

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte PFIZER, INC.,
Patent Owner and Appellant

Appeal 2009-004106
Merged Reexamination Control Nos.
90/006,617; 90/006,886;
90/007,110; and 90/007,478
Patent 6,469,012 B1¹
Technology Center 3900

Decided: February 12, 2010

Before EDWARD C. KIMLIN, CAROL A. SPIEGEL, and
ROMULO H. DELMENDO, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

¹U.S. Patent No. 6,469,012 B1, *Pyrazolopyrimidinones for the Treatment of Impotence*, issued 22 October 2002 to Ellis et al. (hereinafter "the 012 patent"), based on application 08/549,792, filed 4 March 1996, under 35 U.S.C. § 371 as the national phase of PCT/EP94/01580, filed 13 May 1994, which claims benefit under 35 U.S.C. § 119 of GB application 9311920, filed 9 June 1993. The real party in interest is PFIZER, INC. (Appeal Brief filed 24 July 2006; Supplemental Appeal Brief filed 14 November 2008 (hereinafter "App. Br.") at 2).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Appellant Pfizer, Inc. appeals under 35 U.S.C. §§ 134(b) and 306 from an Examiner's final rejection of claim 24. Claims 1-23, 25, and 26, the only other pending claims, have been found patentable (App. Br. 2; Ans.² 2). Oral arguments were heard June 3, 2009. We have jurisdiction under 35 U.S.C. §§ 134(b) and 306. We AFFIRM.

I. Statement of the Case

A. Background

The 012 patent issued on October 22, 2002. A first reexamination, Control No. 90/006,617, was ordered by the Director of the Patent and Trademark Office on September 29, 2003. A second request for reexamination, Control No. 90/006,886, was filed by third party requester Lilly ICOS LLC on December 15, 2003. Reexamination was ordered in the '886 reexamination proceeding on February 6, 2004. A third request for reexamination, Control No. 90/007,110, was filed by third party requester Bayer AG and Bayer Pharmaceuticals Corporation on July 7, 2004. Reexamination was ordered in the '110 reexamination proceeding on September 13, 2004. A fourth request for reexamination, Control No. 90/007,478, was filed by third party Requester ICOS Corporation on March 23, 2005. Reexamination was ordered in the '478 reexamination proceeding on May 16, 2005. A Patent Owner statement was filed with respect to the first reexamination proceeding only. The '478 reexamination proceeding was merged with the three previously merged '617, '886, and '110 reexamination proceedings. (*See* Decision Merging Reexamination

² Examiner's Answer mailed 20 July 2007 (hereinafter "Ans.").

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Proceedings mailed August 19, 2005; App. Br. 6³). A fifth request for reexamination, Control NO. 90/007,614, was filed by third party requester Lilly Corporation on July 5, 2005. This request was denied because it was determined not to cite any new and different patents or printed publications which would raise a new substantial new question not already of record in the pending merged reexamination proceeding.⁴

There is also a pending litigation involving the 012 patent. The Patent Owner sued Lilly ICOS, LLC, Eli Lilly & Company, and ICOS Corporation for infringing the 012 patent by making the drug product Cialis® (Complaint, *Pfizer Inc., et al. v. Lilly ICOS LLC et al*, Civil Action No. 02-1561 (D. Del. Oct. 22, 2005))⁵.

We have fully considered the respective positions and arguments of the Appellant and the Examiner, as well as all of the evidence submitted in support thereof unless expressly noted otherwise.

B. The subject matter on appeal

The subject matter on appeal is directed to a method of treating male erectile dysfunction (hereinafter "ED") by oral administration of a selective inhibitor of a particular enzyme found in the penis, i.e., cyclic guanosine

³ The Appeal Brief incorrectly stated that the Decision Merging Reexamination Proceedings was mailed 19 July 2005.

⁴ See Order Denying Request for Ex Parte Reexamination mailed 18 August 2005 and Decision Dismissing Petition mailed 8 November 2005 in Reexamination 90/007,614.

⁵ Complaint filed 22 October 2002 in *Pfizer Inc., Pfizer Limited, and Pfizer Ireland Pharmaceuticals, Plaintiffs, v. Lilly ICOS LLC, Eli Lilly & Company, and ICOS Corporation*, Civil Action No. 02-1561 (JJF) (D. Del.) attached to the Appeal Brief as Exhibit A (hereinafter "Complaint").

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

3',5' monophosphate phosphodiesterase V, also referred to as "cGMP
PDE_V," "PDE_V," and "PDE5" (hereinafter "PDE_V").

Claim 24, the only claim on appeal, reads (App. Br. Clm. App'x 1):

A method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a selective cGMP PDE_V inhibitor, or a pharmaceutically acceptable salt thereof, of [sic, or] a pharmaceutical composition containing either entity.

Claim 24 broadly encompasses treating ED by oral administration of Pfizer's drug Viagra®, Lilly/ICOS LLC's drug Cialis®, and Bayer Pharmaceuticals Corporation's drug Levitra® (Viagra Package Insert 12;⁶ Cialis Package Insert 9;⁷ Levitra Package Insert 10⁸).

C. The rejections

The Examiner rejected claim 24 under 35 U.S.C. § 102(b) as anticipated by any of Korenman,⁹ Bensky,¹⁰ Hsu,¹¹ Chang,¹² and Yin¹³ (Ans.

⁶ Viagra® package insert 69-5485-00-9, (Pfizer Labs Revised August 2003). (Appeal Brief Exhibit F-12 (hereinafter "Viagra Package Insert").)

⁷ Cialis® package insert PV 3530 AMP, (Lilly ICOA LLC Issued November 2003). (Appeal Brief Exhibit F-9 (hereinafter "Cialis Package Insert").)

⁸ Levitra® package insert 08669034M (Bayer Pharmaceuticals Corporation August 2003). (Appeal Brief Exhibit F-10 (hereinafter "Levitra Package Insert").)

⁹ Stanley G. Korenman & Sharon P. Viosca, *Treatment of Vasculogenic Sexual Dysfunction with Pentoxifylline*, 41 J. Am. Geriatrics 363-366 (April 1993). (Appeal Brief Exhibit F-2 (hereinafter "Korenman").)

¹⁰ *Chinese Herbal Medicine Materia Medica*, 3-27, 490-92 (Dan Bensky & Andrew Gamble with Ted Kaptchuk eds. and trans., Eastland Press 1986). (Appeal Brief Exhibit J (hereinafter "Bensky").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

4-5). The Examiner relied on Florio Declaration I,¹⁴ Florio Declaration II,¹⁵ and Iversen Declaration I¹⁶ to support the anticipation rejections.

The Examiner also rejected claim 24 under the judicially created doctrine of obviousness-type double patenting over claim 1 of any of Campbell 270,¹⁷ Campbell 511,¹⁸ and Campbell 945¹⁹ (Ans. 5-8).

¹¹ Hong-Yen Hsu et al., *Oriental Materia Medica: A Concise Guide*, 563-65 (Oriental Healing Arts Institute 1986). (Appeal Brief Exhibit H (hereinafter "Hsu").)

¹² *2 Pharmacology and Applications of Chinese Materia Medica*, 1135-39 (Hson-Mou Chang & Paul Pui-Hay But eds., Shem Chang-Shing Yeung et al. trans., World Scientific Publishing Co. Pte. Ltd. 1987). (Appeal Brief Exhibit I (This decision cites to the English translation of Chang by Dennis Goldwater) (hereinafter "Chang").)

¹³ Ai-Hua Yin et al., *50 Cases of Treating Male Impotence Using Powdered YinYangHuo and TuSiZi*, 10(6) *Yunnan J. Traditional Chinese Med.* 13 (1989). (Appeal Brief Exhibit G (hereinafter "Yin").)

¹⁴ Declaration under Rule 37 C.F.R. § 1.132 of Vincent Allen Florio, Ph.D., dated 12 December 2003. (Answer Exhibit G, Appeal Brief Exhibit UU-7 (hereinafter "Florio Decl. I").)

¹⁵ Declaration under Rule 37 C.F.R. § 1.132 of Vincent Allen Florio, Ph.D., dated 21 March 2005. (Answer Exhibit F (hereinafter "Florio Decl. II").)

¹⁶ Declaration under Rule 37 C.F.R. § 1.132 of Philip W. Iversen, Ph.D., dated 14 December 2003. (Answer Exhibit H, Appeal Brief Exhibit UU-8 (hereinafter "Iversen Decl. I").)

¹⁷ U.S. Patent 6,100,270, *Bicyclic Heterocyclic Compounds for the Treatment of Impotence*, issued 8 August 2000, to Simon Fraser Campbell (hereinafter "Campbell 270"). (Appeal Brief Exhibit L.)

¹⁸ U.S. Patent 6,534,511 B1, *Bicyclic Heterocyclic Compounds for the Treatment of Impotence*, issued 18 March 2003, to Simon Fraser Campbell (hereinafter "Campbell 511"). (Appeal Brief Exhibit M.)

¹⁹ U.S. Patent 6,656,945 B2, *6-Heterocyclyl Pyrazolo[3,4-D]Pyrimidin-4-one cGMP-PDE Inhibitors for the Treatment of Erectile Dysfunction*, issued 2

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

II. The Anticipation Rejections

Claim 24 is rejected under 35 U.S.C. § 102(b) as anticipated by each of Korenman, Bensky, Hsu, Chang, and Yin.

A. Anticipation based on Korenman

1. the Examiner's findings

The Examiner found that Korenman successfully treated ED in about half a patient population by oral administration of pentoxifylline (Ans. 4). Citing the Florio I and Iversen I declarations,²⁰ the Examiner found that selective PDE_V inhibition is an inherent property of pentoxifylline (*id.*). Thus, the Examiner found claim 24 to be anticipated by Korenman (*id.*).

2. Appellant's arguments

Appellant essentially argues that (i) Korenman does not provide any meaningful data showing successful treatment of ED or disclose successful treatment of ED by inhibition of PDE_V, (ii) the evidence relied on by the Examiner to show that pentoxifylline is necessarily a selective inhibitor of PDE_V is flawed and unreliable, and (iii) the Examiner improperly dismissed rebuttal evidence showing that pentoxifylline is a nonselective PDE_V inhibitor as mere opinion lacking "hard factual evidence" (App. Br. 11-15). In particular, Appellant argues that "data that lacks statistical significance

December 2003, to Campbell et al. (hereinafter "Campbell 945"). (Appeal Brief Exhibit N.)

²⁰ The Examiner directed attention to "all of page 38 and the table on page 39 and exhibits J and K" (Ans. 4). Exhibits J and K referred to in the Answer are identical to Appeal Brief Exhibits UU7 and UU8, respectively. However, the Examiner did not identify which exhibit contained the referenced pages 38 and 39 and, therefore, these pages have not been considered.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

cannot be relied upon to prove or even support a scientific assertion, in this case that pentoxifylline is selective for PDE_v" (App. Br. 41).

3. the issue

The dispositive issue is whether the preponderance of the evidence establishes that pentoxifylline is inherently a selective PDE_v inhibitor.

