

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MONOSOL RX, LLC
Petitioner

v.

ICOS CORPORATION,
Patent Owner

Case: IPR2017-00412
Patent 6,943,166

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

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PETITIONERS' EXHIBIT LIST

Description	Exh #
U.S. Patent 6,943,166	1001
U.S. Patent 5,859,006	1002
U.S. Patent 6,140,329	1003
U.S. Patent 6,087,362	1004
WO 9703675	1005
VIAGRA® (sildenafil citrate) label	1006
CIALIS® (tadalafil) label	1007
D. Eros, et al., Structure-Activity Relationships of PDE5 Inhibitors, Current Medicinal Chemistry, 2008 (15), 1570-1585.	1008
Prosecution History for U.S. Patent No. 6,943,166	1009
Expert Declaration of Roger Williams, M.D. Regarding U.S. Patent No. 6,943,166	1010
Excerpt from Viagra Approval Pkg	1011
Filloon, Estimating the minimum therapeutically effective dose of a compound via regression modelling and percentile estimation, <i>Stat Med.</i> 1995 May 15-30;14(9-10):925-32	1012
Effects of sildenafil citrate on human hemodynamics, <i>Am. J. of Cardiology</i> , 83(5), Supp. 1, pp. 13-20 (March 4, 1999)	1013
The Guideline for Industry, Dose Response Information to Support Drug Registration (“Guideline for Industry”)	1014
Petition To Add Information About Sildenafil’s Danger’s To The Drug Label	1015
Cutler, et al., Defining the Maximum Tolerated Dose: Investigator, Academic, Industry and Regulatory Perspectives, <i>J. Clin. Pharmacol.</i> 1997; 37:767-783	1016
ICOS 10K FY 1998	1017
FDA Clinical Hold - 21-368 FDA Cialis Correspondence P5	1018
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Pursuant to 35 U.S.C. § 311, MonoSol Rx, LLC (“Petitioner”) respectfully petitions for Inter Partes Review, seeking cancellation of claims 1-12 of U.S. Patent No. **6,943,166** (the ‘166 Patent). According to USPTO records, the ‘166 patent is assigned to ICOS CORP c/o Eli Lilly and Co. (“Patent Owner”). A copy of the ‘166 Patent is attached as Exh. 1001. As demonstrated by the grounds presented below, the alleged invention of the challenged claims are obvious and should be canceled under 35 U.S.C. § 103.

I. PAYMENT OF FEES

Pursuant to 37 C.F.R. section 42.103, \$23,000 is being paid at the time of filing this petition, charged to Deposit Account 19-4293. Should any further fees be required by the present Petition, the Patent Trial and Appeal Board (“PTAB”) is hereby authorized to charge the above referenced Deposit Account.

II. REQUEST FOR *INTER PARTES* REVIEW OF CLAIMS 1-12 OF THE ‘166 PATENT

Pursuant to 37 C.F.R. §42.104(b), Petitioner requests that the PTAB find unpatentable Claims 1-12 of the ‘166 patent. Such relief is justified as the alleged invention of the ‘166 patent was described by others prior to the filing date of the ‘166 patent and obvious to one of skill in the art.

Petitioner is aware that the ‘166 patent was previously challenged by IntelGenx Corp. in a request for Inter Partes Review, and that this Petition was

denied institution on September 1, 2016. IPR2016-00678, Paper 13. That Petition raised two grounds of unpatentability: (1) Daugan and (2) Daugan and SNDA (the Viagra® Approval Package). However, in that case, the PTAB found that the Petitioner “ignored the maximum-total dose requirement” in failing to “point to the asserted prior art or otherwise explain why an ordinary artisan would limit the tadalafil dose to 20 mg per day.” *Id.* at 7. The PTAB therefore concluded that the Petitioner had “not established a reasonable likelihood it would prevail in showing that claim 1 would have been obvious over Daugan, either alone or in combination with SNDA.” *Id.*

A. The Alleged Invention of the ‘166 Patent

The ’166 patent relates generally to a method of treating sexual dysfunction by orally administering tadalafil in a specific dose range that is encompassed by the prior art. The ‘166 patent acknowledges that tadalafil was already known to be administered in doses of 0.2-400 mg without apparent “significant side effects” Ex. 1001, col. 2, lines 12-21. The ‘166 patent therefore sought to claim a method of administering a specific dose of tadalafil, namely “about 1 to about 20 mg, up to a maximum total dose of 20 mg per day.” *Id.* at claim 1.

During prosecution, there was no dispute that the prior art taught methods of treating sexual dysfunction by orally administering to a patient in need thereof one or more unit dose of tadalafil, in 0.2 to 400 mg, once or several times per day and

in fact, taught 50 mg of oral dosage forms and noted that “other strengths may be prepared...” Daugan ‘675 at 5, 12-16. However, the applicants argued that there were “unexpected results” for this claimed dose of “one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day.” Ex. 1010, Decl. ¶¶ 64-76. The ‘166 patent was prosecuted and issued before 2007, prior to development of the current applicable legal standard for obviousness under *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

B. Brief Description of the Technology

Erectile dysfunction was a well-known condition prior to ‘166 patent. Before ‘166 patent (or its alleged priority date of April 30, 1999), it was also well known that sildenafil and tadalafil were highly selective phosphodiesterase (PDE) enzyme inhibitors that were effective in treating sexual dysfunction. Ex. 1010, Decl. ¶¶ 15-21. Sildenafil and tadalafil each share a common mechanism of action and are only pharmacologically active when cGMP synthesis is activated. Ex. 1010, Decl. ¶¶ 20-21.

It was an accepted premise that PDE5 inhibitor such as sildenafil had certain side effects that limited its use in certain individuals. Ex. 1001, col. 1, lines 58-65. The ‘166 patent teaches that orally administered tetracyclic derivatives such as tadalafil have been previously administered in doses of **0.2-400 mg**, without “significant side effects.” *Id.* (emphasis added). The ‘166 patent therefore attempts

to address a known problem with a known solution: orally administering tadalafil in an optimal dose that maintains efficacy while minimizing its side effects.

C. Critical Date

The '166 patent claims was filed as U.S. Patent Application No. 10/031,556. This was a national stage application of the PCT Application No. PCT/US2000/011129 that claimed priority to a provisional patent application number 60/132,036 filed on April 30, 1999. Ex. 1009, Prosecution History, Transmittal Letter. However, the claimed feature of “maximum total dose” was not present in the provision patent application. Rather, this feature first appears in the file wrapper on October 19, 2001, the transmittal date of U.S. Patent Application No. 10/031,556. Thus, Petitioner notes that the claimed subject matter does not appear to be fully supported as of April 30, 1999. Regardless, as set forth herein, Petitioner submits that the claims are obvious even if April 30, 1999 is deemed the critical date.

