Federal Court  Cour fédérale

**Date: 20111110**

**Docket: T-1048-07**

**Citation: 2011 FC 1288**

**Ottawa, Ontario, November 10, 2011**

**PRESENT: The Honourable Mr. Justice O'Reilly**

**BETWEEN:**

**ELI LILLY CANADA INC.,**
**ELI LILLY AND COMPANY,**
**ELI LILLY AND COMPANY LIMITED AND**
**ELI LILLY SA**

**Plaintiffs**
**(Defendants by Counterclaim)**

**and**

**NOVOPHARM LIMITED**

**Defendant**
**(Plaintiff by Counterclaim)**

## REASONS FOR JUDGMENT AND JUDGMENT

### I. Overview

[1] The plaintiffs [collectively "Lilly"] sued Novopharm for infringement of a patent for a medicine called olanzapine, whose brand name is Zyprexa. Psychiatrists prescribe olanzapine primarily for the treatment of schizophrenia. Novopharm markets a generic version of olanzapine,

called novo-olanzapine. Olanzapine is the subject of a Canadian patent (No 2,041,113) [the ‘113 patent]. Lilly applied for the ‘113 patent in 1991 and was granted it in 1998.

[2] Olanzapine was also included within an earlier Lilly patent (No 1,075,687) [the ‘687 patent]. The ‘687 patent was a so-called “genus patent”. It covered 15 trillion compounds all with a similar chemical structure – three-ring molecules called “thienobenzodiazepines”. The ‘113 patent, therefore, is a so-called “selection patent” which identifies an already-patented compound for separate patent protection based on its alleged advantage over the other members of its chemical family.

[3] In an earlier judgment, *Eli Lilly Canada Inc v Novopharm Limited*, 2009 FC 1018 [Trial Judgment], I dismissed Lilly’s action for infringement primarily on the basis that Lilly was not entitled to a second patent for olanzapine. I found that Novopharm had proved on the balance of probabilities that, at the 1991 filing date for the ‘113 patent, Lilly did not have enough information about olanzapine either to have shown or soundly predicted that it would have the utility described in the patent. In addition, I found that the patent did not set out a sufficient description of the alleged invention. Because I concluded that olanzapine did not amount to a separate and distinct invention from the ‘687 patent, I also found that the ‘113 patent had been anticipated by the ‘687 patent and that olanzapine had been double-patented. However, I found that olanzapine was not an obvious choice for the inventors of the ‘113 patent to take into development. But this alone, I concluded, did not mean that olanzapine met the definition of an invention in s 2 of the *Patent Act* because it did not represent an invention over and above the compounds of the ‘687 patent.

[4] Lilly appealed my decision and the Federal Court of Appeal allowed the appeal: *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 [FCA Judgment]. Justice Layden-Stevenson, writing for the Court, found that I had erred in my approach to selection patents. She also concluded that the '113 patent was not invalid for anticipation, double patenting or obviousness. However, she referred the issues of utility and sufficiency back to me. A fuller discussion of my original judgment and Justice Layden-Stevenson's decision is set out below in order to make clear the task now assigned to me. I will also briefly consider below two other Federal Court decisions involving Lilly, olanzapine, and the '113 patent that arose out of proceedings under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/98-166, as amended SOR 93-113 [*PMNOC Regulations*].

[5] The parties agreed that the issues of utility and sufficiency could be determined on the basis of the evidentiary record generated by the first trial. In fact, as will be seen below, there are actually few disputes between the parties about the evidence. The main controversies relate to the inferences and conclusions that can be drawn from that evidence. Accordingly, many of the findings of fact I made during the first trial are repeated here.

[6] For ease of reference, I have set out relevant statutory provisions in Annex "A", and a summary of expert witnesses' backgrounds and qualifications in Annex "B".

[7] As mentioned, the issues before me are whether Novopharm has established that the '113 patent is invalid on one or both of these grounds:

1. Lack of Utility

2. Insufficient Disclosure

[8] I find that Novopharm has met its burden in relation to the issue of utility, but not on the issue of sufficiency. Therefore, I conclude that the ‘113 patent is invalid and must dismiss Lilly’s action for infringement.

## II. Factual Background

[9] Schizophrenia is a chronic form of psychosis affecting about 1 percent of the population. Generally speaking, symptoms fall into two categories. The first, called “positive” symptoms, includes hallucinations and delusions. The second, called “negative” symptoms, includes withdrawal, lack of motivation and impaired mental functioning.

[10] There is no known cure for schizophrenia. However, over the course of the past 50 or 60 years, scientists have found some drugs that mitigate some of the worst symptoms. Patients typically remain on drug treatment for many years. The drug chlorpromazine was a breakthrough in the early 1950s. But chlorpromazine had a serious side-effect liability. In particular, it induced an array of uncomfortable motor effects called “extra-pyramidal symptoms”, or EPS. EPS include restlessness, stiffness, twitching and facial contortions. Chlorpromazine and analogous drugs that share this liability to cause EPS are referred to as “typical” or “first-generation” antipsychotics.

[11] A better drug, clozapine, came onto the market in the late 1960s. Clozapine’s main advantage was that it did not induce EPS. However, after years on the market, it was found to cause

a rare but serious blood disorder, called agranulocytosis, in which the body abruptly stops making white blood cells. Clozapine was taken off the market in the 1970s, but returned in the late 1980s. Patients taking clozapine must take frequent blood tests to ensure their white blood cell count is normal. Clozapine and other drugs with a low EPS liability are referred to as “atypical” or “second-generation” antipsychotics.

[12] Once clozapine was off the market, many scientists, including those at Lilly, looked for a safe, clozapine-like compound - one that would treat both the positive and negative symptoms of schizophrenia, have little liability to produce EPS, and not affect production of white blood cells.

[13] Various tests can be used to determine a compound’s potential as an antipsychotic. The same tests have been used for decades. Compounds are tested in mice to see if they reduce locomotor activity and induce hypothermia (good signs for an antipsychotic). A compound’s capacity to block a conditioned avoidance response [CAR] in rats is of interest because it, too, indicates antipsychotic activity. Essentially, a CAR test measures a compound’s ability to interfere with rats’ learned behaviour (e.g., avoiding electric shock). On the other hand, a compound’s liability to induce catalepsy [CAT] in rodents is an important indicator of its liability to produce EPS in humans. A compound will be a potential atypical or second-generation antipsychotic if it shows good CAR-CAT separation (i.e., its CAR score is high and its CAT score is low).

[14] As described above, in the 1970s, scientists were looking for a safe clozapine-like compound. Lilly was exploring compounds that were chemically similar to clozapine as part of that quest.

[15] Having heard about clozapine and its potential as an antipsychotic, Dr. Jiban Chakrabarti, a Lilly chemist, attended a conference in Prague in the early 1970s. He met the scientists who had made and developed clozapine. Dr. David Tupper, another Lilly chemist, recalls that, when Dr. Chakrabarti returned, he was very excited about what he had heard there. He believed that he could make compounds that would be clozapine-like in terms of their antipsychotic effect but would avoid the problems associated with clozapine. Dr. Chakrabarti suggested replacing one of clozapine's phenyl rings with a thiophene ring.

[16] Dr. Tupper, after visiting the library and determining that no such compounds had previously been made, worked out ways to synthesize them. The end result was the family of compounds covered by the '687 patent.

[17] The '687 patent was filed in 1975 and issued to Lilly in 1980. Its inventors were Dr. Chakrabarti and Dr. Tupper, both of whom worked at Erl Wood, Lilly's research facility in Sussex, United Kingdom. The '687 patent described a "novel class of compounds" called "thienobenzodiazepines" with a three-ring chemical structure, similar to clozapine's. The patent asserted that this family of compounds had displayed useful central nervous system activity in animal tests, and had potent neuroleptic, sedative, relaxant and anti-emetic properties. They showed good CAR-CAT separation. These properties, the patent stated, rendered the compounds useful in the treatment of mild anxiety states, and certain kinds of psychotic conditions such as schizophrenia. Further, the compounds had a high therapeutic index (meaning that there was a wide margin

between the effective dose and a gross toxic effect) and were effective across a broad dosage range (from 0.1 mg/kg/day to 10 mg/kg/day).

[18] The focus of the ‘687 patent was clearly on the nature of the compounds themselves – their constituents, their structure, the processes by which they could be made, and the possibilities for formulating the active ingredients. Still, the patent specifically asserted that the utility of the compounds of the invention lay in their potential use in the treatment of central nervous system disorders, including schizophrenia. Dr. Ian Pullar testified that Lilly was hopeful that the class of compounds described in the ‘687 patent would be effective in treating both the positive and negative symptoms of schizophrenia, and have low EPS liability. One of the vast number of compounds covered by the ‘687 patent (15 trillion) was olanzapine. In fact, it fell within a group of the “most preferred compounds” of the invention, although it was not specifically named.

[19] Over the years following the filing of the ‘687 patent, Lilly scientists worked at bringing some of the compounds of the invention to market. A few dozen were synthesized and tested *in vitro*. Dr. Chakrabarti published a paper in 1980 that gave data on 45 of the ‘687 compounds, including their CAR and CAT values. From that study, flumezapine and ethyl flumezapine, which had been specifically identified in the ‘687 patent, looked promising. A few others also looked favourable, but Dr. Chakrabarti noted that the “profile of activity needs further development of this class of compounds” (D-39, at p 883).

[20] Lilly began tests on ethyl flumezapine, but discontinued this work in 1978 after dog studies showed the compound caused a reduction in white blood cells, just as clozapine had been known to

do, which was the major side effect sought to be avoided. At that point, Lilly turned its attention to flumezapine. Dog studies on flumezapine did not show any problem with white blood cells, although other problems were detected – weight loss, anemia and elevated prolactin. Still, in due course, in 1981, Lilly was granted permission by the U.S. Food and Drug Administration [FDA] to administer flumezapine to healthy volunteers, and then to begin clinical trials with patients experiencing schizophrenia.

[21] Lilly halted its clinical trials on flumezapine in April 1982 after receiving reports of elevated liver enzymes and a muscle enzyme called creatine phosphokinase [CPK] in some patients. Lilly passed on those reports to officials at the FDA who asked Lilly to discontinue treating patients with flumezapine.