4. findings of fact

The following findings of fact (hereinafter "FF") are supported by a preponderance of the evidence of record.

a. Korenman

- [1] Korenman characterizes pentoxifylline as a drug which renders red blood cells more deformable, thereby allowing them to pass more readily through partially obstructed arterial channels (Korenman 363, c. 1, ¶ 1).
- [2] Korenman hypothesized that pentoxifylline would be similarly effective in improving blood flow through the penis, thereby facilitating erection in men with a vascular component of impotence (Korenman 363, c. 1, ¶ 1).
- [3] Study subjects were treated with either placebo or 400 mg tid of pentoxifylline for twelve weeks (Korenman 364, c. 1, ¶ 3).
- [4] Four of eight subjects receiving pentoxifylline initially and none of ten subjects receiving placebo showed any improvement (Korenman 364, c. 2, ¶ 4), i.e., four of eight subjects receiving pentoxifylline initially experienced successful intercourse.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- [5] When the ten subjects initially receiving placebo were subsequently placed on pentoxifylline, five of them experienced successful intercourse (Korenman 364, c. 2, ¶ 4).
- [6] Korenman concluded that these preliminary results suggested a well tolerated alternative therapy for ED in patients with mild to moderate penile vascular disease (Korenman 363, abstract).
- b. Florio I and Iversen I declarations
- [7] Vincent Allen Florio, Ph.D., is a principal scientist and project leader for phosphodiesterase research at ICOS Corporation and the research leader for Cialis® on behalf of Lilly-ICOS (Florio Decl. I ¶ 2).
- [8] Both Lilly ICOS and ICOS Corporation requested reexamination of the 012 patent (see the requests for reexamination in Reexamination Control Nos. 90/006,886 and 90/007,478).
- [9] From late October 2003 through early November 2003, Dr. Florio supervised testing to determine and compare pentoxifylline's IC_{50} ²¹ against PDE_{IA}, PDE_{II}, PDE_{IIIA}, PDE_{IIIB}, PDE_{IVB}, and PDE_V (Florio Decl. I ¶¶ 9-11).
- [10] The test protocol supervised by Dr. Florio was run in 8-strip cluster tubes in a 96-well format, i.e., an 8 row (A-H) x 12 tube (well) matrix and comprised

²¹ IC_{50} is the concentration of an inhibitor at which 50% inhibition of a target response, such as enzyme activity, is seen. *See e.g.*, International Patent Publication WO 93/06104, *Pyrazolopyrimidinone Antianginal Agents*, published 1 April 1993, at 7-8. (Appeal Brief Exhibit Z (hereinafter "WO 6104").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

(i) adding 50 μ l assay buffer into each well from A1 to H11 and 75 μ l of 250 μ M pentoxifylline into wells A12 to H12,

(ii) transferring 25 μ l of wells A12 to H12 into wells A11 to H11 with an 8-channel pipettor, mixing and serially repeating through wells A3 to H3 to make a 1:3 serial dilution over 10 wells in each row,

(iii) adding 100 μ l 3 H-cGMP substrate to each well in rows A to D and 100 μ l 3 H-cAMP substrate to each well in rows E to H,

(iv) adding 50 μ l enzyme to each well as follows to initiate the enzyme reaction: PDE_{IA3} to row A, PDE_{IIA} to row B, PDE_{VA} to rows C and D, PDE_{IIIA} to rows E and F, PDE_{IIIB} to row G, and PDE_{IVB2} to row H, and

(v) measuring enzymatic cleavage products using a scintillation counter (Florio Decl. I, Exhibit A, "Methology [sic]").

[11] Dr. Florio summarized his results as follows (Florio Decl. I ¶11):

	PDE _{IA3}	PDE _{IIA}	PDE _{IIIA}	PDE _{IIIB}	PDE _{IVB2}	PDE _{VA}
IC ₅₀ (in μ M)	233	109	275	333	79.4	63.8
Selectivity Ratio	3.65	1.71	4.31	5.22	1.25	1.00

[12] Florio Declaration I did not contain any raw data.

[13] Phillip W. Iversen, Ph.D., is a statistician employed as a research scientist by Lilly company (Iversen Decl. I ¶¶ 2-4).

[14] Dr. Iversen testified that he applied a 3-parameter logistic model fit to analyze the data summarized in the table at paragraph 11 of Florio Declaration I (Iversen Decl. I ¶¶ 6-7).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[15] Dr. Iversen concluded that the selectivity ratios for PDE_I through PDE_{IV} versus PDE_{VA} "are statistically significantly different from a ratio value of 1" (Iversen Decl. I ¶ 8).

c. Appellant's rebuttal evidence

[16] Martyn Frank Burslem, Ph.D., is a research biochemist for patentee Pfizer (Burslem Decl.²² ¶¶ 2-6).

[17] Mr. Burslem testified that the "relative selectivity" of a compound can be calculated by dividing the summary statistic for potency, typically the IC₅₀ of the compound, at a nontarget protein by the summary statistic for potency at the target compound (Burslem Decl. ¶ 12).

[18] Specifically, Mr. Burslem testified that a compound could be described as relatively selective for PDE_V if the IC₅₀ for PDE_{I, II, III, or IV} divided by the IC₅₀ for PDE_V is statistically greater than 1 (Burslem Decl. ¶ 12), i.e., "the difference in potency of the drug at the two enzymes must be greater than the variation occurring in the test system" (*id.* ¶ 13).

[19] Ian Colin Marschner, Ph.D., is a statistician employed by Pfizer Australia Pty. Limited as Director of its Asia Biometrics Centre (Marschner Decl.²³ ¶¶ 1-4).

²² First Declaration under 37 CFR 1.132 of Martyn Frank Burslem, dated 4 June 2005. (Appeal Brief Exhibit P (hereinafter "Burslem Decl.")) The Burslem Declaration was submitted in *Eli Lilly and Company v. Pfizer Overseas Pharmaceuticals*, Federal Court of Australia, Victoria District Registry, and filed in Reexamination 90/006,886 (Burslem Decl. ¶ 18).

²³ First Declaration under 37 CFR 1.132 by Ian Colin Marschner, dated 5 April 2005. (Appeal Brief Exhibit UU (hereinafter "Marschner Decl."))

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- [20] The dates, experimental protocol, and data summary described in Florio Declaration I are identical to the dates, experimental protocol, and data summary testified to by Lothar Uher, a technical scientist at ICOS, and by Dr. Florio as described in the Florio²⁴ and Uher²⁵ Affidavits attached to the Marschner Declaration (hereinafter "the Florio PDE experiment") (see Florio Aff. ¶¶ 9-17 and attached ICOS Corporation Laboratory Notebook No. 47057, Project 1410, 1-4; Uher Aff. ¶¶ 4-8 and attached ICOS Corporation Laboratory Notebook No. 47057, Project 1410, 1-4; Florio II Decl. ¶ 13).
- [21] The Florio Affidavit provided the raw data collected from the October 28, 2003 to November 18, 2003 PDE testing (Florio Aff. ICOS Corporation Laboratory Notebook No. 47056, 103-138).
- [22] According to Dr. Florio, the data files, including the raw data, were sent to Dr. Iversen for statistical analysis (Florio Aff. ¶ 18).
- [23] Dr. Burslem opined that the Florio PDE experiment was flawed for a number of reasons including failure to account for expected experimental variations, such as systemic bias and random

The Marschner Declaration was submitted in *Eli Lilly and Company v. Pfizer Overseas Pharmaceuticals*, Federal Court of Australia, Victoria District Registry, and filed in Reexamination 90/006,886 (Marschner Decl. ¶ 6).

²⁴ Affidavit of Vincent Allen Florio in *Eli Lilly and Company v. Pfizer Overseas Pharmaceuticals*, Federal Court of Australia, Victoria District Registry. (Appeal Brief Exhibit UU-2 (hereinafter "Florio Aff.").)

²⁵ Affidavit of Lothar Josef Uher in *Eli Lilly and Company v. Pfizer Overseas Pharmaceuticals*, Federal Court of Australia, Victoria District Registry. (Appeal Brief Exhibit UU-3 (hereinafter "Uher Aff.").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- experimental error, e.g., the Florio PDE experiment did not run independent or replicate experiments using new enzyme, inhibitor, and reagent solutions in order to differentiate meaningful data from random effects of batch-to-batch enzyme, inhibitor, and reagent solution or vary the positions of the test samples to account for positional effects such as edge effects in a matrix plate format (Burslem Decl. ¶¶ 8-10, 13, 19, and 25-29).
- [24] Dr. Burslem reviewed the raw data from the Florio PDE experiment, determined the intra- and inter-plate variation, and concluded that a relative selectivity of between 1.2 and 2.2 was within experimental error (Burslem Decl. ¶¶ 33-34).
- [25] Dr. Burslem explained that (Burslem Decl. ¶ 36 (footnote omitted)),
- [a]lthough . . . Uher never measured the variability that arises from the enzyme and pentoxifylline preparations, he did at least measure the variability that arises simply from taking multiple measurements from the same preparations. He measured the inhibition of the PDE enzymes 4 times for PDE1A, PDE2, PDE3B and PDE4B2 and 8 times for PDE3A and PDE5. This variability that arises from taking multiple measurements from the same experiment is generally less than the variability that arises from independent experiments because in the former the enzyme and inhibitor preparations are the same for each measurement. Nevertheless, even this degree of variability can be significant to affect the validity of any analysis of the data and must therefore be taken into account.
- [26] According to Dr. Burslem, based on his own experience over 17 years, variations of 2 to 3.5 fold in IC_{50} values between replications of

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- an experiment using different preparations of enzyme, inhibitor, and reagent preparations were commonplace (Burslem Decl. ¶¶ 3 and 29).
- [27] Dr. Iversen similarly stated that "[f]or many of the assays I have consulted on, in my experience, the reproducibility of the IC₅₀s is in the range of 2 to 3" (Australian proceeding transcript²⁶ 754), and he acknowledged that edge effect and single batch experiment problems may raise concerns where it is critical to establish that a particular selectivity ratio was a real effect (*id.* 752-756).
- [28] Dr. Marschner faulted the Florio PDE experiment for failing to include high enough concentrations of pentoxifylline to assess the entire dose-response curve as well as for not including replicate experiments to confirm the statistical validity of its conclusions in view of known sources of experimental error, such as positional edge effect (Marschner Decl. ¶¶ 6-25).
- [29] Instead of analyzing the raw data *per se*, Dr. Iversen simply calculated an average of the observed data across all of the runs conducted at each concentration of a single PDE inhibition experiment and only analyzed the difference between the averaged data and the theoretical

²⁶ Transcript of proceedings in *Eli Lilly and Co. v. Pfizer Research and Development Co.* and *Bayer Aktiengesellschaft v. Pfizer Ireland Pharmaceuticals*, Federal Court of Australia, Victoria District Registry. (Appeal Brief Exhibit Q-2 attached to Appeal Brief Exhibit Q, First Declaration under 37 CFR 1.132 of Matthew Guy Swinn, dated 6 April 2005 (hereinafter "Australian proceeding transcript").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- IC₅₀ curve generated by software that fit a curve to the data (Burslem Decl. ¶¶ 35-38; Iversen Aff.²⁷ ¶¶ 6-8).
- [30] It is well known that "no quantitative experimental result is of any value unless it is accompanied by an estimate of the errors involved in its measurement" (STATISTICS²⁸ 44).
- [31] PDE_V has been called the cGMP-specific PDE or the cGMP-binding PDE (Beavo²⁹ 738, c. 1, ¶ 2).
- [32] Pentoxifylline has been recognized as a cAMP PDE inhibitor or a nonspecific PDE inhibitor in the scientific literature, e.g.,
- Pentoxifylline "increased significantly the level of cAMP" but "[n]o significant increase of the cGMP level was observed . . ." (Vittone³⁰ 1090, c. 1, ¶ 3).
- "[N]on-selective PDE inhibitors, . . . pentoxifylline . . ."
(Cortijo³¹ 562, c. 1, ¶ 3).