III. CLAIM CONSTRUCTION

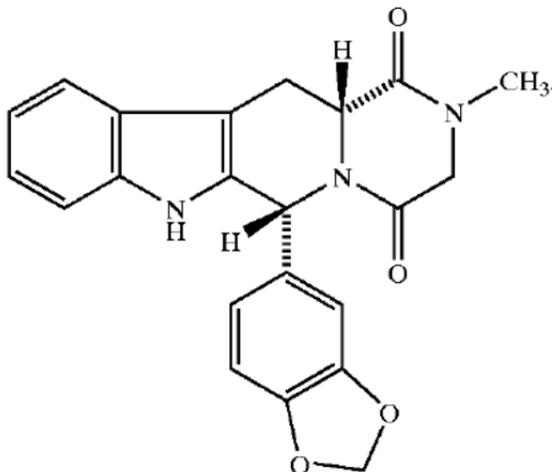
A. Standards For Claim Construction

37 C.F.R. § 42.100(b) provides that claims are construed according to the “broadest reasonable interpretation” at the Patent Trial and Appeal Board (PTAB). Under the broadest reasonable interpretation, claim terms are given their broadest reasonable interpretation in view of the specification to one having ordinary skill in the art at the time of the invention..

B. Construction of Terms

Claim 1 of the '166 patent, shown below, is the only independent 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



The term “**about 1 to about 20 mg**” of tadalafil should be interpreted according to its plain and ordinary meaning. In view of the intrinsic record, this would be understood as the dose range purported to have unexpected results.

The term “**up to a maximum total dose of 20 mg per day**” of tadalafil should be interpreted according to its plain and ordinary meaning. In view of the intrinsic record, this would be understood as the maximum end of a daily dose range.

The term “**compound having the structure**” is defined in the '166 patent, which states that “[t]he present invention provides a pharmaceutical dosage form for human pharmaceutical use, comprising about 1 to about 20 mg of (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 in a unit dosage form suitable for oral administration, alternatively named (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methylpyrazino-[1',2':1,6]pyrido[3,4-b]indole-1,4-dione.” Id. at col. 2, lines 23-28. To a person of ordinary skill in the art, the term would be interpreted as the common chemical name for tadalafil.

Any other term not specifically discussed above should be interpreted according to its plain and ordinary meaning to a person of ordinary skill in the art (POSA) in view of the specification.

IV. GROUNDS FOR UNPATENTABILITY OF EACH CLAIM

In light of the disclosures detailed below, the ‘166 patent is unpatentable for at least the reasons summarized in the chart below and discussed in more detail herein.

No.	Ground	Prior art	Exhibit Nos.	Claims
1	103(a)	Daugan ‘675 in View of Guideline for Industry, Dose	1005, 1014	1-12

		Response Information to Support Drug Registration		
2	103(a)	Daugan '675 Alone or In View of the Petition To Add Information About Sildenafil's Danger's To The Drug Label	1005, 1015	1-12
3	103(a)	Daugan '675	1005	1-12

A. Ground 1: Claims 1-12 are Unpatentable Under 35 U.S.C. § 103(a) As Being Obvious Over Daugan '675 In View of the Guideline for Industry, Dose Response Information to Support Drug Registration

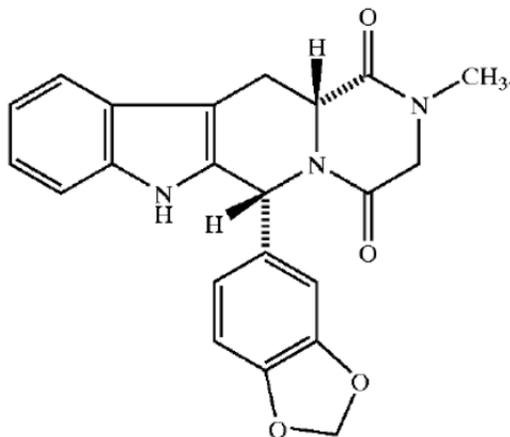
Claims 1-12 are directed to a known method of treating sexual dysfunction by orally administering a known drug (tadalafil) in a dose range that was taught in the prior art. Claim 1 is independent. Daugan '675 alone or in view of The Guideline for Industry, Dose Response Information to Support Drug Registration ("Guideline for Industry") teaches every element of claims 1-12 of the '166 patent as set forth in more detail below, and therefore renders those claims unpatentable under 35 U.S.C. §103(a). *See* Ex. 1010, Decl. ¶¶ 122-133.

Daugan '675 discloses and teaches tadalafil as one of the two preferred tetracyclic derivatives for treating erectile dysfunction. Ex. 1010, Decl. ¶¶ 103-112, 131-157. It teaches that tadalafil can be orally administered daily. Ex. 1005, Daugan '675, 5:4-7 (for a typical adult patient, tadalafil can be orally administered in "a range of from 0.5-800 mg **daily** for an average adult patient," including "**0.2-400 mg** of active compound, . . . for administration in single or multiple doses, once

or several times per day.”) *Id.* at 5:4-7 (emphasis added). Thus, at the very least, Daugan ‘675 teaches a dosage range from 0.2-400 mg per day.

Moreover, in several examples, Daugan ‘675 discloses 50 mg of tadalafil in oral dosage form. Daugan ‘675, p. 5, line 5. Daugan ‘675 also noted that “other strengths may be prepared...” *Id.* at 12-16. Daugan ‘675 also teaches that in practice, the physician will determine the actual dosing regimen most suitable for an individual patient. *Id.* at 5, lines 9-14. Thus, Daugan ‘675 teaches that an actual dosing regimen can be narrower within the described range.

In view of the foregoing, Daugan ‘675 teaches 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



Since Daugan ‘675 teaches that for a typical adult patient, individual tablets can be provided in single or multiple doses of 0.2-400 mg for oral administration

“**once** or several times **per day**,” a POSA would only need routine optimization to find that 1 to about 20 mg, up to a maximum total dose of 20 mg per day would be obvious even in view of Daugan ‘675 alone. Daugan ‘675, 5:5-7, Ex. 1010, Decl. ¶¶ 105, 131-155.

Under post-*KSR* law, the specific dose range need not be expressly found in Daugan ‘675. Rather, a POSA can apply common sense, particularly when there is a “**design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions.**” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). In such a situation, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. In view of these principles, a POSA would have found the claimed range of “about 1 to about 20 mg, up to a maximum total dose of 20 mg per day” to be obvious in view of the prior art including known optimization methods.

To the extent it was not obvious based on Daugan ‘675 alone, it would have been obvious to a POSA to optimize the dose range to minimize adverse side effects while maintaining pharmaceutical efficacy, as was typical for the pharmaceutical industry. Ex. 1010, Decl. ¶¶ 158-188. Specifically, a POSA would be motivated to administer tadalafil in the claimed dose range, “up to a maximum total dose of 20 mg per day” in order to maintain efficacy, minimize side effects, and comply with the accepted guidance in the field of drug design. A POSA would

also have been motivated to optimize the dose of tadalafil to arrive at “about 1 to about 20 mg, up to a maximum total dose of 20 mg per day” in view of market pressure to compete with Viagra® and the design need to avoid side effects of the claimed drug. See ‘166 patent at col. 1, line 58-col. 2, line 21 (acknowledging that certain side effects limited sildenafil’s use in certain individuals). Ex. 1010, Decl. ¶¶ 22-26, 168-188, 191.

The Guideline for Industry, Dose Response Information to Support Drug Registration (“Guideline for Industry”) was published in the Federal Register on November 9, 1994 (59 FR 55972), and was viewed by POSA’s prior to the critical date. Ex. 1010, Decl.¶ 122. It is therefore prior art to the’166 patent.

