Federal Court  Cour fédérale

Date: 20150107

Docket: T-296-13

Citation: 2015 FC 17

Ottawa, Ontario, January 7, 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 2,226,784 (the '784 Patent).

[2] Mylan, on the other hand, argues that Lilly's application should be dismissed because the '784 Patent is invalid for lack of utility and for obviousness-type double patenting.

[3] For the reasons that follow, I have come to the conclusion that the Applicant has met its burden of proof on the balance of probabilities to establish for the purpose of these proceedings that the '784 Patent is valid, and that an order prohibiting the Minister of Health from issuing an NOC should issue.

I. Background

[4] Erectile dysfunction, commonly referred to as ED, is a medical condition described as the inability of a man to obtain and maintain an erection sufficiently hard for vaginal penetration and sexual intercourse. ED is an extremely common medical condition believed to affect upwards of 50 percent of men aged 40 to 70.

[5] A muscle is usually considered to be in its resting state when relaxed. In the case of the penis, the reverse is true. The penis contains two symmetrical compartments above and on either side of the urethra, each of which is called a corpus cavernosum. They consist of small blood vessels or passages surrounded by smooth muscle which can contract or relax as with any form

of muscle. When constricted, the smooth muscle restricts the flow of blood through the blood vessels in the arterial network entering the corpora cavernosa, acting much like a ligature. Blood exits the corpora cavernosa through veins at approximately the same rate as it enters through the arteries, maintaining the penis in a non-erect state. When an erection is triggered, the smooth muscle surrounding the vessels in the arterial network and the cavernous smooth muscle relax, no longer constricting the arteries delivering blood to the corpora cavernosa. Blood then floods into the highly vascularized tissue of the corpora cavernosa, causing them to swell. That swelling, in turn, squeezes the venules of the membrane enclosing the corpora cavernosa, thereby reducing the size of their internal passages and reducing their ability to drain blood from the corpora cavernosa. The result is that the penis becomes engorged with blood and rigid.

[6] Relaxation of smooth muscle in the penis is therefore a key to the erectile process. What, then, causes smooth muscle to relax and contract? Smooth muscle, which is found in many parts of the body, is under the control of the involuntary autonomic system. Smooth muscle relaxation results from a cascade or series of highly complex biochemical reactions within the body involving chemical messengers operating on communication systems called “pathways”.

[7] By the priority date of the ‘784 Patent, it was known that there are many different pathways that lead to penile smooth muscle relaxation. The pathway to which the Patent is directed is the NO/cGMP pathway. In this pathway, sexual stimulation results in the non-adrenergic non-cholinergic (NANC) nerves releasing nitric oxide (NO). Upon stimulation, the NANC nerves release a flood or rush, of NO. It is known that this flood of NO is primarily responsible for producing an erection.

[8] The nitric oxide diffuses through the cell membrane. Inside the cell, the nitric oxide stimulates guanylate cyclase to convert guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). An increase in the amount of cGMP inside a smooth muscle cell leads to relaxation of the smooth muscle and eventually to an erection.

[9] A class of enzymes known as phosphodiesterases (PDEs) also regulates the intracellular concentrations of the cGMP. One of these PDEs, PDE V, breaks down the cGMP to its non-cyclic form, GMP. In contrast to cGMP, GMP does not cause smooth muscle relaxation. Tadalafil works by inhibiting PDE V, thereby preventing PDE V from breaking down cGMP to the inactive GMP. Increased concentrations of cGMP then facilitate smooth muscle relaxation.

[10] Tadalafil was initially developed by Drs. Daugan and Grondin and their colleagues at GlaxoSmithKline (Glaxo). It was first disclosed and claimed in Canadian Patent No. 2,181,377 (the '377 Patent), which was filed in Canada on January 19, 1995 with a priority date of January 21, 1994. It was published on July 27, 1995. The '377 Patent claims novel compounds, including tadalafil, pharmaceutical compositions, and the use of tadalafil in the treatment of various disorders where smooth muscle relaxation was thought to be beneficial, including cardiovascular disorders. This Patent is entitled "Tetracyclic Derivatives, Process of Preparation and Use".

II. The Impugned Patent

[11] The '784 Patent was filed in Canada on July 11, 1996, with a priority date of July 14, 1995. It is entitled "Use of cGMP-Phosphodiesterase Inhibitors to Treat Impotence", and its sole

inventor is Dr. Daugan. The ‘784 Patent relates to the use of certain tetracyclic derivatives which are potent and selective inhibitors of PDE V in the treatment of impotence.

[12] According to the specification part of the disclosure, many different drugs have been shown to induce penile erection but are only effective after direct injection into the penis, and are not approved for ED. Current medical treatment involves either injection of vasoactive substances or the use of glyceryl trinitrate patches applied to the penis; while these treatments are effective, they often produce undesirable side effects.

[13] The specification goes on to describe the compounds of the invention (tadalafil and 3-methyl tadalafil), and states that these compounds, “unexpectedly”, have been found to be useful in the treatment of ED. “Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration” (pp 3-4 of the Patent).

[14] The gist of the invention is described in the following way:

> It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP specific PDE. It has now been surprisingly found that human corpus cavernosum contains three distinct PDE enzymes. The predominant PDE has further surprisingly been found to be cGMP PDE. As a consequence of the selective PDE V inhibition exhibited by compounds of the present invention, the subject compounds can elevate cGMP levels, which in turn can mediate relaxation of the corpus cavernosum tissue and consequent penile erection.
>
> (‘784 Patent, p 4)

[15] Oral administration is said to be the “preferred route”, because it is the most convenient and avoids the disadvantages associated with intracavernosal (i.c.) administration, but the drug

can also be administered sublingually or buccally. Oral dosages of the compound for curative or prophylactic treatment of ED are said to be in the range of from 0.5 to 800 mg daily, the actual dosing regimen being determined by a physician. For human use, the compounds will be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration: "For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents" ('784 Patent, p 5).

[16] The '784 Patent includes data from two *in vitro* tests on tadalafil and 3-methyl tadalafil. The first test shows that, when in proximity to the PDE V enzyme, the compounds inhibit its activity. The second test shows that the compounds can penetrate and prolong the cGMP response in rat aortic smooth muscle cells. Taken together, these data indicate that the compounds are potent inhibitors of PDE V *in vitro*. The Patent also states that the compounds were shown to be highly selective inhibitors of PDE V over other PDE enzymes, but does not provide these data. The '784 Patent contains no *in vivo* testing or clinical studies of any of its compounds.

[17] The '784 Patent has 28 claims, which relate generally to pharmaceutical uses of the compounds of the Patent, including use in the treatment of ED. The narrowest claims are limited to tadalafil and 3-methyl tadalafil. Dependent claim 18 is limited to the oral route of administration; other claims provide generally for "treatment", without being limited to a particular route.

[18] Lilly initially asserted ten claims of the '784 Patent in its Notice of Application. It addressed only claims 2, 4, 12, 14 and 15 in its evidence, and Mylan prepared its evidence accordingly. There is a dispute as to whether Lilly asserts claim 18 as well. After receiving Mylan's evidence, Lilly served reply evidence in which its experts addressed claim 18, and it asserted the claim in its factum. Mylan argues that this attempt to “reassert a withdrawn claim” is improper, but did not provide any evidence to the effect that Lilly had effectively renounced that claim. The fact that both of its experts state in their affidavit that they have been “advised” by counsel to Mylan that only claims 2, 4, 12, 14 and 15 are at issue, is clearly insufficient to establish that Lilly made representations that it was not asserting claim 18. Indeed, Mylan did not strenuously pursue that argument at the hearing.

[19] The claims themselves are reproduced in the Annex. There is no dispute as to the construction of these claims as set out by Lilly.

[20] Claim 2 claims a pharmaceutical composition for the treatment of ED in a male animal comprising a compound selected from the group consisting of two compounds, tadalafil and 3-methyl tadalafil.

[21] Claim 4 relates to the composition of claim 2 for use in human males.

[22] Claim 12 claims the use of tadalafil or 3-methyl tadalafil for the treatment of ED in a male animal. Unlike claims 2, 4 and 15, claim 12 is not limited to a particular pharmaceutical composition but it is still promising that either of the compounds will treat ED in a male animal.

[23] Claim 14 merely adds to claim 12 the element that the male animal is human.

[24] Claim 15 relates to the use of the compositions of claims 2 and 4 for the treatment of ED in a male animal.

[25] Claim 18 may be dependent upon either or both of claims 12 and 14. When one combines claim 18 with both claims 12 and 14, one has a claim to the use of tadalafil or 3-methyl tadalafil in treating ED upon oral administration, including in human males.

III. Issues

[26] By letter dated December 21, 2012, Mylan provided a purported Notice of Allegation (NOA) relating to, *inter alia*, the '784 Patent. In its NOA, Mylan alleges that it does not infringe a number of claims in the '784 Patent, while other claims are invalid on the basis of lack of utility or, in the alternative, obviousness-type double patenting. As previously mentioned, the relevant claims for the purpose of this application are claims 2, 4, 12, 14, 15 and allegedly 18. As Mylan did not allege non-infringement of these claims, the debate therefore rests entirely on the validity of these claims.

[27] On October 3, 2014, the Applicant filed a motion to strike from the record paragraphs 11-35 and Exhibits 10-33 from the affidavit of Carol Yau, the last two sentences of paragraph 19 and Footnotes 25 and 26 from Mylan's Memorandum of Fact and Law, and the last sentence of paragraph 106, the quote that follows it, and footnote 159 from Mylan's Memorandum of Fact and Law. All of these relate to documents alleged to have been filed by Lilly in a European

opposition proceeding to a patent relating to VIAGRA sildenafil. At the hearing, I indicated that the motion would be dismissed because the arguments raised go to the weight more than to the admissibility of the documents. I shall now expand briefly on the reasons provided at the hearing.

[28] This matter therefore raises the following issues:

A. Should Lilly's motion to strike be granted?

B. Is the allegation that the '784 Patent is invalid for lack of utility justified?

C. Is the allegation that the '784 Patent is invalid for obviousness-type double patenting over the '377 Patent justified?

IV. Analysis

The burden of proof and the person skilled in the art

[29] The parties generally agree as to the legal burden and the person skilled in the art. With respect to the burden of proof, the Court of Appeal stated that the second person must first lead evidence which is sufficient to put the allegations of invalidity "in play" and which is "not clearly incapable of establishing its allegations": *Pfizer Canada v Canada (Health)*, 2007 FCA 209, at para 109 [*Pfizer Apo-Quinapril*]. The second person cannot satisfy its initial burden merely by detailing the allegation in the NOA. Once the allegation is in play, the first person is required to meet its burden by proving that the allegation is unjustified on a balance of probabilities: *Pharmascience v Canada (Health)*, 2014 FCA 133, at paras 33-36; *Pfizer Canada v Apotex*, 2007 FC 971, at para 51 [*Pfizer sildenafil*], aff'd 2009 FCA 8. If the evidence is evenly

balanced, the first person will have failed to prove that the allegation of invalidity is not justified: *Eli Lilly Canada v Apotex*, 2009 FC 320, at paras 37-40.