²⁷ Affidavit of Philip Iversen dated 29 September 2004. (Appeal Brief Exhibit P-4 attached to the Burslem Declaration (hereinafter "Iversen Aff."))

²⁸ J.C. Miller & J.N. Miller, Statistics for Analytical Chemistry ch. 2, 33-52 (Ellis Horwood ed., PTR Prentice Hall) (3d ed. 1993). (Appeal Brief Exhibit P-9 attached to the Burslem Declaration (hereinafter "STATISTICS").)

²⁹ Joseph A. Beavo, *Cyclic Nucleotide Phosphodiesterases: Functional Implications of Multiple Isoforms*, 75 *Am. Physiology Soc'y* 725-48 (1995). (Appeal Exhibit F-3 (hereinafter "Beavo").)

³⁰ Vittone et al., *The Mechanical and Biochemical Effects of Pentoxifylline on the Perfused Rat Heart*, 36 *Experientia* 1088-90 (1980). (Appeal Brief Exhibit F-6 (hereinafter "Vittone").)

³¹ Cortijo et al., *Investigation into the Role of Phosphodiesterase IV in Bronchorelaxation, Including Studies with Human Bronchus*, 108 *Brit. J. Pharmacology* 562-568 (1993). (Appeal Brief Exhibit F-17 (hereinafter "Cortijo").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

"As expected, . . . pentoxifylline (non-specific cAMP-PDE inhibitor) increased cAMP levels without affecting cGMP levels" (Valente³² 229 abstract); "[T]he cAMP-dependent PDE inhibitor, pentoxifylline . . ." (*id.* 234, c. 2, ¶ 2); and, "[T]he respective PDE5 and cAMP-dependent PDE inhibitors, sildenafil and pentoxifylline . . ." (*id.* 240, c. 2, ¶ 1).

"[A]n increase in cAMP but not cGMP during pentoxifylline infusion . . . suggests that if pentoxifylline exerts its actions as a PDE inhibitor, it is most likely to inhibit the cAMP-specific PDE more than the other PDEs" (Kruuse³³ 636, c. 2, ¶ 4).

Pentoxifylline "increased cAMP in a dose-dependent manner . . . but not cGMP level" (Chen³⁴ 773 abstract).

- [33] The Food and Drug Administration approved package insert for Trental® (pentoxifylline) describes its mode of action as "improv[ing] the flow properties of blood by decreasing its viscosity" and "increas[ing] leukocyte deformability and . . . inhibit[ing] neutrophil

³² Valente et al., *L-Arginine and Phosphodiesterase (PDE) Inhibitors Counteract Fibrosis in the Peyronie's Fibrotic Plaque and Related Fibroblast Cultures*, 9 Nitrous Oxide 229-244 (2003). (Appeal Brief Exhibit F-4 (hereinafter "Valente").)

³³ Kruuse et al., *Effects of the Non-selective Phosphodiesterase Inhibitor Pentoxifylline on Regional Cerebral Blood Flow and Large Arteries in Healthy Subjects*, 7 Eur. J. Neurology 629-638 (2000). (Appeal Brief Exhibit F-5 (hereinafter "Kruuse").)

³⁴ Chen et al., *Pentoxifylline Inhibits PDGF-induced Proliferation of and TGF- β -stimulated Collagen Synthesis by Vascular Smooth Muscle Cells*, 31 J. Molecular & Cellular Cardiology 773-83 (1999). (Appeal Brief Exhibit F-7 (hereinafter "Chen").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

adhesion and activation" (Trental Package Insert³⁵ c. 1 "Mode of Action").

[34] Peter Ellis, Ph.D., co-inventor of the 012 patent, testified that pentoxifylline's mode of action as described by Korenman and the Trental Package Insert are "not indicative of the effects of PDE_v inhibition" (Ellis I Decl.³⁶ ¶¶ 28-29).

d. Florio II declaration

[35] Dr. Florio disagreed that the Florio PDE experiment would have had any material edge effect because a water bath was used to keep each reaction well at a consistent and uniform temperature (Florio II Decl. ¶ 13).

[36] As to random experimental variation in the Florio PDE experiment, Dr. Florio testified that the protocol specified in the 012 patent

describes a partial purification of PDE enzymes. It does not describe an assay for PDE inhibitors, per se, but rather, provides a method to measure phosphodiesterase activity of the partially purified PDEs. As such, it is decidedly imprecise regarding the nature of the PDEs being tested, is silent regarding any need for use of additional batches of substrate, and is also silent on the other issues raised by Pfizer in Australia. [Florio II Decl. ¶ 14.]

Other findings of fact follow below.

³⁵ Trental® package insert TRE-MAY03-F-A, (Aventis Pharmaceuticals Revised May 2003). (Appeal Brief Exhibit F-14 (hereinafter "Trental Package Insert").)

³⁶ First Declaration under 37 CFR 1.132 of Peter Ellis, dated 29 March 2005. (Appeal Brief Exhibit F (hereinafter "Ellis I Decl.").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

5. legal principles

A reference anticipates a claim under § 102(b) when it discloses each and every element of the claimed invention, either explicitly or inherently. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981). "If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed." *In re Hedges*, 783 F.2d 1038, 1038 (Fed. Cir. 1986).

6. analysis

The Examiner's *prima facie* case of anticipation is based on his finding that pentoxifylline treatment was successful in about half of patients suffering from impotence and that pentoxifylline is necessarily a selective cGMP PDE_V inhibitor as shown in the Florio I and Iversen I declarations (Ans. 4). Dr. Florio supervised an experiment, the Florio PDE experiment, which determined the average IC₅₀ of pentoxifylline for PDE_{IA}, PDE_{IIA}, PDE_{IIIA}, PDE_{IIIB}, PDE_{IVB}, and PDE_{VA} as well as their respective "selectivity ratio" vis-à-vis the IC₅₀ for PDE_{VA} (FF 9-11, 20, 29). Dr. Florio summarized the results of the Florio PDE experiment as (FF 11):

	PDE _{IA3}	PDE _{IIA}	PDE _{IIIA}	PDE _{IIIB}	PDE _{IVB2}	PDE _{VA}
IC ₅₀ (in μM)	233	109	275	333	79.4	63.8
Selectivity Ratio	3.65	1.71	4.31	5.22	1.25	1.00

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Dr. Iversen evaluated the summary data and concluded that the selectivity ratios for PDE_I through PDE_{IV} versus PDE_{VA} were scientifically reliable, i.e., statistically and significantly different from a ratio value of 1 (FF 14, 15, 29).

In rebuttal, Appellant submitted testimony by Drs. Burslem and Marschner attacking the scientific reliability of the Florio PDE experimental data (FF 16-26, 28). According to Drs. Burslem and Marschner, the Florio PDE experiment did not control for expected experimental variations, such as systemic bias and random experimental error, e.g., by running independent or replicate experiments using new enzyme, inhibitor, and reagent solutions in order to differentiate meaningful data from random effects of batch-to-batch enzyme, inhibitor, and reagent solution and by varying the positions of the test samples to account for positional effects such as edge effects in a matrix format (FF 23, 25, 28). Furthermore, both Drs. Burslem and Iversen agreed, based on their own experiences, that it was not unusual for the reproducibility of IC₅₀s to be in the range of 2 to 3 or 3.5 (FF 26-27). Moreover, Dr. Iversen acknowledged that edge effect and single batch experiment problems may raise concerns where it is critical to establish that a particular selectivity ratio was credible (FF 27). Indeed, it is well known that "no quantitative experimental result is of any value unless it is accompanied by an estimate of the errors involved in its measurement" (FF 30). Furthermore, Appellant submitted a sampling of scientific literature which characterized pentoxifylline as a cAMP PDE inhibitor or as a nonspecific PDE inhibitor (FF 32).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

According to the Examiner, the rebuttal "opinions are not hard factual evidence" (Ans. 12) and "the experimental details stressed by the patent owner . . . would be more pertinent before the FDA . . ." (*id.* 13; *see also* 14 ("In other words, the analysis is more suitable for the FDA.")). The Examiner complains that Appellant has been repeatedly invited to supply evidence comparing the IC_{50} s of pentoxifylline for PDE_V and PDE_{III} using the protocol described in the 012 patent under reexamination to determine if pentoxifylline is a selective PDE_V inhibitor, but Appellant has failed to do so (Ans. 16 and 17). According to the Examiner, there is no need to respond to Appellant's arguments regarding the experimental methodology and statistical analysis of the Florio PDE experiment because the evidence weighs heavily on the side of the declaration by Philip Iversen showing that pentoxifylline is a selective PDE_V inhibitor (Ans. 16).

We disagree. While the Florio I and Iversen I declarations appear to support the contention that pentoxifylline is a selective PDE_V inhibitor, when Appellant comes forward with reasonable rebuttal, buttressed by prior art references and argument, as is the case here, the entire merits of the matter must be reweighed. *In re Hedges*, 783 F.2d at 1038. This the Examiner has not done. Here, the weight of the evidence calls the reliability of the relative selectivity ratios calculated from the Florio PDE experimental data into question based on the expected systemic and random errors of the experiment (FF 23, 25, 28). In our opinion, while Dr. Florio addressed the edge effect systemic error (FF 35), he did not meaningfully address the expected random errors in the Florio PDE experiment (FF 36), including enzyme, inhibitor, and reagent batch-to-batch variations. Moreover, the

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

expected random errors highlighted by Appellant are not all inclusive. For example, the Florio PDE experiment serially diluted the pentoxifylline (FF 10). It is well known that transfer inaccuracies lead to less accurate and less precise dispensing with each sequential serial dilution step, resulting in the highest dilutions having the most inaccurate results. If the Florio PDE experiment cannot meaningfully discriminate between an IC_{50} ratio of 1 or 2 or 3 or 3.5 because of systemic and/or random experimental errors, then a ratio of 1.71 or 1.25 has the same statistical significance as a ratio of 1.00 and does not establish that pentoxifylline is necessarily a selective PDE_V inhibitor. Rather, it reasonably appears that the Florio I and Iversen I declarations understated the actual variability measured and overstated the statistical significance of the data from the Florio PDE experiment testing of pentoxifylline. This conclusion is consistent with the characterization of pentoxifylline as a cAMP PDE inhibitor or as a nonspecific PDE inhibitor in the scientific literature (FF 32) and with the testimony of Dr. Ellis, a co-inventor of the 012 patent, that the reported mode of action of pentoxifylline is not indicative of the effects of PDE_V inhibition (FF 1, 33, 34). In summary, claim 24 recites treating ED by orally administering an effective amount of a selective PDE_V inhibitor and the Examiner has failed to establish, by a preponderance of the evidence of record, that pentoxifylline is inherently a selective PDE_V inhibitor.

