Federal Court Cour fédérale

Date: 20150202

Docket: T-298-13

Citation: 2015 FC 125

Ottawa, Ontario, February 2, 2015

PRESENT: The Honourable Mr. Justice de Montigny

BETWEEN:

ELI LILLY CANADA INC.

Applicant

and

MYLAN PHARMACEUTICALS ULC AND THE MINISTER OF HEALTH

Respondents

and

ICOS CORPORATION

Respondent Patentee

JUDGMENT AND REASONS

[1] This is an application by Eli Lilly Canada Inc. (Lilly) for an order under section 55.2(4) of the *Patent Act*, RSC 1985, c P-4, and section 6 of the *Patented Medicines (Notice of*

Compliance) Regulations, SOR/93-133, to prohibit the issuance of a Notice of Compliance (NOC) to Mylan Pharmaceuticals ULC (Mylan) for a generic version of tadalafil, sold by Lilly under the brand name CIALIS, until after the expiration of the Canadian Patent 2,371,684 (the '684 Patent). The '684 Patent is directed to a unit dosage form of tadalafil, including the use of that unit dosage form for the treatment of erectile dysfunction (ED).

[2] Mylan, on the other hand, submits that the '684 Patent is a selection patent and that its utility was neither demonstrated nor soundly predicted at the filing date, and that the utility is not met today. In the alternative, if the '684 Patent is not interpreted as a selection patent, it is argued that the claimed invention is anticipated by the Canadian Patent No. 2,226,784 (the '784 Patent) and is clearly obvious.

[3] For the reasons that follow, I have come to the conclusion that the Applicant has not met its burden of proof on the balance of probabilities to establish for the purpose of these proceedings that the '684 Patent is valid, and that an order prohibiting the Minister of Health from issuing an NOC should issue.

I. Background

[4] The compound tadalafil was claimed and disclosed in Canadian Patent No. 2,181,377 (the '377 Patent), which was published in July 1995. The use of tadalafil for the treatment of ED was claimed and disclosed in the '784 Patent, which was published in February 1997 and was the subject of another application to prohibit the issuance of an NOC to Mylan (see 2015 FC 17).

The ‘784 Patent disclosed that oral administration was the preferred route, and it disclosed unit doses of tadalafil from 0.2 to 400 mg.

[5] Another compound, sildenafil, had previously been developed for the treatment of ED. Sildenafil was known to treat ED by the same mechanism of action as tadalafil – inhibition of the PDE5 enzyme. The mechanics of ED and of PDE5 inhibitors are described in my previous decision dealing with the ‘784 Patent.

[6] By the time the ‘684 Patent was filed, sildenafil had been approved by regulatory authorities for the treatment of ED. Sildenafil was marketed in doses of 25 mg, 50 mg, and 100 mg. VIAGRA (the commercial name under which sildenafil was sold) had shortcomings, including high rates of flushing, blue-green vision and an interaction with nitrates that caused a drastic drop in blood pressure over nitrates alone (Pullman affidavit, paras 70-72, 78, Application Record (AR) Vol 2, pp 358-359). Indeed, sildenafil was marketed with a labeled contraindication for concomitant administration with nitrates.

[7] Sildenafil also had other, less serious shortcomings, as it was sometimes associated with such adverse events as headache, back pain, rhinitis and conjunctivitis. The medication also had to be taken within one hour of the anticipated sexual activity (Goldstein affidavit, para 107, AR Vol 2, pp 257-258). Finally, it was known that sildenafil should be taken on an empty stomach, because a high-fat meal can interfere with absorption (Goldstein affidavit, para 331, AR Vol 3, p 515). For those reasons, a great amount of research started into other PDE5 inhibitors, and even other neurotransmitters.

[8] Tadalafil was such a potent, selective and reversible PDE5 inhibitor. Early studies with tadalafil used large doses, including doses up to 100 mg. Studies testing the safety of tadalafil went up to 500 mg doses. The selection of these large doses was based on the only approved PDE5 inhibitor known at the time, sildenafil, and the similar potencies of the two compounds. It was also known that with sildenafil, the effectiveness of the compound was proportional to the dose.

[9] One of the earliest efficacy studies, using protocol LVBI, used a 100 mg dose of tadalafil. The objective of that study was to evaluate the tolerability, safety and efficacy of a single dose of 100 mg of tadalafil compared to placebo in a three-center, two-by-two crossover study in patients with ED. The study concluded that tadalafil significantly enhanced erectile function in response to visual sexual stimulation in patients with mild to moderate ED at single doses of 100 mg. This was the very first proof of concept study in patients to show evidence of activity (Pullman affidavit, para 31, AR Vol 3, p 543 and Exh "B", Vol 15, p 3485; Pullman cross-examination, pp 47-49, AR Vol 28, p 6413-6415).

[10] Lilly chose to use the 100 mg dose for tadalafil because they were expecting its response to be similar to sildenafil, since the two compounds have more or less the same potency. Potency is described by the use of a test to determine the $IC_{50,}$ or the concentration of a test drug that is necessary to inhibit 50% of the enzyme activity. The most common dose for sildenafil is a 100 mg dose, although the typical starting dose is 50 mg. Dr. Pullman's choice of a starting dose for tadalafil was also informed by people with experience in pharmacokinetics who would have looked at scaling from animals to humans (Goldstein affidavit, paras 269-270, 370, AR Vol 3, pp

505, 524; Pullman affidavit, para 29, AR Vol 2, p 350). Mylan agrees that to determine the starting dose, "[t]he skilled person would also be guided by looking at dosage levels for similar products, such as sildenafil, that were known to treat the same condition by the same mechanism of action" (Notice of Allegation (NOA), Potter affidavit, Exh "B", AR Vol 1, p 111).

[11] Another study conducted between November 1997 and April 1998, referred to as LVBH, showed that the quantity of tadalafil absorbed appeared to increase proportionally with doses from 10 mg to 50 mg. However, in the majority of subjects, a less than dose proportional increase in area under the curve (AUC) was observed when the dose was increased from 50 mg to 100 mg. AUC is used to describe the total amount of drug absorbed by the body. This was true for both single dose and multi-dose administration, and all doses were safe and generally well tolerated. This study taught that a lower daily dose of tadalafil can provide a constant therapeutic effect without reaching a toxic level (see Pullman affidavit, paras 35-39, AR Vol 3, p 544 and Exh "C", AR Vol 15, p 3538).

[12] In summary, Phase II clinical trials and the pharmacokinetic profile surprisingly started to show that, despite it being equipotent with sildenafil, tadalafil did not need higher doses, and using more drug made it less reliable. This was apparently the genesis and the basis for Dr. Pullman's hypothesis that with tadalafil, unlike sildenafil, less is more. It was believed that 50 mg and 100 mg were not optimal dosage strengths and that lower doses may be more desirable (Pullman affidavit, paras 44-47, AR Vol 2, pp 352-353). In later testing, it was decided to use even lower doses of tadalafil and to look at their safety and efficacy. These are described as Examples 5, 6 and 7 in the '684 Patent, to which I will now turn.

II. The '684 Patent

[13] The '684 Patent is entitled "Compositions Comprising Phosphodiesterase Inhibitors for the Treatment of Sexual Dysfunction". It was filed in Canada on April 26, 2000 and has a priority date of April 30, 1999. There are two inventors, one of whom is a witness in this proceeding, Dr. William Pullman.

[14] The '684 Patent is directed to a unit dosage form of tadalafil, including the use of that unit dosage form for the treatment of ED. The very first paragraph of the Patent states that the unit dosage form herein described provides a benefit in therapeutic areas where inhibition of PDE5 is desired, "with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes".

[15] The Background of the Invention section explains that despite its commercial success, sildenafil has "fallen short" due to its significant adverse side effects. The patentee focuses on three side effects: "Adverse side effects limit the use of sildenafil in patients suffering from vision abnormalities, hypertension, and, most significantly, by individuals who use organic nitrates" ('684 Patent, pp 2-3).

[16] The Patent goes on to describe the shortcoming of sildenafil for patients taking nitrates, because of the significant drop in blood pressure that can result from the interaction of these two drugs. For that reason, "the package label for sildenafil provides strict contraindications against its use in combination with organic nitrates (…) and other nitric oxide donors in any form, either

regularly or intermittently, because sildenafil potentiates the hypotensive effects of nitrates" ('684 Patent, p 3).

[17] The Patent then goes on to state that the patent applicants have discovered that tadalafil "can be administered in a unit dose that provides an effective treatment without the side effects associated" with sildenafil ('684 Patent, p 4). The penultimate paragraph of the Background section states:

> Significantly, applicants' clinical studies also reveal that an effective product having a reduced tendency to cause flushing in susceptible individuals can be provided. Most unexpectedly, the product also can be administered with clinically insignificant side effects associated with the combined effects of a PDE5 inhibitor and an organic nitrate. Thus, the contraindication once believed necessary for a product containing a PDE5 inhibitor is unnecessary when Compound (I) [tadalafil] is administered as a unit dose of about 1 to about 20 mg, as disclosed herein. Thus, the present invention provides an effective therapy for sexual dysfunction in individuals who previously were untreatable or suffered from unacceptable side effects, including individuals having cardiovascular disease, such as in individuals requiring nitrate therapy, having suffered a myocardial infarction more than three months before the onset of sexual dysfunction therapy, and suffering from class 1 congestive heart failure, or individuals suffering from vision abnormalities.
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> ('684 Patent, p 4)

[18] In the Summary of the Invention section, the invention is again described as a "pharmaceutical dosage form", comprising about 1 to about 20 mg of tadalafil, in a unit dosage form suitable for oral administration. The term "oral dosage form" is described a little bit further as being used in a general sense to reference pharmaceutical products administered orally (including liquid formulations, tablets, capsules and gelcaps) ('684 Patent, p 7). The following

paragraph is the subject of conflicting interpretations by the parties and is therefore worth reproducing:

> The present invention further provides a method of treating conditions where inhibition of PDE5 is desired, which comprises administering to a patient in need thereof an oral dosage form containing about 1 to about 20 mg of a selective PDE5 inhibitor, as needed, up to a total dose of 20 mg per day. The invention further provides the use of an oral dosage form comprising a selective PDE5 inhibitor at a dosage of about 1 to about 20 mg for the treatment of sexual dysfunction.
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> ('684 Patent, p 5)

[19] After providing the structural formula of tadalafil, the Patent defines a number of terms and abbreviations (see '684 Patent, p 7). The term "vision abnormalities" is defined as an "abnormal vision characterized by blue-green vision believed to be caused by PDE6 inhibition", while the term "flushing" means "an episodic redness of the face and neck attributed to vasodilation caused by ingestion of a drug, usually accompanied by a feeling of warmth over the face and neck and sometimes accompanied by perspiration". The "package insert" is also described as the "information accompanying the product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding the use of the product".

[20] Another paragraph that has been the subject of much discussion and to which I will deal with in the analysis portion of these reasons relates to the package insert:

> Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from a retinal disease, for example, diabetic retinopathy or retinitis pigmentosa, or in patients who are using organic nitrates. Thus, the package insert preferably is free of contraindications associated with these conditions, and particularly the administration of the dosage form

> with an organic nitrate. More preferably, the package insert also is free of any cautions or warnings both associated with retinal diseases, particularly retinitis pigmentosa, and associated with individuals prone to vision abnormalities. Preferably, the package insert also reports incidences of flushing below 2%, preferably below 1%, and most preferably below 0.5%, of the patients administered the dosage form. The incidence rate of flushing demonstrates marked improvement over prior pharmaceutical products containing a PDE5 inhibitor.
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> ('684 Patent, pp 8-9)

[21] The Detailed Description then discusses the container used in the article of manufacture, the oral dosage forms and the excipients, none of which is at issue in the present application. The next section, dealing with Preparations, is not at issue either in this application.

[22] The first four examples set out in the '684 Patent relate to different formulations containing tadalafil. More relevant for the purposes of this application are Examples 5, 6 and 7, which relate to testing of tadalafil. I will now summarize each of them on the basis of what is disclosed in the Patent. Of course, the teachings of these clinical trials are the subject of strong disagreement between the parties, and I will address these issues in my analysis.

[23] The first clinical study, referred to as LVAB, describes a randomized, double-blind, placebo-controlled, two-way crossover design clinical pharmacology drug interaction study that evaluated the hemodynamic effects of concomitant administration of tadalafil and short-acting nitrates on healthy male volunteers. It is the only study prior to the filing date assessing the interaction of tadalafil and nitrates, and it is the subject of Example 5 in the '684 Patent.

[24] The subjects received either 10 mg tadalafil or placebo daily for seven days. On the sixth or seventh day, the subjects received sublingual nitroglycerin while lying on their back on a tilt table. The nitroglycerin was administered 3 hours after tadalafil dosing, and all subjects kept the nitroglycerin tablet under their tongue until it completely dissolved.

[25] According to the '684 Patent, this clinical study showed that tadalafil was well tolerated and that there were no serious adverse events. Tadalafil demonstrated minimal, if any, effect on mean systolic blood pressure, and mean maximal nitroglycerin-induced decrease in systolic blood pressure.

[26] Example 6 describes two randomized, double-blinded placebo-controlled clinical studies of tadalafil for the treatment of ED (these studies are referred to as LVBG and LVBF). Doses from 5 to 20 mg of tadalafil were efficacious and demonstrated less than 1% flushing and no reports of vision abnormalities. The '684 Patent describes how tadalafil significantly improved the percentage of successful intercourse attempts as measured by Questions 3 and 4 of the International Index of Erectile Function (IIEF). The IIEF was developed to create a brief, reliable, self-administered measure of erectile function that is cross-culturally valid and psychometrically sound, with the sensitivity and specificity for detecting treatment-related changes in patients with ED. Although the IIEF contains 15 questions, two key questions are evaluated for many studies: question 3 measures the ability to penetrate their partner, and question 4 measures the ability to maintain an erection after penetrating their partner.

[27] Example 7 of the '684 Patent describes a randomized, double-blind, placebo-controlled study of tadalafil administered on demand to patients with male ED: this is the LVAC study. "On demand" is defined as intermittent administration of tadalafil prior to the expected sexual activity. Example 7 concludes that this study demonstrated that all four doses of tadalafil, namely 2 mg, 5 mg, 10 mg, and 25 mg, taken on demand, produced significant improvement, relative to placebo, in the sexual performance of men with ED as assessed by the IIEF. The Patent states that treatment with nitrates was not allowed in this study.

[28] Following Example 7, the '684 Patent includes two tables of combined results from clinical studies – a table reporting efficacy results (p 31) and a table reporting side effects (p 32). The Patent does not indicate which clinical studies are included in these combined results, although Dr. Pullman indicates in his affidavit that the tables use the cumulative responses from Examples 6 and 7 (Pullman affidavit, para 71, AR Vol 2, p 358). It appears from the first table that all unit doses of 2, 5, 10, 25, 50 and 100 mg of tadalafil show statistically significant change from placebo, on the basis of the IIEF erectile function domain previously referred to. This first table also appears to demonstrate the plateau effect described in some of Lilly's earlier studies, where there is a sharp rise in efficacy at low doses but efficacy levels off between the 10 and 25 mg doses.