[22] Lilly decided not to resume the clinical trials on flumezapine, even though there were signs that it was an effective antipsychotic. Investigators "were very impressed with the efficacy of the drug, as well as the significant absence of extrapyramidal side effects . . ." (D-84, at p 8). Lilly could have changed the clinical trial protocols, for example, by reducing the maximum dose, or by monitoring patients more closely for liver enzymes and CPK. Dr. Paul Leber, an FDA official who was involved in the discussions about flumezapine at the time, testified that the FDA did not halt Lilly's development of flumezapine:

> It was simply an assertion that, in the current state, they should not do further clinical testing until they submitted new reports to us and we reviewed them. Then we would explain to them what they could or could not do.
> (Transcript, Vol 6, p 150, lines 15-20)

[23] However, continuing with flumezapine would have required considerable time and effort. Lilly would have had to persuade the FDA to allow it to continue clinical trials. While the project

team felt that studies of flumezapine should be continued, Lilly management concluded that further investment in flumezapine was unwarranted. Lilly discontinued, but did not completely abandon, its request to have flumezapine approved. Still, in effect, as of 1982, flumezapine was for Lilly a tainted product.

[24] Dr. Pullar, who was the chairman of the flumezapine project team, described this as a "black time" at Erl Wood. Yet, the team felt there was enough promise within the '687 compounds that they went looking for another candidate. There was pressure coming from Lilly management to show that the substantial corporate investment in developing an antipsychotic would pay off. Erl Wood, established in 1967, had only produced one drug in its then 15-year existence that had actually made it to market.

[25] Within a few weeks of the discontinuation of flumezapine, Dr. Tupper and his colleague, Mr. Terrence Hotten, synthesized seven more of the '687 compounds, one of which was olanzapine. Dr. Tupper felt that, given that flumezapine had gone quite far in its development, the focus should be on methyl compounds like olanzapine, not ethyl. Ethyl flumezapine had been an abject failure. At first, Dr. Pullar did not think that olanzapine would be a good choice for development because it did not show particularly dramatic potency in animal tests. But the rest of the team favoured olanzapine based on its overall performance on an array of animal and *in vitro* tests. Dr. Pullar now feels glad he was outvoted and, naturally, is proud of his association with a drug that treats many patients effectively. As he said, the team "carried out very good research in order to put [olanzapine] on the market". Dr. Tupper expressed similar sentiments and cited numerous prizes the Lilly scientists had received for their work.

[26] So, by 1983, Lilly was satisfied, based on animal and *in vitro* tests, that olanzapine showed potential as an antipsychotic. Studies continued and Lilly's hopes were confirmed by further preliminary results. Beginning in 1986, Lilly gave olanzapine to healthy volunteers and, in 1989, started clinical trials in patients. By 1990, bringing olanzapine to market became a top priority for Lilly. It recognized a market opportunity, given that clozapine was about to be reintroduced, and new drugs, such as risperidone, were about to come on stream. A patent for olanzapine was filed in the United Kingdom in 1990 and in Canada in April 1991. Lilly was granted its Canadian patent, the '113, in 1998.

[27] By the time it filed the '113 patent, Lilly had received the results of its healthy volunteer studies, as well as some preliminary data from clinical trials. It had also concluded a six-month study in dogs. The patent mentions some of these studies and provides some general information about what they disclosed.

## III. The '113 Patent

[28] The '113 patent is entitled "Thienobenzodiazepine Derivatives and Their Use as Pharmaceuticals". The introduction describes the side-effect issues encountered with antipsychotic drugs, particularly EPS, and the "need for better products that control or eliminate the symptoms in a safer and more effective way".

[29] The patent explains that schizophrenia patients are prone to drug-induced EPS, including drug-induced Parkinsonism, acute dystonic reactions, akathisia, tardive dyskinesia and tardive dystonia. Most antipsychotics produce these symptoms at therapeutic doses, which frequently results in poor compliance rates in patients who must take them. Long-term use can lead to irreversible EPS.

[30] The patent cites the example of haloperidol which was known to cause EPS and tardive dyskinesia. Clozapine is also mentioned, with reference to its liability to cause agranulocytosis.

[31] The patent refers to the British Patent (No 1533235), the equivalent of the ‘687 patent, and the experience with flumezapine – termination of the clinical trial due to concerns about CPK and liver enzymes. In addition, two patients on flumezapine appeared to experience EPS.

[32] Then the inventors of the ‘113 patent announce that “[w]e have now discovered a compound which possesses surprising and unexpected properties by comparison with flumezapine and other related compounds”. The patent sets out a drawing of olanzapine and its chemical nomenclature and goes on to say that the “compound of the invention has given surprising and excellent results . . . in experimental screens for testing activity on the central nervous system and in clinical trials, which results indicate its usefulness for the relatively safe and effective treatment of a wide range of disorders of the central nervous system”.

[33] The test results for olanzapine are then described, beginning with *in vitro* tests showing that it operates as an antagonist of dopamine at the D-1 and D-2 receptors, has antimuscarinic and

anticholinergic properties, and has antagonist activity at noradrenergic receptors. These properties, the patent states, indicate that olanzapine is "a potential neuroleptic with relaxant, anxiolytic or anti-emetic properties" and that it is "useful in treating psychotic conditions such as schizophrenia, schizophreniform diseases and acute mania".

[34] Later in the patent, the results of rodent tests are set out. These are described as "standard behavioural tests predictive of antipsychotic activity". Olanzapine antagonized apomorphine-induced climbing behaviour and hypothermia in mice. CAR and CAT data are provided, noting that the separation "indicates that the compound is less likely to induce extrapyramidal side effects in the clinic".

[35] Regarding testing in humans, the patent states that olanzapine has shown a "high level of activity in the clinical evaluation of psychiatric patients suffering from schizophrenia . . . at surprisingly low dosage levels". A summary of the results of an open label study follows. The patent states that six of eight patients who completed at least two weeks of treatment showed between 66% and 87% improvement at four weeks at dosages of between 5 and 30 mg. The patent mentions that other trials are ongoing and that preliminary results suggest high efficacy at low doses.

[36] The '113 patent sets out a number of advantageous qualities of olanzapine. These can be grouped into two main categories. First, the patent identifies certain advantages of olanzapine over the other compounds from the '687 patent. Second, the '113 patent states that olanzapine is superior to other known antipsychotic drugs used in the treatment of schizophrenia and related conditions.

(a) Olanzapine's advantages over the other '687 compounds

[37] As mentioned, the '113 patent says that olanzapine displays "surprising and unexpected properties" as compared to flumezapine and other related compounds; i.e. compounds of the '687 patent. There are four specific comparisons in the patent.

[38] The first two comparisons relate specifically to flumezapine. The patent summarizes Lilly's experience with flumezapine, and the concerns about elevated liver enzymes and CPK. In contrast, the '113 patent states that patients treated with therapeutic doses of olanzapine experienced "a low incidence of only mild and transient elevation of liver enzymes", and CPK levels were lower than with flumezapine.

[39] There is a third comparison with flumezapine regarding EPS. Early in the patent, the inventors explain that many antipsychotic drugs cause EPS. The patent also states that "[i]n clinical trials with flumezapine two of the patients showed the emergence of extra pyramidal side effects . . ." Immediately thereafter, the assertion appears that "[w]e have now discovered a compound which possesses surprising and unexpected properties by comparison with flumezapine and other related compounds". Then, further on in the patent, the inventors state that olanzapine "is less likely to induce extrapyramidal side effects in the clinic".

[40] The '113 patent also mentions a dog study in which olanzapine was compared with ethyl olanzapine, another of the '687 compounds. The patent reports the outcome of the study as

indicating “that four out of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the invention did not show any rise in cholesterol levels” at a dosage of 8 mg/kg.

[41] Therefore, the ‘113 patent explicitly compares olanzapine favourably to two other compounds of the ‘687 patent in respect of the following parameters:

- lower incidence of liver enzyme elevations compared to flumezapine;
- lower CPK levels than flumezapine;
- lower EPS than flumezapine; and
- no increase in cholesterol compared to ethyl olanzapine.

(b) Olanzapine’s advantages over other antipsychotic drugs

[42] The patent declares that olanzapine shows “surprising and excellent results” in experimental screens and clinical trials. In particular, olanzapine shows a “high level of activity in the clinical evaluation of psychiatric patients suffering schizophrenia” at doses lower than were expected based on animal models. The patent refers to the open-label study and preliminary results from three other ongoing clinical trials.

[43] The patent states that olanzapine caused a “low incidence of only mild and transient elevation of liver enzymes in patients treated with therapeutic doses”. Further, olanzapine “causes lower elevation of prolactin levels than other currently used neuroleptic drugs”.

[44] The patent also states that no alteration of white blood cell count was observed during clinical studies of olanzapine.

[45] These statements are followed by the following broad assertion about olanzapine:

> Overall, therefore, in clinical situations, the compound of the invention shows marked superiority and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level.

[46] The introductory words of the sentence ("overall, therefore") appear to preface a summary of the collective advantages of olanzapine in respect both of efficacy and the particular side effects discussed in the preceding passages. I will come back to this statement below when discussing the "promise" of the '113 patent.

[47] For the moment, however, I would simply point out that this statement, despite its apparent breadth, does not appear to assert the superiority of olanzapine in respect of all possible side effects. However, a fair interpretation of the patent is that it asserts the superiority of olanzapine in respect of the side effects specifically identified in it, including the ones that presented the greatest concern to schizophrenia patients – EPS and agranulocytosis. No antipsychotic would be considered to be markedly superior or have a better side effects profile than other antipsychotics if its EPS or agranulocytosis liability was disadvantageous.

[48] Therefore, the advantages of olanzapine over other antipsychotic drugs addressed in the '113 patent include:

- a high level of efficacy at low doses;

- lower elevation of prolactin;
- lower EPS liability; and
- no alteration of white blood cell count.

[49] There is also an implied comparison with respect to liver enzymes, given the linkage made between flumezapine and chlorpromazine in that area. The patent says that "in respect of its tendency to raise liver enzyme levels, flumezapine is similar to chlorpromazine, an antipsychotic which has long been in use but whose safety has been called into question". However, it is unnecessary to discuss this characteristic separately as it is covered by the comparison with flumezapine.