Furthermore, while the Examiner may suggest possible types of rebuttal evidence, the Examiner must evaluate the rebuttal evidence submitted by Appellant.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

7. conclusion

Based on the foregoing, we reverse the rejection of claim 24 under 35 U.S.C. § 102(b) as anticipated by Korenman. The preponderance of the evidence of record establishes that pentoxifylline is not a selective PDE_V inhibitor.

B. Anticipation based on the Yin Yang Huo references: Bensky, Hsu, Chang, and Yin

1. the Examiner's findings

The Examiner found that each of Bensky, Hsu, Chang, and Yin (collectively "the Yin Yang Huo references") treats impotence by oral administration of the herb Yin Yang Huo (Ans. 5). The Examiner found that "[t]he Declarations of . . . Florio and . . . Iversen, clearly establish that icariin is an ingredient of Yin Yang Huo and that icariin is a selective cGMP PDE_V inhibitor" (*id.*). Thus, the Examiner found claim 24 anticipated by each of the Yin Yang Huo references (*id.* 5, 23).

2. Appellant's arguments

Appellant argues that there is no credible evidence that Yin Yang Huo treats ED or any basis for concluding that the Yin Yang Huo references disclose using an "effective amount" of a selective PDE_V inhibitor to treat ED (App. Br. 15-17). Specifically, Appellant argues that none of the Yin Yang Huo references identify which compound in Yin Yang Huo is responsible for efficacious treatment of impotence (App. Br. 15-17, 90-91, and 98) and that the Examiner improperly credited evidence lacking scientific credibility over substantial rebuttal evidence in the form declarations by experts in Chinese herbal medicines and clinical trials (*id.*

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

15-17 and 90-91). As to Yin in particular, Appellant argues that the disclosed treatment comprises a mixture of Yin Yang Huo and Tu Si Zi, as well as yellow rice wine, genital massage, rest, bathing in a herbal mixture, and abstinence from intercourse and, therefore, does not establish that the treatment effect was due to Yin Yang Huo alone (*id.* 16). Essentially, Appellant argues that the Yin Yang Huo references are not enabled.

3. the issue

The dispositive issue is whether the Yin Yang Huo references describe oral administration of the selective PDE_v inhibitor icariin in an amount effective to treat ED.

4. additional findings of fact

a. the Yin Yang Huo references

[37] The pharmaceutical name for Yin Yang Huo is "Herba Epimedii" (Bensky 490; Yin 1), which includes the species *E. sagittatum*, *E. brevicornum*, and *E. macranthum* (Chang 1135; Hsu 563)

[38] According to Bensky, Yin Yang Huo is "used for Deficient Kidney Yang patterns with such symptoms as impotence, spermatorrhea, frequent urination, forgetfulness, withdrawal, and painful cold lower back and knees" (Bensky 490) and is combined with Wu Wei Zi, Gou Qui Zi, and Sha Yuan Ji Li "for Deficient Kidney impotence and infertility" (*id.* 491).

[39] Bensky lists icariin, benzene, sterols, tanin, palmitic acid, linolenic acid, oleic acid, and vitamin E as the major known ingredients of Yin Yang Huo (Bensky 491).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- [40] Bensky reports a dosage of 1-4 quian of Yin Yang Huo, i.e., 3 to 12 g (Bensky 20, 491).
- [41] According to Hsu, Yin Yang Huo is traditionally used to treat impotence, weakness in the loins and knees, arthralgia due to wind, cold, and damp, general paralysis (Hsu 564).
- [42] Specifically, Hsu reports (Hsu 564) that Yin Yang Huo has an aphrodisiac action mainly because it stimulates secretion of semen, causing the filling up of the scrotum, thereby stimulating the sensing nerves, and indirectly promoting sexual desire. The leaf and the root are most potent in this action, the fruit is intermediate, and the stem is the least potent.
- [43] Hsu lists the chemical constituents of the Yin Yang Huo root and rhizome as O-methylcariin, magnoflorin, and vitamin E; and, of the leaf and stem as icariin, olivil, and icariresinol (Hsu 564).
- [44] Hsu reports a dosage of Yin Yang Huo of 6 to 12 g (Hsu 565).
- [45] According to Chang, Yin Yang Huo "is used for impotence, atrophy and weakness of the low-back and knee, numbness of limbs, neurasthenia, amnesia and climacteric hypertension" (Chang 1135).
- [46] Specifically, Chang reports (Chang 1135, footnotes omitted) that [t]he aqueous extract of <Yinyanghuo> given to dogs intragastrically did not cause erection (or mounting behavior) though it promoted semen secretion. The rank of potency of the various plant parts was leaf and root > fruit > stem. [] The weight-increase experiment on mouse prostate, seminal vesicle, and levator ani proved that the injection of the <Yinyanghuo> extract 20-40 mg was as efficacious as androgen 7.5 µg. [] A significant rise in the mean 24-hour urinary 17-ketosteroids . . . but

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

no significant change in the 24-hour 17-hydroxycorticosteroid excretion was obtained. These results suggest that <Yinyanghuo> has gonadotropic effects [].

- [47] According to Chang, the stem and leaf of *E. sagittatum* contain icariin, des-O-methylcaritin, β -anhydroicaritin, and magnoflorine, while the underground part contains des-O-methyl- β -anhydroicaritin, icariins A, B, C, D, and E, and 4 kinds of lignan (Chang 1135).
- [48] Chang does not report any specific regimen for treating impotence using Yin Yang Huo.
- [49] According to Yin, the authors have satisfactorily treated 50 cases of male impotence with their own formulation of Yin Yang Huo and TuSiZi (Yin 1).
- [50] Yin describes a typical case involving a 27 year old male, Mr. Qi, diagnosed with impotence caused by excessive sex who achieved an erection after 10 days and was reported cured after 17 days of treatment (Yin 2).
- [51] Yin describes the method of treatment as follows (Yin 1):
- Formula components: 15 grams each of YinYangHuo and TuSiZi, powdered together and bottled in preparation for use. Dosage: 5 grams per time, 3 times per day, taken with huang-jiu [Chinese rice wine], for a period of 20 days as one course of treatment. Supplemental treatment: 1. Massage the area of the lower abdomen and the perineum, 10 times, beginning from left to right followed by from right to left. Do this for 1 minute each before arising in the morning, before the noon nap, and before going to bed in the evening. 2. Every evening boil 15 grams each of ChuanXiong (Radix Ligustici

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Chuanxiong) and XiXin (Herba cum Radice Asari) in water and then sit in it for 20 minutes. Precautions: Abstain from intercourse for 100 days, and avoid becoming over-tired or exposed to cold.

[52] According to Yin, the formulation was taken for a minimum of 7 days and a maximum of 4 courses of treatment, with an average of 48.5 days (Yin 1).

b. the Florio II declaration

[53] Dr. Florio testified that he supervised testing to determine and compare the IC₅₀s of icariin against PDE_I through PDE_V (Florio II Decl. ¶ 9).

[54] According to Dr. Florio, the experimental protocol was largely identical to that used to test pentoxifylline except that dimethyl sulfoxide was used to help solubilize the icariin (Florio II Decl. ¶ 10).

[55] According to Dr. Florio, a first experiment was conducted using 0.00254 to 50 µM icariin and second and third experiments were conducted using 0.01 to 200 µM icariin (Florio II Decl. ¶ 11 n.5).

[56] Dr. Florio summarized his results as follows (Florio II Decl. ¶11):

	PDE _{IA3}	PDE _{IIA}	PDE _{IIIA}	PDE _{IIIB}	PDE _{IVB2}	PDE _{VA}
IC ₅₀ (in µM) ± SE	312±71	203±48	1460±914	1228±375	159±33	1.08±0.16
Selectivity Ratio	289	188	1352	1137	147	1.00

[57] Appellant does not dispute that the experimental data shows the selectivity of icariin for PDE_V (App. Br. 51).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

c. Appellant's rebuttal evidence³⁷

- [58] Eric J. Lien, Ph.D., Emeritus Professor of Pharmaceutical Sciences at the University of Southern California, reported that amounts of icariin found in 67 different samples of Yin Yang Huo ranging from 0.00307 (sample #14) to 3.692 (sample #13) weight percent (Lien Decl.³⁸ ¶¶ 1, 15; Lien Decl. Exhibits 6-11).
- [59] Wu reported that as of 2003 the *Epimedium* genus reportedly contained about sixty flavonoid glycosides, including icariin, nearly thirty flavones, and around fifty icarisides (Wu³⁹ 27).
- [60] Dr. Ellis testified that a 5 gram dose of Yin Yang Huo tid, such as disclosed by Yin, is insufficient to treat ED through inhibition of PDE_V (Ellis II Decl.⁴⁰ ¶ 4).
- [61] Specifically, Dr. Ellis testified that the mere fact that a compound administered to an impotent man contains some amount of a selective PDE_V inhibitor does not mean that the amount administered will inhibit PDE_V in the body sufficiently to produce any relief in the treatment of ED (Ellis II Decl. ¶ 9).

³⁷ We have not considered the Second Declaration under 37 CFR 1.132 of Emilia Bagiella, Appeal Brief Exhibit VV, because it is not signed or dated.

³⁸ First Declaration under 37 CFR 1.132 by Eric J. Lien, Ph.D., dated 11 November 2005. (Appeal Brief Exhibit AAA (hereinafter "Lien Decl."))

³⁹ Wu et al., *Chemical and Pharmacological Investigations of Epimedium Species: A Survey*, 60 Progress in Drug Research 1-57 (2003). (Appeal Brief Exhibit BBB (hereinafter "Wu").)

⁴⁰ Second Declaration under 37 CFR 1.132 of Peter Ellis, dated 11 November 2005. (Appeal Brief Exhibit CCC (hereinafter "Ellis II Decl."))

Appeal 2009-004106
 Reexamination Control Nos. 90/006,617;
 90/006,886; 90/007,110; and 90/007,478
 Patent 6,469,012 B1

[62] According to Dr. Ellis, the maximum plasma concentration (C_{max}) of icariin achieved following a 5 g oral dosing of Yin Yang Huo tid as described by Yin is well below its IC_{50} for PDE_V (Ellis II Decl. ¶ 11).