As shown in the Guideline for Industry, a POSA would recognize that every drug has a maximum daily dose insofar as after a certain dose, additional dosing fails to confer additional clinical benefit and the beneficial effects of a drug are outweighed by risks of adverse effects. Ex. 1010, Decl. ¶¶ 122-127. POSAs often refer to this concept as the maximum tolerated dose (MTD). Ex. 1010, Decl. ¶¶ 128-129. A POSA would understand that a MTD, which is typically determined in a Phase 1 safety/tolerance study in a target population, defines the “upper limit of the therapeutic dose range to be investigated in a Phase II efficacy study.” *Id.* An example of such a MTD is shown below. The figure notes the MTD as “the upper limit of a therapeutic dose range for efficacy”:

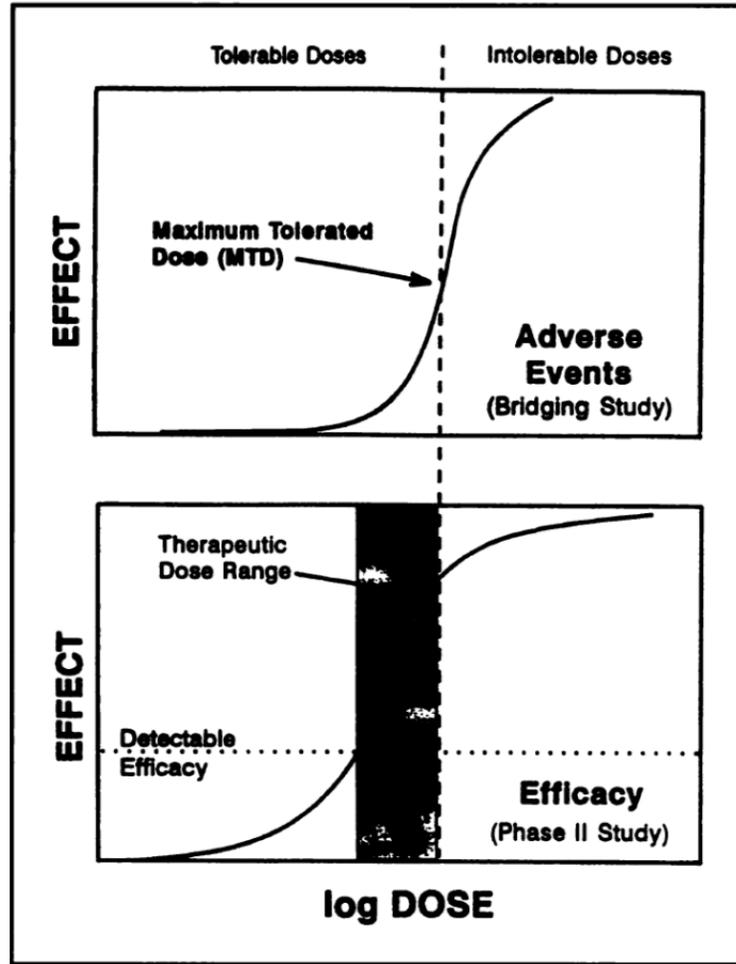


Figure 2. The maximum tolerated dose, determined in a Phase I safety/tolerance study in the target population (a bridging study, top panel) defines the upper limit of the therapeutic dose range to be investigated in a Phase II efficacy study (bottom panel).

See, e.g., Ex. 1016, Cutler, et al., *Defining the Maximum Tolerated Dose: Investigator, Academic, Industry and Regulatory Perspectives* at Fig. 2.

A POSA would have known prior to the critical date that “An acceptable balance of observed undesired effects and beneficial effects” is required to “make marketing at one of those doses reasonable.” See Ex. 1014, *The Guideline for Industry*, p. 6. A POSA would be motivated to find a maximum dose that would maintain efficacy and lower side effects.

Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir.2007). Such is the case here. The Guideline for Industry states that a drug sponsor should “Identify a reasonable starting dose, ideally with specific adjustments...” *Id.* at 13. Then, the sponsor should “identify reasonable, response-guided titration steps, and the interval at which they should be taken, again with appropriate adjustments for patient characteristics.” *Id.* at 14. Then, the sponsor should “identify a dose, or a response (desirable or undesirable), beyond which titration should not ordinarily be attempted because of a lack of further benefit or an unacceptable increase in undesirable effects. This guidance applies here, as is typical for pharmaceutical testing.

In this case, the drug sponsor already had a reasonable starting dose: a range of from “0.5-800 mg **daily** for an average adult patient,” including a range of “0.2-400 mg of active compound. . . for administration in single or multiple doses, once or several times per day,” and a further exemplary dose of 50 mg as taught in Daugan ‘675 at 5:4-7. In short, Daugan ‘675 taught “per day” dosing in a range that included the claimed dose range.

In view of Daugan '675's teachings, the drug sponsor could then identify reasonable, response-guided titration steps and the intervals at which they should be taken, with appropriate adjustments. Then, the sponsor can identify a dose beyond which titration should not ordinarily be attempted because of a lack of further benefit or an unacceptable increase in undesirable effects. This is routine and conventional testing, as shown in the Guideline for Industry. Routine titration or optimization would have shown that in doses higher than 20 mg per day, there were increased side effects without any significant added benefit. Ex. 1010, Decl. ¶¶ 122-130.

This is confirmed by the prosecution history of the patent, in which the patent applicant submitted a Declaration that stated:

“Phase 3 studies were conducted using 20 mg or lower doses because higher doses above 20 mg of Compound (I) had a sufficient number of adverse events such that the dose would have reduced tolerability to the general public.”

See Ex. 1009, Pros. History, Sides Affidavit dated 1-15-2004.

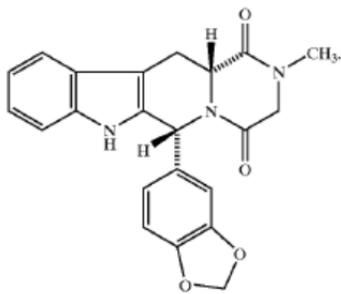
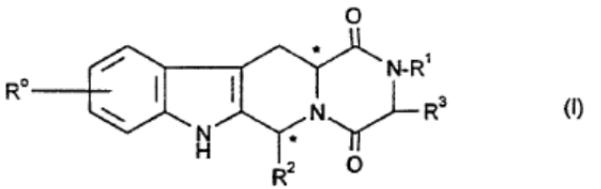
A POSA would recognize that beyond a certain maximum dose, the beneficial effects of a drug are outweighed by risks of adverse effects. Indeed, a POSA would recognize that a “balance of observed undesired effects and beneficial effects” is accepted to “make marketing at one of those doses reasonable.” See The Guideline for Industry, p. 6. In view of this industry

guidance, a POSA would be motivated to find a maximum daily dose, in this case, 20 mg, that would maintain efficacy and lower side effects.

The claim chart below provides more detail regarding the obviousness of claims 1-12 over Daugan '675 in view of Guideline for Industry.