[29] According to the Patent, the second table shows an increase in adverse events at 25 mg through 100 mg unit doses, without the corresponding increase in efficacy as shown in the previous table. It is also worth mentioning that the incidences of flushing and vision

abnormalities were very low. There is, however, no direct comparative testing between tadalafil and sildenafil in this table, nor anywhere else in the Patent.

[30] Before stating the claims of the Patent, we find the following paragraph:

> In accordance with the present invention, a unit dose of about 1 to about 20 mg, preferably about 2 to about 20 mg, more preferably about 5 to about 20 mg, and most preferably about 5 to about 15 mg, of Compound (I) [tadalafil], administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED and minimizes or eliminates the occurrence of adverse side effects. Importantly, no vision abnormalities were reported and flushing was essentially eliminated. Surprisingly, in addition to treating ED, with at about 1 to about 20 mg unit dose Compound (I), with a minimum of adverse side effects, individuals undergoing nitrate therapy also can be treated for ED by the method and composition of the present invention.
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> ('684 Patent, pp 32-33)

[31] Claims 1 to 8 claim pharmaceutical unit dosage forms and claims 9 to 18 claim use of a unit dose. Claims 1 to 6 claim a pharmaceutical unit dosage form suitable for oral administration, and differ only by the amount of tadalafil they contain. They are not restricted to any particular use. The different dosage ranges or specific dosages are the following: 1 to 20 mg (claim 1); 2 to 20 mg (claim 2); 5 to 20 mg (claim 3); 2.5 mg (claim 4); 5 mg (claim 5); and 10 mg (claim 6). Claim 9 recites a dosage form of any one of claims 1 through 6 for use in treating sexual dysfunction. Claim 10 recites a dosage form of claim 9 wherein the sexual dysfunction is male ED. All of these claims are reproduced in the Annex of these reasons.

[32] Lilly does not assert claim 1, because there is no efficacy data to support it. Lilly therefore asserts claims 2 to 6, 9 and 10. Indeed, claim 10 depends on claim 9, which itself depends on claims 2 to 6.

III. The evidence

A. Lilly's witnesses

[33] Lilly has put forward one fact witness, Dr. William Pullman, who is also one of the named inventors of the '684 Patent. Lilly has also offered two expert witnesses, Dr. Gerald Brock and Dr. Irwin Goldstein.

Dr. William Pullman

[34] Dr. Pullman is a clinical pharmacologist. He joined Pfizer in 1992, where he was responsible for the Phase II trials and the authorship of the Phase III development plan in the VIAGRA sildenafil team. Following his time at Pfizer, Dr. Pullman began to work with Eli Lilly Australia in 1995, and then moved to the United States to begin work with Eli Lilly & Co. as head of Clinical Pharmacology. As a result of his previous experience with VIAGRA sildenafil, he assisted in securing an in-license opportunity with ICOS Corporation, and became the Director, Medical Affairs, for the Lilly-ICOS joint venture. His affidavit reviews his involvement with Lilly's clinical trials of tadalafil. He presents a number of the clinical trials related to dosing levels, some of which form the examples to the '684 Patent, and the implications for tadalafil's side effects. Because he had determined that tadalafil was effective at lower doses, Dr. Pullman saw its potential to avoid some of sildenafil's side effects, including

possibly nitrate interaction. The affidavit describes the results of the trials with respect to side effects.

[35] In his affidavit, he states that he was aware of all of the clinical data up to and including the filing of the New Drug Application (NDA) with the US Food and Drug Administration (FDA) in 2001 (Pullman affidavit, para 14, AR Vol 2, p 347). On cross-examination, however, he recognized that he had no personal knowledge of the initial clinical testing of tadalafil, including studies testing multiple doses of tadalafil (Pullman cross-examination, pp 215-216, AR Vol 28, pp 6581-6582). This clinical testing was performed by two different companies (GlaxoSmithKline (GSK) and ICOS) prior to the involvement of Lilly. Dr. Pullman learned of these studies and was aware of their general findings in the context of the due diligence work that he oversaw before Lilly decided to enter into a joint venture with ICOS. While it is no doubt true that Lilly could have put forward a fact witness with knowledge of GSK or ICOS clinical testing, it is of no significance in the context of the present application and Mylan has certainly not impugned Dr. Pullman's credibility with respect to this particular aspect of his testimony.

[36] Of more concern is the fact that Dr. Pullman professed to know nothing of two nitrate studies (LVBY and LVCM) that were conducted by Lilly prior to filing the NDA and that were apparently provided to the FDA. On cross-examination, Dr. Pullman stated that he was only aware of the nitrate study (LVAB) that is the subject of Example 5 in the '684 Patent (Pullman cross-examination, pp 202-206, AR Vol 28, pp 6568-6572). This lack of knowledge, combined with the refusal by Lilly's counsel of all questions relating to the FDA, despite evidence that Dr. Pullman met with the FDA prior to filing the '684 Patent to discuss the LVAB study on August

30, 1999, most certainly undermines Dr. Pullman's evidence with respect to post-filing issues such as the sequence of events leading to tadalafil's nitrate contraindication. Little weight will therefore be given to his view that a "class contraindication" of PDE5 inhibitors with nitrates emerged within the FDA in view of the experience with VIAGRA (see Pullman affidavit, para 82, AR Vol 2, p 360).

Dr. Gerald B. Brock

[37] Dr. Brock is a urologist, specialized in erectile dysfunction. He was involved in clinical trials of sildenafil and tadalafil, among other drugs. He consults for many pharmaceutical companies, including Lilly. His evidence consists of an affidavit and cross-examination, with exhibits.

[38] After providing background information on ED and the state of the art up to 1995, essentially repeating his affidavit in Court file T-296-13, he then gives his construction of claim 10, the claim he has been asked to limit himself to, as it is dependent upon claim 9, itself dependent upon claims 2-6. He construes claim 10 as having the following essential elements:

a. a pharmaceutical unit dosage form;

b. comprising an amount of tadalafil;

c. which amount of tadalafil is selected from the following list

i. about 2 to about 20 mg;

ii. about 5 to about 20 mg;

iii. about 2.5 mg;

iv. about 5 mg; and

v. about 10 mg;

d. for use in treating male erectile dysfunction;

e. in a patient where inhibition of PDE5 provides a benefit; and

f. said unit dosage form being suitable for oral administration.

(Brock affidavit, para 84, AR Vol 2, p 194)

[39] Relying on the specification of the '684 Patent, he construes the term "pharmaceutical unit dosage form" as being one that is used to a maximum daily dose of 20 mg per day. Although the Patent does have a maximum daily dose, there is no requirement that the medication be taken daily, or on demand.

[40] Opining on anticipation, he states that the '784 Patent does not describe efficacy at low doses and a daily dose maximum of 20 mg to avoid or minimize certain side effects, and finds therefore that the invention of claim 10 of the '684 Patent is not disclosed and enabled in the '784 Patent. He states at paragraph 94 of his affidavit:

> While the '784 Patent describes an efficacious product across the wide range of dosages, the '684 Patent describes the surprising efficacy at the low doses and the reduced side effects, such as flushing and vision disturbances for example. While this purpose behind the invention of the '684 Patent is not set out in the claims, including claim 10, it is the rationale for the dose limitations discussed above. Therefore, it is not surprising that the '784 Application does not disclose these dose limitations because the issue of reducing these side effects is not discussed in the '784 Application either.
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> (Brock affidavit, para 94, AR Vol 2, p 196)

[41] With respect to obviousness, he first reviews and comments on the prior art cited by Mylan. On that basis, he finds that the prior art suggests a dosage range only as narrow as 0.2 to 400 mg, instead of a maximum daily dose of 20 mg as set out in claim 10. The concept that the limitation of the doses as is done in claim 10 would provide the benefit that it does would not have been considered by a person of skill in the art (PSA). As the only approved oral ED medication, sildenafil would have been used to help guide the research with future medications. Since sildenafil was prescribed with 25, 50 and 100 mg doses, with the 100 mg dose being the most common, and the normal starting dose being 50 mg, it would be expected that other PDE5 inhibitors with a similar potency would be dosed the same. In his view, there was no motivation to limit doses as was done in claim 10.

[42] Moreover, a person of skill in the art would have considered flushing to be an inherent side effect of PDE5 inhibition at the time, and would not have expected to see the lack of flushing with tadalafil as reported on the table at page 32 of the '684 Patent. Similarly, it was not obvious that tadalafil could minimize or eliminate abnormal vision, as it was theorized that sildenafil's relative lack of selectivity for PDE6 was the basis for abnormalities related to colour vision. The finding that tadalafil did not demonstrate any vision abnormalities at any dose was not only positive but was not obvious because vision abnormalities were viewed at the time as an uncommon, transient effect; Lilly had identified and avoided a problem that did not yet form a part of the prior art.

[43] Finally, Dr. Brock expresses the view that the utility of the invention as claimed in claim 10 was demonstrated by the Canadian filing date. That view is based on his review of the results

in the ‘684 Patent and of the clinical trial reports as appended to the affidavit of Dr. Pullman. In his view, the purpose of the invention (which is the claimed pharmaceutical unit dosage form) is to minimize or eliminate the adverse side effects known to occur with the administration of sildenafil while still providing an effective dose. These side effects are characterized to include facial flushing, vision abnormalities and a significant decrease in blood pressure when tadalafil is administered with organic nitrates. The promise would not be interpreted as a promise to minimize or eliminate all side effects, in his view, since a person skilled in the art would understand that this is not possible when using a drug that inhibits PDE5.

[44] On the basis of clinical trials, Dr. Brock states that Lilly had enough information to demonstrate that oral doses of tadalafil of about 2 mg to about 20 mg would be efficacious to treat ED in men, and that these lower doses would also result in lower incidences of flushing and vision abnormalities, and lead to better results in subjects also taking nitrates as compared to sildenafil (Brock affidavit, para 211, AR Vol 2, p 225). In Dr. Brock’s opinion, the ‘684 Patent does not promise to be “safer” than sildenafil, but promises only the efficacy at a very low dose together with the lower incidences of adverse effects that these lower doses provide (Brock affidavit, para 216, AR Vol 2, p 226). The reduction of flushing and colour abnormalities is clearly demonstrated by the clinical trials when compared to the prior art for sildenafil, in Dr. Brock’s view. As for the administration of tadalafil with nitrates, Dr. Brock only comments that “tadalafil did not cause the same drop in blood pressure when administered with nitrates that was seen with sildenafil”, as shown by Example 5 of the Patent (Brock affidavit, para 220, AR Vol 2, p 227).

[45] Mylan argued that Dr. Brock has extensive ties to Lilly, having received payment from Lilly for consulting services and providing lectures to physicians, and had access to inside information prior to the filing date. Indeed, Dr. Brock confirmed on cross-examination that he sat on the Lilly-ICOS advisory board at the relevant dates for the '684 Patent (1999-2000), and that he was a principal investigator on the clinical trial (LVAC) that is included as Example 7 of the '684 Patent. I do not think, however, that this is sufficient to diminish the weight of his evidence.

[46] First of all, most experts in the field are consulted and remunerated by the industry, and this does not in and of itself disqualify them as experts. Dr. Brock has read and understood the Code of Conduct for Expert Witnesses, and has agreed to be bound by it. As for the insight he would have gained into the strengths and weaknesses of tadalafil as a result of sitting on the advisory board and acting as an investigator on clinical trials of tadalafil, I accept his statement on cross-examination that a study investigator only sees a very small part of the whole study, and that it doesn't make a huge difference in terms of one's insight into the actual study (Brock cross-examination, pp 243-245, AR Vol 23, pp 5100-5102). I also note that Dr. Brock was not specifically asked how the information he may have gained as a result of sitting on the advisory board may have had an impact on the opinion that he gave. For all of the above reasons, plus the fact that Dr. Brock has been accepted as a qualified expert in other cases before this Court (most notably in the case dealing with the application from Pfizer to seek an order prohibiting the Minister from issuing an NOC for sildenafil: *Pfizer Canada v Apotex*, 2007 FC 971), I would reject Mylan's attempt to impugn the credibility of Dr. Brock.

Dr. Irwin Goldstein

[47] Dr. Goldstein is a urologist, specialized in sexual dysfunction, and is a Clinical Professor of Surgery at the University of California – San Diego. Like Dr. Brock, he has been involved in clinical research dealing with sildenafil and tadalafil, and has appeared as an expert witness for Pfizer in the sildenafil litigation mentioned in the previous paragraph of these reasons.

[48] In his 116-page affidavit, Dr. Goldstein reviews the state of the art and gives his opinion on every issue in dispute. He gives a basic science tutorial and describes ED treatment before and after 1995; that part of his affidavit is mainly a repetition of the one he gave in Court file T-296-13. He then reviews the common general knowledge in April 1999 (the relevant date for considering obviousness) and April 2000 (the relevant date for utility). He discusses the breakthrough occasioned by sildenafil, as it was previously thought that an oral medication could not be used to treat erectile dysfunction, and of the great amount of research that followed because of the characteristics that still made sildenafil less than ideal. He then reviews Mylan's prior art, giving more detail on vision abnormalities and flushing. He is of the view that in April 1999, the larger differential in IC_{50} between PDE5 and PDE6 for tadalafil versus sildenafil could have led a person skilled in the art to hypothesize that there could be less effect of tadalafil with respect to colour vision abnormalities, but that any difference between the two drugs would need to be confirmed in human studies in light of all the conflicting evidence. The same is true for flushing, which was thought to be inherent to PDE5 inhibition but was less of an issue with tadalafil.

[49] Dr. Goldstein subsequently reviews Mylan's documents on the art after 2000, as well as Lilly's confidential clinical trial results that were obtained before the filing of the '684 Patent (these are the studies that were summarized above, referred to as LVBI, LVBH, LVBG, LVBF, LVAC, LVAB and LVAI, as well as other studies that are not relevant for the purpose of the present application). Dr. Goldstein then construes claims 2-6, 9 and 10, including the term "unit dosage form", in much the same way as Dr. Brock.

[50] Dealing with anticipation, Dr. Goldstein opines that the dosage strength of 2 to 20 mg or any subset within that range, and the daily dose maximum of 20 mg, are essential elements of claim 10 of the '684 Patent and would not be found to be disclosed in the '784 Patent by a person skilled in the art. In the eventuality that disclosure would be found, he further states that there are no instructions in the '784 Patent that a person skilled in the art could follow to arrive at the claimed subject matter of claim 10 of the '684 Patent:

> A POSITA could not arrive at the dosage strengths covered by claim 10 of the '684 Patent by using the teachings of PA3 ['784 Patent] and conducting routine work that is not prolonged or arduous. This work would not be routine and it would necessarily be prolonged and arduous. This information could only be determined by designing and performing complex experiments, as Lilly had to do, reviewing those results, and then repeating the cycle taking into account what has been learned. Lilly spent years performing clinical trials across continents and in hundreds if not thousands of patients. At paragraph 270 I further describe how Lilly's clinical trials were not simple and routine. Knowing that work has to be done is not the same as knowing how to perform the experiments, and what results those trials will provide.
>
> (Goldstein affidavit, para 359, AR Vol 2, pp 328-329)

[51] As for obviousness, Dr. Goldstein opines that a person skilled in the art would find the dose limitations of 2 to 20 mg and the daily maximum dose of 20 mg to be inventive and not

obvious. It would not have been self-evident to a person skilled in the art that such dose limitation would still be effective in treating ED and would lead to a better side effect profile than sildenafil. The driving force behind the work that led to the invention of claim 10 of the '684 Patent was the desire to obtain a product with a better side effect profile than sildenafil. Yet in April 1999, not enough was known about inhibition of the PDE family of enzymes to know that any PDE5 inhibitor could be developed with better results in respect of flushing or vision problems. According to Dr. Goldstein, the clinical trials that were developed and conducted to determine the effectiveness of low doses of tadalafil and its better side effect profile than sildenafil were not simple and routine.