[30] As for the person skilled in the art to which the '784 Patent is directed, it is agreed between the parties that it is a skilled drug development and discovery team whose members have expertise in chemistry, enzymology, pharmacology, pre-clinical and clinical evaluation of candidate therapeutics, and clinical management of ED. The lead chemistry and pharmacology team members would have a Ph.D. level education, while the clinician(s) would have an M.D. or equivalent. The skilled person has clinical trial experience, as well as knowledge of the physiology of penile erection and the pharmacology of NO, cGMP, and PDE enzymes, including inhibitors of PDE activity, and is familiar with important developments and literature in these areas.

The evidence

[31] The parties have submitted voluminous evidence comprised of affidavits and cross-examinations, each with numerous exhibits, including scientific papers and pharmaceutical testing results.

[32] Lilly filed affidavits of two fact witnesses: Dr. Daugan and Dr. Grondin. Lilly also put forth two expert witnesses: Dr. Brock and Dr. Goldstein. Finally, Lilly submitted the affidavit of Cindy Sue Potter, a law clerk, to introduce a number of exhibits including the '784 Patent itself, the NOA, and the numerous scientific papers submitted with the NOA. Mylan put forth two expert witnesses: Dr. Murray and Dr. Melman. The affidavits, cross-examinations and exhibits for all these witnesses form part of Lilly's record. Mylan also submitted the affidavit of Carol

Yau introducing several exhibits; by way of a motion to strike, Lilly contests the admissibility of many of these exhibits.

Dr. Daugan

[33] Dr. Daugan is a French pharmaceutical researcher (medicinal chemist) with Glaxo, a French pharmaceutical company. He is the listed inventor of the '784 Patent. In his affidavit, he describes his involvement in the development of tadalafil, as part of a research project to identify PDE V inhibitors. He recounts that a patent was filed when tadalafil was first developed (international version of the '377 Patent), but this patent did not contemplate tadalafil's use in treating ED. After this patent was filed, and after discussions with colleagues at Glaxo in light of the scientific literature and Phase I clinical trials of tadalafil, he began to consider that tadalafil could be used to treat ED. At this point, the second patent was filed (the international version of the '784 Patent). The exhibits to the affidavit are his curriculum vitae, two published papers about the discovery of tadalafil, and lab notebooks.

Dr. Grondin

[34] Dr. Grondin is also a researcher for Glaxo. His affidavit describes his role in supervising the *in vitro* experiments on tadalafil, leading up to the international filing of the '784 Patent. Like Dr. Daugan, he describes the decision to file the '784 Patent after the researchers predicted that tadalafil – initially developed to treat hypertension – could also be used to treat ED. The exhibits to the affidavit include his curriculum vitae, published papers, and lab notebooks.

Dr. Brock

[35] 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 Eli Lilly. His evidence consists of an affidavit, cross-examination (both with exhibits, primarily scientific papers), and reply affidavit.

[36] In his affidavit, Dr. Brock states that the development of an oral agent for the treatment of erectile dysfunction was an ongoing active area of medical research for decades, prior to the discovery of tadalafil. Sildenafil citrate had been discovered only shortly before the patent for the compound tadalafil (the ‘377 Patent) was filed. Prior to the discovery of sildenafil citrate, the important conceptual limitations were the general belief and understanding that a general vasodilator, while being able to enhance blood flow to the penis, would almost certainly also evoke significant generalized systemic hypotension to the detriment of the individual and, as a consequence, likely be of little clinical utility. Previous experimental work in the area of erectile dysfunction had demonstrated the lack of efficacy of earlier oral agents and the widespread use and acceptance of drugs that were injected directly into the penis was believed to be the gold standard therapy delivery system at the time (1990-1994).

[37] The understanding of the potential therapeutic role of NANC nerve pathway effectors and the identification of PDE inhibitors was also known at that time (July 1995), although it was not known how that might be achieved. Several leading experts had speculated that use of a cGMP PDE inhibitor could be considered for the treatment of erectile dysfunction, but this was not done. The leading research was designed to study the physiological pathways involved in the erectile process; it was not focused on the development of a clinical drug to treat the condition. The experts acknowledged that further research was required before there would be any realistic ability to target a specific mechanism through which erectile dysfunction could be treated. In

1994 and 1995, the leading researchers continued to investigate the use of a nitric oxide donor for the treatment of impotence, as many believed that this would be a better alternative than PDE inhibition.

[38] Therefore further research and investigation were required before one would have been able to predict that the use of a PDE V inhibitor, let alone an orally administered PDE V inhibitor, would be efficacious in the treatment of erectile dysfunction. It was unknown that an orally administered PDE V inhibitor could be effective in treating erectile dysfunction because of the expected systemic effects of administering such a compound orally. According to Dr. Brock, "[t]hat there would exist selectivity in the distribution of PDE enzymes in the penile circulation to a level not found in other essential vascular structures would have been fool-hardy speculation" (Brock affidavit, para 33, Application Record (AR) Vol 2, p 193).

[39] The nature of the ability of a PDE V inhibitor such as sildenafil citrate as a selective PDE V inhibitor to be an effective and safe oral agent for the use of enhancing erectile function in men was fortuitous and insightful. While there was now the idea that PDE V inhibitors could be used clinically, the complete understanding of how best to inhibit cGMP metabolism and augment erectile mechanisms was still in an infantile state. While sildenafil changed the thinking, it did not do so entirely or immediately, as changing scientific theories takes time. Theoretically, any selective and potent PDE V inhibitor could possibly work but one could not say that it was self-evident that it would work, as many characteristics such as metabolism, side effects and absorption of these new agents all needed to be tested.

[40] The inventive concept found in claims 2, 4, 12, 14 and 15 is the treatment of erectile dysfunction using tadalafil or 3-methyl tadalafil. This concept did not appear in the prior art, and Dr. Brock is of the view that a person skilled in the art would not consider the use of tadalafil or 3-methyl tadalafil to be obvious. It would be inventive, because:

> [o]ne of skill in the art would have reason to hope that either compound could be used to treat erectile dysfunction, particularly in light of the publication of the patent claiming the use of sildenafil citrate for the same use, but it would not reach the level of self-evident that either compound would be successful in treating erectile dysfunction or that the person of skill in the art would consider that either compound ought to work to treat erectile dysfunction.
>
> (Brock affidavit, para 38, AR Vol 2, p 194)

[41] Finally, Dr. Brock determined that the promise of the ‘784 Patent is the treatment of erectile dysfunction. In his view, a person skilled in the art would consider this promise to be soundly predicted based on the information disclosed in the Patent and the common general knowledge, and there was sufficient information available with respect to PDE V inhibitors and particularly sildenafil citrate, to allow the inventor to predict the use of potent and selective PDE V inhibitors like tadalafil and 3-methyl tadalafil in the treatment of ED.

[42] In his reply affidavit, Dr. Brock addresses Mylan’s construction of the promise, namely that the disclosed tetracyclic derivatives (tadalafil or 3-methyl tadalafil) will be effective in treating erectile dysfunction when administered orally. In his view, the person skilled in the art would not view the promise of the Patent as a whole so narrowly. That the compounds may be administered orally is only one aspect of the invention. That being said, he believes that the ‘784

Patent is still soundly predicted if it is found that the promise of the Patent as a whole relates to oral administration.

Dr. Goldstein

[43] Dr. Goldstein is also a urologist, specialized in sexual dysfunction. He was involved in clinical research involving sildenafil and tadalafil, among other drugs. He has also served as an expert witness for Pfizer in VIAGRA sildenafil litigation.

[44] He states that in 1994, no effective oral therapy for ED was available prior to sildenafil. The "gold-standard" drug treatment for ED in 1994 did not involve oral pills but did involve the injection of vasodilator drugs into the corpus cavernosum. Vasodilator medications in 1994 could not be administered systemically (e.g. orally) for the treatment of ED, as this led to smooth muscle relaxation throughout the vasculature and serious hypotension could result. Systemic vasodilation, a common mechanism of oral antihypertensive drugs, actually causes ED rather than treats it.

[45] In 1994, penile erection was known to occur after smooth muscle relaxation of the penis. The neurologic system, including the NANC nerves, the central nervous system, and the peripheral nervous system were, in part, implicated in affecting penile erection. It was also known that a number of chemical messengers, including nitric oxide, were involved in the biological processes affecting local penile smooth muscle tone. In 1994, it was also known that the vascular system and the endocrine system were in part affecting penile erection.

[46] Dr. Goldstein also states that a handful of basic science groups were examining the mechanism of action of nitric oxide/cGMP on smooth muscle relaxation in penile tissue, but it had not been demonstrated conclusively that nitric oxide was the NANC transmitter to the exclusion of other NANC vasodilator substances. Research was focussed primarily on increasing the production of cGMP with nitric oxide donors. There was minimal research on preventing the degradation of cGMP within the cell (PDE inhibitors). Moreover, the distribution of PDE enzymes in the corpus cavernosum was not known publicly until 1999.

[47] Finally, Dr. Goldstein indicates that the publication of Pfizer's patent on the use of sildenafil and related compounds as treatments for impotence in December 1994 was the first public disclosure of an invention claiming that a PDE inhibitor, taken orally and present systemically, could effectively treat erectile dysfunction in men. The mechanism of the preferential therapeutic activity for sildenafil and related compounds was not fully understood until a study examining the selective tissue distribution of PDE V was published in 1999. Therefore, "the claims for sildenafil in Pfizer's 1994 patents served as a prototype for an orally active therapy for the treatment of ED, but did not yet provide a rational basis for the development of other selective PDE V inhibitors. Further, the potency, selectivity, and safety of other compounds with chemical structures unrelated to sildenafil could not have been predicted in 1994" (Goldstein affidavit, para 16, AR Vol 2, pp 275-276). He concludes that the claims of the '784 Patent are novel and inventive over the claims of the '377 Patent.

[48] In his view, the promise of the '784 Patent is that either of the compounds, tadalafil or 3-methyl tadalafil, can be used to treat erectile dysfunction. He finds that this promise is soundly

predicted at the filing date based on testing disclosed in the Patent and the advances in the field up to 1996.

