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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

ICOS CORPORATION,
Patent Owner.

Case No. IPR2017-00323
Patent No. 6,943,166

**PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 6,943,166**

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I. INTRODUCTION

Pursuant to the provisions of 35 U.S.C. § 311 and § 6 of the Leahy-Smith America Invents Act (“AIA”), and to 37 C.F.R. Part 42, Mylan Pharmaceuticals Inc., (“Petitioner”) hereby requests *inter partes* review of United States Patent No. 6,943,166 to Pullman (“the ’166 patent,” EX1001), which issued on September 13, 2005, and is currently assigned to ICOS Corp., which is owned by Eli Lilly and Co. (collectively “Patent Owner”).

The ’166 patent is directed to a dosing regimen for treating sexual dysfunction using a prior art compound now known as tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor with previously reported and previously claimed utility for treating sexual dysfunction. The dosing regimen claimed in the ’166 is the administration of about 1 to about 20 mg of tadalafil, where the total maximum daily dose is no larger than 20 mg. The art taught not only the compound tadalafil itself, but that (i) orally administered tadalafil was useful in treating sexual dysfunction at daily dosages as low as 0.5 mg (EX1007); and (ii) tadalafil was nearly twice as potent as sildenafil citrate (Viagra[®]), another inhibitor of the same PDE5 enzyme that gained FDA approval in March 1998. EX1008.

Sildenafil (25 mg, 50 mg, and 100mg) was approved, as a once-daily treatment for male erectile dysfunction, and it was known to produce only minor adverse events at the approved once-daily doses of 25 and 50 mg. As tadalafil was

nearly twice as potent as sildenafil for the same PDE5 enzyme, the person of ordinary skill in the art would have been motivated to adjust the dosing of tadalafil proportionately based on known data regarding the approved doses of sildenafil.

Dose response analyses of sildenafil for treatment of sexual dysfunction were documented in the prior art. *See, e.g.*, EX1008 at 0070. Skilled artisans routinely produced these dose-response curves to inform dosage decisions and, following FDA Guidelines (*e.g.*, EX1009), routinely selected doses below a dose-response plateau as a preferred daily dosage. In accordance with this, and as discussed in detail below, a 25 mg daily dose of sildenafil falls near the top of the dose-response curve but below its plateau. EX1008 at 0070. In other words, the dose response curve generated for sildenafil identified that daily dose as within the optimal dose range with respect to efficacy and adverse events.

As explained by Dr. George Grass, a pharmacokineticist with over 30 years of experience in drug development and drug delivery, to determine an appropriate daily dose of tadalafil a person of ordinary skill would have compared the potency data for tadalafil and sildenafil (consisting of IC_{50} values for the PDE5 enzyme) that were reported in the prior art. Based on this comparison (3.5 nM to 2.0 nM), tadalafil would have been expected to be nearly twice as potent as sildenafil, and the dose response for tadalafil would have been expected to be analogous to that reported for sildenafil except similar efficacies would be obtained at lower doses of

tadalafil. Thus, the efficacy and adverse events reported for a once-daily dose of 25 mg sildenafil would have been expected by the skilled artisan to be approximately equivalent to those occurring with a once-daily dose of roughly 15 mg of tadalafil. *Id.* From the Patent Owner's own press releases, it was already known in the art that tadalafil had been used for treating sexual dysfunction in a variety of clinical trials in Europe and the U.S., that the drug was safe and well tolerated, and that patients showed significant improvement.

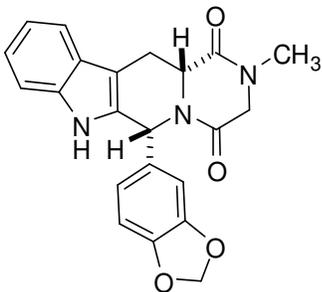
Administering a once-daily dose of 15 mg of tadalafil to a patient with sexual dysfunction satisfies each element of claim 1 of the '166 patent, including that that the unit dose contains about 1 to about 20 mg of tadalafil, and that the daily dose is no larger than 20 mg. Moreover, each of claims 1-12 of the '166 patent merely recite doses that would have been expected to be efficacious and cause only minimal adverse events based on comparison to sildenafil's known potency and approved dosing. EX1008.

A. Brief Overview of the '166 Patent

Generally, the '166 patent is directed to a dosing regimen used in methods to treat sexual dysfunction with tadalafil, a highly-selective PDE5 inhibitor. *See, e.g.,* EX1001, abstract. The '166 patent has only one independent claim, claim 1, which recites:

1. A method of treating sexual dysfunction in a patient in need thereof comprising orally administering one or more unit dose

containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day, of a compound having the structure



Dependent claims 4, 5, 8, and 12 recite specific dosage values within the 1-20 mg range, and dependent claims 6, 9, and 10 additionally recite specific dosage values that are to be administered once per day. Dependent claims 2 and 3 recite that the sexual dysfunction is male erectile dysfunction and female arousal disorder, respectively. Dependent claims 7 and 11 recite dosage forms in which the unit dose is to be given (*i.e.*, formulated as a liquid, tablet, capsule or gelcap, or as a free drug).

The '166 patent admits that the prior art had previously identified "certain tetracyclic derivatives" including tadalafil and that such compounds are potent PDE5 inhibitors, have an "oral dosage" of "0.58 mg daily for an average adult patient (70 kg)," and have unit doses between "0.2 to 400 mg of active compound." *Id.* at 2:12-22 (citing disclosures that include tadalafil). The '166 patent also acknowledges that no significant adverse side effects are disclosed for these prior art tetracyclic derivatives. *Id.*

The '166 patent then states: “Applicants have discovered that one such tetracyclic derivative, [tadalafil], can be administered in a unit dose that provides an effective treatment without the side effects associated with the presently marketed PDE5 inhibitor, sildenafil.” *Id.* at 2:23-32. The '166 patent subsequently states: “The present invention is based on detailed experiments and clinical trials, and the unexpected observations that side effects previously believed to be indicative of PDE5 inhibition can be reduced to clinically insignificant levels by the selection of a compound and unit dose.” *Id.* at 5:15-19.

As discussed in this Petition and in the accompanying declaration of Dr. Grass (EX1002), however, the compound and claimed dosing regimens were both disclosed and suggested in the art. At most, the unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day as claimed in the '166 patent is simply the result of routine optimization. EX1002, ¶¶22-28.

B. Brief Overview of the Prosecution History

U.S. Patent Application No. 10/031,556 (“the '556 application”) was filed on April 26, 2000 and issued on September 13, 2005 as U.S. Patent No. 6,943,166. The '556 application was a national stage entry of PCT/US00/11129, which claims priority to Provisional Application No. 60/132,036, filed on April 30, 1999. The earliest claimed priority date of the '166 patent is April 30, 1999.

During prosecution, the examiner rejected claims under 35 U.S.C. § 103(a) over U.S. Patent No. 6,140,329, which discloses “oral administration and a dosage within the recited range” of the “the instant compound and a method of using it to treat sexual dysfunction.” EX1006 at 0385. In response, applicants argued that the range of about 1-20 mg “is critical because this dose range exhibits the surprising and unexpected results of low adverse events *and* still being unexpectedly efficacious in treating sexual dysfunction.” EX1006 at 0053.

As purported evidence of alleged unexpected results, Applicants submitted two declarations of Dr. Gregory Sides, an employee of Patent Owner. EX1006 at 0058-62, 0296-0301; EX1002, ¶¶18-21. Dr. Sides compared the efficacy and adverse events associated with 20 mg to 50 mg of tadalafil, but he did not submit data sufficient to permit any conclusion of statistical significance, nor did he provide a statistical analysis of the data. EX1002, ¶21. A Notice of Allowability followed thereafter. *Id.* at 0034-36. In the “Reasons for Allowance,” the examiner stated that there was no *statistical* difference between the two doses with respect to efficacy (*id.* at 0035) despite the fact that the Sides declarations did not provide a statistical analysis. The examiner also stated that “the adverse side effects at 20 mg are dramatically reduced when compared to 50 mg” and concluded that the data was sufficient to show unexpected results. *Id.*; EX1002, ¶21.

As shown in this Petition and by the supporting evidence, the data presented during prosecution and in the specification of the '166 patent do not establish unexpected results. In fact, they merely confirm the predictable results of routine dose optimization studies. Moreover, the data comparison used in the Sides declarations suffer from various defects that undermine any legitimate conclusion of unexpected results. As such, Petitioner respectfully submits that the examiner's acquiescence to Patent Owner's one-sided attorney argument and accompanying declarations regarding unexpected results should receive little if any deference by the Board.

C. Brief Overview of the Scope and Content of the Prior Art

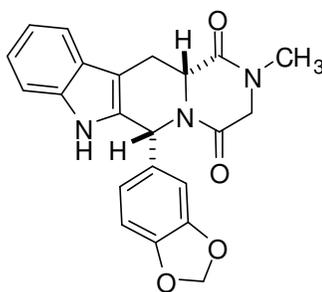
In obviousness cases, *Graham v. John Deere Co. of Kansas City*, requires an evaluation of any differences between the claimed subject matter and the asserted prior art. 383 U.S. 1, 17-18 (1966). As noted in *KSR Int'l Co. v. Teleflex Inc.*, the obviousness inquiry may account for inferences that would be employed by a person of ordinary skill in the art. 550 U.S. 398, 418 (2007).

1. International Patent Publication No. WO 1997/03675 ("the '675 PCT") (EX1007).

The '675 PCT published on February 6, 1997, and is prior art to the claims of the '166 patent under 35 U.S.C. § 102(b).

The '675 PCT prominently discloses Compound A ((6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-

pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione)(EX1007 at 3, lines 24-25), now known, and referred to herein as tadalafil (*see*, “Cialis[®] label,” EX1010), as one of two “highly selective” PDE5 inhibitors that are useful in the treatment of male sexual dysfunction disorders, including erectile dysfunction, as well as female sexual dysfunction disorders. EX1007 at 3-4; EX1002, ¶¶57-60; EX1004, ¶¶37, 39.



Compound A (Tadalafil)
The '675 PCT; EX1007

The '675 PCT teaches tadalafil has an IC₅₀ of 2 nM for PDE5 and “hence [has] utility in the treatment of erectile dysfunction substantially as hereinbefore described.” EX1007 at 17; EX1002, ¶59; EX1004, ¶38.

The '675 PCT teaches that tadalafil may be administered orally, for example using “individual tablets or capsules [which] contain from 0.2-400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day.” EX1007 at 5; EX1002, ¶¶57, 60. The '675 PCT also notes that “[f]or human use, compounds of formula (I), and in particular compounds A [(tadalafil)] and B [(3-

methyl-tadalafil)] can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier[.]” EX1007 at 5; EX1002, ¶¶60.

2. *Sildenafil Citrate (VIAGRA[®]) Approval Package for New Drug Application No. 020895 (“Sildenafil NDA,” EX1008).*

a) *Brief Description of the SNDA*

The Sildenafil NDA is the Center for Drug Evaluation and Research Approval Package for the use of sildenafil citrate (Viagra[®]) in the treatment of erectile dysfunction. The Sildenafil NDA includes a joint clinical review, which outlines clinical trial data available for sildenafil citrate, as well as pharmacokinetic, pharmacological, toxicological, safety and efficacy data compiled for review by FDA for formal drug approval. EX1002, ¶¶63; EX1004, ¶¶41, 42.

The Sildenafil NDA identifies sildenafil’s mechanism of action, teaching: Sildenafil is a selective inhibitor of phosphodiesterase, an enzyme that catalyzes cleavage of cAMP or cGMP. Different tissues have different forms of this enzyme, and these different forms have different affinities for sildenafil. Sildenafil has the lowest IC₅₀ for PDE5 . . . PDE5 is found in the corpus cavernosum, platelets, skeletal muscle, and vascular and visceral smooth muscle.