## IV. Other Federal Court Proceedings involving the '113 Patent

[50] The '113 patent was litigated in two previous applications before the Federal Court under the *PMNOC Regulations*. In the first, before Justice Johanne Gauthier, Lilly sought and obtained an order prohibiting the Minister of Health from issuing a Notice of Compliance [NOC] that would have allowed Apotex Inc. to make and sell a generic version of olanzapine (*Eli Lilly Canada Inc v Apotex Inc*, 2007 FC 455) [*Lilly (1)*].

[51] Justice Gauthier construed the '113 patent and found that it disclosed a number of advantages of olanzapine which, taken together, amounted to an assertion that olanzapine was "an antipsychotic that, in clinical situations, had overall a better profile than prior known antipsychotic agents (including the compounds encompassed in the '687 Patent)" (para 334).

[52] Apotex had alleged that the ‘113 patent was invalid on grounds of anticipation, obviousness, double patenting, and violation of s 53 of the *Patent Act*, RSC 1985, c P-4. Justice Gauthier found that Apotex’s allegations were not justified. However, she also found that the additional question of whether the ‘113 met the criteria for a valid selection patent was not properly before her as it had not been specifically alleged by Apotex. The Federal Court of Appeal confirmed that finding: *Eli Lilly Canada Inc v Apotex Inc*, 2008 FCA 44.

[53] In a separate proceeding under the *PMNOC Regulations*, involving, essentially, the same parties as are before me, Justice Roger Hughes concluded that the advantages described in the ‘113 patent amounted to a promise and had to be adequately described in the patent specification.

[54] He found that they were not adequately described, and that Novopharm’s allegation that the ‘113 patent’s disclosure was insufficient was justified. He refused to issue an order prohibiting the Minister from granting Novopharm a NOC to enter the olanzapine market (*Eli Lilly Canada Inc v Novopharm Limited*, 2007 FC 596) [*Lilly (2)*]. Soon thereafter, Novopharm obtained its NOC. Lilly launched an appeal, but the Federal Court of Appeal found the proceeding to be moot, given that Novopharm had already obtained its NOC (*Eli Lilly Canada Inc v Novopharm Limited*, 2007 FCA 359). By then, Lilly had commenced this action for infringement of the ‘113 patent.

[55] Justice Hughes addressed a key issue that was not before Justice Gauthier – whether the ‘113 is a valid selection patent – in particular, whether the ‘113 patent’s disclosure was sufficient. He found that the ‘113 patent failed to describe what the “surprising and unexpected properties” of olanzapine were in comparison with the other compounds of the ‘687 patent. On appeal, Lilly

argued that Justice Hughes erred by requiring patents to set out comparative data. However, the Court did not agree that Justice Hughes had stipulated that comparative data were required in selection patents.

[56] The essence of Justice Hughes' decision is set out in the following paragraph (para 162):

> I find that the '113 patent fails to provide sufficient disclosure in its specification as to the invention, if any, in selecting olanzapine from a previously disclosed group of compounds. The prior art British Patent teaches the whole class of compounds [is] to be useful in treating central nervous system disorders. The invention in selecting olanzapine is the so called "surprising and unexpected" properties of olanzapine in "comparison with flumezapine and other related compounds". No such comparison is made anywhere in the '113 patent. No data was given. We are left only with rhetoric such as "high level of efficiency" and "mild and transient" and "lower" side effects. The puzzling and scant mention of a dog study refers only to ethyl olanzapine and tells nothing of flumezapine or other compounds.

[57] Justice Hughes concluded that the '113 did not adequately distinguish between olanzapine's qualities and the characteristics of the previously patented family of compounds, of which olanzapine was a member. Therefore, the '113 was not a valid selection patent.

## V. The Federal Court of Appeal's Approach to Selection Patents

### 1. *The Trial Judgment*

#### (a) The Nature of the Action

[58] Lilly alleged in its Statement of Claim that Novopharm's generic version of olanzapine would infringe the '113 patent.

[59] Novopharm responded by alleging that the ‘113 patent was invalid on numerous grounds, including anticipation, obviousness, and double-patenting. In addition, Novopharm alleged that the ‘113 patent was an invalid selection patent, given that olanzapine fell within the claims of the ‘687 patent and failed to meet the criteria set out in long-standing case law, that selected compounds must be “previously undiscovered, constituting a special advantage, particular to themselves, not attributable to them by virtue of their belonging to the class of the [genus patent], and defined in clear terms in the specification” (Third Amended Statement of Defence and Counterclaim, para 14).

[60] In the same vein, Novopharm maintained that the ‘113 patent failed to satisfy the requirements for a valid selection patent because the “inventors of the ‘113 Patent had not made and tested a sufficient number of the compounds from the ‘687 Patent in order to support or soundly predict any of the asserted advantages in the ‘113 Patent and in particular the assertion that ‘overall, therefore, in clinical situations, the compound of the invention shows marked superiority, and a better side effect profile than prior known antipsychotic agents, and has a highly advantageous activity level’” (para 14.2). Further, according to Novopharm, Lilly did not have sufficient information to soundly predict that olanzapine would have the characteristics described in the ‘113 patent, or possess an articulable and sound line of reasoning to support that prediction, or provide proper disclosure in the patent (para 25).

[61] In its Reply and Defence to Counterclaim, Lilly disputed Novopharm’s assertion that the ‘113 was not a valid selection patent. Lilly contended that the ‘113 was a valid selection patent given that olanzapine has a number of substantial and peculiar advantages that are described in the patent. In addition, olanzapine has a better side effect profile than prior-known antipsychotic

agents, has a high activity level at low doses, and a number of advantages over the compounds of the ‘687 patent. Lilly maintained that the ‘113 patent was a valid selection patent because olanzapine has special advantages that could not have been predicted before it was made and tested. In particular, olanzapine avoided problems associated with the compounds of the ‘687 patent, namely, elevation of liver enzymes, muscle enzymes, prolactin, and cholesterol, and did not cause blood disorders or EPS.

[62] Lilly also asserted that olanzapine had been proven, as of the filing date, to be an effective antipsychotic based on the clinical trials conducted to that point. Accordingly, the issue of sound prediction had no application. However, Lilly also contended that it had a factual basis for all of the characteristics of olanzapine promised in the ‘113 patent, had an articulable and sound line of reasoning supporting the prediction of those characteristics, and had provided proper disclosure in the ‘113 patent.

[63] As can be seen from the pleadings, the question of the ‘113’s validity as a selection patent was at the forefront of this action. The bulk of the evidence and the legal arguments surrounded that issue.

(b) The Reasons

(i) Utility

[64] In my original judgment, I started from the premise that a valid patent must disclose an invention. Section 2 of the *Patent Act* defines an invention as a “new and useful . . . composition of matter, or any new and useful improvement in any . . . composition of matter”. This is true of

selection patents, just as it is with any other kind of patent. However, I noted that a selection patent must disclose an invention over and above what was contained in the prior patent – the "genus patent" – covering the selected compound. In other words, there must be something distinctly useful about the selected compound as compared to the class of compounds defined by the genus patent.

[65] I relied on Justice Marshall Rothstein's statement that selection patents must define their utility. Justice Rothstein set out the relevant principles in *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61, [2008] 3 SCR 265 [*Sanofi-Synthelabo*], relying on the well-known precedent of *Re I.G. Farbenindustrie AG's Patents* (1930), 47 RPC 289 (Ch D) [*Farbenindustrie*]:

> 1. There must be a substantial advantage to be secured or disadvantage to be avoided by the use of the selected members.
>
> 2. The whole of the selected members (subject to "a few exceptions here and there") [must] possess the advantage in question.
>
> 3. The selection must be in respect of a quality of a special character peculiar to the selected group. If further research revealed a small number of unselected compounds possessing the same advantage, that would not invalidate the selection patent. However, if research showed that a larger number of unselected compounds possessed the same advantage, the quality of the compound claimed in the selection patent would not be of a special character (para 10).

[66] I interpreted these principles as setting out a requirement that olanzapine have a substantial and peculiar advantage over the other compounds of the '687 patent. In addition, the patent must clearly describe the selected compound's substantial and special advantage. Justice Rothstein said that "the specification of the selection patent [must] define in clear terms the nature of the

characteristic which the patentee alleges to be possessed by the selection for which he claims a monopoly" (para 114).

[67] I then reviewed the '113 patent to determine what advantages were being asserted for olanzapine. I found there to be a general assertion in the '113 patent that olanzapine is superior to the class of compounds covered by the '687 patent. The patent states that olanzapine displays "surprising and unexpected properties" as compared to flumezapine and other related compounds. As described above, the patent specifies four examples of superiority in respect of two '687 comparator compounds (flumezapine and ethyl olanzapine). The patent says that olanzapine is better and different from those two compounds in the following respects:

(i) Olanzapine has lower elevations of liver enzymes than flumezapine;

(ii) Olanzapine has lower elevations of CPK than flumezapine;

(iii) Olanzapine has less EPS liability than flumezapine; and

(iv) Olanzapine does not elevate cholesterol, but ethyl olanzapine does.

[68] I did not find it necessary to refer to expert testimony to construe this aspect of the patent, given that the asserted advantages were clearly stated in the patent.

[69] I went on to consider the other advantages of olanzapine that are asserted in the patent. In this respect, I considered how a skilled reader familiar with the history of the development of anti-psychotics would read the patent. I found that "reading the '113 patent as a whole, the skilled reader, aware of the '687 patent, would interpret the alleged superiority of olanzapine over other

antipsychotic drugs on the market as being another major advantage of olanzapine over the other '687 compounds" (Trial Judgment, para 53).

[70] While the '113 patent refers only to two of the '687 compounds and their disadvantages, it is clear that neither of them had been used for the treatment of schizophrenia or any other condition. By contrast, according to the '113 patent, not only could olanzapine be used for that purpose, it was, "overall", markedly superior to, and had a better side effects profile than, other drugs on the market. That assertion related both to olanzapine's efficacy and the particular advantages of olanzapine in respect of the side effects that were discussed in the patent. I found that a fair reading of that statement was that the patent "asserts the superiority of olanzapine in respect of the side effects specifically identified in it, including the ones that presented the greatest concern to schizophrenia patients – EPS and agranulocytosis" (Trial Judgment, para 47).