[49] In his reply affidavit, he addressed the alternative promise put forward by Mylan, namely that tadalafil or 3-methyl tadalafil will be effective in treating ED upon oral administration. In his view, a person skilled in the art would not consider this to be the promise of the Patent; the invention as claimed is not that narrow, except for claim 18. Even if the promise was to include oral administration, he remains of the view that the invention is soundly predicted.

Dr. Murray

[50] Dr. Murray is a clinical pharmacologist. He is a professor of medicine and pharmacology and a clinical researcher.

[51] According to Dr. Murray, the skilled person in the art would consider the promise of the '784 Patent to be that tadalafil or 3-methyl tadalafil will be effective in treating ED upon oral administration, including in human males. Demonstration of that promise would require efficacy and toxicity data from oral dosing in humans, and such testing had not been conducted by the '784 filing date.

[52] Moreover, the promise of oral effectiveness could not have been soundly predicted by the skilled person in the art at that time. The only data in the '784 Patent pertain to *in vitro* potency of tadalafil and 3-methyl tadalafil in inhibiting the PDE V enzyme, which was known to be involved in the erectile process:

> [t]here is no testing of the compounds in corpus cavernosum tissue from any species, nor are there any *in vivo* data on whether the compounds could be adequately absorbed across the gastrointestinal barrier, or whether they could sufficiently distribute to, and penetrate into, the penis before being metabolized and/or excreted by the body.
>
> (Murray affidavit, para 19, AR Vol 10, pp 1752-53)

[53] There are also no data on whether an effective oral dose could be achieved that was not so high as to cause unacceptable side effects in other tissues. Moreover, no inferences could be drawn from the fact of sildenafil having been successfully orally administered because sildenafil is chemically distinct from tadalafil and 3-methyl tadalafil.

[54] In contrast, the use of tadalafil to treat ED by direct injection would have been obvious to the skilled person in the art at the '784 Patent priority date in light of the '377 Patent claims. It was known that PDE V inhibitors enhanced the erectile process if sufficient concentrations could be achieved in the corpus cavernosum, and since direct injection bypasses potential problems associated with absorption and distribution and often allows lower dosing to avoid systemic toxicities, a skilled person would have a reasonable expectation of success in using tadalafil in this way.

Dr. Melman

[55] Dr. Melman is a professor of urology and a physician. As part of his practice, he administers sildenafil, tadalafil, and other drugs to patients with ED.

[56] He is also of the view that a skilled person would understand the '784 Patent to be promising that tadalafil and 3-methyl tadalafil are effective for treatment of ED in humans,

including by oral administration. As of the filing date of the ‘784 Patent, the inventors had tested these two compounds in *in vitro* assays, and tadalafil had additionally been tested by oral administration in an *in vivo* model of hypertension in rats. However, no testing had been conducted to evaluate the therapeutic efficacy of the compounds in humans with ED. As such, the promise of the Patent had not been demonstrated.

[57] Dr. Melman adds that the promise had not been soundly predicted as of the ‘784 filing date. The two *in vitro* tests disclosed in the ‘784 Patent did not provide a sufficient factual basis for a prediction of therapeutic utility on oral administration to humans with ED. For a skilled person to make any prediction of a therapeutic effect in ED on oral administration, he or she would need some information about the absorption, metabolism and tissue distribution of the compounds in question when orally administered. No such information is provided in the ‘784 Patent, and as such, the skilled person cannot draw any meaningful inferences as to the efficacy or safety of the compounds on oral administration.

[58] Finally, Dr. Melman states that, in light of the claims of the ‘377 Patent, it would have been obvious at the ‘784 priority date that tadalafil would be useful in the treatment of ED if administered by intracavernosal injection. The ‘377 claims are premised on tadalafil’s activity as a selective PDE V inhibitor, and this same biochemical activity forms the basis for the ‘784 relevant claims to therapeutic use in ED. Because intracavernosal administration would ensure delivery of the compound to the target tissue, many of the pharmacokinetic concerns relevant to oral administration would be alleviated. Therefore, the skilled person would have a reasonable expectation that tadalafil would work to treat ED by this route of administration.

A. *Should Lilly's motion to strike be granted?*

[59] In its NOA, Mylan referenced and quoted excerpts from documents alleged to have been filed by Eli Lilly and Company (the parent corporation of Lilly) and ICOS in a European opposition proceeding to a patent relating to VIAGRA sildenafil. Mylan thereby attempted to rely on purported admissions made by Eli Lilly and Company and ICOS in the section of its NOA relating to obviousness-type double patenting. In its Notice of Application, Lilly denied that any admissions were made, or that these documents and statements within them were relevant to this proceeding.

[60] Lilly did not comment on these documents in its evidence, and neither did Mylan. Mylan merely attached them to an affidavit of its law clerk, Carol Yau, and included it in its evidence served on Lilly on December 6, 2013. Lilly did not voice any objection to that affidavit, and did not examine Ms. Yau. However, Lilly excluded the Yau affidavit and its exhibits from its Application Record.

[61] Mylan included the Yau affidavit in its Responding Application Record, which was served and filed on August 22, 2014. Lilly did not see fit to bring its motion to strike until October 3, 2014, six business days before the hearing of this Application. According to Lilly, these documents have been improperly introduced into evidence, are not relevant to any issue in this proceeding, and constitute hearsay.

[62] This Court has repeated on more than one occasion, that the discretion to strike affidavits or portions thereof should be exercised sparingly and only where it is in the interests of justice to do so: see e.g. *Armstrong v Canada (Attorney General)*, 2005 FC 1013, at para 40.

[63] It is no doubt true that merely attaching a document to an affidavit is generally not proof of a document: *Inhesion Industrial Co v Anglo Canadian Mercantile Co* (2000), 6 CPR (4th) 362 (FCTD), at para 22. At the end of the day, however, the test for authentication of documentary evidence is that the trier of fact be satisfied that the document in issue is what it purports to be: Sopinka, Lederman & Bryant, *The Law of Evidence in Canada*, 4th ed (Markham, Ont: LexisNexis, 2014) at para 18.6.

[64] The impugned documents purport on their face to have been filed with the European Patent Office (EPO), by or on behalf of Eli Lilly and Company and/or ICOS. They appear to be listed on the Register in relation to European Patent 0 702 555 (EP 555) and the affidavit included particulars as to the date each document was listed and the way in which it was described on the Register.

[65] Despite speculative submissions by Lilly to the effect that the documents may not be complete copies and may not form a “complete picture” of the record on the opposition, there is no reason to doubt the authenticity and accuracy of the impugned exhibits. Lilly has offered no evidence that the documents are incomplete, modified or anything other than what they purport on their face to be. The Register is a matter of public record, and Lilly could have determined if the documents were true and complete copies. It was also open to Lilly to call witnesses with

first-hand knowledge of the impugned documents, either to question their authenticity or to explain the statements made in them. The evidence is that they were authored by the parent company of Lilly, and as the Supreme Court noted in *Evans*, "a party can hardly object that he had no opportunity to cross-examine himself": *R v Evans*, [1993] 3 SCR 653, at 664. As for Lilly's argument that Mylan could have introduced the impugned documents pursuant to section 23 of the *Canada Evidence Act*, RSC 1985, c C-5, it is of no merit. That provision allows for the evidence of any proceeding or record to be given by way of exemplification or certified copy if it originates from courts in Canada, Great Britain, the United States "or of any other foreign country". No argument has been presented in support of the proposition that the EPO is a court of record of a foreign country. In any event, it is clear that section 23 of the *Canada Evidence Act* is not the only procedure by which foreign evidence can be proven, and Lilly has not successfully impugned the authenticity of the material to which it now objects.

[66] Lilly also argued that the documents in question are not relevant to any issue in this proceeding. They relate to a different type of proceeding unknown in Canada, to revoke a different patent on a different basis than the allegations made by Mylan in this proceeding. There is no doubt that the Court is not bound by the decisions of foreign courts dealing with corresponding patents, to say nothing of different patents. As this Court stated in *Eli Lilly v Apotex*, 2007 FC 455, at para 244 (aff'd 2008 FCA 44):

> This Court is not bound by the decisions of foreign courts dealing with corresponding patents. In the words of the Federal Court of Appeal: "Although foreign patents may be practically identical, foreign law is unlikely to be so and must, in any case, be proved" (*Lubrizol Corp. v Imperial Oil Ltd.* (1992), 45 C.P.R.(3d) 449). These words are especially apt in the present matter which can be differentiated from what occurred in the United States on a number

> of grounds, including the nature of the proceedings, the evidence, and the burden of proof.

[67] That being said, the evidence offered by Mylan is not relied upon to establish a point of law, but only to show that Lilly's previous statements with respect to the state of the common general knowledge regarding ED and its treatment in the early 1990s, are inconsistent with the position it is now taking. These statements would be insufficient to establish that the '784 Patent is invalid for obviousness-type double patenting, not only because European patent law differs from Canadian patent law but also because they were not meant to be a conclusion of law but the expression of a factor to be taken into consideration in applying the applicable legal test in the EPO. In other words, Mylan is referring to these statements not for the truth of their content, but for the fact that they were made. To that extent, they are not inadmissible as hearsay evidence and they are relevant to Mylan's allegation of obviousness-type double patenting.

[68] The weight to be given to these statements in assessing the reliability of Lilly's evidence with respect to the state of the common general knowledge at the relevant date, and with respect to the inference that could be drawn at the time from prior art documents, is obviously another matter. For the reasons advanced by counsel for Lilly (different patent, different type of proceeding, different applicable legal principles), caution must be exercised when importing into a proceeding submissions made in a different context. Indeed, this Court does not even know how the EPO ruled on these submissions.

[69] For all of the foregoing reasons, I find that Lilly's motion to strike ought to be dismissed. This is not to say that the impugned statements should carry the same weight as if they had been

made by Lilly itself in a prior Canadian proceeding involving the same patent. Accordingly, the documents sought to be struck by Lilly will remain part of the evidence, but will be given the weight commensurate to the circumstances and the legal context in which they were drafted.

B. *Is the allegation that the '784 Patent is invalid for lack of utility justified?*

[70] Utility is part of the definition of "invention" in section 2 of the *Patent Act*, which states that the claimed art must be "useful". A patent's utility must therefore either be demonstrated or soundly predicted at the filing date, when the new use is the essence of the invention: *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77, [2002] 4 SCR 153, at para 56 [*AZT*]; *Eli Lilly Canada v Novopharm Ltd*, 2010 FCA 197, at para 74 [*Olanzapine*]; *Pfizer Apo-Quinapril*, above, at para 153.