[52] Dr. Goldstein then addresses Mylan's allegation that the concepts in the '684 Patent are not inventive; an argument that is no more at issue. With respect to utility, Dr. Goldstein opines that the data contained in the '684 Patent and discussed in Examples 5, 6 and 7 is sufficient without reference to the other clinical studies to conclude that the promise (which he identifies as being that the claimed unit dosage form when administered to patients for the treatment of ED will have a better side effect profile than sildenafil) is demonstrated. In this connection, he adds:

> It is true that tadalafil may not be better in a statistically significant manner for all possible side effects, including those listed in the Table on page 32 of the '684 Patent, but the inventors in my opinion definitively demonstrated that tadalafil, when administered with the dosing restrictions set out in claim 10 of the '684 Patent as I have already discussed, clearly has fewer or lower incidences of side effects in respect to the ones that the inventors focused on, namely flushing, vision abnormalities and hypotension resulting from the concomitant use with nitrates. As such, the promise of the patent is demonstrated.
>
> (Goldstein affidavit, para 379, AR Vol 2, pp 333-334)

[53] Dr. Goldstein also addresses Mylan's allegation that the utility of tadalafil was not demonstrated in the '684 Patent because comparative testing was not performed with sildenafil and no data were included on testing in patients with cardiovascular disease, with or without organic nitrates. First, he states that the data in the published literature in the form of abstracts and full peer-reviewed research publications on sildenafil would have been readily available at the time of the '684 Patent application filing date, and reasonable comparisons could have been made to tadalafil. Second, he asserts that direct head to head studies with PDE5 inhibitors are rare in the post art and Mylan's expectation that this type of study would be done routinely by a pharmaceutical company seems "unreasonable" (at para 381 of his affidavit).

[54] Dr. Goldstein adds that a person of skill in the art would not believe the '684 was promising to minimize or eliminate all adverse effects that were seen with sildenafil, as such a person knows that all drugs have side effects. A person of skill in the art would expect there to be some side effects from PDE5 inhibition, as drugs of the same class frequently have similar side effects. What would not have been obvious, therefore, would be tadalafil's reduced flushing and the lack of blue vision, as these are the side effects that were considered inherent to the inhibition of PDE5. Clinical studies such as those reported as Examples 6 and 7 have demonstrated that tadalafil minimizes the amount of flushing and that it essentially eliminated the blue vision abnormalities seen with sildenafil. These results are in accordance with what he has seen in his clinic.

[55] As for Mylan's argument that tadalafil is not better than sildenafil when the patient is also using nitrates, because both are labeled such that use with nitrates is not recommended, Dr. Goldstein writes:

> While it is true that the specification at page 8 in the last paragraph does state that the package insert for tadalafil "preferably" will not contain a contraindication for the use of nitrates, this does not rule out that it could and it does not change the fact that the inventors demonstrated that tadalafil when administered with the dosage restrictions of claim 10 of the '684 Patent was better than sildenafil in this regard. In essence, tadalafil was better than sildenafil, but the standard for the FDA to allow it to avoid the contraindication in its label was higher. This is apparent from Example 5 of the '684 Patent by itself and is further supported by the clinical trials that I discussed in this regard as well.
>
> (…)
>
> The "potentiation of hypotensive effects of nitrates" that is stated in the contraindication for tadalafil occurs under a daily dosing regimen of 20 mg of tadalafil. This daily dosing regimen has been shown to increase the steady state concentration of tadalafil in the blood by 60% compared to single use, on-demand dosing. Thus, the contraindication arises from an appropriate, but conservative public safety policy. In my view, the actual data included in the '684 Patent and the post art confirms the utility of tadalafil in minimizing adverse effects, including interactions with organic nitrates. Warnings and contraindications imposed by drug regulatory policies do not necessarily define actual risk or utility.
>
> (Goldstein affidavit, paras 399 and 402, AR Vol 2, pp 338-339)

[56] Finally, Dr. Goldstein comments on Mylan's allegation that 1 to 2 mg dosage forms would not be effective for on demand therapy for the treatment of ED. First, he points out that claim 10 is not limited to on demand therapy, and second, that the lowest dosage strength he was asked to consider (claims 2 and 4) is 2 mg. On the basis of the studies referred to in Examples 6 and 7, it is clear that the 2 mg dose had a significant improvement, relative to placebo, in the sexual performance of men with ED. Even if the 2.5 mg tablet currently marketed was not

specifically tested, there is no doubt that a person skilled in the art would know that a 2.5 mg dose (which contains 25% more active ingredients than a 2 mg dose) would also be effective for either on demand or daily treatment. As for the adverse effect profile of a 2.5 mg dose, it would be between the adverse effect profiles for the 2 and 5 mg doses; as no flushing or vision abnormalities were seen at either of those doses, a person skilled in the art would know that the same would be true for the 2.5 mg dose.

[57] Mylan's counsel levelled the same concerns with respect to Dr. Goldstein's impartiality as it did for Dr. Brock. For the reasons set out above, I find that Dr. Goldstein's access to confidential information prior to the filing date and his involvement with the development of tadalafil are insufficient to impact the weight of his testimony. As for the allegation that Dr. Goldstein provided his evidence with a view to upholding the validity of the '684 Patent, it is not borne out by a close reading of his affidavit or, for that matter, by his answers on cross-examination. The volunteered statement that he made after the conclusion of his re-examination may have been somewhat improper, but it appears to have been given in good faith to bring clarity on an issue he was questioned about earlier; it can certainly not be interpreted as an attempt to stray from his role as an independent expert to that of a biased witness.

B. Mylan's witnesses

[58] Mylan has put forward two expert witnesses: Dr. Arnold Melman and Dr. Evan Siegel.

Dr. Arnold Melman

[59] Dr. Melman is a Professor of Urology at Albert Einstein College of Medicine in New York City and an attending physician in the Department of Urology at Mount Sinai School of Medicine and at Montefiore Medical Centre.

[60] The gist of his opinion is found in his own summary and is to the following effect. First of all, he is of the view that a skilled person in the art would understand the patentee to be promising that the claimed unit dose of tadalafil will reduce three adverse effects associated with sildenafil (flushing, vision abnormalities and the negative effects associated with nitrate interactions) to clinically insignificant levels. "Clinically insignificant levels" would mean that the adverse effects would occur with sufficient rarity, and/or would be sufficiently mild, such that they would not affect a clinician's judgment when prescribing a treatment for erectile dysfunction. As it relates more particularly to nitrate interaction, it would mean that a contraindication of tadalafil is not necessary.

[61] Second, he believes this promise is not achieved because there is a strict contraindication by the regulatory authorities in both the United States and Canada against the co-administration of tadalafil and nitrates for all unit dosages claimed in the '684 Patent. This contraindication, which is reflected in the US Product Label and the Canadian Product Monograph, is based on the results from studies that were sponsored by Lilly and results from the potential of tadalafil to amplify the hypotensive effects of nitrates. Those effects can lead to clinically significant decreases in blood pressure and associated adverse events, including death.

[62] Dr. Melman further states that as of the '684 Patent filing date, the patentee had not demonstrated that tadalafil could be safely co-administered with nitrates at any unit dose. As of that date, it was known that sildenafil interacted with nitrates because it is a PDE5 inhibitor. Since tadalafil is also a PDE5 inhibitor, a skilled person in the art would have expected tadalafil to have a similar interaction. The only study that had been conducted on tadalafil and nitrates by the '684 Patent filing date (the LVAB study) used healthy volunteers and did not demonstrate a statistically significant difference in cardiovascular effects between tadalafil and sildenafil when used with nitrates. A skilled person would not have predicted either that tadalafil could be safely co-administered with nitrates, based on the information disclosed in the '684 Patent, given the known interaction of sildenafil and the limitations of Example 5.

[63] Dr. Melman then reviewed the '684 Patent, the skilled person's knowledge about the use of PDE5 inhibitors to treat ED in April 1999 and April 2000, and the various clinical trials conducted by Lilly prior to filing the '684 Patent as disclosed by Dr. Pullman. In particular, Dr. Melman states that Example 5 only describes part of the LVAB study and does not discuss the sildenafil testing in the LVAB study. He stresses that it is apparent from the LVAB study that there was no statistically significant difference between the head to head comparison of tadalafil and sildenafil. He adds that as of today, the claimed unit dose of tadalafil fails to achieve an improvement over sildenafil on the most important adverse effect identified in the '684 Patent – the interaction with nitrates. Both the Canadian Product Monograph and the US Product Label for CIALIS unequivocally state that tadalafil is contraindicated in patients using any form of nitrates, and as a clinician he states that he will not prescribe tadalafil to a patient who has been prescribed nitrates. This contraindication is based on tadalafil-specific studies, which all show

that tadalafil has clinically significant interactions with nitrates and should not be co-administered with nitrates, regardless of dose or dose regimen. Therefore, the contraindication is not simply a "class contraindication" applied reflexively to all PDE5 inhibitors.

[64] Dr. Melman also comments on the publicly available version of the FDA Review of the New Drug Application for CIALIS (tadalafil), which confirms his opinion that tadalafil has clinically significant interactions with nitrates. The FDA Review recommended, based on the studies conducted by Lilly, that short-acting nitrates be contraindicated up to 48 hours following a dose of CIALIS.

[65] Dr. Melman also opines that the claimed unit dose of tadalafil does not produce an improvement over sildenafil with respect to nitrate co-administration; to the extent that there is any difference, tadalafil is contraindicated with nitrates for a longer period of time because of its longer half-life.

[66] Finally, Dr. Melman reviews Dr. Brock's and Dr. Goldstein's opinions and sets out several points of disagreement, particularly with respect to their views on the interaction between tadalafil and nitrates. In conclusion, he reaffirms that there was no evidence that tadalafil could be safely co-administered with nitrates at any unit dose as of the '684 Patent filing date. Given the frailties of the only nitrate study performed prior to the '684 filing date (LVAB), it has not been demonstrated either that the claimed dose of tadalafil had any improvement over sildenafil in terms of co-administration with nitrates. He also expresses the view that as of April 2000, it could not be predicted from Example 5 that tadalafil could be safely co-administered with

nitrates at any unit dose, or that the claimed dose of tadalafil would have any improvement over sildenafil in terms of co-administration with nitrates. Even as of today, tadalafil does not have a better overall side effect profile than sildenafil. With respect to the most important safety concern – the interaction with organic nitrate – both drugs are absolutely contraindicated. With respect to other adverse effects, sildenafil has higher incidence rates for some adverse effects, whereas tadalafil has higher incidence rates for other adverse effects.

Dr. Evan Siegel

[67] Dr. Siegel is a toxicologist with expertise in drug development, including dose selection and side effects. He considers himself an expert in development and clinical testing of drugs across many areas. He does not have a particular specialization or experience in the field of sexual dysfunction.

[68] After reciting his qualifications and mandate, Dr. Siegel provides a general primer regarding the drug development process, particularly as it relates to the determination of an appropriate human dosage amount for a given drug, the relationship between dosing and adverse effects, and general information about different types of adverse effects. Of particular relevance is Dr. Siegel's statement that in some cases, an adverse effect is severe and/or frequent enough that it warrants the inclusion of a caution, warning or contraindication on the product monograph, label or packaging. Such notices are intended to alert patients and physicians to the potential harm that can result from use of the product. He states:

> I understand a contraindication to be the most severe notice about potential adverse effects associated with using the product. Essentially, a contraindication is a statement that advises

> prescribing healthcare providers and patients against using the product if the patient suffers from a certain condition or is taking another product that will interact negatively and potentially cause harm. A contraindication effectively says "do not use this product if these circumstances apply".
>
> (Siegel affidavit, para 70, AR Vol 18, p 4278)

[69] Dr. Siegel then goes on to review the '684 Patent, including the clinical studies disclosed therein and offers his construction of the claims. He understands the '684 Patent to promise that the unit dosages of tadalafil claimed (1 to 20 mg) provide an improvement over sildenafil by reducing three specific adverse effects (vision abnormalities, flushing, and the negative effects associated with co-administration with nitrates) to "clinically insignificant levels", while higher dosages of tadalafil (such as 25 or 50 mg) do not provide this improvement.

[70] Dr. Siegel responds to and critiques the Pullman affidavit, and sets out three issues with Dr. Pullman's narrative: first, the Pullman affidavit omitted important parts of the tadalafil development story, such as animal testing and early human testing; second, this narrative is focused on efficacy, whereas the '684 Patent is directed to the avoidance of three specific adverse effects; and third, the Pullman affidavit does not adequately explain the interaction of tadalafil with nitrates. Much like Dr. Melman, he is of the view that in the LVAB study, there were no statistically significant differences between the combined effect of tadalafil and nitrates versus the combined effect of sildenafil and nitrates. Moreover, the LVAB study did not demonstrate that tadalafil could safely be co-administered with nitrates. He also disagrees with Dr. Pullman that tadalafil is contraindicated because it is in the same class as sildenafil; tadalafil is contraindicated with nitrates because it has been shown to have clinically significant interactions with nitrates.

[71] Dr. Siegel agrees with Drs. Goldstein and Brock that the '684 Patent promises that the claimed unit dosage of tadalafil provides an improvement by reducing the three specific adverse effects (flushing, vision abnormalities and the negative effects associated with co-administration with nitrates) known to occur with sildenafil. However, he disagrees with them on the degree of improvement that is promised. Based on the evidence in the '684 Patent and the evidence submitted by Lilly in this proceeding, he is further of the view that there was no basis on which to conclude that the unit dosages of tadalafil selected in the '684 Patent (1 to 20 mg) provided an improvement by reducing the three specific adverse effects relative to sildenafil, or relative to higher dosages of tadalafil (such as 25 or 50 mg). Example 5, in particular, was conducted with healthy and relatively young male volunteers, not with chronic nitrate users or with patients suffering from ED. Moreover, the example only provides information about a 10 mg dosage of tadalafil.

[72] In addition to these views, he is also of the opinion that there is no basis upon which to conclude today that any dosage of tadalafil, either within or higher than the selected dosage range, can be safely co-administered with nitrates. Accordingly, the claimed dosages of tadalafil do not exhibit a better adverse effect profile than sildenafil in this regard. He bases this opinion on his review of the data provided in the '684 Patent, the evidence provided in the Pullman affidavit, and a review of several different sources of current information regarding tadalafil. He examines the FDA Review and the published literature post 2000 and comes to the same conclusions as Dr. Melman that a unit dose of 1 to 20 mg of tadalafil cannot be co-administered with nitrates and that the contraindication is the result of testing specifically directed towards the interaction of tadalafil and nitrates, not due to class labeling by regulators. He concludes that

portion of his affidavit by explaining why he disagrees with Dr. Brock's and Dr. Goldstein's views on the interaction of tadalafil and nitrates.