[63] Based on the average amounts of icariin in Yin Yang Huo reported by Dr. Lien and the molecular weights and reported pharmacokinetic data for Viagra®, Levitra®, Cialis®, and icariin in rats and/or man, Dr.

Ellis calculated the following comparative summary:

Brand name	Viagra®	Levitra®	Cialis®	Yin Yang Huo
Generic Name or Active	Sildenafil Citrate	Vardenafil HCl	Tadalafil	Icariin
Minimum effective clinical oral dose of Viagra®, Levitra® and Cialis® vs. Yin's dose of icariin in Yin Yang Huo	25 mg	5 mg	5 mg	25.4 mg
PDE_V Inhibitor IC_{50}	3.5 nM	0.14 nM	6.7 nM	1080 nM
Blood Plasma Free Drug Concentration at C_{max}	4.5 µg/L	0.225 µg/L	4.9 µg/L	7.8 µg/L
Percent Inhibition of PDE_V at C_{max}	73%	75%	62%	0.5%

(Ellis II Decl. ¶¶ 12-17; Ellis II Decl. Exhibit 1; Viagra Package Insert 19; Levitra Package Insert 10; Cialis Package Insert 10; Florio II Decl.).

[64] Dr. Ellis further opined that, since the only observation Yin obtained of any sexual capability during dosing with icariin is the erection reported by Mr. Qi after taking the treatment for 10 days, any efficacy Yin observed should be correlated with total drug exposure, not C_{max} (Ellis II Decl. ¶ 18).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[65] Based on total drug exposure, Dr. Ellis calculated that Yin Yang Huo would only inhibit 0.14% of PDE_V at average blood levels of icariin (Ellis Decl. II ¶¶ 19-20).

[66] Upon considering the 3 to 12 g dosage of Yin Yang Huo reported by Bensky (FF 40), the 6-12 g dose of Yin Yang Huo reported by Hsu (FF 44), and a description in Chang of using "small oral doses of the herb maceration (60 g of herb in 1 liter of wine)" (Chang 1138), and assuming dose proportionality, Dr. Ellis calculated that a 15 g dose of Yin Yang Huo would correspond to 0.43% inhibition of PDE_V at average blood levels of icariin or to less than 1.5% inhibition at C_{max} (Ellis Decl. II ¶ 22; FF 40).

Other findings of fact follow below.

d. legal principles

A reference is anticipatory under § 102(b) when it (i) discloses each and every element of the claimed invention, either explicitly or inherently, and (ii) enables one of ordinary skill in the art to make the invention. *In re Gleave*, 560 F.3d at 1334.

e. analysis

Claim 24 requires oral administration of a selective PDE_V inhibitor in an amount effective to treat ED.

As found by the Examiner (Ans. 5), each of the Yin Yang Huo references treats impotence by administering herbal Yin Yang Huo (FF 38, 41, 45, 49). It is undisputed that the herb is orally administered (*see e.g.*, FF 46, 51), that icariin is an active component of the herb (FF 39, 43, 47, 58) and that icariin is a selective PDE_V inhibitor (FF 57). Thus, the issue is

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

whether the Yin Yang Huo references describe oral administration of the selective PDE_v inhibitor icariin in *an amount effective to treat ED*.

Bensky, Hsu, Chang, and Yin describe administering Yin Yang Huo in dosages of 3-12 g (FF 40), 6 to 12 g (FF 44), 60 g/liter wine (FF 66) and 15 g (FF 51), respectively. Indeed, Dr. Ellis was able to calculate expected plasma free icariin concentrations at C_{max} and % PDE_v inhibition levels based on a daily dosage of icariin as described by the Yin Yang Huo references (FF 62, 63, 65, 66). However, Yin Yang Huo is orally administered in specific amounts over a period of time, not just in a single dose, to treat impotence. For example, Yin describes taking Yin Yang Huo for a minimum of 7 days and a maximum of 4 courses of treatment, with an average of 48.5 days (FF 52). Appellant argues that a single dosage of Yin Yang Huo fails to provide an amount of icariin sufficient to treat ED based on a comparison of Dr. Ellis' calculated percent inhibition of PDE_v of an average amount of icariin present in a Yin Yang Huo dosage versus the calculated percent inhibition provided by a single dose of Viagra®, Levitra®, and Cialis®. However, the selective PDE_v inhibitor of claim 24 is not required to have a minimum % inhibition at its IC₅₀ or a maximum K_i or other enzyme kinetics inhibition value or other defined parameter that would exclude Yin Yang Huo from the claimed method. Moreover, Yin Yang Huo is not administered as a single daily dosage when treating ED. Yin expressly defines one course of treatment as comprising administering 2.5 grams Yin Yang Huo 3 times per day for 20 days (FF 51). Therefore, this rebuttal evidence is insufficient to establish by a preponderance of the evidence that the Yin Yang Huo references fail to disclose oral

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

administration of icariin in an amount effective to treat ED, particularly in view of Yin's disclosed successful treatment of 50 cases of impotence (FF 49).

f. conclusion

Ergo, based on the foregoing, we sustain the rejections of claim 24 under 35 U.S.C. § 102(b) as anticipated by any of Bensky, Hsu, Chang, and Yin. The Yin Yang Huo references disclose oral administration of a selective PDE_v inhibitor, i.e., icariin, in an amount effective to treat ED.

III. Obviousness-type Double Patenting Rejection

A. The Examiner's findings and conclusion

The Examiner found that claims 1 of Campbell 270, 945, and 511 each recite a method of treating male ED by administering a defined species of selective PDE_v inhibitor, while claim 24 on appeal treats male ED by *oral* administration of *any* selective PDE_v inhibitor (Ans. 5-8). The Examiner concluded that it would have been obvious to administer the specific selective PDE_v inhibitor recited in claim 1 of Campbell 270, claim 1 of 945, and claim 1 of 511 orally because oral administration is the easiest mode to deliver the selective PDE_v inhibitor and because the prior art applied in the anticipation rejections, i.e., Korenman and the Yin Yang Huo references, administered their respective ED treatment drug via the oral route or, alternatively, because the Campbell 270, 945, and 511 patent specifications make clear that oral administration is the preferred route of administration (Ans. 8).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

B. Appellant's arguments

Appellant argues that Campbell 511 and 945 cannot be double patenting references because they issued after the 012 patent (App. Br. 9, 17-21; Reply Br.⁴¹ 1). Specifically, "the unusual circumstance created solely by GATT result[ed] in terms of the '511 and '945 reference patents that are entirely subsumed within the term of [the 012 patent]" (App. Br. 20).

Appellant further argues that the convenience of oral administration is of no use if the drug does not work unless injected locally into the penis (App. Br. 25). According to Appellant, the Examiner improperly relied on the Campbell patent specifications to reach his conclusion of obviousness and ignored the teachings of the prior art that the drugs administered in method claims 1 of Campbell 270, 945, and 511 are known antihypertensives and PDE inhibitors and that the systemic effects of orally administered antihypertensives and PDE inhibitors may cause or worsen ED (App. Br. 8, 21-27, 32-35; Reply Br. 1-7).

Appellant still further argues that the Examiner has failed to establish that the drugs administered in method claims 1 of Campbell 270, 945, and 511 are selective PDE_v inhibitors (App. Br. 27-28; Reply Br. 1 and 7-8). According to Appellant, contrary to the Patent Office's statement, WO 6104 and WO 7149⁴² only teach that the compounds used in method claims 1 of Campbell 270 and 511, respectively, are selective for cGMP PDEs rather

⁴¹ Reply Brief for Appellant under 37 C.F.R. 41.37 filed 24 September 2007 (hereinafter "Reply Br.").

⁴² International Patent Publication WO 93/07149, *Pyrazolopyrimidinone Antianginal Agents*, published 15 April 1993. (Appeal Brief Exhibit AA (hereinafter "WO 7149").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

than cAMP PDEs, i.e., that the compounds are selective for PDE_I or PDE_V (App. Br. 27-28). According to Appellant, neither WO 6104 nor WO 7149 teach that the Campbell compounds are selective PDE_V inhibitors or are useful for treating ED (App. Br. 28).

C. Issues

Therefore, at issue is

(i) whether patent term or patent issue date determines if a claim of a patent issued based on a post-GATT application qualifies as a double patenting reference against a claim of a patent issued based on a pre-GATT application,

(ii) whether the Examiner reversibly erred in relying on the specifications of Campbell 270, 511, and 945 to interpret the coverage of "administering" as recited in their respective method claims 1, and

(iii) whether one of ordinary skill in the art would have had a reasonable expectation of success of treating ED by orally administered the specific compounds recited in method claims 1 of Campbell 270, 511, and 945.

D. Additional findings of fact

1. the Campbell patents

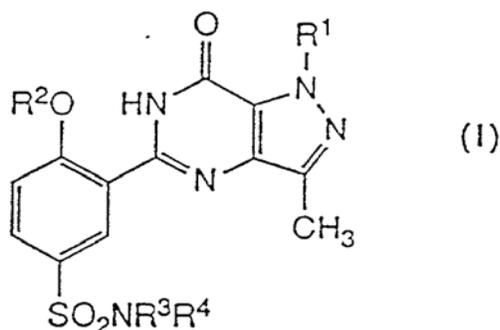
[67] Campbell 270 issued on August 8, 2000 based on application 08/836,671, which is the national phase filing under 35 U.S.C. § 371 of PCT application PCT/EP95/04065, filed October 16, 1995 (Campbell 270 front page).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[68] Campbell 511 issued March 18, 2003 based on application 09/542,489, filed April 3, 2000, which is a division of application 08/836,671, which issued as Campbell 270.

[69] Claim 1 of Campbell 270 reads

A method of treating male erectile dysfunction comprising administering to a male human in need of such treatment an effective amount of a compound of formula (I):



wherein

R¹ is methyl or ethyl;

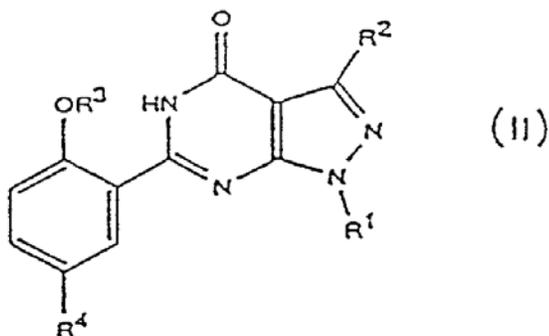
R² is ethyl or n-propyl; and

R³ and R⁴ are each independently H, or C₁-C₆ alkyl optionally substituted with C₅-C₇ cycloalkyl or with morpholino; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

[70] Claim 1 of Campbell 511 reads

A method of treating male erectile dysfunction, comprising administering, to a male human in need of said treatment an effective amount of a compound of formula (II):

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1



wherein

R¹ is C₁-C₆ alkyl;

R² is H; methyl or ethyl;

R³ is C₂-C₄ alkyl;

R⁴ is H; [sic,] C₁-C₄ alkyl optionally substituted with NR⁵R⁶, CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkenyl optionally substituted with CN, CONR⁵R⁶ or CO₂R⁷; C₂-C₄ alkanoyl optionally substituted with NR⁵R⁶; SO₂NR⁵R⁶; CONR⁵R⁶; CO₂R⁷ or halo;

R⁵ and R⁶ are each independently H or C₁-C₄ alkyl; or together with the nitrogen atom to which they are attached, form a pyrrolidino, piperidino, morpholino, 4-(NR⁸)-1-piperazinyl or 1-imidazolyl group wherein said group is optionally substituted with one or two C₁-C₄ alkyl groups;

R⁷ is H or C₁-C₄ alkyl; and

R⁸ is H; C₁-C₃ alkyl or (hydroxy)C₂-C₃ alkyl; or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

[71] According to Campbell 270 and 511, the compounds of claim 1 may be administered orally and have a preferred dosage for a typical man

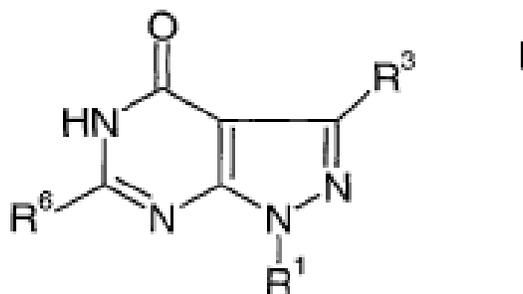
Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

of 5 to 75 mg tid (Campbell 270 1:66-67, 7:25-26; Campbell 511 2:1-2, 7:54-55).