<p>Claim 1 of '166 Patent</p>	<p>Daugan '675, FDA Review and FDA Clinical Hold</p>
<p>1. (A) 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" Daugan '675, 4:25-27</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." Daugan '675, 6:13-15 (emphasis added).</p>
<p>(B) orally administering</p>	<p>"[T]he compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration." Daugan '675, 3:32 to 4:1 (emphasis added).</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</p>

	i.c. administration." Daugan '675, 4:29-31 (emphasis added).
(C) one or more unit dose containing about 1 to about 20 mg,	<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." Daugan '675, 5:4-7.</p> <p>"In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within scope of this invention"</p>
(D) up to a maximum total dose of 20 mg per day,	<p>Up to a maximum total dose of 20 mg Prior art taught tadalafil in "0.5-800 mg daily for an average adult patient," including "0.2-400 mg of active compound, . . . for administration in single or multiple doses, once or several times per day." Daugan '675, 5:4-7. Prior art also disclosed examples of orally administered tadalafil in 50 mg doses. Id. at 12-16 (noting that "other strengths may be prepared...") Id. at 12-16.</p> <p>Per Day Prior art taught tadalafil in "0.5-800 mg <i>daily</i> for an average adult patient," including "0.2-400mg of active compound, . . . for administration in single or multiple doses, once or several times <i>per day</i>." Daugan '675, 5:4-7.</p> <p>20 mg as a maximum total dose would be obvious to try in view of the known clinical data and routine optimization. Ex. 1010, Decl. at ¶¶ 122-130, 158-185</p>

	<p>(noting that Viagra® was known to be effective and administered in 25, 50 and 100 mg doses). Given the known higher efficacy of tadalafil, a POSA would be motivated to use lower doses of tadalafil to achieve the same effects. <i>Id.</i></p> <p><i>See</i> The Guideline for Industry, which states that a drug sponsor should “Identify a reasonable starting dose, ideally with specific adjustments...” <i>Id.</i> at 13. Then, the sponsor should “identify reasonable, response-guided titration steps, and the interval at which they should be taken, again with appropriate adjustments for patient characteristics.” <i>Id.</i> at 14. Then, the sponsor should “identify a dose, or a response (desirable or undesirable), beyond which titration should not ordinarily be attempted because of a lack of further benefit or an unacceptable increase in undesirable effects. This is the case for the 20 mg maximum total dose per day.</p>
<p>(E) of a compound having the structure</p> 	<p>The compounds may be represented by the following general formula (I):</p>  <p>and salts and solvates (e.g. hydrates) thereof, in which:</p> <p>R⁰ represents hydrogen, halogen or C1-6 alkyl;</p> <p>R¹ represents hydrogen, C1-6alkyl, C2-6alkenyl, C2-6 alkynyl, haloC1-6alkyl, C3-8cycloalkyl, C3-8cycloalkylC1-3alkyl, arylC1-3alkyl or heteroarylC1-3alkyl;</p> <p>R² represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and</p>

	<p>pyridine or an optionally substituted bicyclic ring</p>  <p>attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and</p> <p>R³ represents hydrogen or C1-3 alkyl, or R1 and R3 together represent a 3- or 4- membered alkyl or alkenyl chain." Id. at, 2:3-20 (emphasis added).</p> <p>The specific compounds of the invention are: (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 (Compound A); and (3S,6R,12aR)-2,3,6,7,12,12ahexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B); and physiologically acceptable salts and solvates (e.g. hydrates) thereof." Daugan '675, 3:23-29 (emphasis added).</p>
<p>Claim 2</p> <p>2. The method of claim 1 wherein the sexual dysfunction is male erectile dysfunction.</p>	<p>The "present invention concerns the use of compounds of formula (I)...for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man" Daugan '675, 4:2-6.</p>

Claim 3	
3. The method of claim 1 wherein the sexual dysfunction is female arousal disorder.	The [compounds] "may also be used for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances." Daugan '675, 4:26-28.
Claim 4	
4. The method of claim 1 wherein the unit dose contains about 2 to about 20 mg of the compound.	Daugan '675, 5:4-7. A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range of 2-20 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675 and the Guideline for Industry, discussed above.
Claim 5	
5. The method of claim 1 wherein the unit dose contains about 5 mg of the compound.	Daugan '675, 5:4-7. A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose of 5 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, and the Guideline for Industry, discussed above.
Claim 6	
6. The method of claim 1 wherein the unit dose contains about 10 mg of the compound and	"[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." Daugan '675, 5:4-7. <i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1. The motivation to arrive at a narrower dose of about 10 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.

is administered once per day.	"Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day." Daugan '675, 5:5-7.
Claim 7	
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 compounds of formula (I)...may be administered orally, buccally or sublingually, in the form of tablets...or in capsules." Daugan '675 5:15-21.
Claim 8	
8. The method of claim 1 wherein the unit dose contains about 2.5 mg of the compound.	<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." Daugan '675, 5:4-7.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 2.5 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects. A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose of 2.5 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, and the Guideline for Industry, discussed above.</p>
Claim 9	
9. The method of claim 8 wherein the unit dose is administered once per day.	"Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day." Daugan '675, 5:5-7.
Claim 10	

10. The method of claim 5 wherein the unit dose is administered once per day.	"Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day." Daugan '675, 5:5-7.
Claim 11	
11. The method of claim 1 wherein the compound is administered as a free drug.	"For human use, compounds of formula (I), ... can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice." Daugan '675 at 5:15-18.
Claim 12	
12. The method of claim 1 wherein the unit dose contains about 20 mg of the compound.	<p>Daugan '675, 5:4-7.</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." Daugan '675, 5:4-7.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 20 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p> <p>A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range of 2-20 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675 and the Guideline for Industry, discussed above.</p>

The prosecution history of the '166 patent shows that the patent was allowed due to perceived “unexpected results” in the claimed dose range. Ex. 1009, Pros. History, Reasons for Allowance. However, since the '166 patent was allowed, the Federal Circuit has since established that evidence supporting superior efficacy at a specific claimed dose “does nothing to undercut the showing that there was a reasonable expectation of success even if the level of success may have turned out to be somewhat greater than would have been expected.” *Hoffmann-La Roche Inc. v. Apotex Inc.*, No. 2013-1128 (April 11, 2014). In that case, the Federal Circuit held that a 150 mg monthly dose, as compared to a 2.5 mg daily dose, with improved efficacy, does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg.

The same principle applies here. The patent owner’s purported evidence of unexpected results raised during the prosecution of the '166 patent do not overcome the strong showing of obviousness. The prior art disclosed orally administering tadalafil in a dose range that included the claimed dose and there was a motivation to attempt lower doses of “about 1 to about 20 mg, up to a maximum total dose of 20 mg per day” based on market pressure, design need and common sense. Under the current legal standards for obviousness, a POSA would have a reasonable expectation of success at the claimed dose range, and would have discovered this through routine optimization, seeking to maintain efficacy

while minimizing side effects. At the very least, given the finite size of the dose range disclosed in the prior art (0.2-400 mg of orally administered tadalafil, including a specific 50 mg example), the claimed range of “about 1 to about 20 mg, up to a maximum total dose of 20 mg per day” would have been obvious to try. Ex. 1010, Decl. ¶¶ 158-167.

To the extent that the claims are directed to a specific subset of dose ranges, e.g., claims 1, 4, 5, 6, 8 and 12. These claims are obvious in view of Daugan ‘675 both alone and in combination with the Guideline for Industry.

Claim 2 recites the features of claim 1 and further recites “wherein the sexual dysfunction is male erectile dysfunction,” Daugan ‘675 also teaches every feature of this claim. Ex. 1010, Decl. ¶¶ 147-148. Specifically, Daugan ‘675 further discloses and teaches that The “present invention concerns the use of compounds of formula (I)...for the curative or prophylactic treatment of **erectile dysfunction in a male animal, including man**” Daugan ‘675, 4:2-6 (emphasis added). Thus, claim 2 is obvious.