[73] Assuming that the inventive concept of the '684 Patent is "selecting a dose of 1 to 20 mg of tadalafil that results in a generally improved adverse effect profile over higher doses of tadalafil", Dr. Siegel opines that, as of April 30, 1999, it was obvious to use tadalafil to treat ED in the unit dosages claimed in that Patent. Based on the disclosure of the '784 Patent, a drug development team would have been motivated to employ standard dose ranging techniques to determine the adverse effects associated with different dosages within this range and find the dosage(s) that is most effective with the lowest incidence and severity of adverse effects in the cohort of patients intended for treatment. As he states:

> Determining the dosage amount of a known compound is routine work for a drug development team. The goal of this process is always the same: to determine the range of doses that maximize efficacy and minimize adverse effects. As a general matter, it was well-known that the incidence of adverse effects could be reduced by lowering the dosage amount and that this is always desirable, so long as the dosage amount remains effective. The drug development team performing this routine work will inevitably observe specific adverse effects of the target compound because adverse effects are inherent properties of the compound.
>
> (Siegel affidavit, para 34, AR Vol 18, p 4270)

[74] Dr. Siegel is of the view that, based on the comparative *in vitro* potency of tadalafil and sildenafil, the relative molecular weights of these compounds, and the pharmacokinetic profile of sildenafil and tadalafil, a drug development team following the ordinary course of development would likely have begun human dosing of tadalafil at a significantly lower dose than the approved marketed dosages of sildenafil. Conducting routine pharmacokinetic testing in animals

would have led a drug development team to further reduce the initial doses used in human testing. Given that a drug development team will typically start human testing with a low, safe dose and then increase the tested dose slowly to determine a maximum tolerated dose, a skilled person would therefore have likely designed an initial dose escalation study to start at approximately 5 mg of tadalafil and move up to approximately 50 mg.

IV. Issues

[75] Mylan argues that if the '684 Patent is construed as a selection patent of the '784 Patent, the promised utility (namely that tadalafil in specific doses will reduce specific side effects to clinically insignificant levels) was neither demonstrated nor soundly predicted at the filing date, mainly because of the ongoing and serious problem of nitrate interaction. If the '684 Patent is not a selection patent, then Mylan argues alternatively that it fails for obviousness and anticipation by the '784 Patent, because the dose ranges of the '684 fall entirely within those disclosed in the '784, and it would have been obvious to test lower doses.

[76] To respond to the lack of utility argument, Lilly ignores the selection patent doctrine and argues that the '684 Patent merely promises to reduce side effects while remaining effective. This promise was both demonstrated and soundly predicted. Moreover, Lilly argues that the 684 Patent's narrower dose range was not obvious because it required extensive and non-routine testing.

[77] Lilly ignores the anticipation argument, because Lilly was allegedly advised that Mylan was dropping the issue. Two weeks before the hearing of this matter, Lilly brought a motion to

strike from the record the portion of Mylan's Memorandum of Fact and Law pertaining to anticipation (paragraphs 170-191 and accompanying footnotes). Lilly acknowledged that Mylan did allege in its NOA the invalidity of the '684 Patent on the basis of anticipation, but argues that the issue was never put into play as Mylan's affiants never opined on the anticipation allegation. Lilly also relies on the fact that it was stopped from asking questions relating to anticipation during the cross-examination of one of Mylan's experts, allegedly because counsel for Mylan confirmed that "anticipation is no longer an issue in the case".

[78] As I previously indicated, this motion must be rejected for the following reasons. First of all, it seems to me that much clearer evidence would be required to find that the anticipation allegation was abandoned by Mylan. In the portion of questioning relating to the legal principles exhibit, counsel for Lilly asked Dr. Siegel whether the anticipation analysis was performed on a claim-by-claim basis or on the patent as a whole, to which counsel for Mylan interjected: "I don't think it's an issue in the case, if that helps…" (Siegel cross-examination, AR Vol 32, p 7147). Lilly construes the word "it's" as referring to the anticipation allegation, but it is equally possible to read it as referring to the issue of whether the anticipation analysis is done on a claim-by-claim basis or on the patent as a whole. On the basis of that ambiguity, I am unable to find that the anticipation allegation has unequivocally been dropped by Mylan.

[79] As for the argument that this allegation has not been put into play, I am also of the view that it is without merit. Mylan did not need to tender expert opinion evidence on the ultimate issue of whether an allegation is justified. This is a matter exclusively for the Court. What Mylan

was required to do was to give an "air of reality" to its allegation, and it did so as the facts that are relevant to the obviousness allegation are also relevant to the anticipation allegation.

[80] Lilly also claims that it would be prejudiced if Mylan is permitted to raise arguments with respect to anticipation, as it has not had an opportunity to cross-examine Mylan's witnesses and had not made submissions on the allegation. It is no doubt true that Mylan had Lilly's Memorandum of Fact and Law for over 11 weeks, and could see that Lilly understood that anticipation was no longer an allegation. Mylan could no doubt have tried to rectify the issue at that time. But Lilly could equally have raised the issue upon receiving Mylan's original memorandum on August 22, 2014, at which point it ought to have known of Mylan's position that anticipation is still a live issue. Indeed, Lilly brought a motion to strike Mylan's original memorandum for formatting irregularities on September 9, 2014, but remained silent about any intention to bring a motion to strike that same document on substantive grounds despite the Court asking whether any further motions would be brought before the hearing.

[81] For all of the above reasons, the motion to strike from Lilly is dismissed and the allegation of anticipation ought to be addressed by this Court. To ensure that Lilly will not suffer any prejudice as a result of that decision, I indicated at the hearing that the Court would be prepared to entertain any arguments that Lilly may wish to make orally with respect to anticipation.

[82] The Court must therefore decide whether the following three allegations are justified:

(1) Is the allegation that the '684 Patent is invalid for lack of utility justified?

(2) Is the allegation that the claims are invalid for anticipation by the '784 Patent justified?

(3) Is the allegation that the claims are invalid for obviousness justified?

V. Analysis

[83] The parties are substantially in agreement as to the definition of the person skilled in the art. Indeed, the PSA was defined in much the same way by Dr. Goldstein, Dr. Brock and Dr. Melman. The '684 Patent is directed to a person or a drug development team having expertise in areas that are relevant to drug dosing, such as pharmacology and/or pharmacokinetics, physiology, dose ranging and safety assessment of candidate therapeutics, and with experience in the treatment of ED. This team could include physicians, clinicians, research scientists, pharmacologists, toxicologists and statisticians, with at least a couple of years of experience working in a drug development environment in academia or in the pharmaceutical industry.

(1) Is the allegation that the '684 Patent is invalid for lack of utility justified?

[84] The parties are in substantial agreement with respect to the law of utility, and there is no need to revisit the applicable principles as I have already canvassed them in the related case dealing with the '784 Patent (see 2015 FC 17, at paras 70 ff). Because the *Patent Act* requires that every invention be new and useful (see the definition of "invention" at section 2 of the Act), utility must either be demonstrated or soundly predicted as of the filing date where the gist of an invention is the new use of a compound: *Apotex v Wellcome Foundation Ltd*, 2002 SCC 77, at

para 56, [2002] 4 SCR 153 [*AZT*]; *Eli Lilly Canada v Novopharm Limited*, 2010 FCA 197, at para 74 [*Olanzapine*].

(a) The Promise of the Patent

[85] The promise of a patent is fundamental to the utility analysis and must be ascertained at its outset. As stated by the Federal Court of Appeal in *Sanofi-Aventis v Apotex*, 2013 FCA 186, at para 47, "[t]he promise of the patent is the standard against which the utility of the invention described in the patent is measured".

[86] If the parties agree on the relevant legal principles in the abstract, they differ on their application to the case at bar and diverge on the actual promise of the '684 Patent. Lilly submits that the promise must be determined by focusing on the claims, and on that basis asserts that the promise of the '684 Patent is that the claimed doses are efficacious and, when administered to patients for the treatment of ED, will have a better side effect profile than sildenafil. While not disagreeing with that construction of the promise, Mylan is of the view that the '684 Patent goes much beyond it and promises that the selection of a unit dose of 1 to 20 mg of tadalafil provides an improvement over sildenafil by reducing three side effects (flushing, vision abnormalities, and the negative effects associated with co-administration with nitrates) to "clinically insignificant levels" , while higher dosages of tadalafil (i.e. greater than 20 mg) do not provide this improvement.

[87] Lilly argued that Mylan has elevated its promise beyond the allegations in its NOA, wherein the promise of the '684 Patent was described as "the claimed dosage range of tadalafil

(a) provides an effective treatment for ED; and (b) produces an improved side effect profile relative to sildenafil, including the ability to be co-administered with organic nitrates" (NOA, Potter affidavit, Exh "B", AR Vol 1, p 113). According to Lilly, Mylan now refers to three specific side effects rather than to the side effect profile in general, and also states that the side effects will not only be better relative to sildenafil, but that they will be clinically insignificant.

[88] I agree with Mylan that Lilly has misrepresented its allegations by quoting from a single sentence in the NOA. A careful reading of the NOA reveals that Mylan provides additional details with respect to what it calls the "Improved Therapeutic Profile Concept" construction of the promise. On the very same page quoted by Lilly, we find the following additions:

> As set out above, the 684 Patent promises that the unit dosage selection results in an improved side effect profile that includes:
>
> > •Tadalafil can be co-administered with an organic nitrate;
> >
> > •Other side effects previously believed to be indicative of PDE5 inhibition, such as flushing and vision abnormalities, can be reduced to clinically insignificant levels; and
> >
> > •Accordingly, tadalafil can be administered to individuals who previously were untreatable or suffered from unacceptable side effects, including individuals having cardiovascular disease, such as in individuals requiring nitrate therapy, having suffered a myocardial infarction more than three months before the onset of sexual dysfunction therapy, and suffering from class 1 congestive heart failure, or individuals suffering from vision abnormalities.
>
> (NOA, Potter affidavit, Exh "B", AR Vol 1, p 113)

[89] On the basis of that extract, it is fair to say that the NOA does contain the factual basis upon which Mylan relies in support of its allegations, and it cannot be argued that Lilly is taken by surprise by the construction of the promise put forward by Mylan in its Memorandum of Fact and Law. The Court must therefore turn to the divergent constructions of the promise offered by the parties and come to its own conclusion as to the proper interpretation of the promise made by the patentee.

[90] While sildenafil is associated with a number of adverse side effects, all the experts agree that the '684 Patent focuses on three side effects associated with sildenafil – flushing, vision abnormalities, and the negative effects associated with co-administration with nitrates. The first two are mild and transient, in the sense that the side effect will go away when the person stops taking the drug. The third one is by far sildenafil's most significant side effect, as the co-administration of sildenafil with nitrates can result in potentially life-threatening hypotension. As Dr. Brock conceded, "death trumps most other side effects" (Brock cross-examination, p 207, AR Vol 23, p 5064). It is clear, therefore, that the promise of the '684 Patent is not just that the claimed doses will have a better side effect profile than sildenafil; the promise is more focused and targets specifically three side effects, one of which can be life-threatening.

[91] As noted above, the parties strongly disagree not only as to the side effects to be considered but also as to the extent of the side effect reduction promised by the '684 Patent. Despite the clear language of the Patent that the side effects previously believed to be associated with PDE5 inhibitors "can be reduced to clinically insignificant levels" by tadalafil at the selected dose, Lilly asserts that complete elimination of side effects is impossible and that the

person skilled in the art would not believe the '684 Patent was promising to minimize or eliminate all adverse effects that were seen with sildenafil. In other words, as Dr. Brock would have it, "the promise of the '684 Patent is the efficacy at a very low dose together with the lower incidences of adverse effects that these lower doses provide" (Brock affidavit, para 216, AR Vol 2, p 226; see also, to the same effect, Goldstein affidavit, paras 384-385 AR Vol 2, pp 335-336).

[92] Having carefully read the '684 Patent and the affidavits of the experts, I am unable to read down the promise of that Patent as Lilly would construct it. Such an interpretation would fly in the face of the clear language of the '684 Patent, which explicitly promises much more than a marginal improvement over sildenafil.

[93] As previously mentioned, the very first paragraph of the '684 Patent states that the unit dosage form described therein provides a benefit in therapeutic areas where inhibition of PDE5 is desired, "with minimization or elimination of adverse side effects resulting from inhibition of other phosphodiesterase enzymes". It then goes on to state that the product can be administered with "clinically insignificant" side effects associated with the combined effects of a PDE5 inhibitor and an organic nitrate. While this may plausibly be characterized as a mere observation drawn from clinical studies, as Lilly argued, the next sentence goes much further and clearly reads as a promise: "[t]hus, the contraindication once believed necessary for a product containing a PDE5 inhibitor *is unnecessary*…" (emphasis added).

[94] The Patent further reiterates (at p 10, line 29 to p 11, line 5) that the selection of a unit dosage form of 1 to 20 mg of tadalafil minimizes undesirable side effects previously believed

unavoidable, including facial flushing, vision abnormalities, and a significant decrease in blood pressure when a PDE5 inhibitor is administered in combination with nitrates. Read in conjunction with the previous sentence, according to which the present invention is based on detailed experiments and clinical trials showing that side effects can be reduced to "clinically insignificant levels" by the selection of a compound and unit dose, it is a fair assumption that the minimization of the undesirable side effects with the selected doses of tadalafil is more than marginal. The language of elimination or minimization of adverse side effects also finds its way into the penultimate paragraph, both for vision abnormalities, flushing and the negative effects for individuals undergoing nitrate therapy.

[95] On the basis of these ambitious and explicit statements throughout the Patent, I agree with Mylan that the promise is not merely a *de minimis* improvement over sildenafil; the language of the disclosure makes it clear that the promised improvement when it comes to adverse side effects is not just marginal but significant. In this respect, I prefer the opinions of Mylan's experts to those of Lilly's experts on the construction of the promise, because they are more in line with the wording of the Patent. Accordingly, I would adopt the following characterization of the promise offered by Dr. Melman in his affidavit:

> In my opinion, based on a complete reading of the '684 Patent, a Skilled Person would understand the patentee to be promising that the claimed unit dose of tadalafil (1 to 20 mg) will reduce all three of the adverse effects associated with sildenafil (flushing, vision abnormalities, and the negative effects associated with nitrate interactions) to clinically insignificant levels. In my opinion, reducing adverse events to "clinically insignificant levels" would mean that the adverse effects would occur with sufficient rarity, and/or would be sufficiently mild, such that they would not affect a clinician's judgment when prescribing a treatment for erectile dysfunction.