EX1008 at 0088.

The Sildenafil NDA also teaches that sildenafil’s PDE6 IC₅₀ is only 10-fold higher (less potent) than its PDE5 IC₅₀. *Id.* PDE6 is present in ocular tissues, providing the probable cause of the visual adverse events that sometimes occur

following administration of sildenafil. *Id.*; EX1002, ¶48. As phosphodiesterase enzymes are found in a variety of tissues throughout the body, the on-target effects of PDE inhibition are predictable adverse events:

On the basis of the proposed mechanism of action, relative affinities of sildenafil for different forms of phosphodiesterase, and the distribution of phosphodiesterase in different tissues, there are effects of sildenafil that can be predicted. These effects include (a) penile erection resulting from relaxation of smooth muscle controlling inflow of blood to the corpus cavernosum, (b) systemic vasodilation and, possibly hypotension, (c) inhibition of platelet aggregation and increased risk of hemorrhage, (d) skeletal muscle weakness, (e) reduced activity of the gastrointestinal tract, and (f) interference with vision.

EX1008 at 0088-89. Accordingly, the Sildenafil NDA concludes that “common treatment-related adverse events—notably headache, vasodilation, dyspepsia, and vision disturbance—were clearly dose-related.” EX1008 at 0095.

The Sildenafil NDA states that sildenafil has an IC_{50} of 3.5 nM for PDE5 (*id.* at 0037), that the therapeutic effectiveness of sildenafil is dose-dependent, and that sildenafil is therapeutically effective for the treatment of erectile dysfunction at doses as low as 5 mg. EX1008 at 0126-28, 0215-16; EX1002, ¶63; EX1004, ¶44. The Sildenafil NDA also teaches that maximum recommended dosing schedule is once per day. EX1008 at 0126, 0132, 0139, 0146, 0155, 0217, 0223, 0238, 0245, 0251; EX1002, ¶63. The Sildenafil NDA also notes where the tested dosages fall

along a dose-response curve, noting, “[t]he 25 mg-placebo difference is more than half of the 100 mg-placebo difference; this suggests that the 25-mg dose is already fairly high on the dose-response curve.” EX1008 at 0070.

b) The Sildenafil NDA was publically available at least as early as March 27, 1998.

Under 35 U.S.C. § 102(b), “a person shall be entitled to a patent unless ... the invention was patented or described in a printed publication ... more than one year prior to the date of the application for patent in the United States.” Because of the variety of ways in which a publication may be disseminated, “public accessibility has been called the touchstone in determining whether a reference constitutes a printed publication bar under 35 U.S.C. § 102(b).” *Kyocera Wireless Corp. v. ITC*, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (quoting *In re Hall*, 781 F.2d 897, 898-899 (Fed. Cir. 1986) (internal quotes omitted). Public accessibility is proven “upon a satisfactory showing that such document has 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.” *Id.* (quoting *SRI Int’l, Inc. v. Internet Sec. Sys. Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008)).

Public accessibility of a printed publication is evaluated on a “case-by-case basis.” *Id.* (citing *In re Cronyn*, 890 F. 2d 1158, 1161 (Fed. Cir 1989)).

Notably, public availability does not require a “show[ing] that particular

members of the public actually received the information.” *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988) (Finding “[e]vidence of routine business practice” sufficient for proving public accessibility.); *see also In re Wyer*, 655 F. 2d 221, 226-227 (C.C.P.A. 1981) (Finding “actual viewing or dissemination of any copy of the application” unnecessary to prove public accessibility “given that there [was] also no genuine issue as to whether the application was properly classified, indexed, or abstracted.”); *In re Hall*, 781 F. 2d at 899 (Dissertation was publicly accessible based on a showing of “routine business practice” of “cataloging and shelving before the critical date.”).

The Sildenafil NDA became publicly available on March 27, 1998, a date more than one year before the April 30, 1999 priority date. Under FDA rules, NDA application documents are accessible to the public immediately upon approval. 21 C.F.R. § 314.430(e) (“After FDA sends an approval letter to the applicant” certain data and information associated with that application become “*immediately available for public disclosure*.”). These data and information available to the public include a “summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the [new drug] application” and a “Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process.” *See* 21 C.F.R.

§ 314.430(e)(2)(ii); *see also*, 21 C.F.R. § 312.130 (Availability for public disclosure of data and information in an Investigation New Drug (IND) application). In the case of sildenafil, the data and information accessible to the public includes over 500 pages of information relevant to the “FDA's Clinical, Statistical and Biopharmacological Review of Viagra Clinical Development.” EX1008; Viagra (Sildenafil) NDA 020895 Approval Package Access Data, http://www.accessdata.fda.gov/drugsatfda_docs/NDA/98/viagra/viagra_toc.cfm (Sildenafil NDA Access Data, “EX1031”) (indicating the files were created on March 27, 1998).

FDA approved sildenafil (VIAGRA[®]) on March 27, 1998. EX1008 at 1; FDA Approval Letter, Sildenafil (Viagra[®]) NDA 020895, March 27, 1998 (“Sildenafil Approval Letter,” EX1032). FDA approval of the sildenafil NDA was publicized broadly that same day. *See, e.g., Drug company’s shares rise on FDA approval of pill to treat impotence*, CNNMoney.com, March 27, 1998 (“CNN Article,” EX1033) reporting: “Shares of pharmaceutical giant Pfizer Inc. were pushed higher Friday on news that the U.S. Food and Drug Administration has approved its treatment for impotence.”); *Pfizer’s Eagerly Anticipated Impotence Drug Viagra Wins FDA Approval*, Dow Jones Online News, March 27, 1998 (“Dow Jones Article,” EX1034) reporting: “The Food and Drug Administration Friday announced approval of a long-awaited impotence drug,

Pfizer Inc.’s Viagra, which is the first pill for the disorder.” (original formatting removed)). Thus, as of March 27, 1998, the general public and skilled artisans alike would have been aware that FDA had approved the sildenafil NDA.

FDA sent Pfizer the approval letter on March 27, 1998, and this event resulted in “immediate” public availability of the Sildenafil NDA documents. EX1032; 21 C.F.R. § 314.430(e). A skilled artisan would have been aware of sildenafil’s approval because of the intense publicity the event garnered and could have requested and obtained the documents containing the safety and effectiveness information contained within the NDA (*i.e.* the Sildenafil NDA, EX1008) on March 27, 1998. *Id.* Thus, the Sildenafil NDA is prior art under 35 U.S.C. § 102(b) because it was publically available more than one year before April 30, 1999.

3. *Dose-Response Information to Support Drug Registration*
(“FDA Guideline,” EX1009)

FDA Guideline, which was originally authored by the International Conference on Harmonisation (ICH) and was then adopted and published by FDA in the Federal Register on November 9, 1994 (EX1009 at 55972), is prior art to the claims of the ’166 patent under 35 U.S.C. § 102(b). FDA Guideline discloses that dose-response information “help[s] identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce

unacceptable side effects.” EX1009 at 55972; EX1002, ¶¶65; EX1004, ¶43. FDA Guideline advocates use of dose-ranging studies to identify doses that are sufficient for clinical effect without subjecting patients to unnecessary or excessive dosing. EX1009 at 55973.

FDA Guideline provides examples of dose-ranging study procedures that may be used to obtain dose-response data and further recommends “choos[ing] as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences.” *Id.* at 55974. FDA Guideline cautions against using excessive doses, described as being “well onto the plateau of the dose-response curve[.]” *Id.* at 55973. FDA Guideline notes that using a dosage well onto the plateau in the past has resulted in adverse patient effects that were only realized post-marketing. *Id.*; EX1002, ¶¶65.

D. Brief Overview of the Level of Skill in the Art

A person of ordinary skill in the relevant field as of April 30, 1999, would likely have some combination of (a) experience with the research or development of pharmaceuticals; (b) the ability to gather and interpret pharmacokinetic and pharmacodynamics data including dose-response curves; and (c) the ability to understand results and findings presented or published by others in the field, including the references discussed in this Petition. EX1002, ¶¶38-39; EX1004, ¶¶24-25. Typically this person would have, or would be a member of a team with

individuals having, a Pharm.D. or Ph.D. with experience in clinical pharmacology, medicinal chemistry, or in a related field, or less education but considerable professional experience in one or more of these fields. *Id.* at ¶38. The skilled artisan may also have, or have access as part of a team to a person having, an M.D. with experience in the field of urology, with specific experience in sexual dysfunction.

This Petition is supported by the declaration of Dr. George Grass. Dr. Grass received a Pharm.D. from the University of Nebraska in 1980 and a Ph.D. in pharmaceuticals from the University of Wisconsin, Madison in 1985. EX1002, ¶2; EX1003 (CV). In 1985, Dr. Grass began a research position at the Institute of Pharmaceutical Sciences in Palo Alto, California, where he worked on the development of early stage compounds for oral delivery. *Id.* at ¶3; EX1003. By 1991, Dr. Grass was serving as a pharmaceutical industry consultant. *Id.* Dr. Grass has also served as the Senior Vice President of Research and Development at Sorbent Therapeutics, overseeing the development of novel technologies and product formulation strategies. EX1002, ¶4; EX1003. Currently, Dr. Grass is President of a consulting business, G2 Research Inc., and Senior Vice President of Non-Clinical Development for NeuroVia, Inc. EX1002, ¶1.

Dr. Grass has authored dozens of peer-reviewed journal articles, including articles dealing with oral drug absorption predictions, pharmacokinetic simulation

modeling, and predictive pharmacokinetic simulation models for drug discovery, and is listed as an inventor on at least twelve issued U.S. Patents. EX1002, ¶3, 5; EX1003. Dr. Grass is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of April 30, 1999. *See* EX1003.

This Petition is also supported by the declaration of Dr. Muta M. Issa. EX1004. Dr. Issa is a tenured Professor of Urology in the School of Medicine at Emory University, and also serves as Chief of Urology at the Atlanta Veterans Affairs Medical Center. EX1004, ¶1. Dr. Issa received his M.D. from the Royal College of Surgeons in Ireland in 1983, after which he became Chief Resident in Urology at Stanford Medical Center. EX1004, ¶2; EX1005 (CV).

Dr. Issa has served on the editorial boards of peer-reviewed publications such as *The Scientific World Journal of Urology* and *Urologists in Cancer Care*. EX1004, ¶3. Dr. Issa has also authored more than 100 peer-reviewed journal articles, pertaining to the field of urology, and is listed as an inventor on at least ten issued U.S. Patents. EX1004, ¶4; EX1005. Dr. Issa is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and

training to assist in an understanding of the evidence presented herein. *See* EX1005; EX1004, ¶5.

E. Background Knowledge in the Art Prior to April 30, 1999

The background publications below reflect knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention, *i.e.*, before the earliest claimed priority date of April 30, 1999, and thereby assist in understanding why one would have been motivated to combine or modify the references as asserted in this Petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015). As established in *KSR*, 550 U.S. at 406, the knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

Prior to April 30, 1999, sexual dysfunctions were defined as “disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle in men and women.” Laumann, E. O., *et al.*, *Sexual Dysfunction in the United States*, 281 JAMA 537-544 (Feb. 1999) (“Laumann,” EX1012); EX1002, ¶44. Dysfunctions of this type were identified as belonging to one of four main categories, including desire disorders, arousal disorders, orgasmic disorders and pain disorders. Halvorsen, J. G., *et al.*, *Sexual Dysfunction, Part I: Classification, Etiology, and Pathogenesis*, 5 J. AM. BOARD FAM. PRACT. (1992)

51-61 (“Halvorsen,” EX1026); EX1004, ¶30. While male sexual dysfunction disorders were more heavily studied (EX1004, ¶¶31-32), those in the art taught that female sexual disorders, such as female arousal disorder, may have similar biological origins as male sexual impotence disorders such as erectile function. EX1026 at 56-57; EX1004, ¶32.

