (and the sources cited in those journal articles) disclose other PDE V inhibitors. *See* C. David Nicholson & M. Shadid, *Inhibitors of Cyclic Nucleotide Phosphodiesterase Isoenzymes–Their Potential Utility in the Therapy of Asthma*, 7 PULM. PHARMACOL., No. 1, 1994, at 1-17; T. J. Torphy et al., *Identification, Characterization and Functional Role of Phosphodiesterase Isoenzymes in Human Airway Smooth Muscle*, 265 J. PHARMACOL. EXP. THER., No. 3, 1993, at 1213-23; W. J. Thompson, *Cyclic Nucleotide Phosphodiesterases: Pharmacology, Biochemistry and Function*, 51 PHARMACOL. THER., no. 1, 1991, at 13-33.

Beyond that, the specification describes in some detail pharmacological studies that were used to determine the potency of specific PDE inhibitors. '124 patent, col. 7, ll. 14-34. Those studies involved the use of samples of human prostatic tissue in a solution of a specific PDE inhibitor to

measure the degree of muscle relaxation caused by particular test compounds. The results of those studies showed that "the inhibitors of PDE I, IV and V proved to have the strongest prostatic tissue relaxing effect." *Id.*, col. 7, ll. 32-34.

The specification also states that "the proof of whether a compound is suitable for the purpose according to the invention" is furnished by known methods, citing references from 1989 and 1990. '124 patent, col. 7, ll. 35-39. The specification then describes an assay for determining if a substance is an inhibitor of a specific PDE and determining the potency of that inhibitor. *Id.*, col. 7, line 35, through col. 8, line 16. UroPep points to record evidence that the information provided by that assay would be sufficient to show that the particular inhibitor under examination would have the necessary potency to be therapeutically effective against BPH. Bell Dep., at 111:2-6, 114:15-20 (Aug. 11, 2016), Dkt. No. 140-1. The information provided regarding PDE inhibitors in general, and PDE V inhibitors in particular, is considerably more detailed than the information disclosed regarding the genus of PGSH-2 inhibitors in *Rochester* and antibodies that could neutralize interleukin 12 in *AbbVie*.

To be sure, there is much that the '124 specification does not describe. For example, it does not separately discuss the characteristics of the three identified specific phosphodiesterases, PDE I, PDE IV, and PDE V. Other than the general statement that specific PDEs are distributed differently throughout the body, the specification provides no explanation of how or why one of those three PDEs should be targeted differently within prostate tissue. That is to say, despite the fact that the claims of the '124 patent are directed only to PDE V, the specification

provides no suggestion as to why a person of ordinary skill would single out PDE V rather than the other two PDE inhibitors of interest, PDE I and PDE IV. *See* Defs. Eli Lilly & Co. and Brookshire Brothers, Inc.'s Consolidated Reply Br. in Support of their Mots. for Summ. J. of Non-infringement and for Invalidity for Failure to Meet the Written Description Requirement of 35 U.S.C. § 112, ¶ 6, at 15, Dkt. No. 139. The specification also provides no substantive results for the tests it discusses or the results of any testing demonstrating actual prophylaxis or treatment of BPH in animals or humans.

In response to the defendants' criticisms of the disclosure in the '124 specification, UroPep points out that in assessing the adequacy of a specification's disclosure for written description purposes, the Court must view the disclosure as would one of skill in the art. *See Ariad*, 598 F.3d at 1351 (Possession means possession as shown in the disclosure and "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."); *In re Alonso*, 545 F.3d 1015, 1019 (Fed. Cir. 2008); *Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1365-66 (Fed. Cir. 2003). Because "the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before . . . it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention . . . ." *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

UroPep points to evidence in the record that persons of skill in the art would have been aware of hundreds of PDE V inhibitors in addition to the exemplary compounds

set forth in the '124 specification, *see* the evidence cited at pages 15-16, *supra*. UroPep also points to evidence that persons of skill in the art would have been aware of the structure of tadalafil, the compound used in the defendants' accused method, and the fact that tadalafil is a PDE V inhibitor, *see* Rotella Decl., at ¶ 64; Bell Decl., at ¶ 46; Rotella Dep., at 48:18-22.