> (Melman affidavit, para 88, AR Vol 18, p 4233. See also, to the same effect, Siegel affidavit, para 152, AR Vol 18, p 4299)

[96] As Mylan points out, Lilly's experts read down the promise based on irrelevant considerations: they find that the '684 Patent did not promise "clinically insignificant" nitrate interaction because, at the time, Lilly knew that this had not been achieved. When asked about how a skilled person would interpret specific statements in the '684 Patent, both Dr. Brock and Dr. Goldstein referred to the data that Lilly actually had in hand at the filing date rather than to the language of the Patent itself (see for example Brock cross-examination, AR Vol 26, pp 5987-5988, 5992-5994, 5996-5999; Goldstein cross-examination, pp 133-136, AR Vol 24, pp 5363-5366). Such an approach is clearly unacceptable: a clear promise cannot be narrowed down to fit what has been demonstrated, otherwise utility would never be an issue. As this Court stated in *AstraZeneca v Apotex*, 2014 FC 638, at para 128:

> First, AstraZeneca's approach to utility is tautological. On a high level, the promise is the yardstick against which utility is measured for the purpose of demonstration. Yet, AstraZeneca proposes a backwards approach that establishes that benchmark based on what can ultimately be demonstrated in the patent. To circumscribe the scope of the promise based on what is demonstrated in the patent makes it impossible to ever conclude that a patent is invalid for lack of utility. No matter how broad a promise (e.g. this drug cures cancer), it would always be read down to a narrower promise based on what was demonstrated. Such an approach would run contrary to the policy objectives of patent law which serve to create consistency and clarity in the bargain struck between innovators and the public. Instead, unequivocal promises in patents could in no way be relied upon and would be subordinate to more complex questions of demonstration within the patent.

[97] With respect to the issue relating to nitrates, Lilly focused on the package insert language and on the use of the word "preferably" in the following quotation found at page 8 of the Patent:

> Significantly, the package insert supports the use of the product to treat sexual dysfunction in patients suffering from a retinal disease, for example, diabetic retinopathy or retinitis pigmentosa, or in patients who are using organic nitrates. Thus, the package insert preferably is free of contraindications associated with these conditions, and particularly the administration of the dosage form with an organic nitrate.

[98] Dr. Brock emphasized in his affidavit that warnings and contraindications imposed by drug regulatory policies do not necessarily define actual risk or utility, and that it is up to the FDA, Health Canada and the European Medicines Board to determine whether or not there should be contraindication for the use of tadalafil with nitrates. According to Lilly, this is precisely why the Patent speaks in terms of preference, and does not rule out the possibility of a contraindication.

[99] It is no doubt true that contraindications are regulatory matters, and I accept Lilly's argument that a patentee cannot promise that which it has no control over. Yet, the language of a patent cannot be ignored and a patentee can make an explicit promise that a contraindication is unnecessary even if, at the end of the day, this is a matter primarily for regulators. This is precisely what was done here. As previously mentioned, there is an explicit promise that tadalafil can be safely co-administered with nitrates such that a contraindication is "unnecessary" (see the quotation at para 93). This statement cannot simply be ignored when construing the promise of the Patent, as Lilly's experts seem to be doing. Having made an explicit promise of a specific result in the Patent, the patentee has made the contraindication not only a regulatory issue, but also a patent issue. Indeed, there is nothing wrong with such a promise as contraindications are not the sole purview of regulators. Clinicians and independent organizations do recommend contraindications based on experimental evidence, and Dr. Goldstein himself was apparently part

of an expert panel that reviewed the available evidence and published practical guidelines for doctors who treat ED (Goldstein cross-examination, pp 156-165, AR Vol 24, pp 5386-5395).

[100] On the basis of the foregoing, I am therefore prepared to hold that the promise of the '684 Patent is not merely to lower the incidence of adverse side effects as compared to sildenafil, but to minimize them significantly or even to eliminate them. This is true for all three side effects that are the focus of the '684 Patent, but more particularly with respect to the co-administration of tadalafil with nitrates; this is the inescapable conclusion that one must draw from the statement that a contraindication is unnecessary when tadalafil is administered as a unit dose of about 1 to about 20 mg.

[101] Counsel for Lilly tried to argue that the promise should be construed by focusing on the claims rather than the specification, and relies for that proposition on the decision of this Court in *Fournier Pharma v Canada (Health)*, 2012 FC 741 [*Fournier*] (subsequently followed by the decision of Justice Kane in *Alcon Canada v Apotex*, 2014 FC 699). In *Fournier*, Justice Zinn wrote (at paras 126-127):

> The Federal Court of Appeal in *Eli Lilly Canada Inc v Novopharm* Limited, 2010 FCA 197, citing *Consolboard Inc v MacMillan Bloedel (Sask)* Ltd, [1981] 1 SCR 504, stated at para 76 that "where the specification sets out an explicit 'promise', utility will be measured against that promise [emphasis added]". The promise of a patent, as that term is used in patent law, is nothing more than the utility the inventor claims for his invention. Where that promise – that claimed utility – is clearly and unequivocally expressed by the inventor in the claims of the patent, then that expression ought to be viewed as the promise of the patent. Any statement found elsewhere should be presumed to be a mere statement of advantage unless the inventor clearly and unequivocally states that it is part of the promised utility. […]

> The interpretation should be focused on the claims because an inventor is not obliged to claim a monopoly on everything new, ingenious, and useful disclosed in the specification. If, as here, the claims are certain and unambiguous in stating the promise, then the disclosure should not be examined microscopically to find additional promises that are outside the scope of the inventor's claimed monopoly.

[102] This statement does not detract from the general rule that the promise should be construed within the context of the patent as a whole, as the Federal Court of Appeal explicitly stated later on in that same decision (see *Olanzapine*, above, at para 93), when the promise is not "clearly and unequivocally" expressed in the claims of the patent. This is precisely the situation in the case at bar. The claims of the '684 Patent simply relate to the unit dosage forms of tadalafil to treat ED, and do not "clearly and unequivocally" set out a promise. This is in contrast to the claims of the patent at issue in the *Fournier* case, where the claims themselves laid out specific characteristics (in that case, dissolution profiles) of the claimed invention. For that reason, the claims of the '684 Patent cannot be the exclusive focus for the construction of the promise.

[103] In any event, I agree with Mylan that Lilly's own promise construction, which includes "a better side effect profile than sildenafil", is inconsistent with the argument that the promise should focus on the claims, as none of the '684 claims refer to side effects. Lilly's own construction of the promise relies, therefore, on its own reading of the Patent as a whole.

[104] The last area of disagreement between the parties with respect to the promise has to do with the fact that the improvement of tadalafil over sildenafil is peculiar to the claimed dose range. Mylan takes the position that the '684 Patent is anticipated by the '784 Patent, since the '784 Patent disclosed that tadalafil treated ED and the unit dosages claimed in the '684 Patent (1

to 20 mg) are entirely within the dosage range disclosed in the '784 Patent (0.2 to 400 mg). Accordingly, the only way for Lilly to avoid a finding of anticipation is to construe the '684 Patent as a selection patent.

[105] A selection patent is not different in nature from any other patent; it is merely a way of describing a patent: *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, at para 9, [2008] 3 SCR 265 [*Sanofi-Synthelabo*]. In the field of chemical patents (which includes, of course, pharmaceutical compounds), a selection patent refers to a patent where a single element or segment is selected from a group, based on a particular feature of the element that provides an advantage not shared by the larger group. For example, one patent may claim a group of compounds, and then a subsequent patent – the selection patent – claims a selection from that group based on some "special property of an unexpected character" (*Sanofi-Synthelabo*, at para 9). In *Sanofi-Synthelabo*, Justice Rothstein adopted the conditions set out in *In re I G Farbenindustrie AG's Patents* (1930), 47 RPC 289 (Ch D) that must be satisfied for a selection patent to be valid (*Sanofi-Synthelabo*, at para 10):

> 1. There must be a substantial advantage to be secured or disadvantage to be avoided by the use of the selected members.
>
> 2. The whole of the selected members (subject to "a few exceptions here and there") possess the advantage in question.
>
> 3. The selection must be in respect of a quality of a special character peculiar to the selected group. If further research revealed a small number of unselected compounds possessing the same advantage, that would not invalidate the selection patent. However, if research showed that a larger number of unselected compounds possessed the same advantage, the quality of the compound claimed in the selection patent would not be of a special character.

[106] Characterizing a patent as a selection patent does not make it *prima facie* more or less valid; indeed, Justice Layden-Stevenson held in *Olanzapine* (above, at para 27) that the failure of a patent to meet the conditions for a selection patent does not constitute an independent basis for challenge or invalidity, but merely informs the analysis of other bases for invalidity, ie novelty, obviousness, sufficiency and utility.

[107] Selection patent doctrine is usually encountered in the context of an obviousness or anticipation analysis. For example, a selection patent will be novel, or unanticipated, if the species are discovered to have previously unknown advantages over the genus. Similarly, the special properties of a compound along with its alleged advantages must be considered when undertaking the obviousness analysis if it is a selection compound (*Olanzapine*, above, at para 57). When it comes to utility, the selection patent must promise an advantage over the genus patent. As Justice Layden-Stevenson stated in the *Olanzapine* case, the inventiveness of a selection patent "lies in the making of the selected compound, coupled with its advantage or advantages, over the genus patent" (at para 78). Of course, all of the claimed unit doses must meet the utility requirements, but that would be true whether the '684 Patent is a selection patent or not. Whether the improvement over sildenafil must be peculiar to the claimed dose range is irrelevant for the purpose of a utility analysis, and will only inform the analysis of anticipation and obviousness.

[108] It is indeed quite telling that none of the experts construed the promise through the lens of the selection patent doctrine, and they do not appear to have been instructed by counsel. To the extent that they came to different constructions of the promise, they did so without ever referring

or commenting as to the exact nature of the '684 Patent. This is as it should be, since the jurisprudence has established that a selection patent is like all other patents and is governed by the same legal principles.

[109] In any event, I have not been convinced that the '684 Patent is a selection patent. Whatever Lilly may have represented to the Patent Office, this Patent does not meet the third criterion set out in *In re I G Farbenindustrie AG's Patents* and adopted by Justice Rothstein in *Sanofi-Synthelabo*. While the dosage range claimed is much narrower compared to the broad range disclosed in the '784 Patent and the improvement over sildenafil is said to be a characteristic of the entire dosage range of 1 to 20 mg, there is nothing in the specification (let alone in the claims themselves) to the effect that the promised advantage is peculiar to this particular dosage range to the exclusion of any other unit dose. The first sentence of the Summary of the Invention section states that the invention provides "a pharmaceutical dosage form … comprising about 1 to about 20 mg of [tadalafil]" and that the invention provides "a method of treating conditions where inhibition of PDE5 is desired" (p 5), and similar language is used throughout the Patent. The patentee clearly claims that a dosage range of 1 to 20 mg provides a substantial advantage over sildenafil in treating ED, but does not assert that a larger number of unselected doses do not possess the same advantage. That being an essential characteristic of a selection patent, I am therefore of the view that the '684 Patent is not a selection patent.

[110] In conclusion, I find that the '684 Patent promises that the claimed unit doses of 1 to 20 mg of tadalafil, when administered to patients for the treatment of ED, will be effective and

provide an improvement over sildenafil by minimizing significantly or eliminating three side effects (flushing, vision abnormalities, and the negative effects associated with co-administration with nitrates). It must now be determined whether the Patent meets that promise.

(b) Demonstration and Sound Prediction

[111] Mylan claims that the '684 Patent is invalid because it fails to meet the promised utility in four different ways:

- Any improvement in side effects is not peculiar to the claimed dose range;
- Nitrate interaction has not been reduced to "clinically insignificant levels" because tadalafil is absolutely contraindicated with nitrates;
- There is no improvement in the nitrate interaction over sildenafil; and
- The 1 mg dose of tadalafil is not efficacious.

[112] I need not spend much time on the first ground raised by Mylan, as I have found that it is not part of the promise against which the utility of the '684 Patent must be assessed that an improvement in side effects over sildenafil is peculiar to the selected dose range of 1 to 20 mg. Similarly, no claims relating to a 1 mg dose have been asserted in this proceeding, for the obvious reason that no evidence has been filed (either by Mylan or by Lilly) with respect to the effectiveness of such a dose in treating ED. Accordingly, the fourth ground raised by Mylan to challenge the validity of the '684 Patent will not be addressed.

[113] The most serious attacks on the utility of the '684 Patent are clearly the second and third ones, and they are interrelated. I will nevertheless deal with them separately, starting with the second one.

[114] I agree with Mylan that as of the filing date, the promise of minimizing significantly or eliminating the negative side effects associated with co-administration with nitrates was neither demonstrated nor soundly predicted. The only study dealing with the co-administration of tadalafil with organic nitrates that was available at the time (LVAB, as reported in Example 5) was far from sufficient to establish that a contraindication was unnecessary, as stated in the Patent. First of all, that study used a small group (22) of relatively young, healthy volunteers; the mean and median age was approximately 40 years, which is substantially younger than the patient population with ED, and only 4 out of 22 men were over the age of 50. On cross-examination, Dr. Brock submitted that this was appropriate if the goal is to uncover whether there is a potentially dangerous interaction between nitroglycerin and a PDE5 inhibitor. He added, emphatically, that:

> if you choose a group of old guys with bad ED who have lead pipe blood vessels that have just marginal blood pressure, you would first of all not get it approved through an ethics committee, because it would be potentially dangerous for these guys to have any change in blood pressure, and whatever change in blood pressure they have may reflect more of the pathology of their arteries than the actual interaction between the drugs.
>
> (Brock cross-examination, pp 311-312, AR Vol 23, pp 5168-5169)

While there is no other evidence as to what should be an appropriate cohort for that type of study, it is safe to say that neither the LVAB subjects, nor the straw man offered as an alternative by Dr. Brock, would be representative of the general patient population suffering from ED.

[115] Moreover, that study only used a single dose of tadalafil (10 mg). As Dr. Goldstein himself conceded, a skilled person would have no basis for extrapolating to the higher doses claimed in the '684 Patent, such as a 20 mg dose (Goldstein cross-examination, AR Vol 24, p 5526; see also Siegel affidavit, paras 164, 177, AR Vol 19, pp 4425, 4430). In cross-examination, Dr. Pullman also admitted that Lilly had no evidence by April 2000 that a contraindication was unnecessary (Pullman cross-examination, p 186, AR Vol 28, p 6552). It is also of note that the FDA documents submitted as exhibits to the Potter affidavit indicate that Lilly chose to exclude all nitrate users from Phase III studies based on the results of the LVAB study, which demonstrated the expected potential serious interaction with nitrates.

[116] Lilly did not attempt to establish that the utility of its Patent, if not demonstrated, would have been soundly predicted by a person skilled in the art. Nor should it have tried, as there was no factual basis for such a prediction and there is no evidence that the inventor had an articulable and sound line of reasoning from which the desired result can be inferred from such a factual basis.