The biological mechanism governing penile rigidity and its role in sexual dysfunctions such as erectile dysfunction was well established in the art. For example, Boolell teaches that production of cyclic guanosine monophosphate (cGMP) causes relaxation of smooth muscle cells, which in turn results in penile rigidity. Boolell, M., *et al.*, *Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction*, 8 INT. J. IMPOT. RES., (1996) 47-52 (“Boolell,” EX1015); EX1002, ¶44; EX1004, ¶¶32-33. A group of enzymes known as cyclic nucleotide phosphodiesterase (PDE) isozymes were known to be present in the corpus cavernosum tissues present in the penis, and were known to hydrolyze cGMP. EX1015 at 47. Thus, those in the art recognized that “a pharmacological agent which inhibits the cGMP-specific phosphodiesterase isozyme, should enhance the action of nitric oxide/cGMP on penile erectile activity and have the potential to enhance penile erections during sexual stimulation.” *Id.*; EX1002, ¶44.

One particular isozyme, PDE5, was identified as “the predominant cGMP [for its] hydrolyzing activity,” and oral “inhibitors of type 5 PDE [which] improve erection” were known to serve as pharmaceutical agents in the treatment of sexual dysfunctions. Terrett, N. K., *et al.*, *Sildenafil (ViagraTM), a Potent and Selective Inhibitor of Type 5 cGMP Phosphodiesterase with Utility for the Treatment of Male Erectile Dysfunction*, 6 BIOORG. MED. CHEM. Lett. (1996) 1819-1824 (“Terrett,” EX1013); EX1002, ¶45; EX1004, ¶32. Sildenafil citrate (Viagra[®]), was identified as a PDE5 inhibitor and as an “orally active treatment for male erectile dysfunction” prior to 1999. EX1013 at 1819; EX1002, ¶46; EX1004, ¶34. Those in the art noted sildenafil exhibited dose-dependent efficacy in the treatment of erectile dysfunction, showing effectiveness over placebo at doses at least as low as 5-10 mg. EX1015 at 51; Licht, M.R., *Sildenafil (Viagra) for treating male erectile dysfunction*, 65 CLEVE. CLIN. J. MED., (1998) 301-304 (“Licht,” EX1016) at 302-03; Gingell, C. J. C., *et al.*, *UK-92,480: A New Oral Treatment for Erectile Dysfunction: A Double-Blind, Placebo-Controlled, Once Daily Dose Response Study*, 155 Suppl 5 J. UROL. (1996) Abstract No. 738 (“Gingell,” EX1017) (describing 65% of men reporting improved erections at a 10 mg dosage level of sildenafil); EX1002, ¶47. In addition, Boolell identified sildenafil as having an IC₅₀ of 3.9 nM for PDE5, and noted that sildenafil is at least “70-fold [more] selective

for PDE5 relative to isozymes from PDE families 1-4.” EX1015 at 50; EX1002, ¶46.

The administration of sildenafil was associated with mild adverse events, such as headache, flushing, dyspepsia, rhinitis, and visual disturbances, especially at higher dosage levels. Goldstein, I., *et al.*, *Oral Sildenafil in the Treatment of Erectile Dysfunction*, 338 N. ENGL. J. MED., (1998) 1397-1404 (“Goldstein,” EX1028) at 1403; Morales, A., *et al.*, *Clinical safety of oral sildenafil citrate (VIAGRATM) in the treatment of erectile dysfunction*, 10 INT. J. IMPOT. RES., (1998) 69-74 (“Morales,” EX1018); de Mey, C., *Opportunities for the Treatment of Erectile Dysfunction by Modulation of the NO Axis-Alternatives to Sildenafil Citrate*, 14 CURR. MED. RES. OPIN., (1998) 187-202 (“de Mey,” EX1029) at 188; EX1002, ¶48; EX1004, ¶35-36. In addition, those in the art noted that “[t]he adverse events of sildenafil reflect its pharmacological activity of inhibition of PDE5 in various tissues[.]” Cheitlin, M.D., *et al.*, *Use of Sildenafil (Viagra) in Patients with Cardiovascular Disease*, 33 J. AM. COLL. CARDIOL. (1999) 273-282 (“Cheitlin,” EX1019) at 273; EX1002, ¶49. Thus, some adverse events, like headache, were known to be on-target effects, and thus stem directly from the inhibition of PDE5. EX1002, ¶49.

Sildenafil is approved for the treatment of erectile dysfunction at doses of 25 mg, 50 mg, and 100 mg, with a recommended starting dose of 25 mg for patients

over age 65. VIAGRA[®] Approved Label, 69-5485-00-2, Revised November 1998, downloaded from the Food and Drug Administration website http://www.accessdata.fda.gov/drugsatfda_docs/label/1998/viagra_label2.pdf, last accessed November 1, 2016 (EX1014) at 1, 15. The maximum recommended dosing frequency is once per day. *Id.* at 17-18.

On October 1, 1998, six months after sildenafil received FDA approval, Eli Lilly announced the formation of a joint venture with ICOS for the commercialization of PDE5 inhibitors for the treatment of both male and female sexual dysfunction. *Lilly and ICOS Establish a Joint Venture to Develop and Market PDE5 Compounds to Treat Sexual Dysfunction* Eli Lilly and Company *PRESS RELEASE* 1998 October 1 (“Lilly Press Release,” EX1020) at 1. The Lilly Press Release identified IC351 as the “lead compound in the joint venture,” and reported that clinical studies “showed significant improvement relative to placebo-treated patients” for the treatment of erectile dysfunction and also demonstrated that it is “safe and well tolerated.” *Id.*; EX1002, ¶50. Prior to the joint venture announcement, ICOS itself announced in a *PRESS RELEASE* of September 17, 1998, that IC351-treated patients in a safety and efficacy study (erectile response) in an overseas study showed “significant improvement relative to placebo-treated patients” and that IC351 was “well-tolerated” in another study of safety and pharmacokinetics. EX1035.

As explained by Dr. Grass, IC351 was the ICOS designation for tadalafil, which was also described as Compound A in WO 09703675 (EX1007). EX1002, ¶51. In fact, a May 1999 publication discussing the clinical trials of IC351 for the treatment of male and female sexual dysfunction specifically identified WO 09703675 (EX1007), which discloses tadalafil as Compound A, as a probable disclosure of the structure of IC351. EX1002, ¶51 (discussing Norman, P., IC-351 ICOS Corp, 1 CURR. OPIN. CPNS INVEST. DRUGS (1999) 268-271 (“Norman,” EX1021) at 268). Even a provisional patent application filed by Merck & Co., US60/123,244, filed March 8, 1999, connects ICOS’ IC-351 to Compound A of the ’675 PCT, and noted that IC-351 was in clinical trials, and that “IC351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than sildenafil. EX1036 at 2 (priority document to Merck PCT 00/53148 cited in EX1006 at 0174-0198). The Merck provisional and PCT note that IC-351 “is disclosed in [the ’675 PCT] for the treatment of impotence.” EX1036 at 7; EX1006 at 0181.

Prior to 1999, those skilled in the art knew that a drug’s potency “can largely determine the administered dose of the chosen drug.” Bourne, H. R., and Roberts, J. M., *Drug Receptors & Pharmacodynamics*, BASIC & CLINICAL PHARMACOLOGY (Katzung, B. G. ed., 6th Ed. 1995) 9-32 (“Bourne,” EX1025) at 27; EX1002, ¶55. Potency is measured by identifying the concentration at which 50% inhibition of

the target function is achieved (IC₅₀). EX1025 at 27; EX1015 at 50; EX1002, ¶55. As explained by Dr. Grass, IC₅₀ values allow for the direct comparison of different pharmaceuticals with common targets to evaluate relative potencies, and also determine appropriate comparative dosage values. EX1002, ¶55. It was also routine to identify the therapeutic window for a drug by generating a dose-response curve. Nies, A.S., *Principles of Therapeutics*, GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Gilman, A. G., et al., eds., 8th Ed. 1990) 62-83 ("Nies," EX1023); Oates, J. A. and Wilkinson, G. R., *Principles of Drug Therapy*, HARRISON'S PRINCIPLES OF INTERNAL MEDICINE (Isselbacher, K., J., et al., eds., 13th Ed. 1994) ("Oates," EX1024); EX1002, ¶¶52-54. As explained by Dr. Grass, a routine dose-response analysis was known to identify the portion of the therapeutic window of a drug that did not overlap with an unacceptable level of adverse events. EX1002, ¶53.

II. GROUNDS FOR STANDING

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '166 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '166 patent on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)):

The following real parties-in-interest are identified: Mylan Pharmaceuticals Inc., the Petitioner in this matter and a wholly owned subsidiary of Mylan Inc.; Mylan Inc., which is an indirectly wholly owned subsidiary of Mylan N.V.; and Mylan N.V.

Related Matters (37 C.F.R. § 42.8(b)(2)):

On September 1, 2016, the Board denied a petition for *inter partes* review of claims 1-12 of the '166 patent in IPR2016-00678 based on a petition filed by IntelGenX Corp. IPR2016-00678, Paper 13 at 2. On September 2, 2016, Eli Lilly and Company and ICOS Corporation filed a complaint against Petitioner in the Eastern District of Virginia (EX1030) asserting infringement of the '166 patent in the action styled *Eli Lilly and Company et al v. Mylan Pharmaceuticals Inc.*, No. 1:16-cv-01122. On information and belief, Patent Owner filed nine other complaints in the Eastern District of Virginia asserting infringement of the '166 patent against various defendants on September 2, 2016.

On October 3, 2016, IntelGenX submitted a request for rehearing. IPR2016-00678, Paper 14. On October 26, 2016, the Board requested supplemental briefing from Patent Owner regarding the substance of the request for rehearing. IPR2016-00678, Paper 15 at 2-3. On November 16, 2016, IntelGenX informed the Board that it sought to withdraw its request for rehearing. IPR2016-00678, Paper 16 at 2-3.

On information and belief, the following cases alleging infringement of the '166 patent against a party other than Petitioner remain pending in the Eastern District of Virginia: *Eli Lilly & Co. et al. v. Alembic Pharmaceuticals Ltd. et al.*, Case No. 16-cv-01120; *Eli Lilly & Co. et al. v. Zydus Pharmaceuticals*, Case No. 16-cv-01170; *Eli Lilly & Co. et al. v. Teva Pharmaceuticals USA Inc.*, Case No. 16-cv-01169; *Eli Lilly & Co. et al. v. Aurobindo Pharma Ltd. et al.*, Case No. 16-cv-01121; *Eli Lilly & Co. et al. v. Sun Pharmaceutical Indus., Ltd. et al.*, Case No. 16-cv-01168; *Eli Lilly & Co. et al. v. Actavis Labs. UT, Inc.*, Case No. 16-cv-01119; *Eli Lilly & Co. et al. v. Cipla USA, Inc.*, Case No. 16-cv-01208; *Eli Lilly & Co. et al. v. Accord Healthcare, Inc.*, Case No. 16-cv-01352.

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b) (3)):

Lead Counsel: Steven W. Parmelee (Reg. No. 31,990)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344)

Service Information – 37 C.F.R. § 42.8(b)(4).

Petitioner hereby consents to electronic service.