[72] Campbell 945 issued December 2, 2003 based on application 09/880,141 which is the national phase filing under 35 U.S.C. § 371 of PCT application PCT/EP95/04066, filed October 16, 1995 (Campbell 945 front page).

[73] Claim 1 of Campbell 945 reads

A method of treating erectile dysfunction in a male animal, comprising administering to an animal in need of said treatment an effective amount of a compound of the Formula I:



wherein:

R¹ is a hydrogen, alkyl, cycloalkyl, cycloalkyl substituted by alkyl or hydroxyl; 2- or 3 tetrahydrofuranyl, 3-tetrahydrothienyl 1,1-dioxide, cycloalkylalkyl, carboxyalkyl, carbo-lower-alkoxy-alkyl, dialkylaminoalkyl, phenyl-lower-alkyl, phenyl-lower-alkyl in which the phenyl ring is substituted in the 2,3, or 4-position by one or two substituents, the same or different, selected from the group consisting of amino, halogen, alkyl, carboxyl, carbo-lower-alkoxy, carbamoyl, NHSO₂-(quinolinyl), nitro and cyano;

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

R³ is hydrogen, lower-alkyl, phenyl-lower-alkyl, lower-alkoxyphenyl-lower-alkyl, dilower-alkoxyphenyl-lower-alkyl, pyridyl-lower-alkyl, cycloalkyl-lower-alkyl, phenylamino, dialkylamino, halogen, trifluoromethyl, lower-alkylthio, cyano or nitro; and

R⁶ is a five or six membered heterocyclic ring having from one to two nitrogen atoms, or a nine or ten membered bicyclic ring having from one to two nitrogen atoms, or optionally substituted at any available carbon atom by one or two substituents, the same or different, selected from the group consisting of lower-alkyl, halogen, lower-alkoxy, cycloalkyloxy, 4-morpholinyl-lower-alkoxy-lower-alkoxy, hydroxyl, imidazolyl, oxo and 4-morpholinyl-lower-alkoxy; or at any available nitrogen atom by lower-alkyl, lower alkanoyl, or trifluoroacetyl; or a pharmaceutically acceptable acid-addition salt thereof.

[74] According to Campbell 945, the compounds of claim 1 may be administered orally or parenterally and have a preferred dosage for a typical man of 5 to 75 mg daily (Campbell 945 4:55-59, 64-67).

[75] Appellant acknowledges that "... Campbell claims broadly enough to cover oral routes of administration" (App. Br. 24).

2. the patent terms of the 012 and the Campbell patents

[76] The 012 patent under reexamination issued on October 22, 2002 based on application 08/549,792, which is the national phase filing under 35 U.S.C. § 371 of PCT application PCT/EP94/01580, filed May 13, 1994 (012 patent front page).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[77] The patent term of the 012 patent is seventeen years from date of grant on October 22, 2002, since its parent PCT application was filed before June 8, 1995, whereas the patent terms of Campbell 270, 511, and 945 are all twenty years from their PCT filing dates on October 16, 1995, which are all after June 8, 1995. 35 U.S.C. § 154(c).

3. Appellant's rebuttal evidence

a. common routes of drug administration

[78] Benet discusses common routes of drug administration, including intravenous, subcutaneous, intramuscular, and oral ingestion (Benet⁴³ 6).

[79] Other known routes of drug administration include parenteral (Husa⁴⁴ 6:41-49), intracavitary and intratumor injections (Burzynski⁴⁵ 11:35-37), and intravesical administration (Deininger⁴⁶ 5:39-42).

[80] According to Benet, oral ingestion is the most convenient, economical, and, usually, a safer route of drug administration, but the

⁴³ Leslie Z. Benet & Lewis B. Sheiner, *Pharmacokinetics: Dynamics of Drug Absorption, Distribution, and Elimination*, in *The Pharmacological Basis of Therapeutics*, ch. 1, 3-13 (Goodman & Gilman et al. eds., MacMillan Publishing Co. (7th ed. 1985). (Appeal Brief Exhibit R, (hereinafter "Benet").)

⁴⁴ U.S. Patent 5,180,720, 2- And 3-Alkoxy or Hydroxy-8-Substituted-Dibenz[B,F]-[1,4]Oxazepine-10(11H)-Carboxylic Acid, Substituted Hydrazides and Methods for Treating Pain, issued 19 January 1993 to Husa et al. (Appeal Brief Exhibit T (hereinafter "Husa").)

⁴⁵ U.S. Patent 4,470,970, *Purified Antineoplaston Fractions and Methods of Treating Neoplastic Disease*, issued 11 September 1984 to Stanislaw R. Burzynski. (Appeal Brief Exhibit U (hereinafter "Burzynski").)

⁴⁶ U.S. Patent 4,119,730, *Treating Muscle Spasms*, issued 10 October 1978 to Deininger et al. (Appeal Brief Exhibit V (hereinafter "Deininger").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

pattern of drug absorption is potentially erratic and incomplete for drugs that are poorly soluble, slowly absorbed, unstable, or extensively metabolized by the liver (Benet 6-8).

[81] In contrast, Benet states that parenteral injection provides more rapid and predictable drug absorption in active form and more accurate selection of the effective dose (Benet 6).

b. causes and prior art treatment of ED

[82] According to Goldstein,⁴⁷ impotence has a diversity of possible causes, including diabetes, radical pelvic surgery, peripheral vascular disease, hypertension, hardening of the arteries, side effects from drugs, and hormonal imbalance, and a number of suggested treatments, including direct penile injection of certain vasodilators and/or adrenergic blocking agents (Goldstein 1:34-38, 44-46, 56-60; *see also* Krane⁴⁸ 1649-51 (Pathophysiology of Impotence) and 1654-56 (Therapeutic Options)).

[83] Carrier classifies the causes of impotence as (i) psychogenic, (ii) neurogenic, (iii) endocrinologic, (iv) arterial, (v) cavernosal (including neurotransmitters), and (vi) other contributing factors, including drugs

⁴⁷ U.S. Patent 4,931,445, *Agents for Treatment of Male Impotence*, issued 5 June 1990 to Goldstein et al. (Appeal Brief Exhibit S (hereinafter "Goldstein").)

⁴⁸ Krane et al., *Medical Progress: Impotence*, 321 *New Eng. J. Med.* 1648-58 (1989). (Appeal Brief Exhibit W (hereinafter "Krane").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

(most commonly antihypertensive agents), Peyronie's disease, and diabetes (Carrier⁴⁹ 468-476).

[84] Carrier describes (Carrier 468),

[p]enile erection [as] a complex neurovascular phenomenon involving not only the coordination of three hemodynamic events (increased arterial flow, sinusoidal smooth muscle relaxation, and decreased venous drainage) but also the interaction of nerves, neurotransmitters, striated and smooth muscle, and the tunica albuginea. . . . [N]itric oxide is believed to be the principal neurotransmitter in smooth muscle relaxation.

[85] According to Carrier, nitric oxide elicits smooth muscle relaxation by stimulating the formation of cGMP through activation of guanyl cyclase (Carrier 474).

[86] Carrier theorizes that "defects in neurotransmitter production, release or the presence of antagonists could cause inhibition of cavernosal smooth muscle relaxation, resulting in inhibition of erection" (Carrier 474).

[87] According to Lerner, "nitric oxide is an important factor in the modulation of corporeal smooth muscle tone" (Lerner⁵⁰ 1248).

[88] Indeed, Lerner reports that "recent findings indicated that nitrous [sic, nitric⁵¹] oxide is involved in the nonadrenergic/noncholinergic

⁴⁹ Carrier et al., *Pathophysiology of Erectile Dysfunction*, 42 *Urology* 468-481 (October 1993) (Appeal Brief Exhibit HH (hereinafter "Carrier").)

⁵⁰ Lerner et al., *A Review of Erectile Dysfunction: New Insights and More Questions*, 149 *J. Urology* 1246-55 (1993). (Appeal Brief Exhibit BB (hereinafter "Lerner").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- mediated relaxation of human corporeal smooth muscle, and suggested that defects in this pathway may cause some forms of impotence.⁶³" (Lerner 1251).
- [89] Wein warns that when considering whether a particular drug is responsible for an adverse effect on libido, erection, emission, or ejaculation, one must consider whether the disease being treated is a causative or contributory factor, the substrate with which the drug interacts, and other factors, such as age, personal history, lifestyle, and secondary drug interactions (Wein⁵² 25).
- [90] According to Weiss, sexual dysfunction is a potential side effect of antihypertensives and has been most associated with potassium-sparing diuretics, nonselective β -blockers, and centrally acting antihypertensive agents, but may also be due to underlying disease states or psychogenic factors completely unrelated to drug therapy (Weiss⁵³ 2079-81).
- [91] Goldstein discloses treating ED by oral, rectal, or parenteral administration of etoperidone (Goldstein 1:6-11; 2:60-67; 3:45-51).

⁵¹ Lerner footnote 63 cites to Raifer et al., *Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission*, 326 New Eng. J. Med. 326:90 (1992). Therefore, the recitation of "nitrous oxide" is an apparent typographical error based on the words of the sentence and the title of the cited reference.

⁵² Alan J. Wein & Keith N. Van Arsdalen, *Drug-Induced Male Sexual Dysfunction*, 15 Urologic Clinics N. Am. 23-31 (1988) (Appeal Brief Exhibit NN (hereinafter "Wein").)