[117] Be that as it may, and regardless of what could have been predicted at the filing date, a patent will be invalid if the prediction is later shown to be unsound or if there is evidence of lack of utility in respect of some of the area covered: *AZT*, above, at paras 56, 76. Even as of today, there is an absolute contraindication against the co-administration of tadalafil and nitrates both in the Canadian Product Monograph and in the US Product Label for tadalafil (Potter affidavit, Exh "D", Doc #2, AR Vol 10, p 2344-2345; Melman affidavit, Exh 11, AR Vol 20, pp 4624-4625, 4630, 4633-4634). The contraindication applies to all marketed doses of tadalafil (2, 5, 10 and 20

mg), and it applies regardless of whether tadalafil is administered daily or "on demand". The relevant portion of the Canadian Product Monograph states:

> CIALIS (tadalafil) has been shown to potentiate the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/ cGMP pathway. **Therefore, administration of CIALIS to patients who are using any form of organic nitrate (e.g., oral, sublingual, transdermal, by inhalation), either regularly and/or intermittently, is contraindicated, due to the risk of developing potentially life-threatening hypotension.**
>
> CIALIS should not be prescribed to patients for whom nitrates are prescribed, even though the patient may not have actually used the nitrate therapy.
>
> In a patient prescribed CIALIS, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of CIALIS before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring.
>
> (Potter affidavit, Exh "D", Doc #2, AR Vol 10, p 2344-2345 (emphasis in original))

[118] Lilly tried to argue that the labelled contraindication is a regulatory and not a patentability issue, that it is overly cautious and that it is a "class-based" contraindication which applies to all PDE5 inhibitors. Nothing is further from the reality. As previously mentioned, a contraindication can be a clinical matter as much as a regulatory one. When Health Canada or the FDA decide to include a contraindication in a package insert or in a label, they do so on the basis of clinical studies. For example, a study sponsored by Lilly in 2003 and authored by six cardiologists (three of which were employees of Lilly) concluded that "[s]imilar to other PDE5 inhibitors, tadalafil should not be used in combination with organic nitrates". The authors also concluded that "[i]f the patient has taken tadalafil within 48 h, then organic nitrates should not be

given" (RA Kloner *et al*, "Time Course of the Interaction Between Tadalafil and Nitrates", *J Am Coll Cardi*, 2003, 42(10), p 1855, Potter affidavit, Exh "D", Doc #19, AR Vol 10, pp 2589-2590). In cross-examination, Dr. Brock agreed that this study showed a "clinically significant interaction" between tadalafil and nitrates (Brock cross-examination, pp 347-348, AR Vol 23, pp 5204-5205). These results appear to be the basis for the 48 hour duration of the contraindication of co-administering tadalafil and nitrates (see Goldstein cross-examination, pp 182, 185, AR Vol 24, pp 5412, 5415; Melman affidavit, paras 124-128, AR Vol 18, pp 4240-4242; Siegel affidavit, para 210, AR Vol 18, p 4316).

[119] In its Memorandum of Fact and Law, Lilly relied on an answer given by Dr. Goldstein in cross-examination to suggest that the Kloner 2003 study presents a "worst case scenario" because it used a dosing regimen of 20 mg daily for seven days. Since tadalafil has a long half-life, it accumulates and after five days, it is equivalent to a dose of 32 mg. Yet, as pointed out by Dr. Siegel in his affidavit (at para 219(d)), that dosage regimen is entirely within the scope of claim 10 of the '684 Patent. Moreover, the authors of that study recommend that nitrates not be administered to patients taking any dose of tadalafil at any frequency, not just avoidance of nitrates in patients taking 20 mg tadalafil daily. In a reply to a question asked by a physician following the publication of the 2003 article, the authors reinforce that point by noting that, based on other studies conducted on single doses of tadalafil (5 mg and 10 mg), "the hemodynamic interactions with nitrates after a single dose of tadalafil were comparable to those after steady-state dosing of tadalafil", and repeated that "nitrates are contraindicated whether a patient has been taking daily or intermittent doses of any PDE5 inhibitor" (Melman affidavit, Exh 13, AR Vol 20, p 4654). In a review also published in 2003, Dr. Kloner and others report on

such studies: see "Cardiovascular Effects of Tadalafil", Goldstein affidavit, Exh 60, AR Vol 14, p 3390 [Kloner Review].

[120] In a further article resulting from the Second Princeton Consensus Conference held in 2004, twenty-four (24) scientists reviewed recent safety and drug interaction data for three PDE5 inhibitors (sildenafil, tadalafil and vardenafil) with emphasis on the safety of these agents in men with ED and concomitant cardiovascular disease. This document is meant to provide practical guidelines for doctors who treat ED in patients who have cardiac issues. They came to the conclusion that organic nitrates "are absolutely contraindicated in patients taking PDE-5 inhibitors" (John B Kostis *et al*, "Sexual Dysfunction and Cardiac Risk (the Second Princeton Consensus Conference)", *Am J Cardiology* 2005, 96:313-321, p 317, AR Vol 29, p 6841).

[121] Lilly's own experts agree that nitrates should not be administered to a person who takes tadalafil until at least 48 hours have elapsed since the last dose of tadalafil (see Goldstein cross-examination, pp 145-146, AR Vol 24, pp 537-5376; Brock cross-examination, pp 325-327, AR Vol 23, pp 5182-5184). Dr. Brock did admit that he, like other clinicians, sometimes prescribes tadalafil to patients receiving nitrates in a practice that he described as an "off-label use", but that is insufficient to show that tadalafil can be safely co-administered with nitrates, not only because he does that with less than one percent of his patients, but also because it contradicts the evidence of the other two expert urologists, Dr. Goldstein and Dr. Melman, as well as the evidence of Dr. Siegel (Siegel affidavit, para 70, AR Vol 18, p 4278). According to Dr. Melman, in particular, a contraindication is a "bright line warning", and "[a] physician should never knowingly co-administer tadalafil and nitrates to a patient under any circumstances" (Melman

affidavit, para 122, AR Vol 18, p 4240). Lastly, it is clear from the wording of the US label and of the Canadian Product Monograph that the contraindication is based on tadalafil-specific studies, and is not simply a "class contraindication" applied reflexively to all PDE5 inhibitors.

[122] For all of the above reasons, the '684 Patent fails to meet the promise of reducing the effects of the nitrate interaction significantly (or to a clinically insignificant level), such that a contraindication of tadalafil and nitrates is not necessary.

[123] I am also of the view that as of the filing date, there was no demonstration or sound prediction of any improvement in nitrate interaction of the claimed doses of tadalafil over sildenafil.

[124] In its Memorandum of Fact and Law, Lilly claims that it was "apparent" from the 10 clinical studies described in the Pullman affidavit that the occurrences of adverse effects were "demonstrated" to be better for tadalafil than for sildenafil at the relevant date in respect of flushing, vision abnormalities and hypotension caused by concomitant use with nitrates. This is a surprising claim to make, considering that for 9 of these 10 studies nitrates were either completely prohibited or had not actually been received by any of the subjects. As previously noticed, the only study where nitrates were co-administered with tadalafil and sildenafil is the LVAB study, which is reported as Example 5 in the '684 Patent. I shall say more about that study shortly.

[125] Lilly also makes the dubious statement that direct comparative testing between tadalafil and sildenafil was not necessary, first, because reasonable comparisons could have been made on the basis of readily available data in the published literature at the time of the '684 Patent application filing and second, because direct head to head studies with PDE5 inhibitors are rare. This is an astonishing argument to make for a patentee promising that his product is an improvement over another one on the market. One would expect, on the contrary, that the most critical piece of evidence to support such a promise would be a direct comparison of the two compounds in clinical studies using similar methodologies.

[126] The LVAB study had a primary objective and two secondary objectives. The primary objective was to compare the hemodynamic effects of nitroglycerin administration during short-term multiple daily dosing of tadalafil to those during placebo treatment in healthy volunteers, while the secondary objectives were: 1) to compare the hemodynamic effects of nitroglycerin during administration of a single dose of tadalafil to those during a single dose of sildenafil, and 2) to compare the hemodynamic effects of nitroglycerin after a first daily oral dose of tadalafil to those following short-term multiple daily dosing of tadalafil. To that extent, the LVAB study was the only head to head study against sildenafil of any kind performed before the filing date. Yet Example 5 reports a "preliminary analysis" of only the first part of the LVAB study, and omits any discussion of the comparative part of the study.

[127] I have already referred to the fact that the LVAB study only used a small number of healthy volunteers rather than ED patients, and that these people were relatively younger than the age of the patient population with ED. What is most troubling, however, is that the undisclosed

part of the study comparing the co-administration of tadalafil and nitrates with the co-administration of sildenafil and nitrates demonstrated no statistically significant difference between tadalafil and sildenafil.

[128] In that study, the investigators performed a "frailty factor" analysis to examine the effects of different treatments on sensitivity to intravenous nitroglycerin. On page 32 of their report (AR Vol 17, p 4044), the authors explain that this analysis accounts for variation among study subjects in inherent sensitivity to nitroglycerins. In other words, they take into account in their statistics the people's inherent sensitivity to nitroglycerins; people who were more likely to have a significant blood pressure drop when taking nitroglycerin with placebo were also likely to have a significant drop when they took a study drug with it.

[129] The results of this "frailty factor" analysis are discussed on page 48 and reported in Table 11.7 on page 50 of that study (AR Vol 17, pp 4060-4062). On page 48, the report states that: 1) there was no significant difference between single dose tadalafil and placebo; 2) there were trends to suggest a difference between multiple dose tadalafil and placebo, but these were not statistically significant; and 3) single dose sildenafil was significantly different from placebo. What the LVAB study report fails to discuss, however, despite it being apparent from reviewing Table 11.7 on page 50, is that there was no statistically significant difference between the head to head comparison of tadalafil and sildenafil, both for single dose and multiple dose tadalafil vs sildenafil. These results are based on a survival analysis, measuring heart rate response to nitroglycerin and the occurrence of clinically significant hypotensive symptoms. The subjects received a graded infusion that consisted of up to seven escalating doses of nitroglycerin, each

given for a period of approximately 5 minutes. Blood pressure and heart rate were measured at 2 and 4 minutes after the initiation of each sequential dose. Nitroglycerin infusion was continued until a drop in systolic blood pressure of 30 mm Hg from the average of the preinfusion baseline values or a drop to an absolute systolic blood pressure of ≤85 mm Hg occurred. During intravenous nitroglycerin infusion, subjects were maintained at 70° head-up tilt. Following sublingual nitroglycerin administration, subjects rested in a supine position and were tilted from recumbency to 70° two minutes prior to the measurement time points every 5 minutes for a period of 30 minutes.

[130] The results of this survival analysis are based on observed differences. An observed difference is said to be statistically significant if the chance of having observed that difference (or an even larger difference) is less than the pre-defined level of significance, usually set at 0.05 in clinical studies (see Melman affidavit, para 112 and FN 16, AR Vol 19, p 4360). The "p-value", which is the chance of having observed a difference if there truly is no difference, is essentially the probability of getting a false positive. The smaller the p-value, the more likely it is that the observed difference is due to a real difference as opposed to being due to random chance. In other words, an observed difference is often defined as statistically significant if the probability of having observed that difference (if there truly is no difference) is less than 5% (or 0.05). The p-value when comparing single dose sildenafil with placebo was 0.007 (therefore significant), but the p-value when comparing single dose and multiple dose tadalafil vs single dose sildenafil was respectively 0.166 and 0.353 (therefore not significant). Therefore, the observed difference between sildenafil single dose and tadalafil single dose, as well as the

observed difference between sildenafil single dose and tadalafil multiple dose, is not statistically significant, as noted by Dr. Siegel in his affidavit (para 144, AR Vol 19, p 4419).

[131] Lilly tried to counter these findings with two strategies, neither of which is compelling. First, Lilly tried to argue that the LVAB study was not "powered" to detect a difference between tadalafil and sildenafil, by which it means, I gather, that a different design and a larger sample size would be required for a drug to drug study. The only evidence upon which Lilly relies for that proposition is a short answer given by Dr. Pullman on cross-examination, where he merely made that statement without any further explanation (Pullman cross-examination, p 172, AR Vol 28, p 6538). Not only is Dr. Pullman not an expert in statistical analysis and did not testify as an expert witness, but none of the two experts called by Lilly (who are not qualified as expert statisticians either) offered that explanation to minimize the impact of the drug to drug comparison in the LVAB study. Dr. Brock did speculate in cross-examination that it would be impossible to generate a p-value of less than 0.05 for Part B because there were not enough patients, but he admitted that he had not done the analysis (Brock cross-examination, pp 301-303, AR Vol 26, pp 6071-6073). Moreover, there is nothing in that study itself to the effect that Part B lacked statistical power.

[132] As pointed out by Mylan's counsel, Lilly purported to reject Part B as unreliable while simultaneously relying on results from that same part of the study. Indeed, the only data reported in Table 11.7 that comes from Part A is the data relating to multiple doses of tadalafil. The only comparison in this table that is exclusively from Part A is the comparison between placebo and multiple doses of tadalafil; the comparison between placebo and single dose sildenafil, in

particular, also comes from Part B. It may well be that Part B is sufficiently powered except for drug to drug comparison, but once again no such explanation or evidence was provided by Lilly's experts.

[133] The second strategy used by counsel for Lilly to offset the head to head testing of tadalafil and sildenafil in the LVAB study was to attempt to rely on an indirect comparison between tadalafil testing in the LVAB study and sildenafil testing in a separate study reported by Webb *et al* ("Sildenafil Citrate and Blood-Pressure-Lowering Drugs: Results of Drug Interaction Studies with an Organic Nitrate and a Calcium Antagonist", *Am J of Cardiology*, 1999, 83 (5A), p 21C-28C, AR Vol 6, p 1434). This study is cited in the '684 Patent, was known in the prior art, and was cited in the LVAB nitrate study that Lilly performed as well as in Mylan's NOA. In that study, the subjects were given 25 mg sildenafil three times a day for four days. On the fifth day, the subjects received a sublingual glyceryl trinitrate tablet 1 hour after taking sildenafil or placebo. Within 7 minutes of taking that tablet, subjects who were receiving sildenafil treatment had a mean decrease in systolic blood pressure that was 4 times greater than that during placebo treatment. Moreover, 11 of the 12 subjects removed the glyceryl trinitrate tablet after 2-7 minutes because of symptomatic hypotension or a decrease in systolic blood pressure of >25 mm Hg.

[134] At first sight, this study appears to substantiate the findings of the LVAB study, even though the LVAB study used a better and more appropriate age range and a better number of subjects. The problem, however, is that none of the experts attempted to compare the two studies, and only Dr. Siegel was explicitly asked to compare them in cross-examination. He opined that the results could not be compared because of the challenges involved in comparing

across different studies, especially when such studies involve a very limited number of subjects (Siegel cross-examination, p 61, AR Vol 32, p 7173).

[135] There were, in fact, a number of methodological differences between the two studies, including the dose of nitrate administered, whether the subjects were pre-screened for nitrate tolerance, the time course of the study, whether the subjects received nitrates in a head-up or supine position, the stopping rules and safety mechanisms, and how the results were analyzed. Apart from Dr. Siegel's opinion respecting the risks involved in comparing studies, there is no expert evidence indicating how and whether the results of the Webb study can be compared to the results of the LVAB study, to say nothing of whether the Webb study can be used to show an improvement of tadalafil over sildenafil.

[136] I am of the view, therefore, that as of the filing date, Lilly had failed to demonstrate that doses of 1 to 20 mg of tadalafil had any improvement over sildenafil in terms of nitrate interaction. The only head to head study comparing the nitrate interaction of tadalafil and sildenafil, the LVAB study, shows no statistically significant difference between the two compounds. Counsel for the Applicant asserted that head to head testing was rare in the pharmaceutical industry, but there is no evidence to support that proposition. What is perhaps even more troubling is the fact that Lilly, having filed a patent that is comparing the side effects between tadalafil and sildenafil, did not even address the issue up front; there is simply no credible reason to explain why Lilly's experts failed to mention in their affidavits that such head to head testing had been conducted before the filing date. As for their unexpected and last-ditch explanation that Part B of that study is not reliable because it was not statistically powered for

the purpose of a drug to drug comparison, it appears to be based on pure conjecture and is not grounded in any evidence.