[71] The promise of a patent is fundamental to the utility analysis and must be ascertained at its outset. Promised utility is an aspect of claims construction, and is therefore a question of law: *Apotex v Bristol-Myers Squibb Co*, 2007 FCA 379, at para 27; *Olanzapine*, above, at para 80. The promise is construed in the context of the patent as a whole, through the eyes of the person skilled in the art, and in relation to the science and information available at the filing date: *Olanzapine*, above, at paras 80, 93. The promise must also be interpreted consistently with the inventive concept: *Hoffman-La Roche Ltd v Apotex*, 2011 FC 875, at paras 20-22.

[72] Where the patent includes an explicit "promise", the utility of the patent will be measured against that explicit promise. Utility will be demonstrated if the patent discloses tests that confirm the patent's promise. If utility is not demonstrated, it may nonetheless be soundly

predicted. The three-part test for sound prediction is laid out in *AZT*, above, at para 70: there must be (1) a factual basis for the prediction, (2) an articulable sound line of reasoning from the factual basis to the result, and (3) proper disclosure in the patent of this line of reasoning (see also *Olanzapine*, above, at para 83). The parties agree that these requirements must be met in the present case.

[73] I agree with counsel for Mylan that a sound prediction of utility must be more than a mere speculation, an intriguing idea, or a lucky guess. It must provide a "solid teaching" that permits the desired result to be inferred from the factual basis. There must be a "*prima facie* reasonable inference of utility": *Olanzapine*, above, at para 85; see also *AZT*, above, at paras 69, 83-84. As the Supreme Court stated in *AZT* (at para 84):

> An applicant does not merit a patent on an almost-invention, where the public receives only a promise that a hypothesis might later prove useful; this would permit, and encourage, applicants to put placeholders on intriguing ideas to wait for the science to catch up and make it so.

[74] That being said, a prediction does not need to amount to a certainty to be sound: *Laboratoires Servier v Apotex*, 2008 FC 825, at para 348, aff'd 2009 FCA 222. Moreover, the soundness or otherwise of the prediction is a question of fact.

[75] There is no evidence that either tadalafil or 3-methyl tadalafil was used to treat ED, in any species, by any route of administration, before the filing date. Thus, regardless of how the promise is construed, there is no dispute that the Patent's utility was not demonstrated. One must therefore determine whether the invention was soundly predicted.

[76] The first step of the investigation is to identify the promise of the Patent. Lilly argues that the proper construction of the promise for the ‘784 Patent is the promise of treatment of ED by the use of tadalafil or 3-methyl tadalafil. Mylan retorts that this is too broad a construction, and that the promise also requires that the compounds must be effective on oral administration, and must not have side effects so severe as to make them unusable in treatment.

[77] Before addressing this issue of construction, a word must be said with respect to the sufficiency of the NOA. Lilly argues that Mylan’s version of the promise as expressed in its NOA was silent as to the mode of administration, and that the NOA is therefore improper.

[78] It is beyond dispute that the second person cannot resile from a position taken in the NOA, and has an obligation to raise all the facts and legal arguments upon which it relies in support of its allegations: *Bayer v Apotex*, 2014 FC 436, at para 33. It is therefore incumbent on the second party to make the first party aware of the grounds on which it claims, and to state the basis of an allegation in sufficient detail to enable a patentee to understand and respond to its NOA.

[79] Mylan’s NOA squarely raised the allegation of inutility, including lack of sound prediction. It is true that Mylan did not refer to the mode of administration in construing the promise of the ‘784 Patent. It cannot be said, however, that the NOA is inadequate for that reason or that Mylan changed its construction of the promise.

[80] First of all, the promise of a patent is an issue of construction, and such an issue is a question of law. Of course, the allegation that the invention was not soundly predicted is dependent to some extent on the construction of the promise underlying the patent. There is no evidence, however, that Lilly had difficulty understanding the grounds for the allegation of inutility or that it was misled by the absence of any reference to oral administration in the NOA. Moreover, no affidavit was filed by Lilly stating that they were prejudiced to any extent in this regard: *Novo Nordisk Canada v Cobalt Pharmaceuticals*, 2010 FC 746, at paras 337-340.

[81] Lilly also argued that Mylan changed its construction of the promise to match what was asserted by its experts in evidence. This is not problematic, as promise construction should indeed be based on expert evidence. As pointed out by Mylan, its experts were reacting to Lilly's own experts discussing oral administration in their affidavits. As a result, Mylan cannot be faulted for narrowing down the promise to take into account its interpretation of the expert evidence.

[82] What, then, is the promise of the '784 Patent? In my view, the promise of the Patent does not include oral administration, and I agree with Lilly that the Patent's overall focus is on the effectiveness of the compounds to treat ED, not the specific route of administration. The title itself refers to the "Use of cGMP-Phosphodiesterase Inhibitors to Treat Impotence", and the first sentence of the '784 Patent states that the overall invention relates to the use of tetracyclic derivatives in the treatment of impotence.

[83] It is only after having described the prevalence of erectile dysfunction and the current therapies for ED, and having described the general formula and the specific compounds of the invention, that the Patent states (at the end of p 3): “Furthermore the compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration”. The Patent then goes on to state the present invention “concerns the use of compounds of formula (I), and in particular compounds A and B, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man” (p 4 of the Patent).

[84] That oral administration is only one aspect of the invention is confirmed by the passage that follows a little later on the same page which states that oral administration of the compounds is the “preferred”, but not the sole route of administration. The Patent specifically contemplates that the compounds may be given orally or parenterally (i.e. not via the digestive tract). When describing the general formulation of the compounds, the Patent again does not restrict itself to oral use, and when discussing veterinary use, the Patent leaves the route of administration up to the veterinarian.

[85] Finally, claim 18 is the only claim (apart from claim 28, which is not at issue here) that refers to oral administration. If this claim is to mean anything, other claims have to be interpreted more broadly to encompass other routes of administration.

[86] The fact that an orally administered medication was considered the “Holy Grail” of ED therapy at the time, to use the words of my colleague Justice Mosley in *Pfizer sildenafil*, above, and that a drug that could not be used orally would be of limited utility, may be a relevant factor when considering obviousness, but is certainly not determinative when constructing the promise of a patent. When reading the ‘784 Patent as a whole, I have no hesitation to conclude that oral administration is a preferred feature of the invention and is the substance of claim 18, but is not the promise of the entire Patent.

[87] Mylan also argues for the first time in its factum that the promise requires efficacy in the absence of undue side effects. Even though the ‘784 Patent itself does not address toxicity, the claim term “treatment” imports a consideration of side effects. A compound that produces the desired physiological effect but also has side effects that prevent it from being used clinically would not be useful in “treatment”.

[88] I am unable to agree with this argument. There is absolutely no reference to toxicity in the ‘784 Patent. None of the claims mentions reduced side effects, nor is there any data whatsoever relating to toxicity. While an inventor may be held to a promise when called upon to prove utility, that promise must have been clear and explicit. As the Federal Court of Appeal recently stated, “[t]he promise doctrine will hold an inventor to an elevated standard only where a clear and unambiguous promise has been made”: *Apotex v Pfizer Canada*, 2014 FCA 250, at para 66.

[89] Of course, a promise need not be stated in a patent's claims, and may appear also in the specification. There again, however, the language must be clear and explicit. In the case referred to in the previous paragraph, the patent listed various disorders for which compounds of the formula would be useful in treating, and stated that the compounds are useful as anti-inflammatory agents "with the additional benefit of having significantly less harmful side effects". It also added that the selectivity of the compounds "may" indicate an ability to reduce the incidence of common anti-inflammatory side effects. Yet, the Court refused to interpret these statements as a promise and quoted with approval Justice Zinn in *Fournier Pharma v Canada (Health)*, 2012 FC 741, at para 126, that a utility not expressed in the claim portion of the specification "[…] 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": *Pfizer Canada v Apotex*, 2014 FC 314, at para 36, aff'd 2014 FCA 250.

[90] In the case at bar, the mere mention of the deleterious effects of existing therapies does not amount to a promise that the compounds will obviate such side effects. Indeed, the '784 Patent is clearly drafted in terms of advantages as opposed to promise, to the extent that oral administration is described as avoiding the disadvantages associated with i.c. administration ('784 Patent, p 4). This is undoubtedly insufficient to infer that a clear and unambiguous promise has been made; as this Court stated in *AstraZeneca Canada v Mylan Pharmaceuticals ULC*, 2011 FC 1023, at para 139, aff'd 2012 FCA 109, "…not all statements of advantage in a patent rise to the level of a promise. A goal is not necessarily a promise". The case at bar is plainly one where the Patent shall be construed in favour of the patentee as it can be read by the skilled person as excluding the promise of reduced side effects.

[91] The ‘784 Patent is to be distinguished from the patent at issue in *Latanoprost* (*Apotex v Pfizer Canada*, 2011 FCA 236), relied on by Mylan, where the Court construed the promise as “to treat glaucoma and ocular hypertension on a chronic basis without causing substantial side effects” (at para 38) because latanoprost was claimed to “reduce intraocular pressure without causing substantial ocular irritation” (this was claim 1 of the impugned patent). It may well be, as suggested by Mylan, that a promise has to be interpreted in light of the nature of the disease the patent purported to treat; yet a promise must be made in the first place.

[92] None of the experts went so far as to opine that the promise requires efficacy without undue side effects. Dr. Goldstein agreed that safety was an aspect of the inventive concept and significantly influences therapeutic usefulness; this is a far cry from an explicit promise of efficacy without the risk of dangerous systemic side effects. As for Dr. Brock, he never explicitly stated that safety was an aspect of the inventive concept; he said that he would need information about safety in order to assess obviousness. Moreover, Dr. Brock’s statement was in the context of a question relating to obviousness, and not to sound prediction. As for Dr. Melman, he stated that serious side effects cannot and should not be tolerated in a drug intended to treat ED. Of course, side effects are always an issue with drugs; while regulators must clearly be concerned with side effects, they are not relevant for patent purposes unless the patent contains an explicit promise to that effect. A mere reference to treatment is not sufficient in that respect.

[93] There is no evidence that either tadalafil or 3-methyl tadalafil was used to treat ED, in any species, by any route of administration, before the filing date. The question then becomes:

did the inventor make a sound prediction that tadalafil and 3-methyl tadalafil could be used in the treatment of ED?

[94] The Patent states that the IC_{50} values for both tadalafil and 3-methyl tadalafil was 2 nM. This is a measurement of the concentration of tadalafil or 3-methyl tadalafil that is required to inhibit 50% of the activity of the PDE V enzyme. The lower the concentration required to have this effect, the more potent the compound. Both Dr. Brock and Dr. Goldstein were of the view that a person skilled in the art would consider this IC_{50} value to demonstrate potency of these two compounds.