[71] As mentioned, the specific advantages of olanzapine over other antipsychotic agents as stated in the patent were:

(i) olanzapine has a high level of efficacy at low doses;

(ii) olanzapine has a lower elevation of prolactin;

(iii) olanzapine has lower EPS liability; and

(iv) olanzapine does not alter white blood cell counts.

[72] I considered whether one or more of these asserted advantages of olanzapine was known to exist, or could have been soundly predicted, at the time the '113 patent was filed in 1991. I reviewed the information known about the drugs with which olanzapine was compared and the main thrust of

the expert evidence before me, then applied the test for sound prediction set out by Justice Binnie in *Apotex Inc v Wellcome Foundation Ltd*, [2002] 4 SCR 153 [*AZT*].

[73] I then determined whether at least one of those advantages could be considered a substantial advantage over the ‘687 compounds and somewhat peculiar to olanzapine. I also considered whether the disclosure of that substantial and special advantage in the ‘113 patent was adequate.

[74] I found that the evidence before me showed no advantage for olanzapine over other compounds of the ‘687 patent. Nor was there a sufficient factual basis to support a prediction that olanzapine would have the asserted advantages over those compounds. The tests that had been carried out by the relevant date simply could not support a prediction of any of those advantages. Further, I could find no articulable line of reasoning that would support a sound prediction of the advantages. Finally, the patent did not disclose any factual basis or line of reasoning that would permit a person skilled in the art to appreciate what the alleged invention - a superior compound to the ‘687 class – actually was.

[75] In addition, I found that the evidence before me showed no advantage, and no factual basis for a sound prediction of an advantage, for olanzapine in comparison with other antipsychotic agents. Again, the tests that had been carried out simply did not support a prediction of such an advantage. There was no evidence of a sound line of reasoning leading to a conclusion that olanzapine would display superiority over other drugs. Nor was there any disclosure in the patent of facts or reasoning that would support olanzapine’s alleged superiority.

[76] In turn, I considered whether, even if they had existed, the asserted advantages of olanzapine could be considered "substantial and peculiar". I found the alleged advantages of olanzapine over flumezapine and ethyl olanzapine were not substantial. To the extent they existed at all, their magnitude was insignificant. Further, there was no evidence that olanzapine was superior to any other compounds in the '687 class in respect of the particular characteristics described in the '113 patent. The comparisons did not relate to the class as a whole and there was no evidence that any advantage was peculiar to olanzapine.

[77] On the other hand, I found that olanzapine's alleged superiority over other antipsychotic drugs on the market would certainly have amounted to a substantial advantage over the '687 class of compounds. The invention described in the '687 patent was in respect of a class of compounds that would be useful in the treatment of psychotic conditions and acute mania, and that would have low EPS liability. By contrast, the invention described in the '113 patent was in respect of a drug that was safer and more effective in the clinical treatment of patients than other antipsychotic drugs on the market. This is clearly a substantial advantage that would set olanzapine apart from the rest of the '687 class. However, the evidence did not support that broad assertion or a sound prediction of it at the time Lilly applied for the '113 patent. Nor was there an articulable line of reasoning from the factual basis existing at the time to the prediction, or disclosure in the '113 patent of those facts and reasoning.

[78] Accordingly, I concluded that the evidence did not show olanzapine to have a substantial and peculiar advantage over the other '687 compounds. It was, therefore, not an invention, according to s 2 of the *Patent Act*.

(ii) Sufficiency

[79] I noted that two disclosure requirements applied to the ‘113 patent. The first was the duty to set out the factual basis and an articulable line of reasoning for the sound prediction of olanzapine’s advantages. The second was the duty to describe the invention itself.

[80] I concluded, however, that in a case where an invention consists of a selected compound predicted to have advantages over the genus, the two disclosure requirements are coextensive. I suggested that, if the patent had met the disclosure requirements for sound prediction by setting out the required factual basis and sound line of reasoning, by definition, it would also have described the invention sufficiently. Having found that the ‘113 patent failed to disclose the basis for the prediction of olanzapine’s advantages, I concluded that it also failed sufficiently to disclose the invention.

2. *The Federal Court of Appeal’s Judgment*

(a) Utility

[81] Justice Layden-Stevenson began by describing what selection patents are:

> Although not restricted to chemical patents, selection patents more commonly arise in that context. Simply stated, the originating (or genus) patent typically refers, in general terms, to a group of products or processes from all of which a particular result (or results) may be obtained or predicted. If a property, quality or use in relation to one or more members of the genus is subsequently discovered, that discovery may be an invention giving rise to a valid selection patent. As explained in

> *Pfizer* and *Sanofi*, selection patents exist to encourage researchers to further use their inventive skills so as to discover new advantages for compounds within the known class (para 20).

[82] She then set out (para 22), the well-known "characteristics of a valid selection patent" as originally laid down in *Farbenindustrie*, above, and endorsed by Justice Marshall Rothstein in *Sanofi-Synthelabo*, above.

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

[83] From there, Justice Layden-Stevenson went on to consider where these conditions for a valid selection patent should be analyzed. She concluded that the conditions for a valid selection patent do not constitute an independent basis on which to challenge the patent. Rather, those conditions merely describe a valid selection patent; they are not criteria for validity. The only valid grounds for attacking a patent are those set out in the *Patent Act*, and the Act says nothing about selection patents. They are no different from any other kind of patent.

[84] Regarding the requirement of utility for selection patents, Justice Layden-Stevenson set out the usual requirement – the patent holder need only show a scintilla of utility for the patent to be

valid. But, where a patent makes an explicit promise, "[t]he question is whether the invention does what the patent promises it will do" (para 76, citing *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504, and *Pfizer Canada Inc v Canada (Minister of Health)*, 2008 FCA 108).

[85] According to Justice Layden-Stevenson, the inventiveness inherent in a selection patent "lies in the making of the selected compound, coupled with its advantage or advantages, over the genus patent" (para 78). The patent "must promise an advantage in the sense that, if the advantage is not promised, the patentee will not be able to rely on the advantage to support the patent's validity" (para 78).

[86] I take this to mean that, to be valid, a selection patent must contain an explicit promise of an advantage, and the alleged invention must meet that promise. Justice Layden-Stevenson went on to confirm that the advantage must be substantial, although it may lie in a single beneficial property or be made up of a number of lesser ones.

[87] A trial judge, therefore, must construe the selection patent to determine whether it contains an explicit promise of a substantial advantage, and to identify what it is. The judge construes the patent through the eyes of the skilled person.

[88] From there, the judge must consider whether the patent holder was able, as of the filing date of the patent, to demonstrate or soundly predict the patent's promise. In defining a sound prediction, Justice Layden-Stevenson cited *AZT*, above. From Justice Binnie's analysis of sound prediction, she

drew what she described as the proper “threshold” of sound prediction: “a *prima facie* reasonable inference of utility” (para 85).

[89] With respect to the ‘113 patent specifically, Justice Layden-Stevenson construed it as containing a promise that olanzapine shows marked superiority to flumezapine and other ‘687 compounds in the treatment of schizophrenia, has a better side effects profile than prior known antipsychotic drugs, and has a highly advantageous activity level. However, because I had not found it necessary in my original decision to refer explicitly to expert evidence on the construction of the patent, she felt she did not have sufficient opportunity to consider that evidence in determining what the actual promise of the ‘113 patent was.

[90] In discussing the alleged advantage of olanzapine relating to cholesterol and the dog study supporting it, Justice Layden-Stevenson laid down an important limitation on construing a selection patent. Since virtually all the experts agreed that the dog was not a good model for studies of a cholesterol effect in humans, the promise of the patent should not be construed as asserting an advantage in respect of olanzapine’s cholesterol effect in humans. Accordingly, if a patent appears to assert advantages that skilled persons would not regard as supportable, they should not be construed as forming part of the promise. Further, the question is not whether particular advantages were known or soundly predicted, it is whether the patent holder had sufficient information on which to base the promise as a whole.

[91] Justice Layden-Stevenson concluded that the ‘113 patent sets out a sufficient factual basis for a sound prediction of the patent’s promise. She cited the studies in mice and rats to determine

olanzapine's potential as an anti-psychotic drug, a small open-label clinical trial with 8 patients, and four studies involving a total of 20 healthy volunteers. She stated, therefore, that the real question in respect of the '113 patent's validity was not whether there was a factual basis for a sound prediction of its utility, but whether there was an articulable line of reasoning – that is, a prima facie reasonable inference - from that factual basis to the patent's promise.

(b) Sufficiency

[92] To meet the requirements of s 27(3) of the *Patent Act*, Justice Layden-Stevenson concluded that selection patents must correctly and fully describe the invention – the compound, its advantages, and how it works. This requirement is separate from the disclosure requirement for sound prediction. In her view, the issue of sufficiency was confined to s 27(3) (para 120). Therefore, I need not say anything further about the disclosure requirement for sound prediction; it was not referred back to me.

3. *Summary of the Court of Appeal's Approach*

[93] The following summarizes my understanding of the proper approach to determining the issues of utility and sufficiency in respect of selection patents generally, and the '113 patent in particular:

1. Review the patent to determine whether it sets out a specific promise of a substantial advantage over the genus compounds and, if it does, identify it.

2. In construing the patent, refer explicitly to the expert evidence to determine whether a skilled person would interpret the stated advantage(s) as being truly advantageous; only those advantages regarded as truly advantageous can form part of the patent's promise.

3. The '113 patent contains a sufficient factual basis for a sound prediction of its promise – studies in rodents, an open-label clinical trial with 8 patients, and healthy volunteer studies involving 20 persons.

4. The real issue in respect of sound prediction is whether there is an articulable line of reasoning from the factual basis set out in the '113 patent to the patent's promise; that is, whether there exists a *prima facie* reasonable inference linking the factual basis to the promise.

5. To decide whether a selection patent discloses the invention sufficiently, one must determine whether it identifies the compound, its advantages and how it works; this is distinct from determining whether the patent meets the disclosure requirements for sound prediction (which is not in issue here).