[137] Of course, utility can also be soundly predicted if not demonstrated by the time of filing. At least three requirements must be met for sound prediction to be established: 1) there must be a factual basis for the prediction; 2) the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and 3) there must be proper disclosure (*AZT*, above, at para 70). According to Lilly, a person skilled in the art can conclude the invention was soundly predicted by reviewing only the disclosure of the '684 Patent, in particular Examples 5, 6 and 7 and the table on page 32. Having carefully considered the matter, I am unable to agree with that submission.

[138] As emphasized above, the only factual basis for the prediction of an improvement in the nitrate interaction is limited to Example 5 of the '684 Patent (as opposed to the entire LVAB study). I agree with Mylan's experts that the information disclosed in that Example would have been insufficient to move a skilled person off their expectation that tadalafil, as a PDE5 inhibitor, would also have an interaction with nitrates that was similar to the interaction observed with sildenafil. First of all, there is no evidence that a skilled person could predict an improvement in <u>incidence</u> based on the qualitative statement in Example 5 about <u>mean</u> effects on blood pressure. The incidence represents the proportion of individuals experiencing potentially clinically significant blood pressure changes; these individuals are sometimes referred to as "outliers". The proportion of outliers is the most important measure from a clinical perspective, because it gives an estimate of the number of people in a population who are at risk of having an adverse effect.

As Dr. Siegel pointed out in his affidavit, low frequency adverse effects can translate into relatively large absolute numbers of patients who would experience such adverse effects when a drug is prescribed to a large patient population. If a million patients receive a drug, for example, and 1% of them experience an adverse effect, then this translates to 10,000 "outlier" individuals who will experience that event (Siegel affidavit, para 216, AR Vol 18, pp 4319-4320). This is undoubtedly what really drove regulatory agencies to make that statement about PDE5 inhibitors and nitroglycerin interactions (Brock cross-examination, pp 339-340, AR Vol 23, p 5196-5197; Goldstein cross-examination, p 152, AR Vol 24, p 5382). The mean, by contrast, measures the average effect over the entire study population, and is much less significant because the average response over a population does not reflect individual sensitivity to a drug.

[139] I also agree with Mylan's experts that a skilled person could not extrapolate from the results obtained with doses of 10 mg to other dosages. Dr. Goldstein himself seems to accept that you have to do the trials to find out, and refers to a study where the data showed that a 5 mg dose created a problem where a 10 mg dose did not (Goldstein cross-examination, p 296, AR Vol 24, p 5526). Lilly argued that although the 20 mg dose was not tested, it was "bracketed" by doses of 10 mg and 25 mg, so that the inventors could have predicted the utility of a 20 mg dose using their pharmacokinetic model. Once again, treatment-related adverse events are very difficult to predict, as Lilly itself admitted in its Memorandum of Fact and Law when dealing with obviousness (at para 115); in any event a head to head nitrate testing of a 25 mg tadalafil and 50 mg sildenafil doses was neither disclosed in the Patent nor had even been performed as of the filing date. Similarly, Dr. Melman pointed out that a skilled person would not have been able to extrapolate from the results observed in Example 5 to likely outcomes in the older patient

population with erectile dysfunction, particularly in light of the lack of detail reported in Example 5 (Melman affidavit, para 182, AR Vol 18, p 4255; see also Siegel affidavit, para 163, AR Vol 18, p 4302). To be fair, Dr. Brock and Dr. Goldstein are of the opposite view on this question. Nevertheless, I prefer the opinions of Dr. Melman and Dr. Siegel, if only because the disclosure of the LVAB study in Example 5 is very sketchy. In offering a "preliminary analysis" of that study and describing the results only in a qualitative way, the Patent would unlikely provide a sound basis to make a prediction for an older population.

[140] For all of the above reasons, I am of the view that a skilled person could not have soundly predicted that unit doses of 1 to 20 mg of tadalafil would provide an improvement in the nitrate interaction over sildenafil. Not only is there no factual basis for the prediction and no articulable and sound line of reasoning from which the desired result can be inferred from the factual basis, but the '684 Patent does not even provide a proper disclosure. As the Supreme Court of Canada stated in *AZT*, above, at para 83, "[t]he public is entitled to accurate and meaningful teaching in exchange for suffering the patent monopoly". Example 5 only describes part of the LVAB study, and fails to even refer (let alone explain) the results of the head to head testing against sildenafil. This failure is clearly unacceptable in a Patent that promises not only efficacy in treating ED, but also a better side effect profile as against sildenafil, and a patentee should not be able to benefit from a partial, if not misleading, disclosure.

[141] Even if utility could have been soundly predicted at the filing date, the '684 Patent must be voided if, as of today, the clinical evidence indicates that tadalafil does not significantly improve over sildenafil with respect to nitrate interactions. In a head to head study conducted by

Lilly employees and consultants referred to as LVCM, the results of which were reported in a review article by Dr. Kloner and others (Kloner Review, above), it appears that a similar number of individuals had clinically significant changes in blood pressure following administration of 10 mg dose of tadalafil plus nitrates as with sildenafil plus nitrates, and this was approximately twice the incidence of the group receiving placebo plus nitrates. The authors of the Kloner Review summarize the results of this study as follows (see Kloner Review, pp 41M-42M, AR Vol 14, pp 3394-3395):

> Both tadalafil and sildenafil modestly augmented the mean maximal blood pressure decrease induced by sublingual nitroglycerin when compared with placebo. However, compared with placebo treatment, the frequency of outliers on day 1 was greater during the tadalafil and sildenafil treatment periods. These results suggest that, in a subset of subjects, both tadalafil and sildenafil augment the nitrate-induced decrease in blood pressure.

[142] On that basis, they concluded that "…the frequency of potentially significant blood pressure effects indicates that, as with sildenafil, tadalafil should not be used in combination with nitrates" (p 45M, AR Vol 14, p 3398). This study, along with two other studies reviewed by Kloner *et al* showing that single doses of 5 or 10 mg of tadalafil have clinically significant adverse interactions with nitrates, appear to be the basis for the 48 hour duration of the contraindication of co-administering tadalafil and nitrates (see the FDA Review for the NDA for CIALIS (tadalafil), AR Vol 7, p 1692; see also Siegel affidavit, para 210, AR Vol 18, p 4316; Melman affidavit, paras 124-128, AR Vol 18, pp 4240-4242; Goldstein cross-examination, p 185, AR Vol 24, p 5415).

[143] In his affidavit (at paras 244-248), Dr. Goldstein comments on the Kloner Review and focuses only on the changes in mean blood pressure while ignoring the number of patients with

clinically significant changes in blood pressure (the so-called "outliers"). For the reasons given above, I agree with Dr. Melman and Dr. Siegel that the most significant data are not the results relating to the average blood pressure changes across the study population, but the actual number of patients who experience serious decreases in blood pressure (see Melman affidavit, para 166, AR Vol 18, p 4252; Siegel affidavit, para 219(e)(i), AR Vol 18, p 4324).

[144] Accordingly, I am in agreement with counsel for Mylan that as of today, there is no improvement in nitrate interaction of tadalafil over sildenafil, when considering the incidence of a significant drop in blood pressure. Moreover, to the extent that there is any difference between tadalafil and sildenafil, tadalafil is contraindicated with nitrates for a longer period of time (48 hours vs 24 hours) because of its longer half-life. Therefore, even as of today, the '684 Patent fails to meet the promise of providing any significant improvement in the nitrate interaction as compared to sildenafil. Based on this finding, I note that even if I had accepted Lilly's construction of the promise—namely that the Patent promises a reduction of side effects compared to sildenafil—I would have found that this narrower promise is neither demonstrated nor soundly predicted.

(2) Is the allegation that the claims are invalid for anticipation by the '784 Patent justified?

[145] Pursuant to section 28.2 of the *Patent Act*, a patent will be invalid for anticipation if the essential elements of the claimed invention were disclosed in such a manner that it became available to the public more than one year before the filing date, and were enabled to a skilled person: *Olanzapine*, above, at paras 43-45. The Supreme Court carefully examined that question

in *Sanofi-Synthelabo*, above, and made it clear that the disclosure does not have to be an exact description of the claimed invention; the disclosure must be sufficient so that, when read by a person skilled in the art and willing to understand what is being said, it can be understood without trial and error (at para 32). As noted by Justice Hughes in *Abbott Laboratories v Canada (Minister of Health)*, 2008 FC 1359, at para 75, "[i]f the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation" (aff'd 2009 FCA 94).

[146] At the stage of disclosure, there is no room for trial and error or experimentation by the skilled person; that person is simply reading the prior patent for the purposes of understanding it. If the disclosure requirement is satisfied, however, a certain amount of trial and error experimentation of a kind normally expected may be carried out at the enablement stage. In discussing enablement, Justice Rothstein wrote in *Sanofi-Synthelabo*, at para 37:

> The prior patent must provide enough information to allow the subsequently claimed invention to be performed without undue burden. When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and would not be considered undue burden. But experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be laid down; however, prolonged or arduous trial and error would not be considered routine.

[147] There is no disagreement between the parties as to the applicable law of anticipation. Mylan claims that if the '684 Patent is not a selection patent (as I have found), then it is anticipated by the '784 Patent because the claimed invention was disclosed and enabled by the '784 Patent. I agree.

[148] The '784 Patent disclosed: (1) unit dosage forms of tadalafil, such as tablets or capsules, in the dosage range from 0.2 to 400 mg; (2) with the unit dosage form suitable for oral administration; and (3) for use in treating male ED. It would appear, therefore, that the claimed invention of the '684 Patent was disclosed in the '784 Patent, as all of the essential elements of the claims of the '684 Patent are disclosed in the '784 Patent. I do not think there can be any dispute that the doses of tadalafil in claims 2 to 6 and 10 of the '684 Patent (1 to 20 mg) are entirely within the dosage range disclosed in the '784 Patent. In fact, the '784 Patent itself stated that "[i]n practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient" ('784 Patent, p 5, lines 9-11, AR Vol 21, p 4785). Since the reduced side effect profile is not part of the claimed invention but is merely a result of this invention, it would appear that the '684 Patent was disclosed by the '784 Patent. When a second patent is not interpreted as a selection patent, its advantages do not factor into the inquiry of anticipation and need not be disclosed in a previous patent to be anticipated.

[149] Not only did the '784 Patent disclose all the essential elements of the '684 Patent, but it also provides the skilled person with enough information to perform the invention claimed in the '684 Patent without undue burden. There is no evidence in the record to show that a skilled

person would have had to go through prolonged experiments or trials and errors to come up to unit dosage forms of 1 to 20 mg of tadalafil, administered orally, for the treatment of ED. As a result, I find that the claimed invention of the '684 Patent was both disclosed and enabled by the '784 Patent, and that the '684 Patent was therefore anticipated.

[150] Counsel for Lilly tried to argue that a maximum daily dosage of 20 mg is another essential element of the claims in the '684 Patent and is part of the claimed invention, and that this was not disclosed in the '784 Patent. According to Lilly, the specification of the '684 Patent makes it "abundantly clear" that when the inventors are talking about a "unit dosage form", it must be a unit dosage form that is limited to one administered to a maximum of 20 mg per day. More specifically, Lilly relies on page 8 of the Patent, where the specification sets out that there are preferable dosage strengths but lists the maximum per day dose as 20 mg, and on the statement at the end of the disclosure that "a unit dose of about 1 to about 20 mg … administered up to a maximum of 20 mg per 24-hour period, both effectively treats ED and minimizes or eliminates the occurrence of adverse side effects" ('684 Patent, p 32).

[151] This reading of the '684 Patent is far from convincing. First of all, there is no reference to a daily maximum total in the claims themselves. More importantly, I fail to see how the phrase "pharmaceutical unit dosage form" can be read to imply a daily maximum dose; it more likely refers to the particular way the product is administered. Indeed, the related term "oral dosage form" is defined in the '684 Patent in the following manner:

> The term "oral dosage form" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, tablets, capsules, and gelcaps.
>
> ('684 Patent, p 7)

[152] This is precisely how the expression "unit dosage form" is used in the '684 Patent when describing what was disclosed in a US patent analogous to the '377 Patent (at p 3, lines 26-28), and in claim 7 (at p 34: "[t]he dosage form of any one of claims 1 through 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap").

[153] Furthermore, I agree with Mylan that the daily maximum total dose pertains to an instruction as to how to administer a unit dosage form rather than as an aspect of the unit dosage form itself. This is consistent with the description of the package insert that is found in the '684 Patent, which refers to the daily maximum total dose separately from the "unit dosage form" itself:

> The package insert also provides instructions to administer one or more about 1 to about 20 mg unit dosage forms as needed, up to a maximum total dose of 20 mg per day.
>
> ('684 Patent, p 8)

[154] Finally, the Canadian file history confirms that the daily maximum total dose is a separate element from the unit dosage form itself. The Patent Cooperation Treaty (PCT) file corresponding to the '684 Patent, which was the application originally filed with the Canadian Patent Office, contained claims reciting the method of treating sexual dysfunction comprising

administering about 1 to 20 mg tadalafil, up to a maximum total dose of 20 mg per day. In response to the Examiner having found that such claims were invalid for claiming a method of medical treatment (citing *Tennessee Eastman v Commissioner of Patents*, (1974) SCR 111; *Imperial Chemical Industries v Commissioner of Patents*, (1986) 3 FC 40; see Potter affidavit Exh "C", Doc #2, AR Vol 4, p 654), Lilly redrafted these claims as "use" claims and removed any reference to a maximum total dose per day. While the file history of a patent application is generally considered as extrinsic evidence and not admissible, I have already held that a change in the wording of a claim as a result of an objection from the Patent Office is an objective fact that can be considered and from which an inference may de drawn: *Distrimedic v Dispill*, 2013 FC 1043, paras 209-210.

[155] Therefore, I conclude that the '684 Patent is anticipated by the '784 Patent.

(3) Is the allegation that the claims are invalid for obviousness justified?

[156] Obviousness was an implicit part of the notion of "invention", and is now codified in section 28.3 of the *Patent Act*:

Invention must not be obvious	**Objet non évident**
28.3 The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to	28.3 L'objet que définit la revendication d'une demande de brevet ne doit pas, à la date de la revendication, être évident pour une personne versée dans l'art ou la science dont relève l'objet, eu égard à toute communication :
(a) information disclosed more	a) qui a été faite, plus d'un an

than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and	avant la date de dépôt de la demande, par le demandeur ou un tiers ayant obtenu de lui l'information à cet égard de façon directe ou autrement, de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs;
b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.	b) qui a été faite par toute autre personne avant la date de la revendication de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs.

[157] Pursuant to section 28.1, obviousness must be assessed as of the priority date, i.e. April 30, 1999.