[95] The '784 Patent sets out that tests against other PDE enzymes using standard methodology also showed that compounds of the invention are highly selective for the cGMP specific PDE enzyme (PDE V). These tests would be the same as that used to obtain the PDE V IC_{50} values set out in the Patent using different isoenzymes. There is no data in the Patent relating to the selectivity of tadalafil and 3-methyl tadalafil, but there is no reason to doubt that the tests were performed and that the result, namely that the compounds were selective PDE V inhibitors, was accurately stated.

[96] The Patent also sets out cGMP level measurements that were done using rat aortic smooth muscle cells. The EC_{50} values (another measure of potency) that were reported for tadalafil and 3-methyl tadalafil using these smooth muscle cells would confirm, in the view of Dr. Brock, the potency of the two compounds to the person skilled in the art.

[97] These experiments are the factual basis for the prediction that tadalafil and 3-methyl tadalafil could be used in the treatment of erectile dysfunction, and they are disclosed in the ‘784 Patent.

[98] For the purpose of establishing sound prediction, the specification of the ‘784 Patent is also to be read in light of the common general knowledge: *Bell Helicopter Textron Canada Limitée v Eurocopter, société par actions simplifiée*, 2013 FCA 219, at paras 153-155; *Teva Canada Limited v Novartis AG*, 2013 FC 141, at para 292. Mylan’s experts agreed that, at the filing date of the ‘784 Patent, the ‘377 Patent formed part of the common general knowledge: Murray affidavit, para 116, AR Vol 11, p 1908; Melman affidavit, para 134, AR Vol 10, p 1844. Moreover, a reader of the ‘784 Patent is specifically directed to the Patent Cooperation Treaty (PCT) counterpart of the ‘377 Patent, namely WO 95/19978. The disclosure of the ‘377 Patent teaches that tadalafil and related compounds are potent and selective inhibitors of PDE V.

[99] In light of the experiments set out in the Patents and the common general knowledge, the ‘784 Patent taught to a skilled person that tadalafil and 3-methyl tadalafil inhibit the PDE V enzyme potently and selectively, and that because of this inhibition, cGMP levels in the corpus cavernosum are elevated, causing smooth muscle relaxation and penile erection. See ‘784 Patent, p 4 (lines 17-24) and p 17 (lines 25-27).

[100] I agree with Lilly that this line of reasoning meets the standard of a *prima facie* reasonable inference of utility. Tadalafil’s ability to treat ED was not a mere “lucky guess”, and the invention claimed in the ‘784 Patent is not based on mere speculation. Indeed, in the context

of their obviousness analysis, both Dr. Melman and Dr. Murray stated in their affidavit that a person skilled in the art "would have a reasonable expectation that tadalafil would work to treat ED by this route of administration" (i.e. by direct injection) (Melman affidavit, para 25, AR Vol 10, p 1817) and that the use of tadalafil to treat ED by direct injection "would have been obvious to the Skilled Person in light of the 377 Patent claims" (Murray affidavit, para 23, AR 10, p 1753). The same is true for 3-methyl tadalafil: see Melman cross-examination, p 44, line 9-13, AR Vol 19, p 2983. Accordingly, Mylan's own experts have conceded that a person skilled in the art could have soundly predicted that tadalafil and 3-methyl tadalafil could be used to treat ED as promised in the specification. Since the promise does not specify a mode of administration, all that is necessary for the promise to be fulfilled is that tadalafil and 3-methyl tadalafil could be used to treat ED.

[101] This would be sufficient to dismiss Mylan's argument that the asserted claims of the '784 Patent are invalid for lack of utility. Even if I were to find that the promise includes oral administration, however, I would still be of the view that the promise was soundly predicted at the Canadian filing date. Despite the absence of any *in vivo* clinical data or some evidence of efficacy in valid animal models, I believe that the '377 Patent and the state of the art in 1996 were sufficient to establish a sound line of reasoning that tadalafil could treat ED through oral administration.

[102] When a patient takes a drug orally, the drug must at the very least be absorbed sufficiently from the gastrointestinal tract. One of the concerns expressed by Mylan's experts was that a person skilled in the art did not have information in advance as to the oral

bioavailability in humans of the compounds claimed in the ‘784 Patent. I agree with Lilly, however, that it could be soundly predicted from the ‘377 Patent that tadalafil, claimed in the ‘784 Patent, would be orally bioavailable in humans. Example 122 of the ‘377 Patent demonstrates that a wide variety of the tetracyclic compounds were orally bioavailable in rats, and Dr. Goldstein stated that if a compound was orally bioavailable in rats, it is 99.99% certain that it would also be bioavailable in humans: Goldstein cross-examination, p 59, AR Vol 14, p 2715. Accordingly, the data relating to rats in the ‘377 Patent would have given a person skilled in the art the expectation that tadalafil would be orally bioavailable in humans.

[103] If one knows that a PDE V inhibitor is orally bioavailable, one can expect it to be efficacious in the oral treatment of ED. Dr. Melman agreed with that assumption on cross-examination, and accepted that it would have been reasonable for the person of skill in the art to assume, in 1995, that a PDE V inhibitor could be efficacious for the treatment of ED if it is known to have bioavailability: Melman cross-examination, pp 28-29, AR Vol 19, pp 3967-3968. Counsel for Mylan made much of the fact that Dr. Melman was asked to disregard his concern about safety and merely agreed with a hypothetical question. This may well be the case, but the safety concern is unrelated to bioavailability and shall be addressed head-on, later in these reasons.

[104] The real concern at the time had to do with the systemic hypotension caused by PDE V inhibitors. Even if a particular compound was orally bioavailable, it was thought unlikely that it could have a selective effect in the penis while avoiding systemic side effects. A drug that was expected to have an effect on the smooth muscle of the penis would also be expected to have an

effect on the smooth muscle located in other parts of the body. Scientists thus expected that the vasodilatory effects of a systemically-administered PDE V inhibitor would be seen throughout the body, resulting in a systemic hypotensive effect that could lead to dangerously low blood pressure. Indeed, vasodilation was known to cause, rather than treat, ED. As Dr. Goldstein stated in his affidavit:

> In 1994, a skilled urologist would have understood that a drug could not be administered systemically for the treatment of ED, as it would not be possible to deliver a sufficiently high concentration of the drug to the penis to effectively and reliably relax the vascular smooth muscle without having an effect on the other smooth muscle in the body (e.g. hypotension).
>
> (Goldstein affidavit, para 49, AR Vol 2, p 285. See also Brock cross-examination, p 100, AR Vol 15, p 3075; Melman affidavit, paras 168-169, AR Vol 10, p 1852)

[105] Mylan argues that safety, efficacy and pharmacokinetic/pharmacodynamics issues such as the existence of a dose at which an oral drug would reach an effective concentration in the corpus cavernosum without having serious side effects cannot be determined *in vitro* or extrapolated from one compound to another. In Mylan's submission, such issues cannot be effectively predicted except by dosing the compound *in vivo* and observing the result. Data from valid animal models can provide a basis for extrapolation to human results, but neither tadalafil nor 3-methyl tadalafil were tested in any such model before the filing date.

[106] I agree with Mylan that the experiments apparently conducted by Dr. Daugan and Dr. Grondin with respect to tadalafil and 3-methyl tadalafil cannot be relied upon to support the sound prediction of the '784 Patent's utility. In their affidavits, these scientists then working for Glaxo, stated that they had the results from some preliminary selectivity experiments for tadalafil

and 3-methyl tadalafil, and that tadalafil had successfully been through Phase I clinical trials in humans, when they saw the patent application from Pfizer claiming use of sildenafil to treat impotence. It is apparently on that basis that they predicted that tadalafil and 3-methyl tadalafil could be used to treat impotence. The problem with this evidence relating to preliminary experiments is that none of it was disclosed to the public before the filing date. As a result, it cannot be considered to establish the sound prediction of the promise.

[107] I also agree with Mylan that the experiment in the '377 Patent demonstrating the oral bioavailability of the compounds in a rat is insufficient to soundly predict the usefulness of the same compounds to treat ED orally in humans. Dr. Goldstein accepted as much in his cross-examination (Goldstein cross-examination, pp 75-76, AR Vol 14, pp 2731-2731), indicating that the experiment was not designed to deal with erectile physiology, but merely to show that tadalafil has oral bioavailability.

[108] Lilly is on more solid ground, however, when it relies on a study published in the *International Journal of Impotence Research* under the title: "Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction" (Potter affidavit, Exh "E", AR Vol 6, p 1129). This piece of prior art, it is worth stressing, was published after the priority date of the '784 Patent but before its Canadian filing date, and may therefore be considered for the purpose of establishing sound prediction. This study, which came to be referred to throughout these proceedings as the "Boolell" study (after the name of the first of its listed authors), described detailed clinical studies providing robust evidence of the efficacy

of the PDE V inhibitor sildenafil in the oral therapy of ED. The following paragraph in the introduction of the study captures the gist of its findings:

> There is now ample evidence from both animal experiments and *in vitro* studies with human tissue to suggest that relaxation of the smooth muscle of the corpora cavernosa is mediated by nitric oxide via cyclic guanosine monophosphate (cGMP). During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells. Nitric oxide then stimulates the cytosolic enzyme guanylate cyclase to produce cGMP which results in a decrease in intracellular calcium and allows relaxation of smooth muscle cells. Cyclic nucleotide phosphodiesterase (PDE) isozymes, which are distributed in various tissues, specifically hydrolyse cyclic nucleotides, such as cGMP. Therefore, a pharmacological agent which inhibits the cGMP-specific phosphodiesterase isozyme, should enhance the action of nitric oxide/cGMP on penile erectile activity and have the potential to enhance penile erections during sexual stimulation.
>
> (Potter affidavit, Exh "E", AR Vol 6, p 1131)

[109] This study was critical as it showed that the main PDE activity in human corpora cavernosa is due to PDE V, and that sildenafil, a selective inhibitor of PDE V, had suitable pharmacokinetic and pharmacodynamics properties (rapid absorption, relatively short half-life, no significant effect on heart rate and blood pressure) for an oral agent to be taken prior to sexual activity. Indeed, the study showed that there were no clinically significant effects on pulse rate, blood pressure and laboratory safety tests following administration of single oral doses of up to 200 mg to healthy volunteers (Potter affidavit, Exh "E", AR Vol 6, pp 1134-1135). This information would have provided reassurance that a PDE V inhibitor could be administered orally at dosage levels where an ED effect is observed without hypotensive side effects: see Brock affidavit, para 248, AR Vol 2, p 256; Goldstein affidavit, para 231, AR Vol 2, pp 336-337.