It was not necessary for the patentees to include in the specification a catalog of all then-known PDE V inhibitors, UroPep argues, because persons of skill in the art were aware of the studies listing large number of such inhibitors. In light of the knowledge of persons in the field at the time, according to UroPep, the particular PDE V inhibitors that were described in detail in the specification constitute "a representative number of species falling within the scope of the genus," *AbbVie*, 759 F.3d at 1299, even if the genus is viewed as all compounds capable of inhibiting the catalytic action of PDE V.

Whether the omissions from the specification, viewed in light of the facts known to persons of skill in the art as of the priority date of the '124 patent, render the specification insufficient to provide the necessary written description of the inventions of the '124 patent is a factual issue. The Court is persuaded that what is disclosed in the specification, when viewed in light of what a person of ordinary skill in the art would have known at the time, is sufficient to at least raise a question of fact sufficient to take the written description issue to a jury. The Court therefore DENIES the defendants' motion for partial summary judgment of invalidity based on 35 U.S.C. § 112 ¶ 1.

IT IS SO ORDERED.

Dated: October 21, 2016 /*s*/ William C. Bryson
William C. Bryson
United States Circuit Judge

APPENDIX F

NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

ERFINDERGEMEINSCHAFT UROPEP GBR,
Plaintiff-Appellee

v.

ELI LILLY AND COMPANY,
Defendant-Appellant

2017-2603

Appeal from the United States District Court for the Eastern District of Texas in No. 2:15-cv-01202-WCB, Circuit Judge William C. Bryson.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, and HUGHES, *Circuit Judges*[*].

[*] Circuit Judge Stoll did not participate.

PER CURIAM.

ORDER

Appellant Eli Lilly and Company filed a petition for rehearing en banc. A response to the petition was invited by the court and filed by appellee Erfindergemeinschaft UroPep GbR. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on February 12, 2019.

FOR THE COURT

Dated February 5, 2019 /s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX G

(12) United States Patent Forssmann et al.

(10) Patent No.: US 8,791,124 B2

(45) Date of Patent: *Jul. 29, 2014

(54) USE OF PHOSPHORDIESTERASE INHIBITORS IN THE TREATMENT OF PROSTATIC DISEASES

(75) Inventors: Wolf-Georg Forssmann, Hannover (DE); Christian Georg Stief, Hemmingen (DE); Michael Carsten Truβ, Hannover (DE); Stefan Uckert, Garbsen (DE); Udo Jonas, Hannover (DE)

(73) Assignee: Uropep Biotech GBR, Garbsen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 13/339,561

(22) Filed: Dec. 29, 2011

(65) Prior Publication Data

US 2012/0172365 Al Jul. 5, 2012

Related U.S. Application Data

(63) Continuation of application No. 10/443,870, filed on May 23, 2003, now Pat. No. 8,106,061, which is a continuation of application No. 09/462,090, filed as application No. PCT/EP97/03617 on Jul. 9, 1997, now abandoned.

(51) Int. Cl.

A61K31/52 (2006.01)

A61K 31/502 (2006.01)

A61K31/4174 (2006.01)

(52) U.S. Cl.

CPC…….....A61K 31/52 (2013.01); A61K 31/502 (2013.01); A61K 31/4174 (2013.01)
USPC……..514/261.1; 514/248; 514/396

(58) Field of Classification Search

CPC……..A61K 31/52; A61K 31/502; A61K 31/4174

See application file for complete search history.

(56) References Cited

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Primary Examiner—James D Anderson

(74) *Attorney, Agent, or Firm*—Jacobson Holman, PLLC

(57) ABSTRACT

The present invention pertains to the use of inhibitors of phosphodiesterase I, IV and V for the prophylaxis and treatment of prostatic diseases, in particular the use of

a) 2-(2-propoxy-phenyl)-8-azapurin-6-one(zaprinast);

b) dipyridamole;

c) 1-(3-chlorophenylamino)-4-phenylphthalazine (M5445);

d) 2-(N-(4-carboxypiperidine-6-chloro-4-(3,4-(methylen-dioxy)benzyl)amino)quinazoline (E 4021, ER 21355);

e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);

f) 4-((3,4-(methylendioxy)benzyl)amino)-6,7,8-trimethoxy-quinazoline;

g) 1-methly-3-propyl-6-(5-(N-(4-methylmorpholino)sulfo-ny1)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (sildenafil);

i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d) pyrimidin-4(5H)-one (WIN 58237);

j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydrox-ypropoxy)-2-carboxy-2,3-didehydro-chronan-4-one (PPL-557212);

k) quinazolines and their trimethoxy derivatives;

1) Pyrazolopyrimidones;

as well as pharmacologically compatible salts thereof,

quinazolines and their trimethoxy derivatives, pyrazolopy-rimidones or compatible salts thereof, in local and systemic administration.