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IV. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioner requests review of claims 1-12 of the '166 patent under 35 U.S.C. § 311 and AIA § 6 and that claims 1-12 of the '166 patent be canceled as unpatentable:

Ground	Claims	Obvious under 35 U.S.C. § 103 over
1	1-12	The '675 PCT in view of the Sildenafil NDA and FDA Guideline

V. CLAIM CONSTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. ---, 136 S. Ct. 2131, 2146 (2016). Claims terms are also “generally given their ordinary and customary meaning,” which is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. A few terms are discussed below.

A. “up to a maximum total dose”

Claim 1 of the '166 patent recites that the claimed method requires “administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day.” EX1001, 14:66-15:1. This phrase means the unit dose is in the range of 1 to 20 mg *and* that the total daily dose does not exceed 20 mg. EX1002, ¶41. For, instance the '166 patent states that “the dose administered is about 5 to about 20 mg/day, more preferably about 5 to about 15 mg/day. Most preferably, a 10 mg dosage form is administered once per day.” EX1001, 4: 19-21. The most preferred dose, a 10 mg dosage form that is administered once per day, satisfies the limitations of claim 1 because the total daily dose, 10 mg, is within the claimed range, and below the “maximum total dose of 20 mg per day” limitation. EX1002, ¶41. The other preferred dosing schedules (*e.g.*, 5 to 20 mg and 5 to 15 mg) similarly satisfy the limitations of claim 1 because they are between 1 and 20 mg and, when administered once per day, result in daily doses no larger than 20 mg. *Id.*; *see also Globetrotter Software v. Elan Computer Group, Inc.*, 362 F. 3d 1367, 1381 (Fed. Cir. 2004) (“A claim interpretation that excludes a preferred embodiment from the scope of the claim ‘is rarely, if ever, correct.’”) (*quoting Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed.Cir.1996)).

B. “female arousal disorder”

Claim 3 of the '166 patent recites that the method treats sexual dysfunction, wherein the sexual dysfunction is “female arousal disorder.” EX1001 at 15:19-21. The '166 patent specification states that “[s]pecific conditions that can be treated by the present invention, include, but are not limited to, male erectile dysfunction and female sexual dysfunction, particularly female arousal disorder, also known as female sexual arousal disorder.” EX1001, 3:6-4:26. Thus “female arousal disorder” is defined as a type of female sexual dysfunction. EX1004, ¶¶27-28.

C. “free drug”

Claim 11 of the '166 patent recites that the compound administered in the recited method “is administered as a free drug.” EX1001, 16:16-17. The '166 patent specification states that “free drug” means “solid particles of drug not intimately embedded in a polymeric coprecipitate.” *Id.* at 4:1-2. Thus, the broadest reasonable interpretation of the term “free drug” would include solid drug particles in the absence of a carrier or excipient, *i.e.*, administered alone. EX1002, ¶42. It would also include solid drug particles administered with a coprecipitate, including a polymeric coprecipitate, so long as the drug particles are not embedded in said coprecipitate. *Id.*

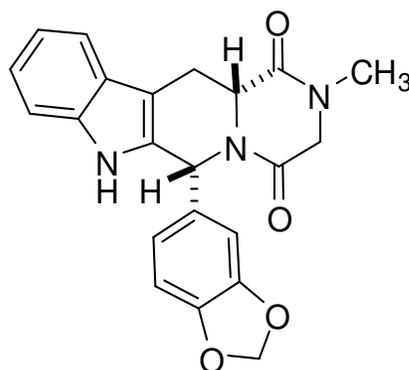
VI. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. [Ground 1] Claims 1-12 are Obvious under 35 U.S.C. § 103 over the '675 PCT (EX1007) in view of the Sildenafil NDA (EX1008) and FDA Guideline (EX1009).

As discussed above, the '675 PCT (EX1007), the Sildenafil NDA (EX1008), and FDA Guideline (EX1009) are prior art to the claims of the '166 patent under 35 U.S.C. § 102(b).

Claim 1

A method of treating sexual dysfunction in a patient in need thereof comprising orally administering one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day, of a compound having the structure



Claim 4

The method of claim 1 wherein the unit dose contains about 2 to about 20 mg of the compound.

Claim 5

The method of claim 1 wherein the unit dose contains about 5 mg of the compound.

Claim 6

The method of claim 1 wherein the unit dose contains about 10 mg of the compound and is administered once per day.

Claim 8

The method of claim 1 wherein the unit dose contains about 2.5 mg of the compound.

Claim 9

The method of claim 8 wherein the unit dose is administered once per day.

Claim 10

The method of claim 5 wherein the unit dose is administered once per day.

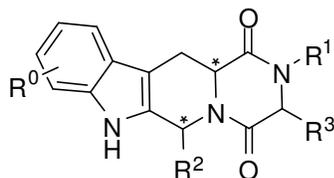
Claim 12

The method of claim 1 wherein the unit dose contains about 20 mg of the compound.

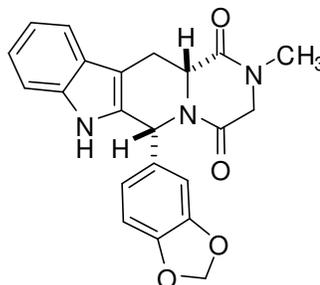
The '675 PCT teaches the tetracyclic compounds of Formula I, shown below, are "potent and selective inhibitors of cyclic guanosine 3', 5'-monophosphate

specific phosphodiesterase (cGMP specific PDE) in the treatment of impotence.”

EX1007 at 1; EX1002, ¶¶67; EX1004, ¶¶45-46.



Formula I,
The '675 Publication; EX1007



Compound A (Tadalafil)
The '675 Publication; EX1007

Tadalafil is encompassed by Formula I and is referred to as Compound A or (6*R*,12*aR*)-2,3,6,7,12,12*a*-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-*b*]indole-1,4-dione, throughout the '166 patent. EX1007 at 3; EX1002, ¶¶67-69. The '675 PCT teaches tadalafil to be useful in the “manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.” EX1007 at 6; EX1002, ¶69.

The '675 PCT teaches oral administration of tadalafil for the treatment of sexual dysfunction, and notes that this treatment approach is an improvement over other known approaches, such as drugs which must be administered by direct injection. EX1007 at 1, 3-4; EX1002, ¶69; EX1004, ¶¶47-49. The '675 PCT also teaches that PDE5 inhibitors such as tadalafil may be formulated into “individual tablets or capsules contain[ing] from 0.2-400mg of active compound, ... for administration in single or multiple doses, once or several times per day.” EX1007

at 5; EX1002, ¶70. The dosage range taught by the '675 PCT encompasses each of the dose ranges claimed in the '166 patent. *Id.*

It was a routine matter for a person of ordinary skill in the art to identify a safe and effective dose range of tadalafil for the treatment of sexual dysfunction. EX1002, ¶71. Standard industry practice, as well as FDA regulatory publications, would have motivated the skilled artisan to perform a dose-ranging study in order to find daily doses that provide efficacious treatment without unnecessary adverse events. EX1009; EX1002, ¶71. For example, FDA Guideline states:

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences.... What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects.

EX1009 at 55973. FDA Guideline teaches that appropriate dosage regimens may be identified by performing a clinical trial “specifically designed to compare several doses.” EX1009 at 55974-76; EX1002, ¶¶72-74. FDA Guidelines teach that “development of dose-response information ... can usually be accomplished with no loss of time and minimal extra effort compared to development plans that

ignore dose-response.” EX1009 at 55973. FDA Guideline further teaches that it is “important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences.” EX1009 at 55974; EX1002, ¶74. These recommendations are meant to guard against common dose-evaluation mistakes, as observed in studies that “used doses that were all too high and, therefore, showed no dose-response slope,” or in studies which only evaluated “doses did not go high enough.” EX1009 at 55975; EX1002, ¶74. A skilled artisan would thus have understood from FDA Guidelines that a dose-ranging trial should be designed such that the tested dosage amounts define a minimum effective dose, the slope, and the plateau on the dose-response curve. EX1002, ¶¶74, 78.

As explained by Dr. Grass, a skilled artisan would be motivated to use a number of doses in the dose ranging study that are adequate to define the dose-response curve. EX1002, ¶¶78-80. The testing of doses to define the different portions of the dose-response curve is routine practice in the industry, as exemplified in FDA Guideline and in the reported clinical trials of sildenafil. EX1002, ¶¶79-80; EX1009 at 55974; EX1015 at 49 (teaching an “oral dose study,” wherein “doses ranging from 1.25 to 90 mg were administered[.]”). The skilled artisan would have good reason to look to the Sildenafil NDA to inform the dose-ranging clinical studies for tadalafil as the compounds were known to have utility

for the same indication, as well as share a common enzymatic target, PDE5, and the adverse events associated with PDE5 inhibition. EX1002, ¶75.

In addition to providing dose-response data for sildenafil, the Sildenafil NDA provides that the compound is to be given “not more than once per day.” EX1008 at 0126, 0132, 0139, 0146, 0155, 0217, 0223, 0238, 0245, 0251; *see also* EX1014 at 17. Sildenafil dose-ranging studies were completed using once-daily dosing. EX1008 at 0126-28, 0132, 0139, 0146, 0155, 0217, 0223, 0238, 0245, 0251. A skilled artisan, would thus routinely evaluate tadalafil doses using once-daily administration and would expect the tadalafil doses to similarly be indicated for administration not more than once per day. EX1002, ¶81.

Those in the art would have been aware that tadalafil is a more potent inhibitor of PDE5 than sildenafil. EX1002, ¶75. The Sildenafil NDA notes the IC_{50} of sildenafil for PDE5 is 3.5 nM. EX1008 at 0037. The '675 PCT teaches that tadalafil has an IC_{50} value of 2 nM. EX1007 at 17. Those in the art were well aware that smaller IC_{50} values indicate higher potency. EX1002, ¶73. With a lower IC_{50} value, the skilled artisan would expect that lower doses of tadalafil would achieve similar efficacy as higher doses of sildenafil in the treatment of sexual dysfunction. EX1007 at 2-4; EX1002, ¶¶77-78. The skilled artisan would also appreciate that the adverse events attributable to PDE5 inhibition, such as headache and dyspepsia, were known to be “clearly dose-related,” and thus would

occur at lower frequencies upon administration of lower doses of tadalafil as compared to sildenafil. EX1008 at 0095; EX1015 at 50-51; Eardley, I., *New Oral Therapies for the Treatment of Erectile Dysfunction*, 81 BR. J. UROL. (1998) 122-127 (“Eardley,” EX1011) at 125; EX1002, ¶¶76. Thus, a skilled artisan would have been motivated to look to the daily doses of sildenafil taught by the Sildenafil NDA to be efficacious, while retaining favorable adverse event profiles, and scale these dosage amounts by the ratio of the IC₅₀ values for tadalafil and sildenafil. EX1002, ¶¶77-78. This routine analysis would allow a skilled artisan to easily identify doses of tadalafil which would likely be efficacious in the treatment of sexual dysfunction, and which should be included in dose-ranging studies for tadalafil. *Id.*

A standard dose-ranging study, informed by the Sildenafil NDA, would allow the skilled artisan to identify the efficacy of a range of doses of tadalafil and the level of adverse events for such doses. EX1002, ¶79; EX1004, ¶49. For instance, it was known that daily doses of sildenafil as low as 5 mg and as high 100 mg were shown to be efficacious in the treatment of erectile dysfunction with a minimum of adverse events, and defined the sildenafil dose-response curve. EX1008 at 0126-28, 0214-16. As explained by Dr. Grass, these doses, adjusted for the increased potency of tadalafil, are expected to be approximately equivalent to tadalafil doses of 2.8 mg and 57 mg, respectively. EX1002, ¶79; EX1007 at 17;

EX1008 at 0037, 0126. In other words, a dose ranging study that included doses between about 2 mg and about 60 mg would be expected to define the slope and the plateau of the tadalafil's dose-response curve. EX1023 at 67; EX1002, ¶79.