## VI. Issue One - Utility

### 1. *The Promise of the '113 Patent*

[94] The claims in issue are the following:

- Claim 3: Olanzapine.
- Claim 6: The use of olanzapine for the manufacture of a drug for the treatment of schizophrenia.
- Claim 13: A pharmaceutical composition comprising olanzapine and a pharmaceutically acceptable diluent or carrier.
- Claim 14: A pharmaceutical composition in capsule or tablet form containing 0.1 to 20 mg of olanzapine.

- Claim 15: A pharmaceutical composition in capsule or tablet form containing 0.5 to 10 mg of olanzapine.
- Claim 16: A pharmaceutical composition in capsule or tablet form containing 2.5 to 5 mg of olanzapine and a pharmaceutically acceptable diluent or carrier.

[95] In construing the patent, I must do so from the perspective of a person skilled in the relevant art and be guided by the expert evidence presented by the parties. The parties agree that a person skilled in the art for present purposes would possess a conglomeration of knowledge and experience in medicinal chemistry, toxicology, psychiatry, and pharmacology, as well as a capacity to interpret data from animal studies and appreciate their relevance to the treatment of human disease.

[96] Lilly maintains that the promise of the ‘113 patent is simply that olanzapine is a relatively safe and effective anti-psychotic. However, most of the experts interpreted the patent as promising something more than what Lilly contends – that it includes the various alleged advantages of olanzapine described above in the clinical treatment of schizophrenia, and expressed in the broad “overall, therefore” statement set out above.

[97] When Dr. Guy Goodwin was asked if the patent promises the advantages identified in it, he answered: “That is my understanding. It is a kind of hypothesis that it will have those advantages, yes” (Transcript, Vol 37, pp 224-5, lines 24-25, 1). He agreed that the “overall, therefore” statement in the patent amounted to a promise of marked superiority and a better side effects profile compared to prior-known anti-psychotic agents in the clinical treatment of schizophrenia (Transcript, Vol 37, p 253, lines 1-9).

[98] Dr. Goodwin acknowledged in his affidavit that the "overall, therefore" statement represents "a summary of the advantages set out in the '113 Patent that olanzapine has over antipsychotics in use in 1991 as well as other members of the '687 Patent" (P-226, at p 33). His affidavit also stated that the '113 patent merely promised a safe and effective anti-psychotic, but he did not discuss the actual wording of the patent in doing so. His affidavit was based on the premise that the use of the compound was distinct from the advantages.

[99] Dr. David Healy testified that "[t]he patent appears to promise. . . that an agent is going to be superior to other agents in the field" (Transcript, Vol 14-C, p 256, lines 7-9). In his report, he found that a person of skill in the art would have understood the "overall, therefore" statement as being "a summary of the promise being made: that overall, in clinical situations, olanzapine would be markedly superior and have a better side effect profile than prior known antipsychotic agents". He found support for that interpretation in the activities of skilled persons at the time: "Researchers were looking for the 'safe clozapine'" (D-104, at p 8). His opinion is supported by the words of the patent itself, as described above, and in Lilly's own assertion that it was looking for a "better clozapine".

[100] Similarly, Dr. Diamond concluded that a "person of skill in the art in April 1991, when reading the patent, would be drawn to conclude that the safety of olanzapine (via a better side effect profile than prior known antipsychotic agents) was being promised" (D-36, at para 30).

[101] Dr. Rosenheck read the "overall, therefore" statement as "a promise made by the inventors with respect to olanzapine's use in the treatment of psychotic conditions such as schizophrenia"

(Rosenheck Expert Report, para 70). He said that the assertion of marked superiority and a better side effect profile was "the meat of this from the perspective of somebody knowledgeable in the art" (Transcript, Vol 18, p 287, lines 8-10). The "overall, therefore" statement "is a claim that olanzapine is a superior drug; that the implications would be that it is more effective and has fewer side effects that prior-known antipsychotic agents, which, since it is plural, must refer to other antipsychotics that are available at the time" (Transcript, Vol 18, p 140, lines 4-10).

[102] In construing the '113 patent, it is also helpful to recall the utility described in its parent patent, the '687. As discussed above, the '687 patent asserted that the compounds of the invention, including olanzapine, had displayed useful central nervous system activity in animal tests, and had potent neuroleptic, sedative, relaxant and anti-emetic properties. They showed good CAR-CAT separation. These properties, the patent stated, rendered the compounds useful in the treatment of mild anxiety states, and certain kinds of psychotic conditions, such as schizophrenia. Further, the compounds had a high therapeutic index and were effective across a broad dosage range.

[103] Dr. Ian Pullar recalled that the preclinical tests on the '687 compounds suggested they would be effective in treating schizophrenia, and have low EPS liability. Indeed, he stated that the goal of Lilly's original thienobenzodiazepine project was "to produce an antipsychotic which . . . produced a lower instance of extrapyramidal side effects and probably had some positive effect on negative symptoms of schizophrenia" (Transcript, Vol 13, p 17, lines 9-13).

[104] Dr. Ronald Diamond noted that the animal models described in the '687 patent are widely used in the development of antipsychotic medications. From his reading of it, the '687 patent appeared to suggest that the compounds of the invention were likely to have antipsychotic

effectiveness with a decreased risk of extrapyramidal or motor side effects: “[T]hat would make sense from the various animal tests that have been used” (Transcript, Vol 10-A, p 19, lines 2-4).

[105] Dr. Allan Young’s understanding from reading the ‘687 patent and the preclinical tests mentioned in it was that the inventors were looking at second-generation antipyschotics. However, “the extent to which you can extrapolate that to the human condition is limited, but inasmuch as you can gain useful information, I think this suggested that the compounds might be potentially atypical antipsychotics” (Transcript, Vol 30, p 46, lines 3-8). In addition, he understood that Lilly was suggesting to the reader that the ‘687 compounds would work in humans because of the reference to a high therapeutic index – “so obviously there’s an indication these drugs would be useful in humans” (Transcript, Vol 30, p 50, lines 4-6). Therefore, Lilly was saying in the ‘687 patent that it had found a class of relatively safe and effective antipyschotics useful in the clinical treatment of schizophrenia and other disorders.

[106] As mentioned, Lilly asserts that the promise of the ‘113 patent is simply that olanzapine is a relatively safe and effective anti-psychotic – the same utility set out in the ‘687 patent. While the ‘113 patent describes certain advantages of olanzapine, those do not, Lilly says, form part of the promise of the patent. Advantages of a compound, Lilly says, are separate from the promise of a particular result. In addition, advantages must be distinguished from the data supporting them. A patent holder need not set out the data supporting the advantages. In particular, Lilly argues that the discussion in the ‘113 patent of olanzapine’s advantages as compared to other compounds merely forms part of the factual basis supporting the true promise of the patent, namely, that olanzapine is a relatively safe and effective drug in the treatment of schizophrenia and related conditions.

[107] By Lilly's interpretation, the "overall, therefore" statement in the patent is simply a summary of olanzapine's advantages. It does not form part of the utility of the invention, and it does not amount to a promise.

[108] Lilly relies on Justice Layden-Stevenson's caution about including in the promise assertions that skilled persons would not regard as supportable (as in the dog study cholesterol example). In Lilly's view, this means that skilled persons would recognize from the patent's disclosure that it had only conducted very limited, uncontrolled, preliminary work on olanzapine. They would not expect anything more than a promise of some early, positive signals about olanzapine's potential as an antipsychotic. Lilly should only be held, therefore, to that level of promise.

[109] Lilly does concede, however, that at its highest, the "overall, therefore" statement amounts to a general assertion of the superiority of olanzapine over the '687 compounds and a better side-effects profile than other known anti-psychotics – but not a promise.

[110] In my view, Lilly's submission with respect to the promise of the '113 patent does not line up with the plain words of the patent. Nor does it accord with the preponderance of the expert evidence about what those words conveyed to them. Nor would that reading, in my view, meet the utility requirement for a selection patent, or conform to the approach to selection patents laid out by Justice Layden-Stevenson. The promise of the '113 patent must be greater than that of the '687 patent which, as outlined above, related to a family of compounds useful in the treatment of

schizophrenia and other disorders, and that would be expected to have low EPS liability (i.e., second generation antipsychotics).

[111] It is simply not enough for a selected compound to achieve what was promised in the genus patent. Justice Brian Malone of the Federal Court of Appeal addressed this point when he said that a valid selection patent involves a "discovery that the selected members possess qualities hitherto undiscovered, particular to themselves and not attributable to them by virtue of the fact of their belonging to a class specified by an earlier invention" (*Pfizer Canada Inc v Canada* (*Minister of Health*), 2006 FCA 214, para 22, citing *Dreyfus and Other Applications* (1945), 62 RPC 125 at 133).

[112] In other words, it is not enough, in my view, for Lilly to maintain that the stated utility of olanzapine – the promise of the '113 patent - is simply that it actually does or could be soundly predicted to do what the '687 patent said that all members of that class did, or were soundly predicted to do.

[113] Lilly also argues that recent Supreme Court of Canada jurisprudence makes clear that a selection patent will be valid if its promise amounts to a single advantage over a single member of the genus patent. Lilly refers to Justice Rothstein's decision in *Sanofi-Synthelabo*, above, and notes that the Court upheld the patent where the selected compound had only one advantage over a compound falling within the genus.

[114] I do not read the *Sanofi-Synthelabo* case in the same manner as Lilly. There, the genus patent covered a broad class of compounds, known as racemates, with useful platelet aggregation

properties. The class was made up of 250,000 compounds. Racemates consist of two constituents, known as isomers. The later selection patent claimed a single isomer of the lead compound of the genus patent. The selected isomer had all of the beneficial platelet aggregation activity of the racemate with little of its toxicity. By contrast, the unselected isomer had none of the beneficial activity of the racemate and most of its toxicity.

[115] Justice Rothstein found that the selection patent was valid. Given that the selected compound had clear advantages over the racemate, he spent little time discussing this aspect of the case. But I would not interpret his decision as permitting a selection patent to be upheld where its utility related to only one advantage over a single compound of the genus patent. On the facts of *Sanofi-Synthelabo*, the existence of the selected isomer was recognized in the genus patent, but no one knew that the selected isomer had all of the activity and little of the toxicity of the racemate. The selection patent stated:

> In an unexpected manner only the dextro-rotatory [isomer] exhibits a platelet aggregation inhibiting activity, the levo-rotatory [isomer] being inactive. Moreover, the inactive levo-rotatory [isomer] is the less well tolerated . . . (See the trial judgment of Justice Michel Shore: *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2005 FC 390, para 22.)