Claim 3 depends from claim 1 and further recites “wherein the sexual dysfunction is female arousal disorder. Daugan ‘675 also teaches every feature of this claim. Ex. 1010, Decl. ¶¶149-150. In particular, Daugan ‘675 teaches that the [compounds] “may also be used for the treatment of female sexual dysfunction

including orgasmic dysfunction related to clitoral disturbances.” Daugan ‘675, 4:26-28. Accordingly, claim 3 is obvious.

For the claims directed to a specific form of oral dosage, e.g. claim 7 (liquid, tablet or gelcap), and claim 11 (free drug), these claims are also obvious over the teachings of Daugan ‘675. Ex. 1010, Decl. ¶¶151-153. Daugan ‘675 teaches that, “The compounds of formula (I)...may be administered orally, buccally or sublingually, in the form of tablets...or in capsules.” Daugan ‘675 5:15-21. Daugan ‘675 also teaches that Daugan ‘675 also expressly discloses that “For human use, compounds of formula (I) . . . can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice.” Daugan ‘675 at 5:15-18. Thus, these claims are also obvious.

For the claims directed to a specific dose frequency, e.g. claim 6 (10 mg and once per day), claim 9 (2.5 mg and once per day), and claim 10 (5 mg and once per day), Daugan ‘675 specifically discusses administering oral tadalafil in a range including these doses once per day. A POSA would be motivated to administer these drugs once per day at the narrower dose ranges to maintain efficacy and limit side effects. Thus, these claims are obvious for the reasons discussed in claim 1, the specific teachings of Daugan ‘675 and the Guideline for Industry.

B. Ground 2: Claims 1-12 are Unpatentable Under 35 U.S.C. §

103(a) As Being Obvious Over Daugan ‘675 Alone Or In View the Petition To Add Information About Sildenafil’s Danger’s To The Drug Label.

Daugan ‘675 teaches the features of claims 1-12 as discussed above. Ex. 1010, Decl. ¶¶ 131-157. Adverse effects of PDE5 inhibitors were known prior to the critical date of April 30, 1999. Ex. 1010, Decl. ¶¶ 15-27. Indeed, at least as of July 1, 1998, there was a public Petition To Add Information About Sildenafil’s Danger’s To The Drug Label (“Petition”). Ex. 1010, Decl. ¶¶ 113-120. This Petition noted the dangers of sildenafil, particularly for conditions that excluded certain patient populations from the drug’s clinical trials, and warned of the dangers of the existing sildenafil label, which did not exclude those same patients from taking the drug. The Petition was available to the public prior to the critical date, being published in July 1, 1998 and routinely viewed by POSA’s. Ex. 1010, Decl. ¶¶ 115-116. Thus, it is prior art to the ‘166 patent.

The Petition states that “[t]here is a serious question as to whether patients, were they adequately informed, would choose to use sildenafil to treat the sexual adverse effects of another drug, **especially if an alternative drug which did not cause sexual dysfunction or a lower dose of the same drug or would obviate the need for sildenafil.**” (emphasis added).

Put another way, the Petition demonstrates that prior to the critical date, there was a known concern to address the side effects of sildenafil and that an

alternative drug was needed, or a lower dose of the same drug, which would obviate the need for sildenafil, if its adverse effects could be addressed. Ex. 1010, Decl. ¶¶ 113-116. A POSA would have known that based on the market pressure to compete with sildenafil, a drug manufacturer would have to market a drug that had the same or better efficacy, and in a dose that maintained efficacy but that also minimized adverse effects. Ex. 1010, Decl. ¶¶ 117-121.

A person of ordinary skill in the art would have been motivated to combine the teachings of Daugan '675, in view of the teachings of the Petition, to use the known compound tadalafil, in doses that would minimize the adverse side effects, and yet maintain the efficacy needed to compete with sildenafil. *In re Hyon*, 679 F.3d 1363, 1366 (Fed. Cir. 2012) (finding motivation to combine where the prior art references were directed to the same class of products).

In *KSR Int'l Co. v. Teleflex, Inc.*, the Supreme Court held that a “combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 420. *KSR* also taught that in many cases a person of ordinary skill will be able to fit the teachings together “like pieces of a puzzle.” *Id.* at 420.

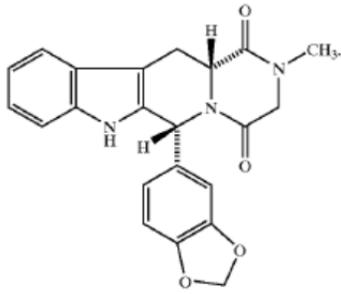
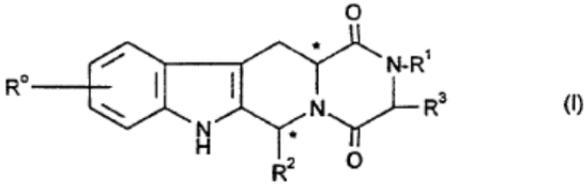
As in *KSR*, Daugan '675 in view the Petition teaches each and every element of claims 1-12 and renders them obvious. *Id.* at ¶ 63. *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1367 (Fed. Cir. 2008) (finding a patent invalid as

obvious where a combination of two prior art references would have resulted in a design having the same benefit and improvement).

The claim chart below provides more detail regarding obviousness of each element of claims 1-12 of the '166 patent by Daugan '675 in view of the Petition:

<p>Claim 1 of '166 Patent</p>	<p>Daugan '675, Sildenafil label, and Petition</p>
<p>1. (A) 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" Daugan '675, 4:25-27</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." Daugan '675, 6:13-15 (emphasis added).</p>
<p>(B) orally administering</p>	<p>"[T]he compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration." Daugan '675, 3:32 to 4:1 (emphasis added).</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</p>

	i.c. administration." Daugan '675, 4:29-31 (emphasis added).
(C) one or more unit dose containing about 1 to about 20 mg,	<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." Daugan '675, 5:4-7.</p> <p>"In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within scope of this invention" Daugan '675, 5:9-14.</p>
(D) up to a maximum total dose of 20 mg per day,	<p>Up to a maximum total dose of 20 mg Prior art taught tadalafil in "0.5-800 mg daily for an average adult patient," including "0.2-400 mg of active compound, . . . for administration in single or multiple doses, once or several times per day." Daugan '675, 5:4-7. Prior art also disclosed examples of orally administered tadalafil in 50 mg doses. Id. at 12-16.</p> <p>Per Day Prior art taught tadalafil in "0.5-800 mg <i>daily</i> for an average adult patient," including "0.2-400mg of active compound, . . . for administration in single or multiple doses, once or several times <i>per day</i>." Daugan '675, 5:4-7.</p> <p>20 mg as a maximum total dose would be obvious to try in view of the known clinical data and routine optimization. Ex. 1010, Decl. at ¶¶ 122-130, 158-185 (noting that Viagra® was known to be effective and administered in 25, 50 and</p>