The Sildenafil NDA reports that a dose of 25 mg “is already fairly high on the dose-response curve.” EX1008 at 0070. That is, the 25 mg dose approaches the plateau of the dose-response curve—the plateau being the point at which no further clinical benefits are realized from increasing dosage. EX1002, ¶¶76-77; EX1009 at 55973 (indicating that excessive doses are those well onto the plateau of the dose-response curve). Based on the ratio of IC₅₀ values for tadalafil (2 nM) and sildenafil (3.5 nM), a 25 mg daily dose of sildenafil is approximately equivalent to a roughly 15 mg daily dose of tadalafil. EX1002, ¶¶77-78; EX1007 at 17; EX1008 at 0037.

As explained by Dr. Grass, one would have reasonably expected a 15 mg dose of tadalafil to be near the top of the tadalafil dose-response curve based on the PDE5 inhibition results disclosed in the Sildenafil NDA. EX1002, ¶78; EX1008 at 0070. This 15 mg dose is within the 2-60 mg tadalafil dosing range, discussed above, that is informed by the doses of sildenafil taught to be efficacious in the treatment of erectile dysfunction (EX1008 at 0126-28, 0214-16; EX1002, ¶79), as well as the tadalafil dose range taught by the '675 PCT to have utility in the treatment of sexual dysfunction. EX1007 at 5. Thus, as explained by Dr. Grass,

the skilled artisan would have performed a routine dose ranging study using doses at, above, and below 15 mg per day to appropriately define the dose-response curve and to identify appropriate daily dosages to provide therapeutic benefit without unnecessary adverse events or toxicity. EX1002, ¶¶78; EX1009 at 55972-73. The 15 mg daily dose of tadalafil itself satisfies each of the limitations of claim 1, including the limitations that the unit dose must be between 1 to 20 mg and that the total daily dose of tadalafil be no larger than 20 mg. EX1002, ¶¶82.

Administering tadalafil unit doses of about 2 to about 20 mg, about 5 mg, about 10 mg, about 2.5 mg, and about 20 mg, as recited in claims 4, 5, 6, 8, and 12, respectively, would similarly be obvious as part of a method of treating sexual dysfunction in a patient in need thereof. EX1002, ¶¶82. All of these doses (except 2.5 mg) are merely common integer doses used to define a dose-response curve for which a daily dose of approximately 15 mg would be expected to fall near the plateau of the curve. *Id.* For doses below 5 mg, it is common practice to select doses that are even fractions of 5 mg, such as 2.5 mg and 1.25 mg. *Id.* (discussing EX1015 at 49).

Thus, daily doses of 2.5 mg, 5 mg, 10 mg, and 20 mg of tadalafil, as recited in claims 4-6, 8-10, and 12, would have been administered to a patient as part of a method of treating sexual dysfunction during a routine dose-ranging study. EX1002, ¶¶83. As discussed more fully in Section VII below, Example 7 of

the '166 patent confirms that the results of a routine dosing study were as expected. EX1001, 14:1-16; EX1002, ¶83.

In view of the foregoing, claims 1, 4-6, 8-10, and 12 of the '166 patent would have been obvious to a person of ordinary skill in the art as of April 30, 1999. *Id.* In addition to the discussion above, the following claim chart explains in further detail how claim 1 of the '166 patent is obvious under 35 U.S.C. § 103 over the '675 PCT (EX1007) in view of the Sildenafil NDA (EX1008) and FDA Guideline (EX1009).

Challenged Claim	The '675 PCT, Sildenafil NDA, and FDA Guideline
<p>1. A method of treating sexual dysfunction in a patient in need thereof comprising</p>	<p>“Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they may also be useful for the treatment of female sexual dysfunction[.]” EX1007 at 4; EX1002, ¶67.</p> <p>“[T]he invention includes the use of a compound of formula (I), ... for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.” EX1007 at 6; EX1002, ¶69.</p> <p>“A double blind, randomised, placebo controlled, four way crossover study followed by a double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of UK-92,480 (sildenafil) in patients with erectile dysfunction with no established organic cause.” EX1008 at 0215; EX1004, ¶51.</p>
<p>orally administering</p>	<p>“[T]he compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration.” EX1007 at 3-4; EX1002, ¶69.</p> <p>“Generally, in man, oral administration of the compounds of the invention is the preferred route, being the most convenient and avoiding the disadvantages associate with i.c. administration.” EX1007 at 4; EX1002, ¶69.</p> <p>“A double-blind, randomised, placebo controlled, four-way crossover study to investigate the efficacy, safety and toleration of single oral dose of sildenafil...” EX1008 at 0152; EX1004, ¶51.</p>
<p>one or more unit dose containing about 1 to</p>	<p>“For administration to man in the curative or prophylactic treatment of the disorders identified above, oral dosages of a compound of formula (I), and in particular compounds A and B will generally be in</p>

about 20 mg,

the range of from **0.5-800mg daily** for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from **0.2-400mg of active compound**, ... for administration in single or multiple doses, once or several times per day.” EX1007 at 5; EX1002, ¶70.

IC₅₀ of Example 1 (Compound A—tadalafil) for PDE5 inhibition is 2 nM. EX1007 at 17.

IC₅₀ of sildenafil for PDE5 inhibition is 3.9 nM. EX1008 at 0037.

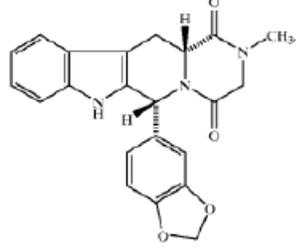
“At the end of a 4-week treatment-free run-in period during which baseline sexual performance data were collected, **subjects were randomized to placebo or sildenafil 5, 25, 50, or 100 mg** and followed for 8 weeks with follow-up at 2 week intervals.” EX1008 at 0126; EX1002, ¶79; EX1004, ¶51.

“The study consisted of two parts. In the first part, subjects received, in random order, **single doses of placebo and sildenafil 10, 25, and 50 mg** on separate study days 3 days apart.” EX1008 at 0215; EX1002, ¶79; EX1004, ¶51.

“[S]ubjects were randomized to placebo or sildenafil 5, 25, 50, or 100 mg and . . . There were monotonic, dose-related increases in the proportion of subjects who said treatment had improved their erections . . . With the exception of questions pertaining to sexual desire, there were highly significant treatment effects for all sexual function questionnaire elements.” EX1008 at 0126-28; *see also* Table 71 at 0128, showing a statistically significant difference between patients receiving 5 mg sildenafil’s ability to obtain erections and those receiving placebo; EX1002, ¶79; EX1004, ¶51.

Historically, drugs have often been initially marketed

	<p>at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences.... What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects. EX1009 at 55973.</p> <p>If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response. EX1009 at 55973.</p> <p>EX1009 at 55974-76 (providing criteria for “Trial intended to evaluate dose- or concentration-response”)</p>
<p>up to a maximum total dose of 20 mg per day,</p>	<p>“[F]or a typical adult patient, individual tablets or capsules contain from 0.2-400mg of active compound, ... for administration in single or multiple doses, once or several times per day.” EX1007 at 5; EX1002, ¶70.</p> <p>“The study consisted of two parts. In the first part, subjects received, in random order, single doses of placebo and sildenafil 10, 25, and 50 mg on separate study days 3 days apart.” EX1008 at 0215; EX1004, ¶51.</p> <p>“not more than once per day.” EX1008 at 0126, 0132, 0139, 0146, 0155, 0217, 0223, 0238, 0245, 0251; EX1002, ¶63.</p>
<p>of a compound having the structure</p>	<p>“The specific compounds of the invention are: (6<i>R</i>,12<i>aR</i>)-2,3,6,7,12,12<i>a</i>-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-<i>b</i>-indole-1,4-dione (Compound A)[.]” EX1007 at 3;</p>

	<p>EX1002, ¶¶68-69.</p>
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Claim 2

The method of claim 1 wherein the sexual dysfunction is male erectile dysfunction.

Claim 3

The method of claim 1 wherein the sexual dysfunction is female arousal disorder.

The '675 PCT teaches that tadalafil is a PDE5 inhibitor, “envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction.” EX1007 at 4; EX1002, ¶¶84-85. As tadalafil is taught to be a potent inhibitor of PDE5, and as it is this inhibition which is taught to enhance erections, a skilled artisan would have found it obvious to use tadalafil in the treatment of male erectile dysfunction, as recited in claim 2 of the '166 patent. EX1002, ¶¶84-85. The artisan would have reasonably expected that tadalafil would be efficacious in the treatment of erectile dysfunction, in view of the Sildenafil NDA, which taught sildenafil-induced inhibition of PDE5 to be therapeutically effective in patients

suffering from erectile dysfunction. EX1008 at 0125-26, 0215-17; EX1004, ¶¶50-51.

In addition, the '675 PCT notes that tadalafil “may also be useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.” EX1007 at 4. As explained by Dr. Issa, female arousal disorder (FAD) is a type of female sexual dysfunction. EX1004, ¶29, 52. As explained by Dr. Issa, the person of ordinary skill would have reasonably expected that tadalafil would have utility in the treatment of FAD, as FAD is the female-equivalent of male erectile dysfunction, and those in the art taught that the origins of female-based disorders are likely to be similar to those in men. EX1004, ¶¶53-54; EX1026 at 52, 56-57; EX1002, ¶85. Further confirming Dr. Issa’s testimony, Eli Lilly and ICOS specifically announced in October 1998 that they had formed a joint venture specifically to develop and commercialize PDE5 inhibitors, including IC351 (tadalafil) specifically for the treatment of both male and female sexual dysfunction. EX1002, ¶¶50, 85 (discussing EX1020 at 1). Thus, the person of ordinary skill would have reason to administer tadalafil in the treatment of female arousal disorder, as in claim 3, in addition to male erectile dysfunction, as in claim 2, each with a reasonable expectation of success. EX1002, ¶85.

Because it was already expressly taught to administer tadalafil to treat erectile dysfunction and female sexual dysfunction, and for the reasons stated

above for claim 1, claims 2 and 3 also would have been obvious to a person of ordinary skill prior to April 30, 1999.

Claim 7

The method of claim 1 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

The '675 PCT teaches methods of formulating tadalafil, stating that tadalafil “may be administered orally . . . in the form of tablets . . . , or in capsules or ovules . . . , or in the form of elixirs or suspensions . . . Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agents[.]” EX1007 at 5; EX1002, ¶86.

In addition, the '675 PCT teaches methods of formulating tadalafil as tablets, film-coated tablets, and capsules, including “hard gelatin capsules.” EX1007 at 12-16; EX1002, ¶86. Thus, it was not only obvious, but also expressly known by those of ordinary skill in the art that tadalafil may be formulated as a liquid, a tablet, a capsule, or a gelcap, as recited in claim 7 of the '166 patent, and the skilled artisan would have had a reasonable expectation of success in achieving such formulations in light of the teachings of the '675 PCT. EX1002, ¶86. Because it was already expressly taught to formulate tadalafil as a liquid, a tablet, a capsule, and a gelcap, as recited in claim 7 of the '166 patent, and for the reasons stated above for claim 1, claim 7 also would have been obvious.

Claim 11

The method of claim 1 wherein the compound is administered as a free drug.