3 Claims, No Drawings

USE OF PHOSPHORDIESTERASE INHIBITORS IN THE TREATMENT OF PROSTATIC DISEASES

This is a continuation of Ser. No. 10/443,870, filed, May 23, 2003 now U.S. Pat. No. 8,106,061, which is a continuation of Ser. No. 09/462,090, filed, Apr. 6, 2000, now abandoned, which is a 371 of PCT/EP97/03617, filed Jul. 9, 1997.

The prostate gland is an organ of about chestnut size which in males surrounds the cervix of the vesical outlet. In 50% of the males in the age of above 50 years, a benign growth of the prostate gland occurs which may result in severe difficulties in the miction up to anuria and which is subject to treatment obligation. Most of the affected patients must be treated with surgical methods.

In the development of benign prostatic hyperplasia (BPH), the glandular portions of the prostate gland increase by double their volume, and the muscular and fibrous portions increase by four times their volume (Christmas and Kirby, W. J. Urol. 9: 36-40, 1991). Since these muscle cells account for a large portion of the total prostatic tissue (at least 35%), a distinct improvement of miction can be achieved by means of a pharmacologically induced relaxation of these muscle cells (Hedlund and Andersson, J. Urol. 130: 275-278, 1983). The substances used

to date mostly belong to the group of alpha-receptor blockers (Lepor et al., J. Urol. 143: 267, 1990), or they interfered with the hormonal regulation of the prostate gland (Kirby and Christmas, W. J. Urol., 9: 41-44, 1991); these medicament treatments were characterized by either a very low effectiveness, a slow onset of action, or significant side-effects, or a combination of such effects.

Therefore, we have examined a completely different pharmacological principle of action, namely the affection of a key enzyme within the smooth muscle cells of the prostate gland, phosphodiesterase.

The physiological transmission of information for the relaxation of smooth muscle cells is effected by messengers of the blood (hormones) or the nerves (neurotransmitters). These messengers and neurotransmitters cause an increase in the levels of the cyclic nucleotides "cyclic adenosine monophosphate" (cAMP) and "cyclic guanosine monophosphate" (cGMP) in the smooth muscle cell, resulting in relaxation. cAMP and cGMP themselves are hydrolized by phosphodiesterases (PDEs). Inhibitors of the PDEs in turn reduce the digestion of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell. This mechanism of action has been described, for instance, by C. D. Nicholson, R. A. Challiss, and M. Shadid: Trends Pharmacol. Sci., 12 (1991), 19-27, C. D. Nicholson and M. Shadid: Pulm. Pharmacol. 7 (1) (1994), 1-17, and T. J. Torphy et al.: J. Pharmacol. Exp. Ther. 265 (3) (1993), 1213-23.

From these publications as well as from W. J. Thompson: Pharmacol. Ther. 51 (1991), 13-33, and J. Beavo in: J. Beavo and M. D. Housley (eds.): Cyclic nucleotide phosphodi-esterases: Structure, regulation and drug action,

Chichester, New York-Brisbane-Toronto-Singapore, Wiley, 1990: 3-15, there is further known the distinction of a number of subesterases of PDE, the specific phosphodiesterases (sPDE). There is distinguished between five different sPDEs which are differently distributed in the individual organs and organ systems and exhibit different levels of effectiveness according to their distribution. In the publications mentioned, there is also discussed the occurrence of the different isoenzymes in various tissues.

An interesting target for the use of PDE isoenzyme selective inhibitors is the lower urinary tract since the medicamental therapy of prostate dysfunctions with conventional substances is often little effective and full of side effects. Therefore, a well-aimed affection of the prostatic muscles by inhibiting a functionally important sPDE isoenzyme appears to be superior to conventional therapy methods.