⁵³ R. J. Weiss, *Effects of Antihypertensive Agents on Sexual Function*, 44 Am. Family Physician 2075-82 (1991). (Appeal Brief Exhibit PP (hereinafter "Weiss").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- [92] According to Goldstein (Goldstein 2:2:62-67),
[a]lthough oral administration of eptoperidone is a preferred route of administration, being both effective and harmless for most patients, nonetheless a parenteral method of administration, direct injection into the penis, is the most preferred route of administration
- [93] In addition to intracavernosal injection of vasoactive drugs, such as papaverine, Krane discloses oral, parenteral, and intramuscular administration of testosterone to treat ED (Krane 1654-55).
- [94] According to Krane, prostaglandin E₁, alone or in combination with papaverine and phentolamine, is a less frequently used intracavernosal agent for treating ED (Krane 1655).
- [95] According to Zentgraf, ED can be diagnosed and treated with intracavernosal injection of the opium alkaloid papaverine, alone or in combination with the α -blocker phentolamine (Zentgraf⁵⁴ 65, 71).
- [96] Specifically, Zentgraf discloses that patients with nonvascular ED usually require low doses of papaverine alone or in combination with phentolamine, whereas arterial ED requires a higher dosage, and venous ED fails to respond at even higher doses (Zentgraf 71).
- [97] However, Zentgraf cautions that possible localized side effects of intracavernous injection of vasoactive agents include hematomas, burning pain on injection, damage to the urethra, infection, fibrotic

⁵⁴ Zentgraf et al., *Diagnosis and Treatment of Erectile Dysfunction Using Papaverine and Phentolamine*, 43 *Urology Int'l* 65-75 (1982). (Appeal Brief Exhibit O (hereinafter "Zentgraf").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

- changes, wearing off of the effect, and "above all, prolonged erection and priapism" (Zentgraf 68).
- [98] As to possible systemic reactions, Zentgraf reports that "[v]asodilatory drugs such as papaverine and phentolamine can produce a fall in blood pressure which may result in collapse" (Zentgraf 69).
- [99] Zentgraf reports that one researcher recommended using a penis clamp after 60 mg of papaverine to prevent systemic reactions, while another researcher found no clinically significant changes in blood pressure following intracavernous injection of papaverine combined with phentolamine (Zentgraf 69, 71).
- [100] Zentgraf concludes that "[c]onsidering the local and systemic side effects following administration of papaverine, combination therapy should be preferred to render treatment as safe as possible" (Zentgraf 72).
- [101] According to Lerner, "intracavernous pharmacotherapy affects penile rigidity independent of the cause of impotence, . . ." (Lerner 1246).
- [102] In 1990, Foreman reported a lack of effective oral drug therapies for the treatment of sexual dysfunction (Foreman⁵⁵ 111) (*Accord Stief*⁵⁶ 1390).

⁵⁵ Mark M. Foreman & Joachim F. Wernicke, *Approaches for the Development of Oral Drug Therapies for Erectile Dysfunction*, 8 *Seminars in Urology* 107-112 (1990). (Appeal Brief Exhibit X (hereinafter "Foreman").)

⁵⁶ Stief et al., *The Effect of the Specific Phosphodiesterase (PDE) Inhibitors on Human and Rabbit Cavernous Tissue In Vitro and In Vivo*, 159 *J.*

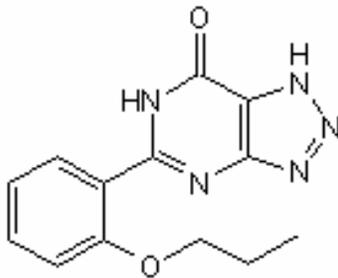
Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[103] According to Foreman, oral medications based on vascular pharmacologic approaches for treating ED "have not been attempted primarily because of the systemic side effects of these agents", e.g., phentolamine, prostaglandin E₁, and papaverine (Foreman 110).

[104] Foreman suggests creating a drug that has selectivity for penile tissue responses in order to minimize or eliminate systemic side effects (Foreman 110).

c. zaprinast

[105] Zaprinast is 2- α -propoxyphenyl-8-azapurin-6-one, i.e.,



(Trapani⁵⁷ abstract).

[106] According to Trapani, data from intravenous infusion of zaprinast, a relatively selective inhibitor of low K_m cGMP PDE, suggests that zaprinast preferentially dilates arterioles and has a less effect on the

Urology 1390-1393 (April 1998). (Appeal Brief Exhibit EE, (hereinafter "Steif").)

⁵⁷ Trapani et al., *Hemodynamic Basis for the Depressor Activity of Zaprinast, a Selective Cyclic GMP Phosphodiesterase Inhibitor*, 258 J. Pharm. and Experimental Therapeutics 269-74 (1991). (Appeal Brief Exhibit KK (hereinafter "Trapani").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

venous circulation (Trapani abstract, 271, 274) (*Accord Lee*⁵⁸ 132 (zaprinast IC₅₀ of 300 nM against 0.2 μM cGMP-PDE), 138 (zaprinast lowered or tended to lower pulmonary mean arterial pressure and systemic vascular resistance)).

d. Campbell's compounds

- [107] According to WO 6104, the compounds utilized in method claim 1 of Campbell 270 are vasodilators useful for treating cardiovascular disorders, including angina and hypertension, as well as selective inhibitors of both cGMP PDEs, i.e., calcium/calmodulin-dependent cGMP PDE (PDE_I) and calcium/calmodulin-independent cGMP PDE (PDE_V) (WO 6104 abstract, 1-2, 7-8).
- [108] According to WO 6104, "oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient . . ." (WO 6104 8-9).
- [109] According to WO 7149, the compounds utilized in method claim 1 of Campbell 511 are vasodilators useful for treating cardiovascular disorders, including angina and hypertension, as well as selective inhibitors of calcium/calmodulin-independent cGMP PDE (PDE_V) (WO 7149 abstract, 1-2, 14-15).

⁵⁸ Lee et al., *Comparative Hemodynamic and Renal Effects of the Low K_m cGMP Phosphodiesterase Inhibitors Cicletanine and Zaprinast in Anesthetized Dogs*, 23 Drug Dev. Res. 127-144 (1991). (Appeal Brief Exhibit LL (hereinafter "Lee").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

[110] According to WO 7149, "oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient . . ." (WO 71409 15).

[111] PDE catalyzes the hydrolysis and inactivation of intracellular cAMP and cGMP (Beavo II⁵⁹ 3).

[112] According to Beavo, PDE comprises five isoenzyme families, i.e., calcium/calmodulin-dependent PDE or PDE_I, cGMP stimulated PDE or PDE_{II}, cGMP-inhibited PDE or PDE_{III}, cAMP-specific PDE or PDE_{IV}, and cGMP-specific PDE or PDE_V (Beavo II 6-11).

E. Legal principles

The PTO may consider double patenting in a reexamination. *In re Lonardo*, 119 F.3d 960, 966 (Fed. Cir. 1997).

"[O]bviousness-type double patenting . . . is a judicially-created doctrine that seeks to prevent the applicant from expanding the grant of the patent right beyond the limits prescribed in Title 35." *In re Dembiczak*, 175 F.3d 994, 1001 (Fed. Cir. 1999). In other words, "[t]he rule against 'double patenting' . . . is to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." *In re Schneller*, 397 F.2d 350, 354 (CCPA 1968).

The level of ordinary skill in the art is evidenced by the references. *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978) ("the PTO usually must evaluate both the scope and content of the prior art and the level of ordinary skill

⁵⁹ Joe Beavo, *Cyclic Nucleotide Phosphodiesterases Structure, Regulation and Drug Interaction* ch. 1, 3-15 (Joe Beavo and Miles D. Houslay eds., John Wiley & Sons 1990). (Appeal Exhibit E (hereinafter "Beavo II").)

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

solely on the cold words of the literature."); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (the Board did not err in adopting the approach that the level of skill in the art was best determined by the references of record).

"It is the claims, not the specification, that define an invention. . . . And it is the claims that are compared when assessing double patenting." *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 943 (Fed. Cir. 1992). However, this does not mean that the specification may not be used at all. *In re Vogel*, 422 F.2d 438, 441-42 (CCPA 1970). Indeed, our reviewing court reaffirmed the holding in *Vogel*, stating that the disclosure may be used to learn the meaning of terms and in "interpreting the coverage of [a] claim." *Id.* at 441. It may also be used to answer the question whether the claims merely define an obvious variation of what is earlier disclosed and claimed. The court stated that the disclosure "sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether [something] has been modified in an obvious manner." *Id.* at 442. The court further stated that "use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. § 103, since only the disclosure of the invention claimed in the patent may be examined." *Id.* See also, *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1378-79 (Fed. Cir. 2008).

The *Longi* court characterized an obviousness-type double patenting rejection as "analogous" to a § 103 rejection. *In re Longi*, 759 F.2d 887, 892 n.4 (Fed. Cir. 1985). An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in deriving the claimed invention in light of the teachings of the prior art. *In re Kubin*,

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

561 F.3d 1351, 1360 (Fed. Cir. 2009); *see also In re Longi*, 759 F.2d at 896–97 (holding that a patent application was properly rejected for obviousness-type double patenting where the prior art references indicated a reasonable expectation of success). Only a reasonable expectation of success, not absolute predictability, is necessary to show obviousness. *In re Longi*, 759 F.2d at 897. Furthermore, "[w]hen chemical compounds have 'very close' structural similarities and similar utilities, without more a *prima facie* case may be made." *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985).

F. Analysis

1. issue: does patent term or patent issue date determine if a claim of a patent issued based on a post-GATT application qualify as a double patenting reference against a claim of a patent issued based on a pre-GATT application?

The rule against double patenting seeks to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about. *In re Schneller*, 397 F.2d at 354. Here, Appellant argues that Campbell 511 and 945 cannot be double patenting references because they issued after the 012 patent (App. Br. 9, 17-21; Reply Br. 1). Although Appellant has cited to several cases which refer to double patenting over a *prior patent*, none of these cases involve the unusual circumstance created here by GATT.

The patent term of the 012 patent under reexamination is seventeen years from its date of grant on October 22, 2002 (i.e., October 22, 2019), whereas the patent term of both Campbell 511 and 945 is twenty years from their October 16, 1995 filing date (i.e., October 16, 2015) (FF 77). Thus, as

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

recognized by Appellant, the "terms of the '511 and '945 reference patents are entirely subsumed by within the term of [the 012 patent]" (App. Br. 20).

Claims 1 of Campbell 511 and 945 each recite a method of treating male ED by administering a defined species of selective PDE_v inhibitor, while claim 24 of the 012 patent recites a method of treating male ED by *oral* administration of *any* selective PDE_v inhibitor (FF 70, 73; App. Br. Clm. App'x 1). According to Appellant, the 012 patent will not prevent the public from using the Campbell compounds to treat ED through non-oral routes of administration after Campbell 511 and 945 expire (App. Br. 20). However, the 012 patent will extend Appellant's right to exclude the public from practicing that portion of the Campbell 511 and 945 patent which treats male ED by oral administration of their specific selective PDE_v inhibitors from October 16, 2015 to October 22, 2019. This is precisely what obviousness-type double patenting was intended to prevent. Therefore, under the circumstances of this case, it is the patent term and not the patent issue date that determines if a claim of Campbell 511 or 945 qualifies as a double patenting reference against a claim of the 012 patent.