The '675 PCT teaches that tadalafil may be administered alone as a free drug. EX1002, ¶87; EX1007 at 5 (teaching that, “compounds of formula (I), ... can be administered alone.”). The term “free drug” is defined in the specification of the '166 patent as “solid particles of drug not intimately embedded in a polymeric coprecipitate[],” and would thus include solid particles of the drug “administered alone” as taught by the '675 PCT. EX1001, 4:1-2; EX1002, ¶¶42, 87.

The '675 PCT also teaches a capsule which comprises tadalafil and up to 1 mL of the water-dispersible surfactant Labrafil M1944CS. EX1007 at 16; EX1002, ¶88. Thus, the '675 PCT discloses a formulation of tadalafil wherein the solid particles of tadalafil are not “intimately embedded in a polymeric coprecipitate.” EX1001, 4:1-2; EX1007 at 16; EX1002, ¶88. Because it was already expressly taught to administer tadalafil as a free drug for the treatment of sexual dysfunction, as recited in claim 11 of the '166 patent, and for the reasons stated above for claim 1, claim 11 also would have been obvious to a person of ordinary skill in the art.

VII. NO OBJECTIVE INDICIA OF NON-OBVIOUSNESS

A. Legal Standard

Where the difference between the claimed invention and the prior art is some range or other variable within the claims, “the applicant must show that the

particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.” *In re Woodruff*, 919 F. 2d 1575, 1578 (Fed. Cir. 1990).

A *prima facie* case of obviousness may be rebutted by secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, and unexpected results. See *Graham v. John Deere Co. of Kansas City*, 383 US 1, 17-18 (1966); *In re Mayne*, 104 F. 3d 1339, 1343 (Fed. Cir. 1997). A showing of unexpected results must be made with “evidence that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected. *Id.*

Secondary considerations are relevant to a determination of obviousness only if they can be linked to novel and claimed features. See, e.g., *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F. 3d 1358, 1369 (Fed. Cir. 2011) (“If commercial success is due to an element in the prior art, no nexus exists.”); *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir.1983) (Claims were obvious because patent owner “failed to show that such commercial success...was due to anything disclosed in the patent in suit which was not readily available in the prior art.”). “If objective indicia of non-obviousness are ‘due to an element in the prior art, no nexus exists.’” *Torrent Pharmaceuticals Limited et al. V. Novartis AG et al.*, IPR2014-00784, Paper 12, at 24-25 (Sep. 24, 2015) (finding lack of unmet need for

claims directed to dosing parameters for an active ingredient where the same active ingredient was previously disclosed for treatment of the condition at issue with broader dosage parameters that included the claimed range) (quoting Tokai Corp. v. Easton Enters., Inc., 632 F.3d 1358, 1369 (Fed. Cir. 2011)).

B. The Claimed Dosing Method Does Not Produce Unexpected Results

In traversing the examiner's obviousness rejections during prosecution of the application that led to the '166 patent, applicants asserted that the claimed "unit dose range of about 1 to about 20 mg [of tadalafil] ... is critical because this dose range exhibits the surprising and unexpected results of low adverse events *and* still being unexpectedly efficacious in treating sexual dysfunction." EX1006 at 0053 (emphasis in original) and at 0352; EX1002, ¶91. Applicants presented two declarations by Dr. Gregory Sides, who was the Medical Director of the Cialis[®] Product Team at Eli Lilly and Company (Patent Owner) (EX1006 at 0058-62; 0296-0301; EX1002, ¶91), in support of the alleged surprising and unexpected results. As explained in more detail below, however, the evidence in the Sides declarations did not establish unexpected efficacy, an unexpectedly low incidence of adverse events, or any unexpected combination of the two. EX1002, ¶¶92, 110. Instead, the data were incomplete and suffered from a large degree of unexplained variability, in some cases a small sample size, and an absence of statistical analysis,

thereby undermining any conclusions regarding the purported results. EX1002, ¶¶92-110.

Patent Owner's evidence of unexpected results included selected data from Example 7 in the specification of the application that became the '166 patent, and other data collected during various clinical trials. EX1001, 14:1-15; *id.* at 14:22-36; EX1006 at 0058-62; 0296-0301; EX1002, ¶91. The first Sides declaration, dated Jan. 12, 2004, primarily addressed adverse events. It compared selected study data from Example 7 of the specification with data pooled from later Phase 3 studies. The second Sides declaration, dated June 14, 2004, primarily addressed efficacy of tadalafil by comparing selected data from Example 7 with pooled data from Phase 3 clinical trials.

In his second declaration, Dr. Sides compared results obtained with 20 and 50 mg doses of tadalafil using the comparative table reproduced below:

	Placebo ⁽¹⁾ (N = 638)	Tadalafil ⁽¹⁾ 20 mg (N = 1143)	Placebo ⁽²⁾ (N = 131)	Tadalafil ⁽²⁾ 50 mg (N = 52)
Efficacy measure	*Change	*Change	*Change	*Change
IIEF EF domain	0.9	8.6	0.8	9.8

⁽¹⁾ Data from an analysis of pooled data from 11 randomized, double-blind, 12-week placebo-controlled trials

⁽²⁾ Data from the table of Example 7 of the specification (an analysis of data pooled from three Phase 2 studies)

* Change = change from baseline in the erectile function domain of the International Index of Erectile Function (IIEF): Mean

EX1006 at 0062; EX1002, ¶101. These data were presented as “new and surprisingly unexpected results,” however, the data are simply the expected results of a typical dose-response investigation (though they suffer from certain methodological problems, discussed further below). EX1002, ¶102.

In fact, as would have been expected by a skilled artisan, the data produced for tadalafil are analogous to those reported in the prior art for sildenafil. The only difference between the dose-response curve of tadalafil and that of sildenafil is that the same responses occur for tadalafil at approximately one-half the daily dose used for sildenafil. *Id.*, discussing EX1007 at 17 and EX1008 at 0037. Given that tadalafil was known to be approximately twice as potent as sildenafil in the inhibition of PDE5, the data were consistent with what a skilled artisan would have expected in view of the daily doses of sildenafil taught to be efficacious by the Sildenafil SNDA. EX1002, ¶102.

Dose-response curves were routinely generated as a matter of course in drug development and were well within the ability of the skilled artisan. EX1002, ¶103; EX1009 at 55972-73. As is typical for such studies, a dose-response curve would have identified a therapeutic window where tadalafil was efficacious but was not associated with an unnecessary number of adverse events. EX1002, ¶103; EX1009 at 55972-73. In general, therapeutic efficacy increases as the dose of the compound is increased, though the efficacy gains tend to taper, appearing on a

dose-response curve as a shoulder, until a point of maximum efficacy is reached.

COLOR ATLAS OF PHARMACOLOGY, (Lüllmann, H., et al., eds., 1993) 44-57 (“Color Atlas,” EX1027) at 52; EX1002, ¶103. Doses at the top of the curve, close to the shoulder, may thus exhibit comparable therapeutic efficacy as those doses on the plateau. *Id.*; EX1023 at 67-69. That a 20 mg dose of tadalafil provided an improvement in IIEF erectile function similar to that of a 50 mg is not indicative of “unexpected results,” but rather, indicates the dose-response for tadalafil plateaued at these dosage levels. EX1002, ¶103. Indeed, a plateau at this dosage level of tadalafil is where it would have been predicted, based on tadalafil’s reported IC₅₀ value, in view of the disclosures in the Sildenafil NDA. EX1002, ¶102

The efficacy data in the second Sides declaration is taken in part from data in the specification of the ’166 patent, reproduced below, using tadalafil doses of 2, 5, 10, 25, 50 or 100 mg, or placebo, and results were tabulated based on IIEF score:

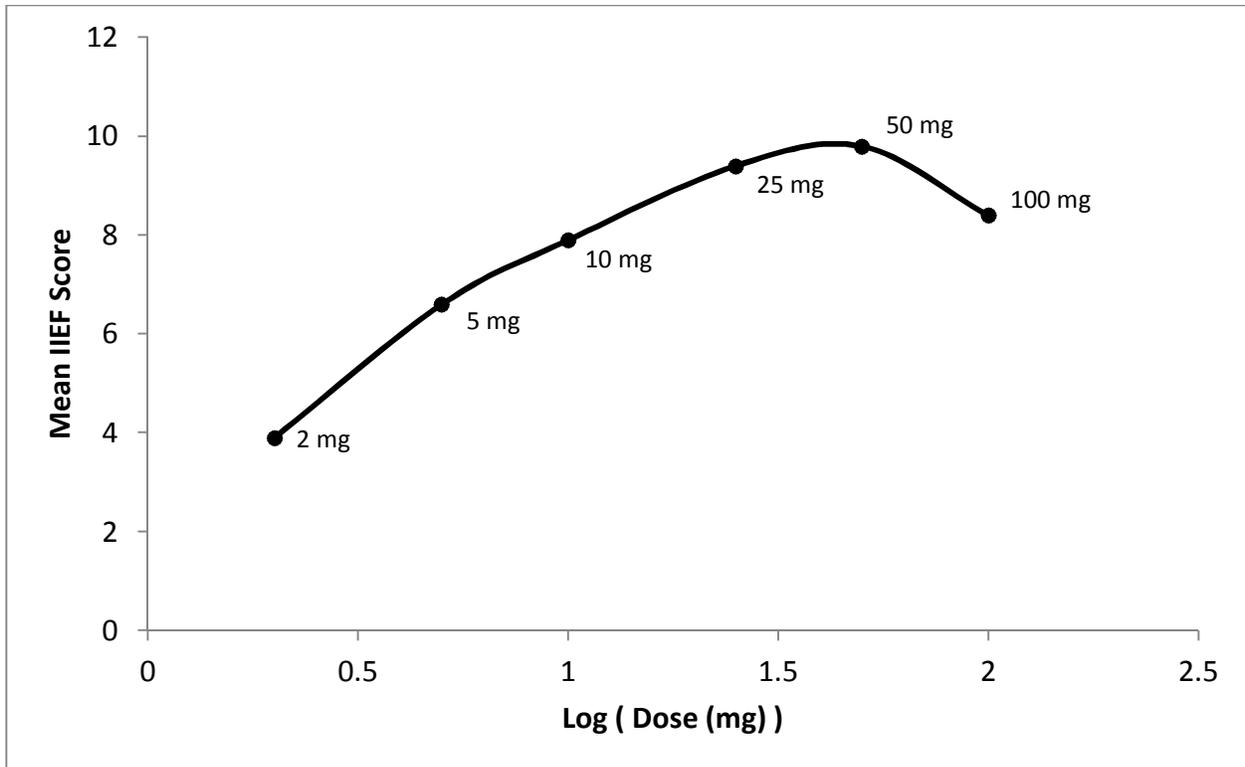
IIEF ERECTILE FUNCTION DOMAIN
(Change from Baseline)

Unit Dose of Compound (I)	n	Mean ± SD	p
placebo	131	0.8 ± 5.3	
2 mg	75	3.9 ± 6.1	<.001
5 mg	79	6.6 ± 7.1	<.001
10 mg	135	7.9 ± 6.7	<.001
25 mg	132	9.4 ± 7.0	<.001
50 mg	52	9.8 ± 5.5	<.001
100 mg	49	8.4 ± 6.1	<.001

n is number of subjects, SD is standard deviation.

EX1001, 14:1-16; EX1002, ¶104.

A dosing study as shown above would have provided a skilled artisan with the ability to generate a dose-response curve, as taught by FDA Guidance. EX1002, ¶105; EX1009 at 55972-73. A Microsoft Excel scatter plot of the therapeutic efficacy data (log value of dose amount vs. mean IIEF Score) can be prepared using smooth lines and markers to plot the dose-response curve defined by the data above. EX1002, ¶106.