[110] Mylan claims that this study is irrelevant to sound prediction as it is focused on sildenafil and gives no information about tadalafil. Relying on answers given by Dr. Brock and Dr. Goldstein on cross-examination, Mylan argues that different molecules and structurally unrelated compounds can have different properties *in vivo*, and that PDE V inhibitors' potential to cause an undesirable reduction in blood pressure may be a function not only of their mode of action but also of their chemical structure.

[111] Having carefully read the evidence, I am of the view that a person skilled in the art could have soundly predicted, in July 1996, that tadalafil could be administered orally to treat ED. It is no doubt true that the Boolell paper gives no information specifically about tadalafil and focuses instead on sildenafil. It is also clear, however, that when that paper states that "a pharmacological agent which inhibits the cGMP-specific phosphodiesterase isozyme, should enhance the action of nitric oxide/cGMP on penile erectile activity and have the potential to enhance penile erections during sexual stimulation", it refers not only to sildenafil and structural analogues, but also to all pharmacological agents having the same mode of actions, i.e. to pharmacological agents inhibiting PDE V. Since we know from the experiments in the '377 Patent that tadalafil is orally bioavailable in humans and is a potent and selective PDE V inhibitor, there is a *prima facie* reasonable inference of utility for the oral administration of tadalafil to treat ED.

[112] The experts agree that structurally unrelated compounds like sildenafil and tadalafil can have different properties *in vivo*. For example, they can have different pharmacokinetics, different half-lives, different effective durations of action, different levels of selectivity for different enzymes and different side effect profiles. But the '377 Patent teaches some of the

properties of tadalafil, namely that this compound is a potent and selective PDE V inhibitor that is bioavailable in humans. When Dr. Brock emphasized in cross-examination that different PDE V inhibitors can have different properties *in vivo*, stating that one may be able to be taken orally while the other may not, that one may not get absorbed whereas another one would, and that one may or may not make it to the proper vascular bed (Brock cross-examination, p 115, AR Vol 15, pp 3090-3091), he was obviously not referring to tadalafil since it was known that this compound was orally bioavailable and selective.

[113] What was unknown was the dose at which tadalafil would improve blood flow to the penis sufficiently to produce an effect on erection, and whether that dose would have significant side effects such as hypotension. The fact that sildenafil could be effective in the treatment of ED at a dose that did not cause significant side effects was not sufficient to soundly predict that tadalafil would likewise work at such a low dosage that it would also be therapeutically useful.

[114] This is irrelevant, however, since the ‘784 Patent did not promise efficacy without undue side effects. As previously mentioned, it would be wrong to elevate the promise of the ‘784 Patent beyond its explicit language to import a requirement that the treatment be not only efficacious, but also free from toxicity or side effects. As the Supreme Court emphasized in *AZT*, above, the notion of toxicity relates to safety and potential commercial success, not patentability. In that case, the appellants had argued that utility must be demonstrated by prior human clinical trials, establishing toxicity, metabolic features, bioavailability and other factors. The Court rejected that argument (at para 77):

> These factors track the requirements of the Minister of Health when dealing with a new drug submission to assess its “safety” and

> "effectiveness". (…) The prerequisites of proof for a manufacturer who wishes to market a new drug are directed to a different purpose than patent law. The former deals with safety and effectiveness. The latter looks at utility, but in the context of inventiveness. The doctrine of sound prediction, in its nature, presupposes that further work remains to be done.
>
> See also: *Alcon Canada v Cobalt Pharmaceuticals Company*, 2014 FC 462, at paras 65, 67; *Pfizer Canada v Mylan Pharmaceuticals ULC*, 2012 FCA 103, at para 57

[115] In the absence of explicit language to the effect that the absence of toxicity or of significant side effects is part of the promise, I am therefore unable to agree with Dr. Murray that the demonstration of the promise that tadalafil or 3-methyl tadalafil will be effective in treating ED upon oral administration would require efficacy and toxicity data from oral dosing in humans: Murray affidavit, paras 20, 22, 152, AR Vol 10, pp 1753, 1794. I agree with Lilly that this is clearly a case where the promise was expanded in order to argue that it is not met. It may well be, as claimed by Mylan and disputed by Lilly, that the clinical trials required to predict clinical efficacy and the absence of adverse effects were available and not too onerous. However, such an argument is irrelevant and beside the point.

[116] Finally, Mylan argues that the utility of 3-methyl tadalafil has not been soundly predicted, since there is no evidence that it was administered to any animal for any purpose before the filing date. The demonstration of oral bioavailability in a rat found in the '377 Patent was done with tadalafil, but not with 3-methyl tadalafil. To the extent that the Court accepts Lilly's submission that all the asserted claims must be interpreted as alternative claims, Mylan relies on subsection 27(5) of the *Patent Act* to argue that they should all fail since one of the alternatives is invalid.

[117] Subsections 27 (1) and (5) of the *Patent Act* provide that:

Commissioner may grant patents	**Délivrance de brevet**
27. (1) The Commissioner shall grant a patent for an invention to the inventor or the inventor's legal representative if an application for the patent in Canada is filed in accordance with this Act and all other requirements for the issuance of a patent under this Act are met.	27. (1) Le commissaire accorde un brevet d'invention à l'inventeur ou à son représentant légal si la demande de brevet est déposée conformément à la présente loi et si les autres conditions de celle-ci sont remplies.
…	…
Alternative definition of subject-matter	**Variantes**
(5) For greater certainty, where a claim defines the subject-matter of an invention in the alternative, each alternative is a separate claim for the purposes of sections 2, 28.1 to 28.3 and 78.3.	(5) Il est entendu que, pour l'application des articles 2, 28.1 à 28.3 et 78.3, si une revendication définit, par variantes, l'objet de l'invention, chacune d'elles constitue une revendication distincte.

[118] I agree with Mylan that if an asserted claim is cast as two alternative claims, the entire claim fails if one of the alternatives is invalid: *Abbott Laboratories v Canada (Health),* 2005 FC 1332, at paras 50-57, aff'd 2007 FCA 153; *Schering-Plough Canada v Pharmascience,* 2009 FC 1128, at paras 88-90. It is not clear, however, that the asserted claims are truly alternative claims. None of the experts have given an opinion on this question.

[119] Claim 2 claims a pharmaceutical composition for the treatment of ED in male animals "comprising a compound selected from the group consisting" of two compounds, tadalafil and 3-methyl tadalafil. Similarly, claim 12 claims the use of a compound "selected from the group consisting of" tadalafil and 3-methyl tadalafil. This does not strike me as the language of alternatives. Quite to the contrary, these claims define a generic expression or genus covering a group of two different compounds, any one of which will work in the combination claimed. They can be properly described as "Markush claims", an expression which originated in the U.S. (*Ex parte Markush* 1925, 340 USOG 839) and which has been acknowledged in the *Manual of Patent Office Practice* (Chapter 11, Section 11.11): "In chemical cases, a claim directed to a genus expressed as a group consisting of certain specified materials is allowable … provided it is clear from the known nature of the alternative materials or from the prior art that the materials in the group possess at least one property in common which is mainly responsible for their function in the claimed relationship." The *Manual* gives the example of "A solvent **selected from the group consisting of** alcohol, ether **and** acetone…" (emphasis in original) as an acceptable format for a Markush claim.

[120] Given the Commissioner's guidance, the use of the words "selected from the group consisting of" as well as the word "and" instead of "or" between the two compounds, I am of the view that the asserted claims are Markush claims and not alternative claims. They are clearly claims to the two compounds, rather than claims to each of the compounds in the alternative. In other words, each of the compounds can be used interchangeably, and any one of the two compounds can be used to obtain the desired result. For that reason, section 27(5) of the *Patent Act* is of no use as it applies only "where a claim defines the subject-matter of an invention in the

alternative". Whether the claims to 3-methyl tadalafil are soundly predicted, therefore, is irrelevant and of no consequence.

[121] For all of the above reasons, I find, therefore, that the promise of the '784 Patent, whether construed as excluding or including oral administration, has been soundly predicted. The first allegation of Mylan must therefore be rejected as it is not justified.

C. *Is the allegation that the '784 Patent is invalid for obviousness-type double patenting over the '377 Patent justified?*

[122] Mylan argues that if the promise does not include oral administration, then the '784 Patent is invalid for obviousness-type double patenting over the '377 Patent. In Mylan's submission, the '377 Patent claims the same compounds as the '784 Patent, and it discloses that these compounds are potent and selective inhibitors of PDE V and may therefore be used to treat conditions where inhibition of PDE V is thought to be beneficial. Therefore, the '784 Patent discloses nothing new, as it was already known that other PDE V inhibitors could be used to treat ED.

[123] Double patenting is a judge-made doctrine of invalidity which rests on the notion that an inventor is only entitled to one patent for each invention. This doctrine, which has been grounded in subsection 36(1) of the *Patent Act* and is devised to prevent the "evergreening" of patents, has been recognized by the Supreme Court for many years: *Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] 2 SCR 1067, at paras 63ff [*Whirlpool*]; *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] 3 SCR 265, at paras 95-97 [*Sanofi-Synthelabo*]; see also *Aventis Pharma v*

Pharmascience, 2006 FCA 229, at para 67. Lilly questioned the legislative foundation of that doctrine, contending that subsection 36(1) of the *Patent Act* relates only to divisional applications and only addresses situations where more than one invention is claimed in one patent. Whatever may be the merit of this textual argument, it is now beyond dispute that double patenting is an accepted ground of invalidity, and it is entirely consistent with the intent and purpose of the *Patent Act*, which is to prevent the undue extension of the statutory monopoly of a patent by means of a series of patents with obvious or uninventive additions. As the Supreme Court stated in *Sanofi-Synthelabo*, at para 97:

> Evergreening is a legitimate concern and, depending on the circumstances, strategies that attempt to extend the time limit of exclusivity of a patent may be contrary to the objectives of the *Patent Act*. The Act aims to promote inventiveness by conferring exclusivity for a limited period of time while providing for public disclosure of the invention to enable others to make or use it after expiry of the period of exclusivity.

[124] Canadian law recognizes both "same invention" double patenting and "obviousness-type" double patenting. Same-invention double patenting asks whether the claims in two patents are identical or conterminous. Obviousness-type double patenting is a more flexible test that prohibits the issuance of a second patent with claims that are not "patentably distinct" from those of the earlier patent: *Whirlpool*, above, at paras 63-66. For example, it has been held that to dilute a medicinal substance for which a patent has been granted does not result in further invention: *Commissioner of Patents v Farbwerke Hoechst Aktiengesellschaft Vormals Meister Lucius & Bruning*, [1964] SCR 49, 41 CPR 9, at 53-54, 57. The rationale behind this prohibition is that a patentee who evergreens a single invention prolongs its monopoly beyond what the public has agreed to pay:

> It is common ground that the bargain between the patentee and the public is in the interest of both sides only if the patent owner acquires real protection in exchange for disclosure, and the public does not for its part surrender a more extended monopoly than the statutory 17 years from the date of the patent grant (now 20 years from the date of the filing of the patent application). A patentee who can "evergreen" a single invention through successive patents by the expedient of obvious or uninventive additions prolongs its monopoly beyond what the public has agreed to pay…
>
> *Whirlpool*, above, at para 37

[125] The parties are in agreement that double patenting calls for an analysis of the claims and not of the disclosure. As the Supreme Court stated in *Whirlpool*, above, at para 63, "[i]t is clear that the prohibition against double patenting involves a comparison of the claims rather than the disclosure, because it is the claims that define the monopoly". See also *Sanofi-Synthelabo*, above, at para 108. They disagree, however, as to whether the claims of the '377 Patent should be read literally or in the context of the specification as a whole.