2. issue: did the Examiner reversibly err in relying on the specifications of Campbell 270, 511, and 945 to interpret the coverage of "administering" as recited in their respective claims 1?

As reaffirmed recently in *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d at 1378-79, the specification may be used to learn the meaning of terms and in interpreting the coverage of a claim. Thus, we discern no reversible error in the Examiner relying on the specifications of Campbell 270, 522,

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

and 945 to interpret the coverage of the term "administering" as recited in their respective claims 1.

3. issue: would one of ordinary skill in the art have had a reasonable expectation of success of treating ED by orally administered the specific compound recited in method claims 1 of Campbell 270, 511, and 945?

We begin with a discussion of the prior art as disclosed in the rebuttal evidence submitted by Appellant.

A number of routes of drug administration, including oral and parenteral, are known (FF 78, 79). Oral administration is the most convenient, economical, and usually, safest route of drug administration, albeit not without drawbacks, such as potentially erratic and incomplete absorption of poorly soluble, slowly absorbed, unstable, or extensively metabolized drugs (FF 80). Alternatively, parenteral injection provides more rapid and predictable drug absorption and more accurate selection of the effective dosage (FF 81).

It is also known that diabetes, pelvic surgery, peripheral vascular disease, hypertension, hormonal imbalances, side effects from drugs (most commonly antihypertensives), and other factors contribute to ED (FF 82-83). When considering whether a particular drug is responsible for ED, for example, one must consider whether the disease being treated is a causative or contributory factor, the substrate that the drug interacts with, and other factors, including age, personal history, lifestyle, and secondary drug interactions (FF 89-90). Thus, ED treatments vary with the causative and contributory factors of the ED and the treatment approach taken. In other words, not all ED treatments are created equal.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Effective ED therapies include direct penile (intracavernosal) injection of certain vasodilators and/or adrenergic blocking agents (FF 82, 95); oral, rectal, or parenteral administration of etoperidone (FF 91); and, oral, parenteral, or intramuscular administration of testosterone (FF 93). While "intracavernous pharmacotherapy affects penile rigidity independent of the cause of impotence" (FF 101), the possible localized side effects, including hematomas, pain, and "above all, prolonged erection and priapism" (FF 97) are undesirable to say the least. Oral medications based on vascular pharmacologic approaches for treating ED "have not been attempted primarily because of the systemic side effects of these agents" (FF 103). For example, vasoactive drugs such as papaverine and phentolamine can produce a drop in blood pressure which may result in collapse (FF 98). One researcher went so far as to recommend using a penile clamp after intracavernous injection of 60 mg papaverine to prevent systemic reactions (FF 99). Not surprisingly, the prior art suggests creating a drug that has selectivity for penile tissue responses in order to minimize or eliminate systemic side effects (FF 104).

Penile erection is a complex neurovascular phenomenon involving the coordination of three hemodynamic events (increased arterial flow, sinusoidal smooth muscle relaxation, and decreased venous drainage) as well as the interactions of nerves, neurotransmitters, striated smooth muscle, and the tunica albuginea (FF 83-84). Nitric oxide is the principal neurotransmitter modulating smooth muscle tone by way of a nonadrenergic/noncholinergic pathway (FF 84, 87, 88). Nitric oxide elicits smooth muscle relaxation by stimulating the formation of cGMP (FF 85).

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

cGMP levels are determined by two enzymes -- guanylate cyclase which stimulates its formation and PDE which facilitates its degradation (FF 85, 111). Reports suggest that defects in this pathway may cause some forms of impotence (FF 86, 88).

We now turn to the issue before us.

The Examiner maintains that oral administration would have been obvious because it is the easiest mode of drug delivery, because Korenman and the Yin Yang Huo references administered their respective ED treatments orally, and because the specifications of Campbell 270, 945, and 511 make clear that oral administration is the preferred route of administration (Ans. 8). The Examiner erred in relying on the disclosure in Campbell 270, 945, and 511 that oral administration is a preferred route of drug administration in order to conclude that it would have been obvious to orally administer a selective PDE_v inhibitor to treat ED. However, the Examiner provided two alternative reasons for concluding that oral drug administration would have been obvious -- ease of delivery and treatment of ED in the prior art by oral drug/herbal remedy administration.

Appellant argues that the prior art teaches successful treatment of ED by intracavernosal injection of a drug and that the systemic effects of orally administered antihypertensives and PDE inhibitors may cause or worsen ED (App. Br. 8, 21-27, 32-35; Reply Br. 1-7). However, the prior art submitted by Appellant, namely Goldstein and Krane (FF 91, 93), also teach successful treatment of ED by orally administering a drug. The real issue is whether one of ordinary skill in the art would have orally administered the *specific*

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

compounds recited in method claims 1 of Campbell 270, 511, and 945 with a reasonable expectation of success of treating ED.

Citing WO 6104, Appellant stated that "[i]n addition to being antihypertensives, the Campbell compounds were known PDE inhibitors, although . . . they were not know [sic] in the prior art as PDE_V selective inhibitors" (Reply Br. 6). Appellant argues that, contrary to the Patent Office's statement, WO 6104 and WO 7149 only teach that the compounds used in method claims 1 of Campbell 270 and 511, respectively, are selective for cGMP PDEs rather than cAMP PDEs, i.e., that the compounds are selective for PDE_I *or* PDE_V (App. Br. 27-28). Appellant further argues that the ordinarily skilled artisan would not have treated ED with oral administration of an antihypertensive because of known systemic effects thereof (App. Br. 32-35).

However, WO 7149 discloses that the compounds of method claim 1 in Campbell 511 are not only antihypertensives, e.g., vasodilators useful for treating hypertension, but also selective PDE_V inhibitors, i.e., inhibitors of calcium/calmodulin-independent cGMP PDE (FF 109, 111, 112). Furthermore, WO 7149 discloses that the oral dosages of the compounds of method claim 1 in Campbell 511 are generally within the range of 4-800 mg daily for an average adult (FF 108), which encompasses the "effective amount" recited in claim 1 of Campbell (5-75 mg tid or 15-255 mg daily for a typical man (FF 71)). Therefore, we agree with the Examiner that it would have been obvious to modify method claim 1 of Campbell 511 by *orally* administering the specified compounds to treat ED because WO 7149 establishes that the specified compounds of Campbell 511 are selective

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

PDE_V inhibitors suitable for oral administration in the claimed "effective amounts." Furthermore, given the very close, and in some cases overlapping, chemical structures of the compounds of Campbell 511 and Campbell 270,⁶⁰ WO 6104 and WO 7149 provide the Examiner with a reasonable basis for concluding that one of ordinary skill in the art would have orally administered the specific compound recited in method claim 1 of Campbell 270 with a reasonable expectation of success of treating ED (FF 71, 107-110; Ans. 11). *In re Grabiak*, 769 F.2d at 731.

Therefore, we sustain the rejection of claim 24 under the judicially created doctrine of obviousness-type double patenting over claim 1 of either Campbell 270 or Campbell 511.

For completeness, we note that the prior art suggests oral administration of a drug that is selective for penile tissue responses in order to minimize or eliminate systemic side effects (FF 104) and that a selective PDE_V inhibitor would prevent the degradation of cGMP formed in response to the neurotransmitter nitric oxide when eliciting smooth muscle relaxation during penile erection (FF 83-88, 111).

As to the obviousness-type double patenting rejection based on method claim 1 of Campbell 945, the Examiner has failed to provide any reasoned basis for concluding that one of ordinary skill in the art would have

⁶⁰ For example, R¹ of Campbell 270 and R² of Campbell 511 can both be methyl or ethyl, R¹ of Campbell 511 can be methyl as shown in Campbell 270, R² of Campbell 270 and R³ of Campbell 511 can both be ethyl or n-propyl, and R⁴ of Campbell 511 and -SO₂NR³R⁴ of Campbell 270 can both be -SO₂NR^{5/3}R^{6/4} where R^{3/5} and R^{4/6} are each independently H, or C₁-C₄ alkyl.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

orally administered the recited compounds of Campbell 945 claim 1 with a reasonable expectation of success of treating ED. We note that the selective PDE_v inhibitor Zaprinist and the compounds recited in claims 1 of Campbell 270 and 511 are all three ring structures (FFs 69, 70, 105), while the compounds recited in claim 1 of Campbell 945 are two ring structures (FF 73). In addition, the preferred adult dosage of the compounds recited in claim 1 of Campbell 945 is one third that of the compounds recited in claims 1 of Campbell 270 and 511. Therefore, we reverse the rejection of claim 24 under the judicially created doctrine of obviousness-type double patenting over claim 1 of Campbell 945.

G. Conclusion

We sustain the rejection of claim 24 under the judicially created doctrine of obviousness-type double patenting over claim 1 of either Campbell 270 or Campbell 511, but reverse the rejection over claim 1 of Campbell 945.

Under the circumstances of this case, it is the patent term and not the patent issue date that determines if a claim of Campbell 511 or 945 qualify as double patenting references against a claim of 012. The Examiner did not err in relying on the specifications of Campbell 270, 511, and 945 to interpret the coverage of the term "administering" as recited in their respective claims 1. Based upon a preponderance of the evidence of record, one of ordinary skill in the art would have had a reasonable expectation of success of treating ED by orally administered the specific compound recited in method claims 1 of either Campbell 270 or 511, but not Campbell 945.

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

IV. Order

Upon consideration of the record, and for the reasons given, it is ORDERED that the decision of the Examiner to reject claim 24 as unpatentable under 35 U.S.C. § 102(b) as anticipated by Korenman is REVERSED;

FURTHER ORDERED that the decision of the Examiner to reject claim 24 as unpatentable under 35 U.S.C. § 102(b) as anticipated by any of Bensky, Hsu, Chang, and Yin is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner to reject claim 24 as unpatentable under the judicially created doctrine of obviousness-type double patenting over claim 1 of Campbell 945 is REVERSED;

FURTHER ORDERED that the decision of the Examiner to reject claim 24 as unpatentable under the judicially created doctrine of obviousness-type double patenting over claim 1 of either Campbell 270 or Campbell 511 is AFFIRMED; and,

FURTHER ORDERED that no time periods for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

KMF

Appeal 2009-004106
Reexamination Control Nos. 90/006,617;
90/006,886; 90/007,110; and 90/007,478
Patent 6,469,012 B1

Patent Owner:

Gregg C. Benson
PFIZER, INC.
Patent Department MS 4159
Eastern Point Road
Groton, CT 06340

1st Third Party Requester:

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
1300 I Street, N.W.
Suite 700
Washington, DC 20005

2nd Third Party Requester:

Larry S. Nixon
NIXON & VANDERHYE, P.C.
901 North Glebe Road
11th Floor
Arlington, VA 22203

3rd Third Party Requester:

Douglas K. Norman
ELI LILLY AND COMPANY
P.O. Box 6288
Indianapolis, MN 46206-6288