EX1001 at 14:1-16; EX1002, ¶106.

The 25 mg dose, 50 mg dose and 100 mg dose are all at or near the top of the dose-response curve, whereas doses from about 2 to about 20 mg are before the shoulder of the curve. *Id.* at ¶¶106-07. It was not only routine to generate such data, as discussed above in Section VI, but also well within the skilled artisan's ability to plot this data, as done by Dr. Grass, above. *Id.* The data confirmed that a daily dose of tadalafil no larger than about 20 mg was effective. *Id.*, ¶103.

Moreover, a daily dose of about 20 mg would avoid unnecessary adverse events. *Id.* Rather than being surprising, this is precisely the outcome a skilled artisan would have predicted given the teachings of the '675 PCT and the Sildenafil NDA.

EX1002, ¶¶107-08; EX1007 at 17; EX1008 at 37, 0125-26.

Moreover, it would not have been surprising to a person of ordinary skill in the art that dosage levels of tadalafil as low as 2.5 mg were efficacious, because 5 mg daily doses of sildenafil were known to provide improvement as compared to placebo. EX1002, ¶108; EX1015 at 50. As sildenafil was known to be approximately only half as potent as tadalafil (EX1002, ¶108 discussing EX1007 and EX1008), daily doses of approximately 2.5 mg would have been expected by the skilled artisan to exhibit similar therapeutic efficacy. EX1002, ¶108.

Furthermore, the differences in efficacy (and adverse events, discussed below) presented during prosecution do not demonstrate a difference in kind, as opposed to merely a difference in degree. *See Bristol-Myers Squibb Co. v. Teva Pharm., Inc.*, 752 F.3d 967, 969-70 (Fed. Cir. 2014) (“While a ‘marked superiority’ in an expected property may be enough in some circumstances to render a compound patentable, a ‘mere difference in degree’ is insufficient”). The skilled artisan would have known to vary the dose of tadalafil to increase efficacy or to decrease adverse events. EX1002, ¶110. A skilled artisan would not have been surprised that tadalafil demonstrates therapeutic efficacy in the treatment of sexual dysfunction along the slope of the dose response curve (*i.e.*, at doses between approximately 2 mg to 20 mg). *Id.* Nor would it have been unexpected for doses at the shoulder and plateau of the dose response curve, *e.g.*, 20 mg and 50 mg, to have comparable therapeutic efficacy. *Id.*

Further, no data were provided in the Sides declarations to suggest that tadalafil doses of about 1 to about 20 mg, 2 to about 20 mg, 5 mg, 10 mg, or 2.5 mg are comparable in efficacy to a 50 mg dose. EX1002, ¶111. Rather, Patent Owner's data simply demonstrated that tadalafil has a typical and predictable dose-response curve for efficacy. EX1002, ¶110. Patent Owner did not provide data for administering tadalafil multiple times a day, administration as a free drug, administration for the treatment of female arousal disorder, or administration for the treatment of any male sexual dysfunction other than male erectile dysfunction. EX1002, ¶112.

In addition, Patent Owner has fallen short of establishing that the comparative efficacy, as well as adverse effect results, associated with the 20 mg and 50 mg tadalafil dosage levels were unexpected or surprising, as the data presented during prosecution was not compared to the closest available prior art. *See Bristol-Myers Squibb Co., Inc.*, 752 F.3d at 969-70 (“To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention. Unexpected properties, however, do not necessarily guarantee that a new compound is nonobvious.”); *see also* EX1002, ¶¶90, 113. As discussed above in Section VI, the '675 PCT teaches administering tadalafil to

humans in amounts encompassing the claimed dose amounts for the treatment of sexual dysfunction. EX1007 at 3-5. Patent Owner has not shown unexpected superiority of the claimed doses over the tadalafil doses disclosed in the '675 PCT. EX1002, ¶113. Nor did Patent Owner show superiority over a comparable dose of sildenafil, e.g., 25 mg. *Id.*

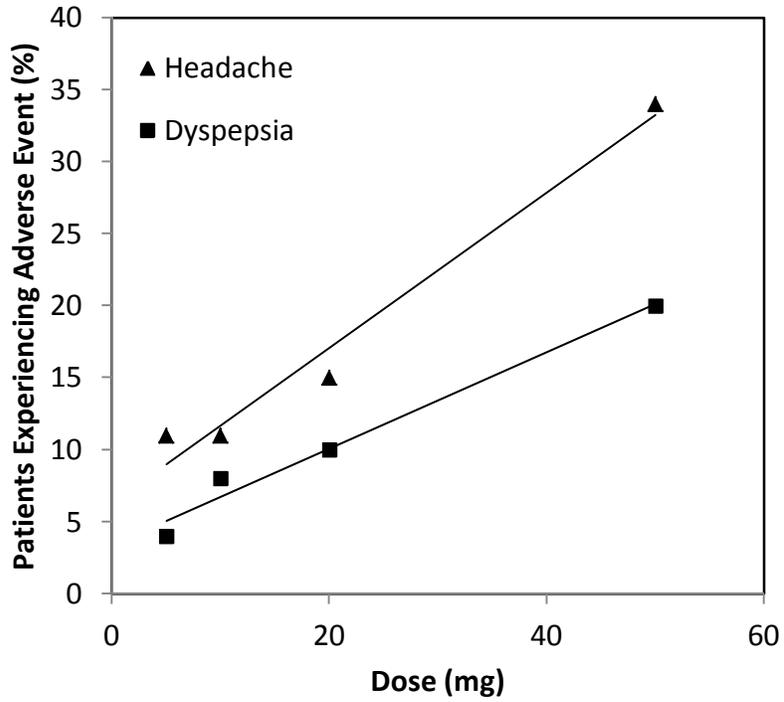
Just as the efficacy data for doses of tadalafil no larger than 20 mg would not have been considered unexpected, so too the adverse events data were not unexpected. The first Sides declaration argued that based on the data, there was a “dramatic reduction” in the common adverse events, such as headache, dyspepsia and back pain between the 20 mg and 50 mg dosages. EX1006 at 0296-301. However, under close scrutiny, the data in the first Sides declaration provides an incomplete presentation of adverse events in a way that suggests their frequencies are unexpectedly low, and the increase in adverse events unexpectedly linear for doses of tadalafil up to 20 mg. EX1002, ¶98. Specifically, the declaration presents the table below, which is said to “show the unexpected decrease in treatment-emergent adverse events” when decreasing the dose of tadalafil. This table compares some data apparently taken from Example 7 of the specification, notably placebo and 50 mg, with subsequent data pooled from eight different Phase 3 studies for placebo, 5, 10, and 20 mg.

	Placebo (1)	Tadalafil 5 mg (1)	Tadalafil 10 mg (1)	Tadalafil 20 mg (1)	Placebo (2)	Tadalafil 50 mg (2)
Adverse Event	(N=476)	(N=151)	(N=394)	(N=635)	(N=134)	(N=59)
Headache	5%	11%	11%	15%	10%	34%
Dyspepsia	1%	4%	8%	10%	6%	20%
Back pain	3%	3%	5%	6%	5%	24%
Myalgia	1%	1%	4%	3%	3%	20%
Nasal congestion	1%	2%	3%	3%	--	--
Flushing	1%	2%	3%	3%	0%	3%
Pain in limb	1%	1%	3%	3%	--	--

(1) Data from an analysis of pooled data from eight controlled Phase 3 studies (Table 7, CIALIS US Packet Insert, Nov 2003) coded using Medical Dictionary for Regulatory Activities (version 5.0); adverse events with $\geq 2\%$ incidence on tadalafil (10 or 20 mg) and more frequent on drug than placebo, and

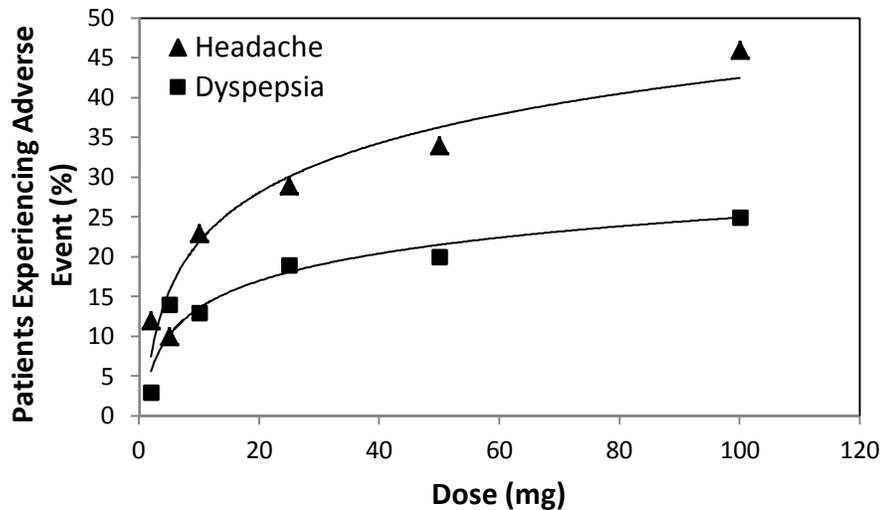
(2) Data from table of Example 7 of specification (an analysis of data pooled from three Phase 2 studies (LVBF/DSD06, LVBG/DSD04 and LVAC); adverse events coded using the COSTART dictionary).

EX1006 at 0300-01. But the pooled Phase 3 data is quite different from that presented in the specification of the '166 patent, and no explanation is provided for deviations between the two data sets. EX1002, ¶99. By providing only a subset of adverse event data, the declaration causes the relationship between dose and adverse events to appear linear. *Id.* This is illustrated in a graph of the reported data on the occurrence of headache and dyspepsia upon administration of tadalafil, reproduced below from the declaration of Dr. Grass, prepared in Microsoft Excel:



EX1002, ¶99.

However, using a more complete set of adverse event data from the specification of the '166 patent shows an initial steep climb at doses below 25 mg (i.e., 2, 5 and 10 mg) of events such as headache and dyspepsia, followed by a plateau from 25-100 mg:



EX1002, ¶¶98; EX1001, 14:22-37. Thus, consideration of all of the data in Example 7 of the '166 patent specification makes clear that adverse events associated with PDE5 inhibition by tadalafil exist along a dose-response curve that mirrors that observed for efficacy. In fact, a person of ordinary skill in the art would have expected on-target adverse events, such as headache and dyspepsia, to exist along a dose-response curve that mirrors that for efficacy, as both are the result of PDE5 inhibition and saturation of receptors for inhibition. Thus, the data in the '166 patent corroborates what the person of ordinary skill in the art would have predicted to occur for adverse events. EX1002, ¶¶99. In addition, unexplained variability in the adverse events data presented in the Sides declaration hampers a meaningful comparison of the pooled data from the Phase 3 studies with those from Example 7 of the specification. EX1002, ¶¶93-96. The first Sides declaration does not present any information regarding the treatment regimen or make-up of

the patient populations involved in the Phase II and Phase III studies. In addition, the pooled clinical trials coded the reported adverse events based on different medical dictionaries, thus the adverse events data cannot be legitimately compared across these multiple studies. EX1002, ¶93.

The variability between the trials relied on by the first Sides declaration is exemplified by the rates of adverse events experienced in the two placebo patient populations. *Id.* at ¶95. For example, the percentage of placebo patients who reported headaches doubled. A similarly unexplained deviation existed when comparing dyspepsia reported among the two placebo groups (1% vs 6%). EX1002, ¶95. This variability is not addressed by the Sides declaration.