	<p>100 mg doses). Given the known higher efficacy of tadalafil, a POSA would be motivated to use lower doses of tadalafil to achieve the same effects. <i>Id.</i></p> <p>There was an identified need to compete with Viagra® (sildenafil), which was administered at 25, 50 and 100 mg. See Viagra® label. Ex. 1010, Decl. at ¶185.</p> <p><i>See</i> Petition to Add Information About Sildenafil's (Viagra's) Dangers to the Drug Label (July 1, 1998) (“There is a serious question as to whether patients, were they adequately informed, would choose to use sildenafil to treat the adverse effects of another drug, especially if an alternative drug which did not cause sexual dysfunction or a lower dose of the same drug or would obviate the need for sildenafil.”)</p> <p>A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range, and set a maximum dose that would be competitive with Viagra® while avoiding adverse side effects. Ex. 1010, Decl. at ¶ 185.</p>
<p>(E) of a compound having the structure</p> 	<p>The compounds may be represented by the following general formula (I):</p>  <p>and salts and solvates (e.g. hydrates) thereof, in which:</p> <p>R⁰ represents hydrogen, halogen or C1-6 alkyl;</p> <p>R¹ represents hydrogen, C1-6alkyl, C2-6alkenyl, C2-6 alkynyl, haloC1-6alkyl, C3-8cycloalkyl, C3-8cycloalkylC1-3alkyl, arylC1-3alkyl or heteroarylC1-3alkyl;</p> <p>R² represents an optionally substituted</p>

	<p>monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring</p>  <p>attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and</p> <p>R³ represents hydrogen or C1-3 alkyl, or R1 and R3 together represent a 3- or 4- membered alkyl or alkenyl chain." Id. at, 2:3-20 (emphasis added).</p> <p>The specific compounds of the invention are: (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 (Compound A); and (3S,6R,12aR)-2,3,6,7,12,12ahexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B); and physiologically acceptable salts and solvates (e.g. hydrates) thereof." Daugan '675, 3:23-29 (emphasis added).</p>
Claim 2	
2. The method of claim 1 wherein the sexual dysfunction is male erectile dysfunction.	The "present invention concerns the use of compounds of formula (I)...for the curative or prophylactic treatment of

	erectile dysfunction in a male animal, including man” Daugan ‘675, 4:2-6.
Claim 3	
3. The method of claim 1 wherein the sexual dysfunction is female arousal disorder.	The [compounds] “may also be used for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.” Daugan ‘675, 4:26-28.
Claim 4	
4. The method of claim 1 wherein the unit dose contains about 2 to about 20 mg of the compound.	<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." Daugan ‘675, 5:4-7.</p> <p>"In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within scope of this invention" Daugan ‘675, 5:9-14.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 2 to about 20 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p>
Claim 5	
5. The method of claim 1 wherein the unit dose contains about 5 mg of the compound.	"[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

	<p>times per day." Daugan '675, 5:4-7.</p> <p>"In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within scope of this invention" Daugan '675, 5:9-14.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 5 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p>
Claim 6	
<p>6. The method of claim 1 wherein the unit dose contains about 10 mg of the compound and</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." Daugan '675, 5:4-7.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 10 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p>
<p>is administered once per day.</p>	<p>"Thus for a typical adult patient, individual tablets . . . for administration in single or multiple doses, once or several times per day." Daugan '675,</p>

	5:5-7.
Claim 7	
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 compounds of formula (I)...may be administered orally, buccally or sublingually, in the form of tablets...or in capsules." Daugan '675 5:15-21.
Claim 8	
8. The method of claim 1 wherein the unit dose contains about 2.5 mg of the compound.	"[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." Daugan '675, 5:4-7. <i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1. The motivation to arrive at a narrower dose of about 2.5 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.
Claim 9	
9. The method of claim 8 wherein the unit dose is administered once per day.	"Thus for a typical adult patient, individual tablets . . . for administration in single or multiple doses, once or several times per day." Daugan '675, 5:5-7.
Claim 10	
10. The method of claim 5 wherein the unit dose is administered once per day.	"Thus for a typical adult patient, individual tablets . . . for administration in single or multiple doses, once or several times per day." Daugan '675, 5:5-7.
Claim 11	
11. The method of claim 1 wherein the compound is administered as a free drug.	"For human use, compounds of formula (I), . . . can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice." Daugan '675 at 5:15-18.
Claim 12	

<p>12. The method of claim 1 wherein the unit dose contains about 20 mg of the compound.</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." Daugan '675, 5:4-7.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 20 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p>
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C. Ground 3: Claims 1-12 are Unpatentable Under 35 U.S.C. § 103(a) Over Daugan '675

Daugan '675 teaches the features of claims 1-12 as discussed above. Ex. 1010, Decl. ¶¶ 131-157. In addition, POSA would be motivated to administer tadalafil in the claimed dose range, up to a maximum total dose of 20 mg per day” in order to obtain FDA approval

As discussed above, Daugan '675 disclosed and taught a method of treating sexual dysfunction by orally administering tadalafil in a dose range of 0.2-400 mg per day, with a specific example of 50 mg. Daugan '675, 5:4-7. A POSA would recognize that to successfully market the drug, a drug sponsor would need FDA approval. Ex. 1010, Decl. ¶¶131 (claim charts), 168-183.

Prior to the critical date, a POSA would have known that tadalafil, like sildenafil, was also effective at treating sexual dysfunction, but that its IC₅₀ value

indicated it was significantly more potent: sildenafil was known to have an IC_{50} of about 3.5 nM (for human corpora cavernosa). Ex. 1010, Decl.¶ 170. Meanwhile, tadalafil was known to have an IC_{50} of 2 nM. See Daugan '675 at 17. A POSA would understand the 2nM value to apply to the treatment of erectile dysfunction, specifically for inhibition of PDE5 and its effects on the human copora cavernosa. Ex. 1010, Decl.¶ 170. A POSA would recognize that a lower IC_{50} value means a more potent drug. *Id.*

Prior to the critical date, it was known that ICOS Corp. and Lilly were engaging in clinical testing for the drug at issue. Ex. 1010, Decl.¶ 174; Ex. 1017, ICOS 10K FY 1998. A POSA would know that Phase 2 are dosing finding studies that support further clinical trials in Phase 3. Ex. 1010, Decl.¶ 174. A POSA would also understand that the FDA reviews the results of these clinical trials. The FDA's correspondence file shows that it was aware of certain adverse effects of tadalafil during testing, particularly in "high dose groups." See Ex. 1019, The FDA Review of Pharmacology and Toxicology Data ("FDA Review") for tadalafil, completed on May 26, 1998. See http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-368_Cialis_Pharmr.pdf (dated May 29, 1998). This document was executed prior to the critical date.

A POSA would recognize that the FDA reviewer noted a “high incidence of arteritis” and placed the IND on “clinical hold.” See, FDA Review (dated May 28, 1998) at 21 (p. 72 of PDF). A POSA would recognize that the IND was placed on clinical hold because of the proposed daily dosing. FDA Review at 94. Thus, therefore, the sponsor later proposed “prn doses up to 10 mg.”. FDA Review at 94.

A POSA would also further recognize that the clinical hold for tadalafil was placed on Dec. 9, 1997 for reasons related to dosing. See Ex. 1010, Decl. ¶¶181-182.