[116] The making of the isomer and the discovery of its special advantages over the racemate and the other compounds of the genus patent constituted a genuine invention. Further, given that the genus patent did not disclose the special advantages of the isomer, the selection patent was not anticipated by the genus patent.

[117] Justice Rothstein specifically referred to the need to compare the selected compound with

the particular racemate from which it derived, as well as the overall class of compounds covered by the genus patent (para 106). Accordingly, the comparison I must make here is between olanzapine and the class of compounds falling within the ‘687 patent.

[118] As described above, the ‘113 patent proclaims a number of advantageous qualities for olanzapine when compared to the other compounds of the ‘687 patent and to other known antipsychotic drugs used in the treatment of schizophrenia and related conditions. In fact, as I read it, the entire patent is based on comparisons between olanzapine and other compounds, whether included in the ‘687 patent or otherwise. It begins with the observation that there was a “need for *better* products that control or eliminate the symptoms of (schizophrenia) in a *safer* and *more effective* way” (emphasis added).

[119] The ‘113 patent goes on to identify the various advantageous properties of olanzapine as compared to the ‘687 compounds and other known antipsychotics. As I read it, Lilly clearly recognized the need to assert a substantial advantage for olanzapine, and the inventors drafted the ‘113 patent accordingly, setting out areas where olanzapine might be said to have some advantageous properties and concluding with an all-encompassing statement about those alleged advantages.

[120] I find, therefore, that the promise of the ‘113 patent is expressed in the broad assertion about olanzapine’s superiority:

> Overall, therefore, in clinical situations, the compound of the invention shows marked superiority and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level.

[121] As discussed above, this statement appears just after a description of particular side effects and olanzapine's comparative advantages. The opening words of the sentence ("overall, therefore"), introduce a summary of the various alleged advantages of olanzapine in respect both of its efficacy and of the particular side effects discussed in the preceding passages.

[122] However, as discussed above, I do not read this statement as asserting the superiority of olanzapine in respect of all possible side effects. Rather, the patent mainly asserts the superiority of olanzapine in respect of the particular side effects specifically mentioned in the patent, most especially EPS and agranulocytosis.

[123] However, I also find that the broad declaration in the '113 patent about olanzapine's superiority suggests that the inventors had some idea of olanzapine's overall side effects liability. This was not a warranty that worrisome side effects could not later come to light. It was a general statement intended by the inventors to assure skilled readers that olanzapine appeared genuinely to represent a significant advance in neuropsychopharmacology.

[124] Therefore, the promise of the '113 patent is that olanzapine is substantially better ("marked superiority") in the clinical treatment of schizophrenia (and related conditions) than other known antipsychotics, with a better side-effects profile, and a high level of activity at low doses. This promise expresses a substantial advantage for olanzapine over the other '687 compounds, which had never actually been used to treat schizophrenia. The individual advantages asserted in the patent (other than in relation to cholesterol) form the foundation for the overall promise of the patent.

[125] This promise involves comparisons between olanzapine and other compounds. As mentioned above, Justice Layden-Stevenson concluded that a sufficient factual basis exists for a sound prediction that olanzapine met the promise of the patent. However, I must consider whether there is a sound and articulable line of reasoning, that is, a *prima facie* reasonable inference, leading from that factual basis to the specific promise of the '113 patent. Before deciding that question, I must set out what the factual basis is, including the information available in April 1991 relating to comparisons between olanzapine and other compounds. Once I have done so, I will consider whether that factual basis shows that the stated utility of the '113 patent, the promise, had been demonstrated as of the filing date. If not, I must then consider whether an articulable and sound line of reasoning – a *prima facie* reasonable inference – links the factual basis with the stated utility of the patent, the promise.

2. *The Factual Basis*

[126] For olanzapine, we know that preclinical studies – *in vitro* assays and tests in mice and rats – a four-week open-label clinical trial (called E001) involving 8 patients, and four studies of healthy volunteers had been completed by the filing date. The '113 patent refers to preliminary results from other clinical trials that were ongoing in 1991, and states that there were some early indications of olanzapine's efficacy from those studies.

[127] As mentioned in the '113 patent, Lilly had done *in vitro* tests (binding assays) showing that olanzapine was an antagonist of dopamine at the D1 and D2 receptors. The patent states that this

activity indicates that "the compound is effective in the treatment of psychotic conditions but is less likely to induce extra pyramidal side-effects".

[128] However, as Dr. Rosenheck cautioned, "it is certainly possible that [olanzapine] has a thrilling binding profile, but that's . . . irrelevant to the evaluation of its potential in humans" (Transcript, Vol 19, p 27, lines 2-6). One "cannot extrapolate from D2 receptor activity to the superiority of a drug in the treatment of human beings" (Transcript, Vol 19, p 26, lines 20-22). Dr. Newcomer accepted that Lilly's *in vitro* studies showed "promising results" but he would not agree that those tests are predictive of a compound's effectiveness in the treatment of psychotic conditions (Transcript, Vol 27-A, p 22, lines 18-21). Dr. Nichols felt the binding assays would indicate to a medicinal chemist "that there was the possibility that olanzapine might be an atypical antipsychotic" (P-191, at para 314).

[129] Regarding the rodent studies, Dr. McEvoy explained their value as follows:

> There were tests for having the potential to be an antipsychotic used in animals that were used as screeners for potential compounds to have efficacy in humans. There were tests for some side effects that one might expect in humans. This has been the entire argument for all of preclinical research, as I understand it. Are these tests perfect? Absolutely not. May there be an effect in humans that you did not pick up in animals? Yes. . . . Is what you learn in animals imperfect for what you will find in humans. Absolutely. But can you learn in animals some stuff that may make more efficient and may tell you a good bit about what will happen in humans, yes, you can. (Transcript, Vol 34, pp 92-3, lines 19-25, 1-23)

[130] Dr. Young referred to the rodent CAR-CAT data for antipsychotics and explained that "[t]he extent to which you can extrapolate that to the human condition is limited, but inasmuch as you can gain useful information, I think this suggested that the compounds might be potentially atypical antipsychotics" (Transcript, Vol 30, p 46, lines 3-8). Generally speaking, "you can't get evidence of

efficacy from animal studies “because animals don’t have schizophrenia or mania” (Transcript, Vol 30, p 67, lines 20-23).

[131] According to Dr. Diamond, references to positive data relating to CAR, CAT and apomorphine-induced behaviour for antipsychotics suggest a compound likely to be effective as an antipsychotic and likely to induce fewer motor side effects at a therapeutic dose – i.e., an atypical antipsychotic (Transcript, Vol 10-A, p 24, lines 20-24).

[132] Dr. Newcomer’s view was that data relating to apomorphine-induced climbing and CAR “suggest that a compound had potential to be an antipsychotic” (Transcript, Vol 27-A, p 20, lines 2-5). In addition, CAT data can indicate a likelihood of low EPS.

[133] Dr. Nichols suggested that the preclinical studies were sufficiently interesting that they would lead him “to believe that this compound would have a profile that [he] would want to test in animal models” (P-191, at para 314).

[134] Dr. Rosenheck felt strongly that to conclude from animal tests alone that olanzapine would be relatively safe and effective in the treatment of mental illness would be “a preposterous claim” (Transcript, Vol 18, p 267, lines 15-25). Dr. Pentel similarly concluded that animal studies “can be used as a guide to anticipating what might be seen in humans. But there are limits to the information, . . .they are a starting point” (Transcript, Vol 8, p 140, lines 15-18).

[135] This evidence suggests that the preclinical studies indicated that olanzapine had the potential to have an antipsychotic effect in humans, possibly with low EPS liability. However, tests on human patients would be required before more could be said about its effectiveness or safety for clinical use.

[136] In respect of the studies of olanzapine in humans, in three of the healthy volunteer studies, four subjects had been given olanzapine, either in a single dose (studies HGAA and HGAB) or over a two-week period (HGAC). In the fourth (E002), eight subjects were given 10 mg/day of olanzapine for a week.

[137] A July 1987 report (D-18) summarized the healthy volunteer studies to that date (HGAA, HGAB and HGAC).

[138] HGAA involved four volunteers who were given single doses of olanzapine ranging from 0.5 mg to 20 mg. They experienced sedation at between 8 mg and 12.5 mg. Two subjects had liver enzyme elevations.

[139] HGAB involved four volunteers given a single dose of olanzapine at 12.5 mg. One subject experienced an increase in liver enzymes.

[140] HGAC was to have involved five individuals, but two were discharged because of high liver enzymes at the beginning of the study. Three subjects were treated with placebo for one week, then 12 mg of olanzapine for 14 days, and then placebo again for another week. One person had elevated

liver enzymes after 12 days on olanzapine. The second also had elevated liver enzymes and a tremor. The third also experienced a tremor, but no increase in liver enzymes.

[141] In summary, of the 11 healthy persons receiving olanzapine to that point, five experienced increases in liver enzymes, as did two persons on placebo. The authors of the report assumed that patients would be receiving much higher doses of olanzapine than had been given to these healthy volunteers and cautioned that "only a limited number of patients should be exposed to this compound until it is clear that [olanzapine] is without any clinically significant effect upon liver function".

[142] The E002 study involved eight healthy volunteers receiving doses of 10 mg of olanzapine for a week. Half of them also received biperiden, which was believed to reduce EPS. Three individuals experienced increases in liver enzymes. Subjects also experienced mild increases in prolactin, which the investigators felt were "clinically unimportant" (D-46, at p 229).

[143] Other observations included a dramatic drop in bilirubin, sedation, low blood pressure, increased heart rate, dizziness, dry mouth, and mild headaches. Still, the investigators suggested that "[f]urther development of [olanzapine] as a potential neuroleptic drug is warranted given evidence of its reliable absorption and manageable pharmacodynamic/safety profile" (D-46, at p 230).

[144] The E001 study of olanzapine involved actual schizophrenia patients. It was carried out by Dr. Stuart Montgomery and Dr. David Baldwin, two experienced clinical psychiatrists at St. Mary's Hospital Medical School in London, England. The purpose of E001 was to study the safety and

efficacy of olanzapine in real patients. The intention was to administer olanzapine to 10 patients over four weeks. However, only seven patients completed four weeks of the study. Two patients discontinued before completing two weeks. Another discontinued in the third week.