Even more variability is observed when the adverse event data presented in the first Sides declaration is compared with that omitted from the declaration but included in the '166 patent specification. EX1002, ¶96, discussing EX1006 at 0300 and EX1001, 14:28-29. For example, 23% of patients receiving 10 mg daily doses of tadalafil experienced headache, as reported by the '166 patent (EX1001, 14:28), but the Sides declaration reports only 11% of patients receiving 10 mg daily doses experienced headache. EX1006 at 0300; EX1002, ¶96. Thus two patient populations, receiving the *same* dose of tadalafil, experienced over a two-fold difference in headache occurrence. *Id.* Similarly, variability can be seen in patients receiving 5 mg daily doses of tadalafil who reported dyspepsia (14%)(EX1001,

14:29), whereas only 4% of patients reported dyspepsia at the 5 mg daily dosage level as reported in the Sides declaration, a 3.5-fold difference. EX1006 at 0300; EX1002, ¶96. The differences urged in the first Sides declaration between the adverse events for the 20 mg and 50 mg tadalafil treatment groups may be confounded by the same apparently inherent variation between studies and data sets. *Id.*

Another problem with the data relied upon in the first Sides declaration is the small sample size for the 50 mg dose of tadalafil. EX1006 at 0300; EX1002, ¶94. Clinical trial data obtained from studies involving a small number of participants may be inconclusive due to small population size. EX 1008 at 0054; Because the sample size in the 50 mg dose group is so low and so different from the sample size used for the 20 mg dose, it becomes difficult to reach a conclusion of a statistically significant difference. EX1002, ¶94.

Because the Sides declarations present data that suffer from numerous deficiencies, it was not established whether any increase in efficacy or adverse events between the 20 mg and 50 mg doses was significant, or merely within the margin of statistical error. EX1002, ¶¶21, 96, 109. As such, this data does not demonstrate an “unexpected decrease” in adverse events at daily doses of tadalafil no larger than 20 mg. EX1002, ¶114.

In short, neither the efficacy nor adverse events reported for the 25 mg and 50 mg doses (presented in the '166 patent) nor those reported for the 20 mg and 50 mg doses (presented in the Sides declarations during prosecution of the '166 patent) were unexpected or surprising in view of the prior art. Thus, Patent Owner failed to show that the narrowed dosing regimen claimed in the '166 patent is critical.

C. No Long-Felt Need for the Claimed Dosing Regimen

To rely on a long-felt, unmet need as objective indicia of non-obviousness of the challenged claims at issue in this proceeding, the burden rests on Patent Owner to provide evidence establishing that (1) the prior art recognized a long-felt need for the claimed invention; (2) this need was not satisfied before the claimed invention; and (3) the claimed invention did, in fact, satisfy the long-felt need. *See Bristol-Myers Squibb Co., Inc.*, 752 F.3d at 971 (“On long-felt need, three other drugs for treating hepatitis B were invented before the filing date of entecavir. These three drugs also gained FDA approval before entecavir. Finally, entecavir’s inventors did not know about its hepatitis B properties until four years after the filing date, and by then the first FDA-approved hepatitis B treatment was launched. Therefore, we agree with the district court that the evidence of long-felt need is of limited value to BMS.”).

Moreover, there must be a nexus between the objective indicia and the claimed invention; in other words, the unmet need must have been satisfied by a

novel aspect of the claimed invention, as opposed to what was already known in the prior art. *See Tokai Corp.*, 632 F. 3d at 1369; *Richdel, Inc.*, 714 F.2d at 1580;

During the prosecution of the '166 patent, applicants alleged that a long-felt need existed for an orally available treatment for erectile dysfunction that presented fewer side effects than sildenafil (Viagra®). EX1006 at 0327, 0348-49. As explained by Dr. Issa, however, applicants did not provide any evidence demonstrating such a long-felt need. EX1004, ¶55.

Furthermore, Dr. Issa also testified that any need for an alternative oral treatment for erectile dysfunction with fewer side effects than sildenafil, to the extent it was filled by tadalafil, would have been satisfied by the disclosure of tadalafil in the '675 PCT as a PDE5 inhibitor for oral administration to patients for the treatment of sexual dysfunction, including erectile disorder. EX1004, ¶¶55-57 (discussing EX1007 at 5, 12-16). Indeed, Patent Owner has presented no evidence that the claimed dosing regimen (daily dose no larger than 20 mg) has a significant or materially more favorable side effect profile than a dosage within the range disclosed in the '675 PCT that is outside the claimed dosing regimen (e.g., daily dose of 21 mg or 25 mg). EX1004, ¶55. Thus, there can be no nexus between the long-felt need asserted by the applicant during prosecution and any alleged novel feature of the claimed methods. For each of these reasons, any purported long-felt need does not provide evidence of non-obviousness of the challenged claims.

VIII. CONCLUSION

For the reasons set forth above, each of claims 1-12 of the '166 patent is unpatentable in view of the prior art. Petitioner therefore requests that an *inter partes* review of these claims be instituted and that claims 1-12 be canceled.

Respectfully submitted,

Dated: November 22, 2016

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IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 12,957 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully,

Dated: November 22, 2016

/ Steven W. Parmelee /
Steven W. Parmelee, Lead Counsel
Reg. No. 31,990

X. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	Pullman, W. E., <i>et al.</i> , <i>Compositions Comprising Phosphodiesterase [Inhibitors] for the Treatment of Sexual Dysfunction</i> , U.S. Patent No. 6,943,166 (filed on April 26, 2000; issued September 13, 2005)
1002	Declaration of Dr. George Grass, Pharm.D., Ph.D.
1003	<i>Curriculum vitae</i> of Dr. George Grass
1004	Declaration of Dr. Muta Issa, M.D.
1005	<i>Curriculum vitae</i> of Dr. Muta Issa
1006	File History for U.S. Patent No. 6,943,166
1007	Daugan, A.C-M., <i>Use of cGMP-Phosphodiesterase Inhibitors to Treat Impotence</i> , Int'l Pub. No. WO 97/03675 (filed on July 11, 1996; published February 6, 1997)
1008	Center for Drug Evaluation and Research, Approval Package for VIAGRA, Approval Date March 27, 1998
1009	<i>Dose-Response Information to Support Drug Registration</i> , 59 FEDERAL REGISTER, (November 9, 1994) 55972-55976
1010	CIALIS® Approved Label, Reference ID: 3820620, Revised September 2015, downloaded from the Food and Drug Administration website http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021368s026lbl.pdf , last accessed November 1, 2016
1011	Eardley, I., <i>New Oral Therapies for the Treatment of Erectile Dysfunction</i> , 81 BR. J. UROL. (1998) 122-127.
1012	Laumann, E.O., <i>et al.</i> , <i>Sexual Dysfunction in the United States</i> , 281 JAMA, (1999) 537-544

1013	Terrett, N.K., <i>et al.</i> , <i>Sildenafil (VIAGRATM), A Potent and Selective Inhibitor of Type 5 cGMP Phosphodiesterase with Utility for the Treatment of Male Erectile Dysfunction</i> , 6 <i>BIOORG. MED. CHEM. LETT.</i> , (1996) 1819-1824
1014	VIAGRA [®] Approved Label, 69-5485-00-2, Revised November 1998, downloaded from the Food and Drug Administration website http://www.accessdata.fda.gov/drugsatfda_docs/label/1998/viagra_label2.pdf , last accessed November 1, 2016
1015	Boolell, M., <i>et al.</i> , <i>Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction</i> , 8 <i>INT. J. IMPOT. RES.</i> , (1996) 47-52
1016	Licht, M.R., <i>Sildenafil (Viagra) for treating male erectile dysfunction</i> , 65 <i>CLEVE. CLIN. J. MED.</i> , (1998) 301-304
1017	Gingell, C. J. C., <i>et al.</i> , <i>A New Oral Treatment for Erectile Dysfunction: A Double-Blind, Placebo-Controlled, Once Daily Dose Response Study</i> , 155 <i>Suppl 5 J. UROL.</i> (1996) Abstract No. 738
1018	Morales, A., <i>et al.</i> , <i>Clinical safety of oral sildenafil citrate (VIAGRATM) in the treatment of erectile dysfunction</i> , 10 <i>INT. J. IMPOT. RES.</i> , (1998) 69-74
1019	Cheitlin, M.D., <i>et al.</i> , <i>Use of Sildenafil (Viagra) in Patients with Cardiovascular Disease</i> , 33 <i>J. AM. COLL. CARDIOL.</i> (1999) 273-282
1020	<i>Lilly and ICOS Establish a Joint Venture to Develop and Market PDE5 Compounds to Treat Sexual Dysfunction</i> Eli Lilly and Company <i>PRESS RELEASE</i> 1998 October 1
1021	Norman, P., <i>IC-351 ICOS Corp</i> , 1 <i>CURR. OPIN. CPNS INVEST. DRUGS</i> (1999) 268-271
1022	<i>Reserved</i>
1023	Nies, A.S., <i>Principles of Therapeutics</i> , GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Gilman, A. G., <i>et al.</i> , eds., 8 th Ed. 1990) 62-83

1024	Oates, J. A. and Wilkinson, G. R., <i>Principles of Drug Therapy</i> , HARRISON'S PRINCIPLES OF INTERNAL MEDICINE (Isselbacher, K. J., et al., eds., 13 th Ed. 1994)
1025	Bourne, H. R., and Roberts, J. M., <i>Drug Receptors & Pharmacodynamics</i> , BASIC & CLINICAL PHARMACOLOGY (Katzung, B. G. ed., 6 th Ed. 1995) 9-32
1026	Halvorsen, J.G., and Metz, M.E., <i>Sexual Dysfunction, Part I: Classification, Etiology, And Pathogenesis</i> , 5 J. AM. BOARD FAM. PRACT., (1992) 51-61
1027	COLOR ATLAS OF PHARMACOLOGY, (Lüllmann, H., et al., eds., 1993) 44-57
1028	Goldstein, I., et al., <i>Oral Sildenafil in the Treatment of Erectile Dysfunction</i> , 338 N. ENGL. J. MED., (1998) 1397-1404
1029	de Mey, C., <i>Opportunities for the Treatment of Erectile Dysfunction by Modulation of the NO Axis-Alternatives to Sildenafil Citrate</i> , 14 CURR. MED. RES. OPIN., (1998) 187-202
1030	<i>Eli Lilly and Company et al v. Mylan Pharmaceuticals Inc.</i> , No. 1:16-cv-01122 (AJT-MSN)
1031	Drug Approval Package: Viagra (Sildenafil) NDA 020895, Date Created March 27, 1998, downloaded from the Food and Drug Administration website http://www.accessdata.fda.gov/drugsatfda_docs/NDA/98/viagra/viagra_toc.cfm , last accessed November 4, 2016
1032	Approval Letter Viagra (Sildenafil) NDA 020895, March 27, 1998.
1033	<i>Drug company's shares rise on FDA approval of pill to treat impotence</i> , CNNMoney.com, March 27, 1998, downloaded from http://money.cnn.com/1998/03/27/companies/impotence/ , last accessed November 17, 2016
1034	<i>Pfizer's Eagerly Anticipated Impotence Drug Viagra Wins FDA Approval</i> , Dow Jones Online News, March 27, 1998

1035	<i>ICOS Announces Clinical Results and Initiation of Trials</i> ICOS Corporation <i>PRESS RELEASE</i> 1998 September 17
1036	U.S. Provisional Patent Application No. 60/123,244, filed March 8, 1999

Certificate of Service

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes review of U.S. Patent No. 6,943,166 (and accompanying Exhibits EX1001-EX1036) by overnight courier (Federal Express or UPS), on this 22nd day of November, 2016, on the Patent Owner at the correspondence address of the Patent Owner as follows:

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