[126] Lilly argues that there is nothing in any of the claims of the '377 Patent to the effect that PDE V inhibition is a key feature of the monopoly defined by those claims. As the claims of the '377 Patent do not include PDE V inhibition and are not related to ED, Lilly argues that Mylan's allegation of obviousness-type double patenting must fail since there is no possible nexus to the invention claimed in the '784 Patent. In my view, this argument overreaches and is not consistent with the case law on claims construction.

[127] It is no doubt true that the claims are the starting point in construing a patent. Yet, the words of the claims must be interpreted in the context of the specification as a whole to ascertain

the true nature of the invention. As Justice Dickson stated in *Consolboard Inc v MacMillan Bloedel (Sask) Ltd*, [1981] 1 SCR 504, 122 DLR (3d) 203 (at 520):

> We must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance, (*Noranda Mines Limited v Minerals Separation North American Corporation*, [1950] S.C.R. 36), being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public.
>
> See also: *Free World Trust v Électro Santé Inc*, 2000 SCC 66, [2000] 2 SCR 1024, at para 31; *Whirlpool*, above, at paras 49(f), (g), 52 and 54

[128] Of course, one should not be permitted to rely on a purposive construction in order to unfairly expand or limit the scope of a claim. At the same time, the invention is at the heart of the patent, and in an obviousness-type double patenting analysis, one must be able to ascertain what is alleged to have been invented in each patent to compare them. In some cases, the wording of a claim will be sufficient to define distinctly what the claimed monopoly is; but in other instances, the person skilled in the art and, ultimately the Court, may have to take the context into account and look at the disclosure to construe the claim and ascertain the true nature of the invention. This is precisely what the Supreme Court did in *Whirlpool*, a double patenting case, and this Court has done the same in other double patenting cases: see *Bayer AG v Novopharm Ltd*, 2006 FC 379; *Merck & Co v Pharmascience*, 2010 FC 510 [*Finasteride*]. Indeed, the Supreme Court acknowledged in *Sanofi-Synthelabo*, above, at para 77, that "[a] bare chemical formula in a patent claim may not be sufficient to determine its inventiveness. In such cases, I think it must be acceptable to read the specification in the patent to determine the inventive concept of the claims."

[129] Lilly claims that there is no element of the claims of the ‘377 Patent that specifies that PDE V inhibition is a determinant of the monopoly defined by those claims. According to counsel, claim 10 of the ‘377 Patent is a claim to tadalafil *per se*, and a person skilled in the art would not import into that claim the role of this compound as a PDE V inhibitor. According to that argument, it would be wrong and inappropriate to limit the claim to one particular mechanism of action, as the claim is silent as to how tadalafil works, its potency, and its selectiveness. That being the case, the claim could be infringed if tadalafil was used for other purposes besides its role as a PDE V inhibitor.

[130] In my view, claim 10 of the ‘377 Patent cannot be read so literally and detached from the context of the entire patent. The very first paragraph of the ‘377 Patent states that the invention relates to a series of “potent and selective inhibitors of [PDE V] having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders”. The compounds’ PDE V inhibitory properties are linked with their therapeutic uses (‘377 Patent, p 6, lines 19-24), and *in vitro* testing indicates that a number of the compounds, including tadalafil, are potent and selective PDE V inhibitors. In that context, I am of the view that claim 10 of the ‘377 Patent is a claim to one compound, tadalafil, as a PDE V inhibitor.

[131] Having found that the impugned claims in the ‘784 Patent are for tadalafil as a PDE V inhibitor to treat ED (whether administered orally or not), the claims in the two patents appear to be patentably distinct. Although both are claims for the same chemical compound, tadalafil, they are claims for different uses of this compound. The ‘377 Patent does not contemplate the use of

tadalafil to treat ED; rather, this is precisely the monopoly claimed in the ‘784 Patent. As Lilly notes, when the ‘377 Patent expires, the public will be free to use tadalafil for the uses claimed in the ‘377 Patent. Therefore, the claims are patentably distinct.

[132] Mylan argues, however, that it would have been obvious for a person skilled in the art that the PDE V inhibitory profile of tadalafil that underlies the ‘377 Patent would treat ED, if administered directly into the penis, at least in January 1994, but certainly as of July 14, 1995 (the priority date of the ‘784 Patent). Therefore, it argues, this new use of tadalafil is not an inventive contribution and the ‘784 Patent is invalid for double patenting because it lacks novelty or ingenuity over the original invention of the ‘377 Patent.

[133] There was much discussion with respect to the correct date for a double patenting analysis. There is very little authority on the subject, and the issue is not even addressed by the Supreme Court in *Whirlpool*, above. This is understandable, given that the analysis is confined to a comparison between the claims in two patents, and does not involve an inquiry into the prior art as would be the case if the alleged invalidity rested on an argument of obviousness. Viewed in this light, the evolution of the science between the two patents should be of no consequence in an obviousness-type double patenting analysis: contrary to the position taken by the Respondent, the question is not whether the use of tadalafil to treat ED was obvious in light of the ‘377 Patent, in which case admissible prior art would be relevant, but whether the claims of the ‘784 Patent disclose novelty or ingenuity over the ‘377 Patent. To resolve that question, the Court (with the help of the persons skilled in the art) must look at the first patent in the context of what was known at the time, with a view to determine whether the claims in the second patent are

patentably distinct from those of the earlier patent. Since the rationale behind this ground of invalidity is the prohibition against an improper extension of the monopoly granted by the first patent, the Court must ascertain whether the invention claimed in the second patent could or should have been included in the first patent.

[134] If, as Mylan would have it, the relevant date was to be the priority date of the second patent (in this case, July 14, 1995), the obviousness-type double patenting analysis would morph into a pure obviousness analysis, with the added benefit that the timing requirements of section 28.3 of the *Patent Act* would be circumvented. It is quite telling that Mylan's written and oral argument relied heavily on the framework for obviousness developed by the Supreme Court in *Sanofi-Synthelabo*, above. To be fair, both sides have at times confused the issue, and all four experts were instructed to consider the issue of double patenting as of July 14, 1995. For the reasons already given, this priority date of the '784 Patent cannot be the relevant date. One cannot read into the claims of the first patent more than what would have been understood by the person skilled in the art at the claim date when comparing the claims of the second patent to those of the first patent. If the focus is to be on the claims, as the Supreme Court teaches in *Whirlpool*, information published after the claim date of the first patent is of no use to determine whether the claims of the second patent are patentably distinct from the claims of the first one. This is indeed what my colleague Justice Hughes found in *Finasteride*, above, where he held that certain documents published immediately before the claim date of the second patent rendered the invention non-obvious, but nevertheless determined that these documents were non-existent as far as the obviousness-type double patenting inquiry was concerned.

[135] If January 1994 (the priority date of the ‘377 Patent) is the relevant date for assessing obviousness-type double patenting, it is clear that the use of tadalafil to treat ED (especially by way of oral administration) would not have been obvious for a person skilled in the art. I need not spend much time with respect to that finding, as Mylan’s own expert agreed on cross-examination that he would not have known of the potential for oral use of PDE V inhibitors in the treatment of ED in January of 1994: Melman cross-examination, pp 28-30, AR Vol 19, pp 3967-3969. Indeed, Mylan’s written and oral argument was focused on the state of the art as of July 1995, not as of January 1994.

[136] In 1994, a person skilled in the art would have understood that a drug could not be administered systemically for the treatment of ED, as it would not be possible to deliver a sufficiently high concentration of the drug to the penis to effectively and reliably relax the vascular smooth muscle without having an effect on the other smooth muscle in the body. According to Dr. Brock, it was only a “matter of speculation” among leading researchers, even in late 1993, whether one might use a PDE V inhibitor and oral administration was not even speculated: Brock affidavit, para 266, AR Vol 2, p 259. Similarly, Dr. Goldstein opined that as of May 1994, the idea that smooth muscle relaxation of the corpus cavernosa and erection could be induced by the administration of a PDE V inhibitor had not been determined in humans: Goldstein affidavit, para 107, AR Vol 2, p 301. In fact, Dr. Goldstein stated that before the introduction of sildenafil, which was well after January 1994, a person skilled in the art would have expected that the systemic administration of antihypertensives would have created a risk that the drug would cause ED in the patient, rather than treat ED: Goldstein affidavit, paras 80-81 AR Vol 2, pp 293-294.

[137] My colleague Justice Mosley came to a similar conclusion in a case relating to a patent claiming the use of VIAGRA sildenafil to treat ED. The date for determining obviousness in that case was June 1993, and the prior art relied upon was common in many respects to the prior art referred to in the case at bar. The Court found that, as late as 1997, there remained conjecture as to whether the NO/cGMP pathway was the major factor in penile erection, and there continued to be concerns about the safety or oral treatment with PDE V inhibitors (*Pfizer sildenafil*, above, at para 99). The Court accepted the evidence of Dr. Brock, one of Pfizer's experts in that case, and concluded that in 1993, a few scientists had merely speculated that PDE inhibition might be a factor in erectile tissue physiology, and that none of them arrived at the solution of using oral administration of sildenafil as a PDE V inhibitor in the treatment of ED. As Justice Mosley wrote (at para 125):

> Although there was a significant amount of evidence indicating that cGMP PDE inhibitors should be further explored with regards to the treatment of ED in the months leading up to the Pfizer discovery, the evidence does not in my view establish that the solution taught by the patent was obvious at the time. At best there was speculation, which in hindsight proved to be correct, that PDE5 inhibitors might treat impotence. Experiments with zaprinast, a cGMP PDE inhibitor, had been performed but in an effort to understand how the erectile process works, not how to treat ED.