[145] Out of the eight patients who completed about three weeks of the study, four of them responded favourably to treatment with reduction in absolute BPRS (Brief Psychiatric Rating Scale) scores of between 65 and 74 percent. One patient was withdrawn from the study due to elevation of liver enzymes.

[146] From the group of six patients treated initially with 5mg, two discontinued early due to continued deterioration, two responded with a 66 and 71 percent reduction of their BPRS scores, and two showed very little change.

[147] Five patients entered an extension of the E001 study for an additional two weeks. Two of them discontinued at the end of the first week, one due to deterioration and the other due to further lack of improvement despite a dose increase. The remaining three patients completed a total of six weeks of the study with final improvement of 80, 77 and 95 percent on their BPRS scores.

[148] With respect to EPS, eight of the 10 original patients showed improvement or no change. The two patients who showed an increase in EPS were those who continued to deteriorate after their admission and they were withdrawn early.

[149] With respect to liver enzymes, one patient had a large increase; two others had mild and transient increases. The investigators noted that attention should be paid in the future to the liver function tests in patients receiving doses exceeding 20mg per day.

[150] Regarding CPK, four patients experienced elevations. However, olanzapine was found to affect prolactin levels very mildly with five out of the seven patients completing four weeks' treatment having values within normal limits; all three of the patients completing six weeks' treatment had values below two times normal limits.

[151] Regarding efficacy, the investigators concluded that six patients appeared to respond to treatment during the four-week study. Two patients deteriorated early and two patients had very little change in their mental state. At six weeks, there were three patients with good improvement, and one patient failed to respond.

[152] The investigators found it difficult to make any conclusions on the efficacy of olanzapine on the basis of this open-label study with so small a sample of patients. However, they suggested that the results appeared to indicate that olanzapine might have efficacy similar to that of conventional antipsychotic drugs. There appeared to be a correlation between clinical improvement and the dose of medication. For example, patients treated with 10 mg/day improved faster than those treated with 5mg/day.

[153] In summary, even though the sample size was very small and the duration very short, the results of the E001 study appeared to indicate the presence of some antipsychotic activity of

olanzapine in some patients. It also appeared that the side effects profile of olanzapine was not a major concern in the short term (except possibly in respect of liver enzymes) and might be relatively favourable compared to some conventional antipsychotic medications.

[154] Of course, it is important to recognize the limitations of a small, open-label study like E001. Dr. Goodwin noted that early studies like E001 often involve patients who would otherwise be difficult to enter into clinical studies. "[I]t is the belief of companies that this kind of study gives them some preliminary information which allows them to . . . plan their proof of concept studies. . . . It is hypothesis-generating" (Transcript, Vol 37, p 246, lines 14-21).

[155] Dr. Diamond believed that some useful information can come from preliminary, open-label studies. However, their value is limited:

> These early studies are hypothesis-generating. They are trying to make educated guesses about what they are later going to ask some questions about, but they are not designed to be able to be definitive about what kind of dose or effectiveness is actually there". (Transcript, Vol 10-A, p 79, lines 13-18).
>
> And we know that with all of these open studies, there is a lot of excitement and buzz about being in a study, and you are going to see significant improvement just from that; so that these very optimistic, positive results are commonly seen in open trials. It's a good signal. It is a good thing to get excited about. But until you have placebo controlled, you don't really know for sure. (Transcript, Vol 11-AM, p 90, lines 15-23).
>
> And many drugs that look really good like this, turn out to be a bust when they do more controlled trials. (Transcript, Vol 11-AM, p 91, lines 1-3). The study provided a "good early signal". (Transcript, Vol 11-AM, p 93, line 6).

[156] Many witnesses noted that this kind of study is susceptible to bias – doctors and patients often exaggerate the study drug's beneficial effects, and patients often show improvement just because they are given more medical attention and better all-around care than they are used to. As

Dr. Goodwin described it, the E001 trial was a pilot study, "a study in which one forms clinical impressions without attempting to prove things statistically" (Transcript, Vol 37, p 74, lines 24-25). It was a hypothesis-generating study that gave Lilly some preliminary information about olanzapine. Even the authors of the study stated that it would be "difficult to make conclusions on the efficacy of [olanzapine] on the basis of an open study with so small a sample of patients" (E001 Clinical Study Report, p 114).

[157] Dr. Newcomer believed that E001 would not even support a conclusion that olanzapine was active: "I mean, you've brought people in off the street and are taking good care of them, and you can get certainly a placebo response" (Transcript, Vol 27-A, p 31, lines 8-10). Dr. Goodwin agreed that one could not know from E001 whether the results were due to chance, or observer bias, or the so-called "halo effect" (Transcript, Vol 37, p 75, lines 15-17).

[158] According to Dr. Young, these types of open trials are susceptible to bias but they can generate "some evidence of a signal of efficacy before moving on to the next stage" (Transcript, Vol 30, p 79, lines 15-16). Dr. Newcomer stated that open-label studies are "traditionally being done to understand more about the safety signals as you move from healthy humans into the patient population" (Transcript, Vol 27-A, p 28, lines 14-16). In a study of eight patients, "you are looking for large effects only, large safety signals only, tolerability. You might get some initial kind of feel for whether or not the compound has got any activity at all" (Transcript, Vol 27-A, p 28, lines 17-22). With respect to E001 in particular, the study "doesn't establish anything one way or another" (Transcript, Vol 27-A, p 31, lines 1-2).

[159] Dr. Healy testified that these kinds of studies are "not going to establish anything with reasonable reliability. . . .[Y]ou could find that the profile of the compound would be just the opposite to what these studies appear to show" (Transcript, Vol 15, p 54, lines 9-13). Further, "[a]t the time Lilly made the statements in the '113 Patent about olanzapine as compared to the other drugs in the '687 Patent and as compared to other antipsychotics, it neither had the data to support the statements nor any sound basis for predicting that they would be true. At most, Lilly had a hope that these statements might someday turn out to be true" (D-104, at para 73). As Dr. Press stated, the E001 study simply gave some "early indications that there was a therapeutic effect (Transcript, Vol 6, p 37, lines 7-8).

[160] In addition to the factual basis relating to olanzapine alone, given the comparisons inherent in the promise of the '113 patent, one must also appreciate what was known about the comparators, including the '687 compounds – particularly, flumezapine and ethyl olanzapine. Detailed results from the flumezapine clinical trial and surrounding documents were available. With respect to ethyl olanzapine, toxicology tests and the results of the dog study were available.

(a) Comparing olanzapine to the other '687 compounds

[161] The '113 patent says that olanzapine displays "surprising and unexpected properties" as compared to flumezapine and other related compounds. This statement involves a direct comparison between olanzapine and the other compounds of the '687 patent. As described above, there are four specific comparisons in the patent between olanzapine and two '687 compounds. The following is a

summary of the specifics of those comparisons and the evidence relating to them.

(i) Olanzapine vs flumezapine – liver enzymes

[162] Several patients on flumezapine experienced a rise in liver enzymes during its clinical trial. In all cases, the levels returned to normal either after the drug was discontinued or while still on the drug. The project team characterized the liver enzyme rises as “mild”.

[163] Dr. Ronald Diamond carried out a comprehensive analysis of the data available for flumezapine and olanzapine. He found that several persons taking olanzapine experienced liver enzyme elevations. Investigators raised concerns about liver enzyme elevations in all of the olanzapine studies conducted before the ‘113 patent was filed. In fact, some subjects were withdrawn from olanzapine studies on that basis. Given that the asserted advantage in the patent relates to liver enzymes in patients taking therapeutic doses, the most relevant study is E001, the only study of olanzapine in schizophrenia patients completed by the filing date. Three patients in E001 experienced elevations of liver enzymes.

[164] In each of the studies of olanzapine in healthy volunteers, increases in liver enzymes were recorded, some after a single dose.

[165] While it is difficult to compare the flumezapine and olanzapine data sets (different doses, different patients, different time frames, different drug potencies), Dr. Diamond concluded that there was no evidence that olanzapine was superior to flumezapine in terms of its effect on liver enzymes.

He also noted that many antipsychotic medications (e.g., chlorpromazine, clozapine, flumezapine, olanzapine and the other "-zines") cause transient elevations of liver enzymes that are not of any clinical significance. Indeed, the '113 patent specifically refers to chlorpromazine's effect on liver enzymes. Yet, it was well-known at the time that chlorpromazine's tendency to cause these elevations was not clinically significant. Chlorpromazine was in widespread use.

[166] Dr. Diamond's conclusion was that the data did not support "the existence of any clear differences in risk" as between flumezapine and olanzapine in respect of liver enzymes (Diamond Expert Report, para 73).

[167] Dr. Alan Young observed that some of the patients and healthy volunteers who had been given olanzapine had some elevations of the liver enzyme SGPT and, less frequently, SGOT. He felt that these elevations could be aptly described as mild and transient, as the '113 patent does. In his view, the results of E001 and the healthy volunteer studies supported the statement that olanzapine causes a low incidence of only mild and transient elevation of liver enzymes. However, he did not make any comparison to flumezapine.

[168] In sum, contrary to the assertion in the '113 patent, the evidence available in 1991 did not suggest that olanzapine had any superiority over flumezapine with respect to liver enzymes. In fact, Lilly was aware, based on its studies in humans, that "both flumezapine and [olanzapine] have illustrated a propensity to cause elevations of liver enzymes" (D-345, at p 15).

(ii) Olanzapine vs flumezapine – CPK

[169] We know that concern about flumezapine's risk for elevating CPK is what brought its clinical trial to a halt and led Lilly to start working on olanzapine. Clearly, flumezapine's potential to elevate CPK was a serious concern both to Lilly and the FDA. Elevation of CPK can be a harbinger of serious conditions such as neuroleptic malignant syndrome [NMS] or rhabdomyolysis.