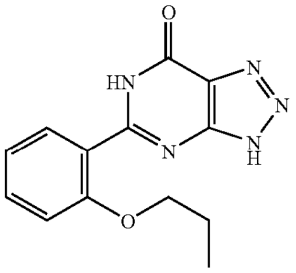
Surprisingly, it has now been found that sPDE I, sPDE IV and sPDE V are of particular importance in human prostatic muscles: After performing Q-sepharose chromatography, there has been found a typical pattern of the human prostatic tissue showing the presence of the PDE isoforms I, IV and V (below). A well-aimed inhibition of these isoenzymes will result in relaxation of the prostatic muscles even when minute doses of a specific inhibitor are administered, with no appreciable effects in other organ strips, in particular vessels, being observed. Therefore, they have an excellent efficiency in the treatment of prostatic diseases.

Therefore, the subject matter of the invention is the use of specific inhibitors of sPDE I, sPDE IV and sPDE V in the prophylaxis and treatment of prostatic diseases,

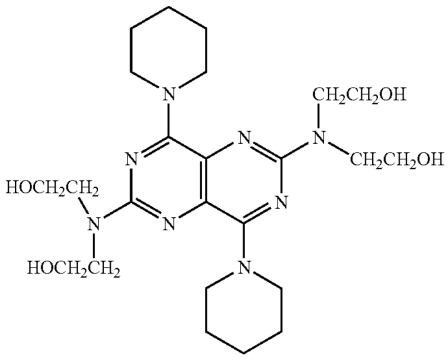
in particular benign prostatic hyperplasia, the so-called urge symptoms, pollacuria (frequent micturition), nycturia (nocturnal micturition), weakened urine jet, urge incontinence (involuntary discharge of urine), prostatism, instabilities of the bladder muscles, impotence, and the use of the inhibitors for the preparation of medicaments useful for this purpose as well as medicaments containing sPDE I, IV and V inhibitors for the objects mentioned.

Preferred selective inhibitors of PDE I, IV and V are:

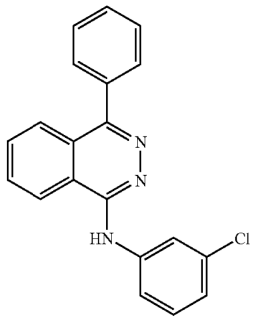
a) 2-(2-propoxyphenyl)-8-azapurin-6-one (zaprinast);



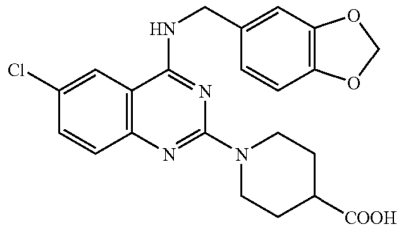
b) dipyridamole;



c) 1-(3-chlorophenylamino)-4-phenylphthalazine (MY5445);

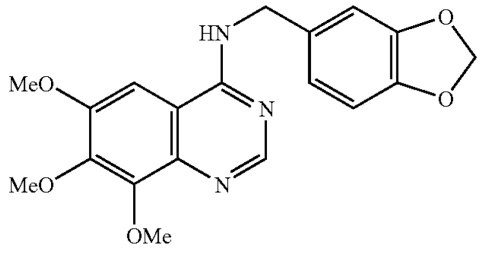


d) 2-(N-(4-carboxypiperidine)-6-chloro-4-(3,4-(methylen-dioxy)benzyl)amino)quinazoline (E 4021, ER 21355);

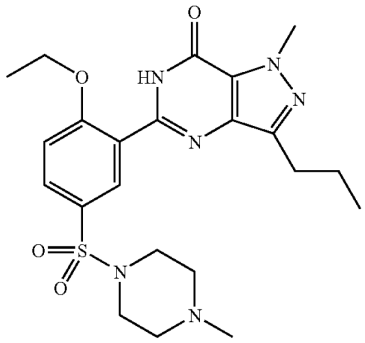


e) 2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate (E 4701);

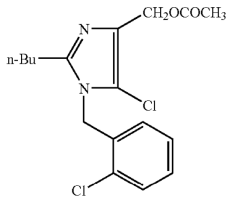
f) 4-((3,4-(methylendioxy)benzyl)amino)-6,7,8-trimethoxy-quinazoline;



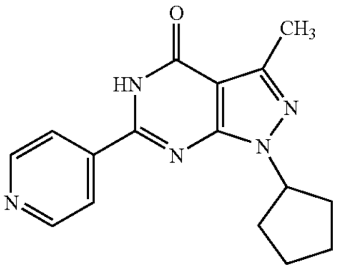
g) 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfo-ny1)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H)one (Sildenafil);