[158] The Supreme Court laid out a four-part test for obviousness in *Sanofi-Synthelabo*, above, at para 67, which can be summarized as follows:

a) Identify the notional "person skilled in the art" and the relevant common general knowledge of that person;

b) Identify the inventive concept claimed in the patent;

c) Identify the differences between the common general knowledge and the inventive concept;

d) Do those differences require a degree of invention, or are they more or less self-evident?

[159] In assessing the "obvious to try" issue at the fourth step, the test is whether it is very plain or more or less self-evident that what is being tested ought to work. The mere possibility that something might turn up is not enough: *Sanofi-Synthelabo*, at para 65. If an obvious to try analysis is warranted, particularly in areas where advances are won by experimentation, the following factors should be taken into consideration:

> 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> 3. Is there a motive provided in the prior art to find the solution the patent addresses?
>
> (*Sanofi-Synthelabo*, above, at para 69)

[160] I have already described the person skilled in the art at paragraph 83 of these reasons as a person or a drug development team having expertise in areas that are relevant to drug dosing, such as pharmacology and/or pharmacokinetics, physiology, dose ranging and safety assessment of candidate therapeutics and with experience in the treatment of ED.

[161] There is substantial agreement between the parties as to the state of the art at the priority date (April 30, 1999). As described above, the '784 Patent disclosed tadalafil, in the dose range of 0.2 to 400 mg, for use in the treatment of ED, by oral administration. It was known that sildenafil's approved doses of 25 mg, 50 mg and 100 mg were effective in treating ED, and that the effectiveness of the compound was proportional to the dose. Lilly's experts also agree that sildenafil's side effects were known to be dose proportional (the lower the dose, the fewer the

side effects): Goldstein cross-examination, pp 293-294, AR Vol 24, pp 5523-5524; Brock cross-examination, p 358, AR Vol 23, p 5215.

[162] According to Dr. Siegel (Siegel affidavit, para 237, AR Vol 18, p 4330-4331), the comparative *in vitro* potency of tadalafil and sildenafil was also known. The IC_{50} of tadalafil against PDE5 was reported as 2 nM in the '784 Patent, while for sildenafil the IC_{50} against PDE5 had been reported as 3 nM and as 3.9 nM ('684 Patent, p 2). This would indicate to the drug development team that an amount of tadalafil would be equally potent as a greater amount of sildenafil. Moreover, the molecular weights of sildenafil and tadalafil were also known as of 1999, the first one being 474.6 g/mol whereas the second was 389.4 g/mol. It would therefore be known that 1 mg of tadalafil would yield more molecules of active agent in the body than 1 mg of sildenafil. Combining the relative molecular weights and *in vitro* potency data, a 25, 50 or 100 mg dose of sildenafil would have been estimated to be equally potent to doses of approximately 11 to 55 mg of tadalafil (depending on which sildenafil potency value one chooses).

[163] On cross-examination, Dr. Siegel admitted that it is not uncommon for IC_{50} values to have some variability. On that basis, counsel for Lilly put to him much higher IC_{50} values for tadalafil from non-public sources, which would make tadalafil slightly less potent than sildenafil (Siegel cross-examination, pp 105-108, AR Vol 32, pp 7217-7220). However, these values are totally irrelevant for the purpose of the obviousness analysis since internal and non-published IC_{50} values are not part of the common general knowledge.

[164] The identification of the inventive concept is laid out with ambiguity in Lilly's submission. Both in its written argument and orally, counsel defined the inventive concept "as a unit dosage form of tadalafil that effectively treats male ED with a maximum daily dosage of 20 mg and a dosage strength for the unit dosage form of between 2 and 20 mg" (Lilly's Memorandum of Fact and Law, para 108). It then goes on to state that the decreased side effect profile is not part of the claimed invention but is a result or a benefit of the invention (para 109). Yet in applying the obviousness framework, Lilly appears to be considering the reduced side effects as it concludes that it would not have been self-evident that the dose limitations "would still be effective in treating ED and would lead to a better side effect profile than sildenafil" (para 122). At the end of the day, I do not think that it matters for the purpose of the obviousness analysis whether or not the improved side effect profile is considered to be part of the inventive concept. The real issue is whether it would have been obvious for the person skilled in the art that unit dosage form of tadalafil between 2 and 20 mg, or more precisely the 2.5 and 5 mg doses asserted by Lilly at the hearing, would effectively treat male ED.

[165] There is no question that sildenafil, as the only approved oral ED medication, would have guided the direction of research with regard to future ED medications acting through PDE5 inhibition. Lilly's thesis is that a person skilled in the art would have believed that tadalafil, based on its PDE5 inhibitory activity, would have similar efficacy in humans to sildenafil. When human efficacy was confirmed at the same dosage levels as sildenafil in the early clinical trials, there would have been no motivation to investigate lower dosages, especially bearing in mind the enormous extra expense and research commitment involved in such a speculative venture. This argument is unconvincing for a number of reasons.

[166] First of all, a drug development team following the ordinary course of development would likely have taken into account the publicly available information relating to molecular weight and *in vitro* potency of tadalafil and sildenafil and, even before doing any testing, would have started with doses of approximately 11 to 55 mg of tadalafil since they would be the equivalent of 25 to 100 mg doses of sildenafil. Indeed, Dr. Brock indicated in cross-examination that there was a study indicating that sildenafil was effective in doses from 10 to 50 mg, which means that a starting dose of as low as 5 mg would have been in order (Brock cross-examination, p 170, AR Vol 23, p 5027; see Potter affidavit, Exh "C", Doc #20, AR Vol 6, p 1374).

[167] Dr. Siegel admitted that there are a number of factors that can affect potency beside molecular weight, such as half-life, selectivity, structure, hydrophobicity and other pharmacokinetic parameters (Siegel cross-examination, pp 108-109, AR Vol 32, pp 7220-7221). This is precisely why testing is required, as Dr. Siegel readily accepts. That being said, it would be an overstatement to claim that there were an infinite number of predictable solutions, or that it was "a long and arduous process involving the design and execution of complex clinical studies and the analysis of massive volumes of data resulting from those studies" that allowed the inventors to reach their conclusions, as Dr. Goldstein would have us believe (Goldstein affidavit, para 366, AR Vol 2, p 330).

[168] First of all, the starting point could be easily ascertained, based on a comparison of the potency and relative molecular weight of tadalafil and sildenafil. Second, lowering the dosage is a standard way to reduce side effects. On cross-examination, Dr. Pullman asserted that the mindset of the pharmaceutical industry is to find the optimal effective dose, by which he means

the highest dose that you "can get away with" that is still safe, because this is the dose which is the most effective, yet still safe (Pullman cross-examination, p 77, AR Vol 28, p 6443). On this question, I prefer Dr. Siegel's opinion, not only because he has been involved in the development of more than 150 drugs across many therapeutic areas and has a vast experience in the development of dosing regimens, but also because he is an independent expert witness as to the state of the art approach to drug dosing, whereas Dr. Pullman is the inventor and gave evidence about his own alleged invention.

[169] Dr. Siegel's opinion is that there is a well-established approach to the process of determining an appropriate dose, which has not changed in 20 to 30 years:

> With respect to dosing, the ultimate goal of a drug development team is to find the dosage range that is the most effective with the least adverse effects in the cohort of patients intended for treatment. In this regard, the team will look for a minimal effective dose and a maximum tolerated dose, where the minimal effective dose is the lowest dose at which an adequate effect is measured in a sufficiently large proportion of the target patient population, and the maximum tolerated dose is the highest dose before onset of intolerable adverse effects in the target patient population.
>
> (Siegel affidavit, para 40, AR Vol 18, p 4272)

[170] Even if one were to take the Pullman affidavit at face value, it would appear therefore that the tadalafil drug development team deviated markedly from the ordinary course of drug development, starting with a 100 mg dose instead of adjusting for the different potencies of tadalafil and sildenafil and for the *in vitro*, pharmacokinetic and animal toxicity data. I agree with Dr. Siegel that this deviation resulted in the tadalafil team starting human testing with a substantially higher dose than would have been selected by a skilled person. Having started with an unnecessarily high dose, the tadalafil team cannot claim to have "surprisingly" found that they

could use a lower dose. I find, therefore, that a person skilled in the art would have likely designed an initial dose escalation study to start at approximately 5 mg of tadalafil and move up to approximately 50 mg; as a result, there was a finite number of predictable solutions.

[171] As for the actual course of conduct, the Pullman affidavit put forward by Lilly is flawed in many respects and has many gaps. First, Dr. Pullman had no knowledge of the initial human clinical testing of tadalafil as he only became involved in the development of tadalafil in late 1998. For example, the earliest efficacy studies in humans (the LVBI study) were completed before Dr. Pullman joined Lilly (see Pullman affidavit, Exh "B", AR Vol 15, p 3486). As a result, the early clinical studies that were conducted to determine the appropriate starting dose in humans are only briefly referred to in his affidavit, without much detail. If only for that reason, Dr. Pullman's evidence is of little weight. Moreover, Mylan put forward some evidence suggesting that ICOS planned to include doses within the range claimed in the '684 Patent prior to actually carrying out any testing of tadalafil for the treatment of ED (Potter affidavit, Exh "D", Doc #1, AR Vol 9, pp 2295-2296; Pullman affidavit, Exh "F", AR Vol 16, p 3730); however, Lilly's counsel refused to produce those clinical trial protocols prepared by ICOS. Since Lilly's own expert agreed that it would be impossible to comment on ICOS' actual course of conduct without reviewing such documents (Brock cross-examination, pp 264, 266-276, AR Vol 26, pp 6034, 6036-6046), it would obviously be inappropriate for this Court to do so.

[172] In the result, I find that it was more or less self-evident that the lower and narrower doses of tadalafil in the '684 Patent would be effective in treating ED in humans and would result in a reduced side effect profile. There was clearly a motive provided in the prior art to find the

solution addressed by the Patent, as a skilled person will look for a minimal effective dose and a maximum tolerated dose. There is no evidence as to the extent and amount of effort required to achieve the invention, but on the basis of the relative potency and relative molecular weight of sildenafil and tadalafil, and of the ordinary course of drug development, there was a finite number of predictable solutions. Therefore, the '684 Patent is invalid for obviousness.

VI. Conclusion

[173] In summary, I find that the following allegations of invalidity regarding the '684 Patent are justified: 1) it lacks utility, as the promise of the patent was neither demonstrated nor soundly predicted at the filing date, and is still not met; 2) it is anticipated by the '784 Patent, as the dosages claimed in the '684 Patent are entirely within the range disclosed in the '784 Patent; and 3) it was obvious that a unit dose of 1 to 20 mg would be effective in treating ED and would lead to a better side effect profile than sildenafil.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. The following allegations of invalidity regarding the '684 Patent are justified:

   a) it lacks utility, as the promise of the patent was neither demonstrated nor soundly predicted at the filing date, and is still not met;

   b) it is anticipated by the '784 Patent, as the dosages claimed in the '684 Patent are entirely within the range disclosed in the '784 Patent; and

   c) it was obvious that a unit dose of 1 to 20 mg would be effective in treating ED and would lead to a better side effect profile than sildenafil;

2. The application for an order prohibiting the Minister of Health from issuing a notice of compliance to Mylan until the expiry of Canadian Patent No 2,371,684 is dismissed;

3. The Respondent Mylan is entitled to recover its costs from the Applicant on the application; there will be no costs with respect to the motion; if the parties cannot agree on the quantum, the question of costs can be brought forward by Notice of Motion; and

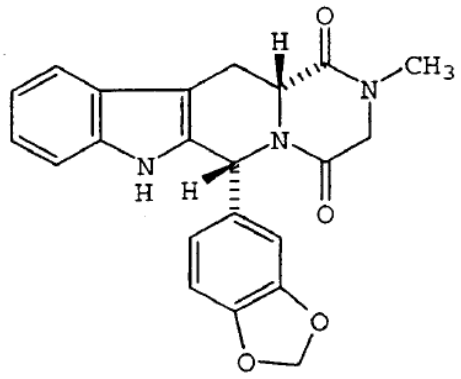
4. No costs will be awarded for or against the Minister.

"Yves de Montigny"

Judge

ANNEX

1. A pharmaceutical unit dosage form comprising about 1 to about 20 mg of a compound having the structural formula:



said unit dosage form being suitable for oral administration.

2. The dosage form of claim 1 comprising about 2 to about 20 mg of the compound in unit dosage form.

3. The dosage form of claim 1 comprising about 5 to about 20 mg of the compound in unit dosage form.

4. The dosage form of claim 2 comprising about 2.5 mg of the compound in unit dosage form.

5. The dosage form of claim 3 comprising about 5 mg of the compound in unit dosage form.

6. The dosage form of claim 3 comprising about 10 mg of the compound in unit dosage form.

7. The dosage form of any one of claims 1 through 6 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

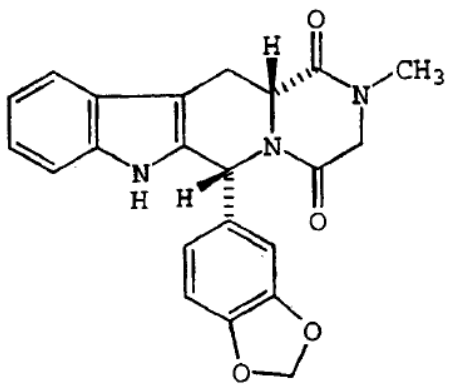
8. The dosage form of any one of claims 1 through 6 wherein the unit dose is in the form of a tablet.

9. The dosage form of any one of claims 1 through 6 for use in treating sexual dysfunction in a patient where inhibition of PDE5 provides a benefit.

10. The dosage form of claim 9 wherein the sexual dysfunction is male erectile dysfunction.

11. The dosage form of claim 9 wherein the sexual dysfunction is female arousal disorder.

12. Use of a unit dose containing about 1 to about 20 mg of a compound having the structure



for treating sexual dysfunction in a patient.

13. The use of claim 12 wherein the unit dose contains about 2 to about 20 mg of the compound.

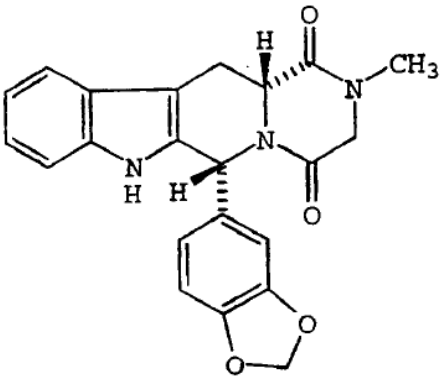
14. The use of claim 12 wherein the unit dose contains about 5 mg of the compound.

15. The use of claim 12 wherein the unit dose contains about 10 mg of the compound.

16. The use of claim 12, wherein the unit dose contains about 20 mg of the compound.

17. The use of claim 12 wherein the unit dose is in a form selected from the group consisting of a liquid, a tablet, a capsule, and a gelcap.

18. Use of a unit dose containing about 1 to about 20 mg of a compound having the structure



for the manufacture of a medicament for the treatment of sexual dysfunction in a patient in need thereof.

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-298-13
STYLE OF CAUSE:	ELI LILLY CANADA INC. v MYLAN PHARMACEUTICALS ULC AND THE MINISTER OF HEALTH AND ICOS CORPORATION
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