A POSA would recognize that there was pressure to use lower doses because, “In fact, studies for tadalafil were on IND “Clinical Hold” **until the sponsor agreed to lower the doses by upwards** of 10-fold and follow patients for clinical evidence of arteritis.” Id. A POSA would also recognize that clinical testing and consequently, FDA approval would be limited if adverse effects were not controlled:

At the time of the presumed End-of Phase 2 (EOP2) meeting, it became clear that a similar toxic effect on animal testes was happening. Therefore, the sponsor was told at the EOP2 meeting that the FDA recommended that they refrain from initiating Phase 3 U.S. trials until the testes-damaging effect was disproved in humans.”

Id.

Despite this, apparently, the drug sponsor conducted testing in South America, Mexico, Canada, Taiwan, Australia and Europe “with no specific

agreement from the FDA.” Id. The FDA eventually lifted the clinical hold later in 1998. FDA Clinical Hold at p. 5. Later, an FDA Reviewer states that “Cialis (5 mg to 10 mg was not shown to be statistically non-inferior to Viagra (50 mg to 100 mg) in this trial. After this study, all pivotal trials were designed to study Cialis 20 mg.” Id. at 9. A POSA would recognize that if Cialis 5 mg to 10 mg was comparable to Viagra® 50 -100mg®, then it is common sense and/or mere optimization to arrive at the conclusion that Cialis® could be provided in 5, 10 and 20 mg doses to compete with Viagra’s 25, 50 and 100 mg per day dosing.

In view of tadalafil’s known potency, the market pressure and design need to obtain FDA approval for a drug, a POSA would therefore be motivated to use the “lower” doses up to a maximum total dose of 20 mg per day.

It is well settled that obviousness can be found where there is “a design need or market pressure to solve a problem and there are a **finite number** of identified, predictable solutions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). Such is the case here. Given the known method of administering tadalafil in oral dosage forms of 0.2-400 mg (see analysis in Ground 1), it would be obvious to optimize the claimed dose, up to a maximum total dose of 20 mg per day, to avoid known adverse side effects, maintain efficacy, and secure FDA approval.

The claim chart below provides more detail regarding the obviousness of claims 1-12 over Daugan ‘675.

Claim 1 of '166 Patent	Daugan '675
1. (A) A method of treating sexual dysfunction in a patient in need thereof comprising	<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" Daugan '675, 4:25-27</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." Daugan '675, 6:13-15 (emphasis added).</p>
(B) orally administering	<p>"[T]he compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration." Daugan '675, 3:32 to 4:1 (emphasis added).</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." Daugan '675, 4:29-31 (emphasis added).</p>
(C) one or more unit dose containing about 1 to about 20 mg,	<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." Daugan '675, 5:4-7.</p> <p>"In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response</p>

	<p>of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within scope of this invention" Daugan '675, 5:9-14.</p>
<p>(D) up to a maximum total dose of 20 mg per day,</p>	<p>Up to a maximum total dose of 20 mg Prior art taught tadalafil in "0.5-800 mg daily for an average adult patient," including "0.2-400 mg of active compound, . . . for administration in single or multiple doses, once or several times per day." Daugan '675, 5:4-7. Prior art also disclosed examples of orally administered tadalafil in 50 mg doses. Id. at 12-16.</p> <p>Per Day Prior art taught tadalafil in "0.5-800 mg <i>daily</i> for an average adult patient," including "0.2-400mg of active compound, . . . for administration in single or multiple doses, once or several times <i>per day</i>." Daugan '675, 5:4-7.</p> <p>20 mg as a maximum total dose would be obvious to try in view of the known clinical data and routine optimization. Ex. 1010, Decl. at ¶122-130, 158-185 (noting that Viagra® was known to be effective and administered in 25, 50 and 100 mg doses). Given the known higher efficacy of tadalafil, a POSA would be motivated to use lower doses of tadalafil to achieve the same effects. Id.</p> <p>Prior to the critical date, it was known that ICOS Corp. and Lilly were engaging in clinical testing for the drug at issue. Ex. 1010, Decl. ¶174. A POSA would know that Phase 2 are dosing finding studies that support further clinical trials in Phase 3. Id.</p> <p>FDA Review noted "high incidence of arteritis" and placed the IND on "clinical hold." See, FDA Review</p>

(completed May 28, 1998) at 21; 26 (pp. 77 of PDF) (dated May 28, 1998). The clinical hold was related to dosing: “The original submission by ICOS Corporation was placed on hold because daily dosing with up to ___ was originally proposed. The sponsor now expects efficacy with prn doses up to 10 mg. The lower dose levels produce parent drug AUC exposures in men which are 10-20 times lower than the AUC exposures in dogs which are associated with vasculitis[s].” See FDA Review at p. 94.

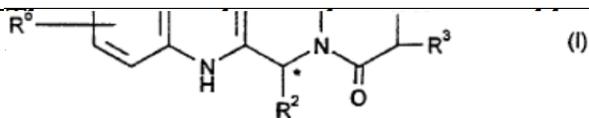
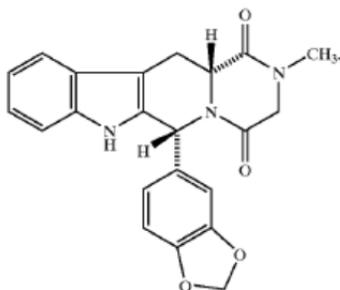
See also FDA Clinical Hold at 5, which notes that: “In fact, studies for tadalafil were on IND “Clinical Hold” until the sponsor agreed to lower the doses by upwards of 10-fold and follow patients for clinical evidence of arteritis.” Id.

In addition:
“At the time of the presumed End-of Phase 2 (EOP2) meeting, it became clear that a similar toxic effect on animal testes was happening. Therefore, the sponsor was told at the EOP2 meeting that the FDA recommended that they refrain from initiating Phase 3 U.S. trials until the testes-damaging effect was disproved in humans.” Id.

This is confirmed by later statements that “Cialis (5 mg to 10 mg was not shown to be statistically non-inferior to Viagra (50 mg to 100 mg) in this trial. After this study, all pivotal trials were designed to study Cialis 20 mg.” Id. at 9.

A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range, and set a maximum dose that would lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval.

(E) of a compound having the structure



and salts and solvates (e.g. hydrates) thereof, in which:

R^0 represents hydrogen, halogen or C1-6 alkyl;

R^1 represents hydrogen, C1-6alkyl, C2-6alkenyl, C2-6 alkynyl, haloC1-6alkyl, C3-8cycloalkyl, C3-8cycloalkylC1-3alkyl, arylC1-3alkyl or heteroarylC1-3alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan and pyridine or an optionally substituted bicyclic ring



attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C1-3 alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain." Id. at, 2:3-20 (emphasis added).

The specific compounds of the invention are: **(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-**

	<p>b]indole-1,4- dione (Compound A); and (3S,6R,12aR)-2,3,6,7,12,12ahexahydro-2,3-dimethyl-6-(3,4-methylene-dioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (Compound B); and physiologically acceptable salts and solvates (e.g. hydrates) thereof." Daugan '675, 3:23-29 (emphasis added).</p>
Claim 2	
2. The method of claim 1 wherein the sexual dysfunction is male erectile dysfunction.	The "present invention concerns the use of compounds of formula (I)...for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man" Daugan '675, 4:2-6.
Claim 3	
3. The method of claim 1 wherein the sexual dysfunction is female arousal disorder.	The [compounds] "may also be used for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances." Daugan '675, 4:26-28.
Claim 4	
4. The method of claim 1 wherein the unit dose contains about 2 to about 20 mg of the compound.	<p>Daugan '675, 5:4-7.</p> <p>A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range of 2-20 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, FDA Review, FDA Clinical Hold.</p>
Claim 5	
5. The method of claim 1 wherein the unit dose contains about 5 mg of the compound.	<p>Daugan '675, 5:4-7.</p> <p>A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose of 5 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, FDA Review, FDA Clinical Hold.</p>
Claim 6	
6. The method of claim 1 wherein the unit dose contains about 10 mg of the compound and	Daugan '675, 5:4-7.