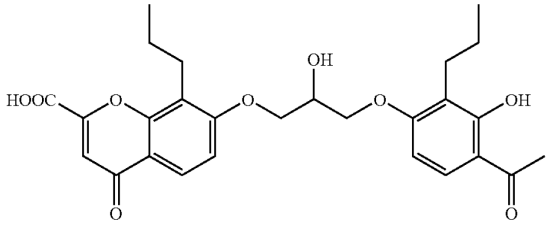
h) 2-n butyl-5-chloro-1-(2-chloronbenzyl)4-methlacetate-imidazole;



i) 1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d) pyrimidin-4(5H)-one (WIN 58237);



j) 7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chronan-4-one (FPL-55712);



k) quinazolines and their trimethoxy derivatives;

1) pyrazolopyrimidones;

as well as pharmacologically compatible salts thereof.

The pharmacologically compatible salts are obtained in a similar manner by neutralizing the bases with inorganic or organic acids. As the inorganic acids, there may be used, for example, hydrochloric acid, sulfuric acid, phosphoric acid or hydrobromic acid, and as the organic acids, for example, carboxylic, sulfo or sulfonic acids, such as acetic acid, tartaric acid, lactic acid, propionic acid, glycolic acid, malonic acid, maleinic acid, fumaric acid, tannic acid, succinic acid, alginic acid, benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, salicylic acid, 3-aminosalicylic acid, ascorbic acid, embonic acid, nicotinic acid, isonicotinic acid, oxalic acid, amino acids, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methyl-benzenesulfonic acid, or naphthalene-2-sulfonic acid.

In the preparation of the medicaments for the treatment of the diseases mentioned, an effective amount of the inhibitors of sPDE I, IV or V or of the salts thereof is used in addition to the usual expedients, vehicles and additives. The dosage depends on the species, body weight, age, individual condition, and kind of administration.

Possible dosage forms are oral, intravenous, transdermal, subcutaneous and intravesicular formulations. The latter are, in particular, those solutions and formulations which are also used for parenteral administration.

Formulations for parenteral administration will contain from 0.15 μg to 1 mg, preferably from 5 to 500 μg, of the compounds mentioned per unit dose and may be present in separate unit dose forms, such as ampoules or vials. Preferably, solutions of the active ingredient are used, more preferably aqueous solutions, and mainly isotonic solutions, but also suspensions. These injection forms may be provided as a ready preparation, or they may be formulated only immediately before use by admixing the active compound, for example, the lyophilizate, optionally together with other solid carriers, with the solvent or suspension medium desired.

For oral administration, there are used the usual galenic preparations, such as tablets, coated tablets, capsules, dispersible powders, granules, aqueous or oily suspensions, syrups, liquors or drops.

Solid preparations may contain inert excipients and vehicles, such as calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginates, gelatin, guar gum, magnesium or aluminium stearate, methylcellulose, talcum, highly dispersed silicic acids, silicone oil, higher-molecular fatty acids (such as stearic

acid), agar-agar, or vegetable or animal fats and oils, solid high-molecular polymers (such as polyethylene glycol); formulations useful for oral administration may optionally contain additional flavoring and/or sweetening agents.

Liquid preparations may be sterilized and/or may optionally contain additives, such as preservatives, stabilizers, wetting agents, penetration agents, emulsifiers, spreading agents, solubilizers, salts for adjusting the osmotic pressure or for buffering, and/or viscosity modifiers.

Such additives are, for instance, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetet-raacetic acid and its non-toxic salts). For adjusting the viscosity, there may be used high-molecular polymers, such as, for example, liquid polyethylene oxide, carboxymethylcelluloses, polyvinylpyrrolidones, dextranes, or gelatin. Solid vehicles are, for instance, starch, lactose, mannitol, methyl-cellulose, talcum, highly dispersed silicic acids, higher-molecular fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycol).