[138] Counsel for Mylan relied on a paper published in the *New England Journal of Medicine* in 1992 (Rajfer 1992), which apparently led a Pfizer scientist to propose that the PDE V inhibitor they were developing should be tested in ED, and claims that Lilly cannot assert that no persons of skill in the art believed that this article would lead to the use of a PDE V inhibitor for the treatment of ED. Mylan takes objection on the basis that Lilly and its partner ICOS took exactly the reverse position when opposing the grant of a Pfizer patent by the EPO. It is true that on the

face of the documents attached to Ms. Yau's affidavit and to which I have already referred, ICOS seems to have made the argument that a person skilled in the art would have inferred from the Rajfer 1992 paper that a PDE V inhibitor would have potential for the treatment of impotence. This is far from sufficient, however, to support the Respondent's thesis that the use of a PDE V inhibitor for the treatment of ED would have been known in early 1994.

[139] First of all, the patents at issue before the EPO were not the same as those at play in the case at bar. Moreover, the proceeding wherein ICOS' submissions were made in Europe has no equivalent in Canada. More importantly, there is no evidence as to how European law may or may not be the same or different from Canadian law. Finally, we have no idea how the EPO ruled in that case. For these reasons alone, the submissions that were made by ICOS in a foreign jurisdiction are insufficient to impeach the credibility of the Applicant.

[140] In any event, it is for the Court to determine, in the last resort and with the help of the experts, to assess what was obvious at any relevant date. I agree with Dr. Brock that the Rajfer 1992 paper was a basic research study designed to investigate the role, if any, of one particular pathway (the NANC pathway) involved in the erectile process. The conclusion of the authors, as formulated in the abstract of the paper, supports this view:

> Our findings support the hypothesis that nitric oxide is involved in the nonadrenergic, noncholinergic neurotransmission that leads to the smooth-muscle relaxation in the corpus cavernosum that permits penile erection. Defects in this pathway may cause some forms of impotence.
>
> (Potter affidavit, Exh "D", Doc #13, AR Vol 5, p 650)
>
> See also Brock affidavit, paras 125-144, AR Vol 2, pp 218-225

[141] My colleague Justice Mosley also agreed with Dr. Brock that this study was very speculative and did not come up with definitive conclusions ("It is conceivable that impairment of this pathway could account for the impairment in relaxation elicited by electrical-field stimulation […] interference with [this pathway] could be one cause of impotence that is treatable by the administration of direct-acting vasodilators": Rajfer 1992, p 94, AR Vol 5, p 654; see Justice Mosley's discussion in *Pfizer sildenafil*, above, at paras 89-98). Considering that language and the focus of the study, it comes as no surprise that this paper would not lead to the use of a PDE V inhibitor for the treatment of ED, especially one that could be taken orally.

[142] On the basis of the foregoing, I have therefore no hesitation to conclude that the use of tadalafil to treat ED, especially by way of oral administration, would not have been obvious for the person skilled in the art in January 1994 and could not have been included in the '377 Patent. In other words, it cannot be said that the '784 Patent is an evergreening of the '377 Patent when it claims a new use of tadalafil by any route of administration, or at the very least a new use of tadalafil by way of oral administration.

[143] If, contrary to my earlier finding, the relevant date to determine whether the '784 Patent is an improper extension of the '377 Patent is July 14, 1995 ('784 Patent priority date) rather than January 21, 1994 ('377 Patent priority date), would Mylan's argument be more compelling? I do not think so.

[144] The only publication of significance that occurred between the '377 priority date and the '784 priority date was the '902 Application (Pfizer's international patent application for

sildenafil), upon which Mylan essentially relies in support of its argument that the use of tadalafil to treat ED was obvious when reading the '377 claims in light of the skilled person's common general knowledge in July 1995. Mylan argued that this application confirmed that a potent and selective PDE V inhibitor could enhance cGMP levels in the corpus cavernosum, thus facilitating penile erection. Most importantly, it allegedly taught that this mechanism was operative *in vivo* in humans with ED and could be successfully exploited to treat their condition. Since the '377 Patent taught that the compounds of the invention, including tadalafil, were potent and selective inhibitors of PDE V, it was therefore obvious to try tadalafil in the treatment of ED.

[145] This argument is fraught with a number of difficulties. First of all, the Canadian equivalent of the '902 Application was severely criticized by the Supreme Court as being deliberately obscure and did not meet the disclosure requirements set out in the *Patent Act* (*Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60, [2012] 3 SCR 625). The Court described the claims as follows (at para 4):

> The specification for Patent'446 [the Canadian equivalent of the '902 Application] explains that the invention concerns the use of a "compound of formula (I)" or a "salt thereof" as a medicament for the treatment of ED. […] Claim 1 sets out formula (I), which produces 260 quintillion possible compounds. Claims 2 to 5 are for successively smaller ranges of compounds of formula (I), with Claim 5 being narrowed down to a range of nine compounds. Claims 6 and 7 relate to a single compound each.

[146] Only sildenafil, the subject of claim 7 and the active compound of VIAGRA, had been shown to be effective in treating ED at the time of the patent application. Although the patent included the statement that "one of the especially preferred compounds induces penile erection in impotent males", the patent application did not disclose that the compound that works is

sildenafil or that the remaining compounds had not been found to be effective in treating ED. In *Teva*, the Supreme Court found that the disclosure in the specification would not have enabled the public to make the same successful use of the invention as the inventor could at the time of his application, because it does not indicate that sildenafil is the effective compound (at paras 69-80). The '902 Application was even less specific, as the compounds identified were even less selective and did not contain a specific claim to sildenafil; it was only one of the nine especially preferred compounds.

[147] Not only was there nothing in the '902 Application to suggest that the especially preferred compound was sildenafil, but at the time of Pfizer's patent publication (December 22, 1994), the person skilled in the art's understanding of ED and PDE action in smooth muscle was counterintuitive to the claims of Pfizer's patent. In an article published in November 1995, Dr. Morales (in a section specifically addressing what was to become known as sildenafil) voiced "concern" that any PDE inhibitor would cause systemic problems (Potter affidavit, Exh "E", Doc #3, AR Vol 6, p 1121). I accept, therefore, Dr. Goldstein's opinion in this respect, according to whom "the claims for sildenafil in Pfizer's 1994 patents served as a prototype for an orally active therapy for the treatment of ED, but did not yet provide a rational basis for the development of other selective PDE V inhibitors" (Goldstein affidavit, para 16, AR Vol 2, p 275). In other words, it would not have been obvious for the person skilled in the art in the summer of 1995 to use tadalafil or 3-methyl tadalafil to treat ED. As a result, there is no basis to find that this invention could or should have been included in the '377 Patent, even when read in light of the state-of-the-art understanding in July 1995 of the physiology of penile erection and PDE action in smooth muscle.

[148] Mylan made much of the fact that Dr. Brock heavily relied on the evidence that he had previously given in the litigation over the use of sildenafil to treat ED (the *Teva* case mentioned earlier), and went as far as stating that "[b]y recycling his earlier evidence wholesale without turning his mind to the differences in the state of the art between June 1993, May 1994, and July 1995, Dr. Brock has failed to assist the Court in understanding the common general knowledge of the Skilled Person as of the Priority Date" (Mylan's Memorandum of Fact and Law, para 161). It is no doubt true that in reviewing the literature cited by Mylan, Dr. Brock borrowed substantially from his previous affidavit, but this is normal since the literature referred to in the two cases was very similar. He did, however, update his opinion and turned his mind specifically to the '902 Application. Since there was nothing else of significance in the scientific literature cited by Mylan between January 1994 and July 1995, Dr. Brock cannot be blamed for having relied to a large extent on his previous affidavit in the *Teva* case. In fact, the real game changer was the Boolell paper published in 1996, because it was the first clinical proof that there was no systemic hypotension from oral administration of a PDE V inhibitor.

[149] Finally, Mylan contends that Dr. Brock's evidence in the case at bar is inconsistent with the evidence that he gave with respect to sildenafil, because he stated that sildenafil is soundly predicted while he is now of the view that tadalafil is not obvious. However, I fail to see where lies the contradiction. The standard for determining whether there is a sound prediction is obviously lower than the standard for determining obviousness. Sound prediction calls for a *prima facie* reasonable inference, whereas obviousness requires that it be evident an alleged invention will work. This is precisely why it is not inconsistent either to determine that the promise of the '784 Patent is soundly predicted but that it was not obvious (to say nothing of the

fact that sound prediction is to be determined about a year later in the case at bar). Therefore, even if I were to focus on obviousness instead of obviousness-type double patenting, I find that Mylan's argument must be rejected.

[150] For all of the foregoing reasons, I am therefore of the view that the Applicant has demonstrated, on a balance of probabilities, that the allegation of obviousness-type double patenting is not justified.

V. Conclusion

[151] In conclusion, I have found Mylan's allegations of invalidity on the basis of lack of utility and obviousness-type double patenting to be unjustified. As a result, I am satisfied on the evidence in this case that Lilly's discovery was truly inventive, and that it has met its legal burden to establish the validity of the '784 Patent on a balance of probabilities. An Order prohibiting the Minister of Health from issuing a Notice of Compliance to Mylan until the expiry of the patent shall therefore issue. The Applicant shall have its costs on the Application; there will be no costs on the motion. If the parties cannot agree on the quantum, the question of costs can be brought forward by Notice of Motion.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. The Application is allowed;

2. The Minister of Health is prohibited from issuing a Notice of Compliance to the Respondent Mylan until the expiry of Canadian Patent No 2,226,784;

3. The Applicant is entitled to recover its costs from the Respondent Mylan on the application; there will be no costs with respect to the motion.

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

"Yves de Montigny"

Judge

ANNEX

Claim 2

A pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, comprising a compound selected from the group consisting of:

> (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione or a physiologically acceptable salt orsolvate thereof; and
>
> (35,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione or a physiologically acceptable salt or solvate thereof,

together with a pharmaceutically acceptable diluent or carrier.

…

Claim 4

The composition according to any one of claims 1 to 3, wherein the animal is human.

…

Claim 12

Use of a compound selected from the group consisting of:

> (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione or a physiologically acceptable salt or solvate thereof; and
>
> (3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione or a physiologically acceptable salt or solvate thereof,

for the curative or prophylactic treatment of erectile dysfunction in a male animal.

…

Claim 14

Use according to any one of claims 9 to 13, wherein the animal is human.

Claim 15

Use of a composition according to any one of claims 1 to 4 for the curative or prophylactic treatment of erectile dysfunction in a male animal.

…

Claim 18

Use according to any one of claims 9 to 17, wherein the compound, medicament, composition, combination or formulation is used or is adapted to be used orally.

FEDERAL COURT

SOLICITORS OF RECORD

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STYLE OF CAUSE:	ELI LILLY CANADA INC. v MYLAN PHARMACEUTICALS ULC AND THE MINISTER OF HEALTH AND ICOS CORPORATION
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