	A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose of 10 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, FDA Review, FDA Clinical Hold..
is administered once per day.	“Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day.” Daugan '675, 5:5-7.
Claim 7	
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 compounds of formula (I)...may be administered orally, buccally or sublingually, in the form of tablets...or in capsules.” Daugan '675 5:15-21.
Claim 8	
8. The method of claim 1 wherein the unit dose contains about 2.5 mg of the compound.	Daugan '675, 5:4-7. A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose of 2.5 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, FDA Review, FDA Clinical Hold.
Claim 9	
9. The method of claim 8 wherein the unit dose is administered once per day.	“Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day.” Daugan '675, 5:5-7.
Claim 10	
10. The method of claim 5 wherein the unit dose is administered once per day.	“Thus for a typical adult patient, individual tablets ... for administration in single or multiple doses, once or several times per day.” Daugan '675, 5:5-7.
Claim 11	

11. The method of claim 1 wherein the compound is administered as a free drug.	"For human use, compounds of formula (I), . . . can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice." Daugan '675 at 5:15-18.
Claim 12	
12. The method of claim 1 wherein the unit dose contains about 20 mg of the compound.	<p>Daugan '675, 5:4-7.</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." Daugan '675, 5:4-7.</p> <p><i>See also</i> routine optimization, design need, market pressure, no unexpected results as discussed for claim 1.</p> <p>The motivation to arrive at a narrower dose of about 20 mg is found in the need to arrive at an effective dose that also minimizes adverse side effects.</p> <p>A POSA would therefore be motivated to optimize within the known dose range of 0.2-400 mg, to arrive at the claimed dose range of 2-20 mg to lower adverse effects, maintain efficacy, compete with Viagra®, and obtain FDA approval, as discussed for claim 1 herein. See Daugan '675, FDA Review, FDA Clinical Hold.</p>

For at least the reasons set forth above, the subject matter of claims 1-12 is obvious in view of the references cited above. There is no dispute that a method of

orally administering tadalafil was known in the prior art, and that the prior art taught a dose range that includes the claimed dose range of one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day. The prosecution history of the '166 patent shows that the patent was allowed because of perceived “unexpected results” associated with “one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day.” Ex. 1010, Decl. ¶¶ 189-199. The Examiner was applying the obviousness standards at the time, which required an express teaching, suggestion, or motivation to arrive at the claimed dose range. While that reasoning was applicable at that time, it is no longer applicable under the post-*KSR* legal standards. Under the current legal standards for obviousness, the claimed dose range is part of a finite range already disclosed in the art, and it would be obvious to optimize, particularly given the market pressure, design need and FDA and industry guidance discussed herein.

V. MANDATORY NOTICES

Pursuant to 37 C.F.R. §42.8, Petitioners provide the following mandatory disclosures:

A. Real Parties-In-Interest

The real party-in-interest is MonoSol Rx, LLC, 30 Technology Drive, Warren, New Jersey, 07059, a Delaware limited liability company.

B. Related Matters

Pursuant to 37 C.F.R. §42.8(b)(2), Petitioners submit that the '166 patent has been challenged in a related IPR proceeding brought by IntelGenx Corp. against ICOS Corp., Case IPR2016-00678. The Patent Trial and Appeal Board denied institution of the IPR. Mylan Pharmaceuticals filed Case IPR2017-00323 against ICOS Corp. on November 22, 2016.

Eli Lilly has also filed suit based the '166 patent against the following entities: Cipla USA, Inc., et al., Case No. 16-cv-1208, Aurobindo Pharma Ltd., et al., Case No. 16-cv-1121, Alembic Pharma., Ltd., et al., Case No. 16-cv-1120, Mylan Pharma., Inc., 16-cv-1122, Actavis Laboratories UT, Inc., Case No. 16-cv-1119, Sun Pharmaceuticals Industries, Ltd., et al., Case No. 16-cv-518, Teva Pharmaceuticals, USA, Inc., Case No. 16-cv-519, Zydus Pharma. (USA), Inc., Case No. 16-cv-520, Sun Pharma. Industries, Case No. 16-cv-1168, Teva Pharma. USA, Inc., Case No. 16-cv-1169, and Zydus Pharma. (USA) Inc., Case No. 16-cv-1170, in the Eastern District of Virginia.

C. Lead and Back-up Counsel

Petitioners provide the following designation and service information for lead and back-up counsel. 37 C.F.R. § 42.8(b)(3) and (b)(4). Please direct all correspondence regarding this proceeding to lead and back-up counsel at their respective email addresses listed below. 37 C.F.R. § 42.8(b)(4).

Lead Counsel	Harold H. Fox Reg. No. 41,498 hfox@steptoe.com 202-429-6284
First Back-up Counsel	Gretchen P. Miller Reg. No. 65,091 gmiller@steptoe.com 202-429-6271

D. Grounds for Standing

Petitioners hereby certify that the patent for which review is sought is available for *inter partes* review and that Petitioners are not barred or estopped from requesting *inter partes* review challenging the patent claims on the grounds identified in the petition. The undersigned authorizes the Commissioner to charge the fee specified by 37 C.F.R. § 42.15(a) to Deposit Acct. No. 19-4293, referencing Attorney Docket Number 18460.0020. In addition, the undersigned representative authorizes the Commissioner to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 19-4293. Proof of Service of this petition pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a) is

provided in the attached certificate of service. Concurrently filed herewith is a powers of attorney and exhibit list per § 42.10(b) and § 42.63(e), respectively.

VI. CONCLUSION

Accordingly, Petitioners request that the PTAB grant this petition for *inter partes* review.

Date: December 6, 2016

Respectfully submitted,

/Harold H. Fox/_____

Harold H. Fox
Gretchen P. Miller
STEPTOE & JOHNSON LLP
1330 Connecticut Ave. NW
Washington, DC 20036
Tel: (202) 429-3000
Fax: (202) 429-3902
hfox@steptoe.com
gmiller@steptoe.com

Attorneys for Petitioner MonoSol RX, LLC

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 1001-1019) by U.S. CERTIFIED MAIL, on this 6th day of December, 2016 on the Patent Owner at the correspondence address of the Patent Owner as follows:

MARSHALL, GERSTEIN & BORUN LLP
233 South Wacker Drive
6300 Willis Tower
Chicago, IL 60606-6357

ICOS CORPORATION
ELI LILLY AND COMPANY
P.O. BOX 6288
Patent Division
Indianapolis, IN 46206-6288

December 6, 2016

By /Harold H. Fox/

Harold H. Fox
Reg. No. 41,498
STEPTOE & JOHNSON LLP
1330 Connecticut Avenue, NW
Washington, DC 20036-1795
Tel: (202) 429-3000
Fax: (202) 429-3902

Counsel for MonoSol Rx, LLC