Oily suspensions for parenteral or topical (in this case intravesicular) administrations may contain vegetable, synthetic or semisynthetic oils, such as, for instance, liquid fatty acid esters having from 8 to 22 carbon atoms in the fatty acid chains, for example, palmitic, lauric, tridecylic, margaric, stearic, arachic, myristic, behenic, pentadecylic, linolic, elaidic, brassidic, erucic or oleic acids, which may be esterified with monohydric to trihydric alcohols having from 1 to 6 carbon atoms, such as, for instance, methanol, ethanol, propanol, butanol, pentanol, or isomers thereof, glycol, or glycerol. Such fatty acid esters

are, for instance, commercially available miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-caprylic acid, caprylates/caprates of saturated fatty alcohols, polyoxyethyleneglycerol trioleates, ethyl oleate, waxy fatty acid esters, such as synthetic duck uropygial fat, coconut oil fatty acid isopropyl ester, oleic acid oleyl ester, oleic acid decyl ester, lactic acid ethyl ester, dibutyl phthalate, adipic acid diisopropyl ester, polyol fatty acid ester, etc. Also useful are silicone oils of various viscosities or fatty alcohols, such as isotridecyl alcohol, 2-octyldode-canol, cetylstearyl alcohol or oleyl alcohol, fatty acids, such as oleic acid. Further, vegetable oils, such as castor oil, almond oil, olive oil, sesame oil, cottonseed oil, peanut oil or soybean oil, may be used. The materials mentioned have the additional property of a spreading agent, i.e. there will be a particularly good spreading on the skin.

As solvents, gelling agents and solubilizers, there may be used water or water-miscible solvents. Useful are alcohols, for example, such as ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethyleneglycols, phthalates, adipates, propylene glycol, glycerol, dipropylene or tripropylene glycol, waxes, methylcellosolve, cellosolve, esters, morpholines, dioxane, dimethylsulfoxide, dimethylformamide, tetrahydrofurane, cyclohexanone, etc.

As film-forming agents, there may be used cellulose ethers which can dissolve or swell both in water and in organic solvents and will form a kind of film after drying, such as hydroxypropylcellulose, methylcellulose, ethylcellulose, or soluble starches. Mixed gelling and film-forming agents are also possible by all means. In this case, there are chiefly used ionic macromolecules, such as sodium carboxymethylcellulose, polyacrylic acid,

polymethacrylic acid, and salts thereof, sodium amylopectine semi-glycolate, alginic acid or propylene glycol alginate as the sodium salt, gum arabic, xanthan gum, guar gum or carrageen.

As additional formulation aids, there may be used: glycerol, paraffins having different viscosities, triethanolamine, collagen, allantoin, novantisolic acid, perfume oils.

The use of surfactants, emulsifiers or wetting agents may also be required for the formulation, such as, for example, sodium lauryl sulfate, fatty alcohol ether sulfates, disodium N-lauryl β-iminodipropionate, polyoxyethylated castor oil, or sorbitan monooleate, sorbitan monostearate, cetyl alcohol, lecithin, glycerol monostearate, polyoxyethylene stearate, alkylphenol polyglycol ether, cetyltrimethylammonium chloride, or monoalkyl/dialkyl polyglycol ether orthophosphoric acid monoethanolamine salts.

Stabilizers, such as montmorillonites or colloidal silicic acids, for the stabilization of emulsions or for preventing decomposition of active substances, such as antioxidants, for example, tocopherols or butylhydroxyanisol, or preservatives, such as p-hydroxybenzoic acid ester, may also be required for the preparation of the formulations desired.

For promoting penetration, intravesicular formulations preferably contain highly compatible organic solvents, such as ethanol, methylpyrrolidone, polyethylene glycol, oleyl alcohol, octanol, linolic acid, triacetin, propylene glycol, glycerol, solketal, or dimethylsulfoxide.

The preparation, filling and sealing of the preparations is done under the usual antimicrobial and aseptic conditions. Also for topical or transdermal application,

the preparations are preferably packed in separate unit doses for easy handling, and if required for stability reasons, as with parenteral forms, also by separately packing the active ingredients or their combinations as lyophilizates, optionally with solid carriers, and the solvents required etc.

EXAMPLE 1

Injection

Fifty milligrams of sildenafil is dissolved in distilled water together with 750 mg of NaCl, the pH is adjusted to 3.7 with 1 N HC1, distilled water is added to give a total of 100 ml, and the solution is packed in 0.5 ml ampoules.

EXAMPLE 2

Solution for Topical Administration

From 500 mg of sildenafil, 2 ml of isopropyl myristate and 10 ml of ethanol, a solution for topical administration is prepared and packed in unit doses of 2 ml each.

The effectiveness of the medicaments according to the teaching of the invention is demonstrated by the following pharmacological studies:

Human prostatic tissue freshly collected in the course of an operation is cut into small strips (about 3 x3 x6 mm). The latter are then installed in a bath containing a nutrient solution ensuring survival of the organic strips. By coupling the organic strips to a measuring element, length and force changes of the organic strip can be recorded, and thus actions of medicaments added to the organ bath nutrient solution can be examined through the length and

force changes (increase or decrease) of the organic strip, At the beginning of the experiment, the organic strips are contracted with an appropriate standard medicament (e.g., carbachol). After the contraction of the organic strips is completed, an inhibitor of a specific phosphodiesterase is now added in incremental dosage (10^{-8}, 10^{-7}, 10^{-6} etc. mo1/1) to the organ bath solution, and the relaxation triggered thereby is measured. The results obtained are essentially applicable to the whole organism since human tissue had been used and the metabolic processes studied proceed faster in the whole organism and thus the medicaments will act still more quickly. In these studies, the inhibitors of PDE I, IV and V proved to have the strongest prostatic tissue relaxing effect.

The proof of whether a compound is suitable for the purpose according to the invention, i.e. is an inhibitor of sPDE I, IV or V, is furnished by known methods, such as described, e.g., by Galwan et al., Arch. Pharmacol. 1990, 342, 221-227; or Nicholson, Br. J. Pharmacol, 1989, 79, 889-897; for example, according to the following general procedure:

Fresh tissue obtained during an operation is homogenized and then ultracentrifuged. Next, the supernatant is filtered, pipetted off and chromatographed, The determination of sPDE is performed as described in M. Truss et al.: Urology 45(5): 893-901, 1995. The determination of the amount of radioactivity permits to calculate the enzyme activity in pmol/ mlxmin. A plot of the activity curve allows to identify fractions in which the phosphodiesterase activity is particularly high. The phosphodiesterase activity of each peak exhibits a different composition with respect to the activity of the different substrates. This special composition of the phosphodiesterase activity allows

for the assignment to a specific phosphodiesterase (sPDE). A substance is considered an inhibitor of an sPDE if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the specific phosphodiesterase than in other peak fractions. For this purpose, enzyme preparations are again prepared, as described above. Now, however, the compound to be tested is added prior to the incubation of the enzyme mixtures according to peak fractions. Then, renewed determination and plotting of the enzyme activity allows to identify a substance as being an inhibitor of the specific phosphodiesterase according to the above-mentioned definition.

The invention claimed is:

1. A method for prophylaxis or treatment of benign prostatic hyperplasia comprising administering to a person in need thereof an effective amount of an inhibitor of phosphodiesterase (PDE) V excluding a compound selected from the group consisting of

dipyridamole,

2-(N-(4-carboxypiperidine)-6-chloro-4(3,4-(methylendioxy)benzyl)amino)quinazoline,

2,3-dihydro-8-hydroxy-7-nitro-1,4-benzodioxine-2-methanol, alpha-nitrate.

4((3,4-(methylendioxy)benzyl 1)amino)-6,7,8-tri-methoxy-quinazoline,

1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfo-nyl)-2-ethoxyphenyl)pyrazole [4,5]pyrimidin-4(5H) one, 2-n-butyl-5-chloro-1-(2-chlorobenzy1)-4-methy-lacetate-imidazole,

1-cyclopentyl-3-methyl-6-(4-pyridinyl)pyrazolo(3,4-d) pyrimidin-4(5H)-one,

7-(3-(4-acetyl-3-hydroxy-2-propyl-phenoxy)-2-hydroxy-propoxy)-2-carboxy-2,3-didehydro-chronan-4-one, 1-methyl-3-propyl-6-(5-(N-(4-methylmorpholino)sulfo-nyl)-2-ethoxyphenyl)pyrazole[4,5]pyrimidin-4(5H) one,

and pharmacologically compatible salts thereof.

2. The method of claim 1 wherein the compound is

2-(2-propoxyphenyl)-8-azapurin-6-one

or a pharmacologically compatible salt thereof.

3. The method of claim 1 wherein the compound in combination with a pharmacologically acceptable excipient is administered in a unit dose form.

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