[170] However, the evidence is not at all clear that flumezapine was, in fact, responsible for the elevations of CPK observed during its clinical trial. Dr. Diamond provided convincing testimony that the CPK results for flumezapine were more a product of the site where the elevations were seen than a consequence of administering the drug. He found it surprising that all of the CPK elevations were seen at a single site, not across the various clinical trial locations. He also noted some peculiarities about that site:

a. One patient had high CPK even before being given flumezapine, yet his CPK levels were not checked again until the nineteenth day of treatment, when they had spiked to 5,500. They then dropped to less than 1,000 a few days later, at which point the treatment was discontinued.

b. One patient was on a high dose of flumezapine for 20 days before his CPK level jumped to 5,000. It went down a few days later after the dose was reduced from 35 mg/day to 20 mg/day. The patient remained on flumezapine for a total of 57 days.

c. One patient on a 20 mg dose of flumezapine had a CPK level of 6,300 on the 22nd day of the study. He was taken off the study 10 days later.

d. One patient had a high level of CPK at a 10 mg dose on the 10th day of the study. The patient remained on flumezapine and his CPK level reduced to normal within a week (this patient was removed from the study after being diagnosed with hepatitis C).

[171] The doctor in charge of the site where these results were obtained noted that other patients, not on flumezapine, also had spikes in their CPK levels. In addition, one of the patients at that site had been exercising vigorously which can elevate CPK. The patient with hepatitis was sharing intravenous drugs and dirty needles with other patients, some of whom also developed hepatitis. Dr. Diamond noted that the high CPK levels could be attributable to the intravenous drugs, the injections themselves, or abscesses from hepatitis.

[172] At Lilly's request, an external physician reviewed the flumezapine data. He concluded that the CPK results were "not well explained". There was no clear connection between the CPK data and flumezapine. Strangely, there was no CPK data recorded at the site where four patients were on the highest dose of flumezapine. On the other hand, there is also no information suggesting that those patients had any side effects of any clinical concern. Indeed, there appear to be no clinical observations in respect of any of the patients with elevated CPK, which may indicate that the peaks were isolated laboratory abnormalities, not affecting anyone's health. Along with elevated CPK levels, one would normally detect fevers or muscle pain in persons who were experiencing NMS or rhabdomyolysis. The patients on flumezapine apparently did not manifest any adverse symptoms.

[173] In contrast to Dr. Diamond's analysis, Dr. John Lehmann's conclusion was that flumezapine's CPK data showed an unacceptable safety profile, whereas olanzapine did not elevate CPK beyond what one would normally find in persons with schizophrenia. Dr. Lehmann concluded that the CPK data showed a statistically-significant dose effect from flumezapine, not a site effect. He divided the flumezapine patients into low-dose and high-dose groups (below and above 20 mg/day, respectively) and found that CPK values correlated with the high dose, suggesting that the

cause of the CPK elevations was flumezapine. Accordingly, in his view, olanzapine had a significant advantage over flumezapine in this respect.

[174] However, Dr. Lehmann did agree with Dr. Diamond that the elevated CPK could have been the result of intravenous drug use, injections or abscesses. He also agreed that between 10 and 20 percent of patients with schizophrenia experience transient CPK elevations up to ten times normal values, or more, for reasons unconnected to their medication. He concurred with Dr. Diamond's view that there were problems at the site where the high CPK values were taken and agreed that Dr. Diamond's hypothesis was a possible alternative explanation for the data. Like Dr. Diamond, he believed that the patient who had a high CPK value before the study began should not have been admitted to it. Overall, he did not see any reason to think that the elevated CPK indicated the onset of NMS or rhabdomyolysis, even if those elevations were caused by flumezapine. He stated that "the hypothesis that flumezapine caused the increases in CPK is not compelling until you take it into more patients and prove that with repeated challenge you elicit the same increases" (Transcript, Vol 39-A, p 120, lines 11-15).

[175] In his reply, Dr. Diamond noted that Lilly's own conclusion regarding CPK was that "the elevations of CPK [in flumezapine patients] are not well explained…". Preliminary results suggested that the drug was efficacious; however, flumezapine was not deemed sufficiently safe for further study (Diamond Expert Report, para 56). Further, notwithstanding the troubling blood chemistry results, the investigators were impressed with flumezapine's efficacy and the absence of EPS. There was no evidence to suggest that the CPK values were accompanied by clinical signs of

health problems.

[176] Dr. Leber pointed out that CPK levels (and liver enzymes) can spike inexplicably. In addition, the fact that some patients had rises in certain enzymes did not prove that those rises were caused by flumezapine.

[177] In 1991, there was evidence that olanzapine also had some liability to elevate CPK based on the results of its first clinical trial. Four patients had CPK elevations. The elevations were not as high as with flumezapine. However, Lilly scientists speculated that if olanzapine had been dosed as high as flumezapine in its clinical trial, one would have seen the same kinds of results for olanzapine's liability for CPK as were seen in the flumezapine trial. But, as Dr. Diamond pointed out, the E001 clinical trial in patients with schizophrenia was a more sophisticated study than the flumezapine trial. Investigators noted that they saw signs of efficacy at low doses of olanzapine (10 mg). Therefore, they scaled back the doses that they had planned to administer. Originally, they had planned to give doses of 10 mg to 120 mg. After two modifications of the study protocol, the doses ranged from 5 mg to 17.5 mg. Dr. Diamond suggested that a similar sensitivity to dose might well have avoided the problems encountered in the flumezapine trial.

[178] Simply put, the flumezapine data on CPK were poor. There was a very small number of patients. Clearly, there were confounding factors at the one site where CPK elevations were recorded as high. Certainly, more testing was needed to determine whether flumezapine really did have an effect on CPK and, if so, whether that effect showed up at therapeutic doses and was clinically significant. Dr. Diamond's analysis of the data was the most thorough of any witness, and

I agree with him that little can be taken from the flumezapine data. As he said, “the problem in dealing with very small samples is there is no fair way to do it; there [are] just different ways of skewing it” (Transcript, Vol 11-AM, pp 153-4, lines 25, 1-2).

[179] In sum, the evidence does not suggest that olanzapine’s CPK liability was lower than flumezapine’s at therapeutic doses.

(iii) Olanzapine vs flumezapine – EPS

[180] The ‘113 patent states that two patients experienced some EPS on flumezapine. Dr. Diamond noted that one of them had previously been taking haloperidol and phenobarbitol, which can cause some difficulties with muscle coordination. The other patient merely had restless legs. There was no clear indication that these symptoms actually were EPS, and no clear connection was made between the symptoms and flumezapine. As mentioned, investigators were impressed with flumezapine’s efficacy and “significant absence of extrapyramidal side effects, akathesia, dysphoria, and marked sedation and/or somnolence commonly associated with all presently available neuroleptic drugs” (D-84, at p 2).

[181] Based on preclinical studies, both flumezapine and olanzapine would be expected to have low EPS liability.

[182] In the only study of schizophrenia patients completed before filing the ‘113 patent (E001), eight patients on olanzapine showed improvement or no change in extrapyramidal symptoms. Two

patients deteriorated. The investigators believed that olanzapine might cause EPS less frequently than conventional antipsychotics. Dr. Diamond interpreted the results of E001 as being consistent with the suggestion that olanzapine might have lower EPS liability than first generation antipsychotics.

[183] In sum, the evidence suggests that flumezapine and olanzapine both appeared to have some EPS liability, but perhaps somewhat lower than conventional antipsychotics.

(iv) Olanzapine vs ethyl olanzapine – cholesterol

[184] The ‘113 patent says that “in dog toxicity studies with a closely analogous compound, [ethyl olanzapine], at a dosage of 8 mg/kg, it was observed that four out of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the invention did not show any rise in cholesterol levels”. The meaning of this sentence was discussed by many expert witnesses.

[185] Clearly, Lilly regarded the results of the dog study as a key component of its application for a patent for olanzapine. It felt bound to make a comparison between olanzapine and its closest analogue in the remaining ‘687 compounds. It recognized the need to show that olanzapine had a significant advantage over the ‘687 compounds and that the best way of making that case was to compare olanzapine to its ethyl cousin. The dog study clearly was conducted solely for purposes of justifying a second patent for olanzapine. Lilly felt that the dog study alone would make the case for being granted that patent. For that reason, the dog study figured largely in the evidence and

arguments at the original trial.

[186] I previously found that this comparison, while valid, is meaningless. It does not support any advantage for olanzapine. I explained this conclusion in my first judgment. As discussed above, Justice Layden-Stevenson pointed out that if a skilled person would not have regarded an asserted advantage, cited by the inventors in the patent, as supportable, then the alleged advantage should not be construed as forming part of the patent's promise. The comparison between olanzapine and ethyl olanzapine was clearly directed to the patent examiner, not the person skilled in the art. Based on Justice Layden-Stevenson's observation, such a comparison, which on its face appears to assert an advantage for the selected compound, does not form part of the promise of the patent. In effect, I found that the dog study was relevant, but meaningless because the dog is a poor model for predicting cholesterol effects in humans. Justice Layden-Stevenson found it to be irrelevant. Still, I believe it is useful to describe briefly the results of the dog study because it contains some relevant information about the properties of olanzapine that were known to exist at the filing date of the '113 patent.

[187] The dog study was carried out at the request of Lilly's patent division in order to compare the effects of olanzapine and ethyl olanzapine, and to identify any differences between them (D-272). This appears to have been the first time that a toxicology study had been requested by the patent division. As Dr. Paul Pentel noted, the timing of the dog study was peculiar in that olanzapine was already being tested in clinical trials. It was an odd time to be testing it in dogs against a failed compound. Lilly expected ethyl olanzapine to cause agranulocytosis in the dog, just as ethyl flumezapine had done (D-269), and expected olanzapine to demonstrate a clear advantage by not

causing serious blood problems.

[188] Lilly knew that it had to show superiority of olanzapine over the ‘687 compounds, including flumezapine, as well as a head-to-head comparison of olanzapine with ethyl olanzapine The patent examiner would naturally want to see those comparisons. (Transcript, Vol 23, p 60, lines 4-15).

[189] Overall, the dog study showed that the two compounds, olanzapine and ethyl olanzapine, caused similar toxic effects in the dogs (D-63, at pp 14, 34). There were differences between the two compounds in some areas (e.g., bilirubin, albumin, alanine transminase, gamma glutamyltransferase, total protein) but the only measure of superiority for olanzapine identified by Lilly was in respect of the cholesterol levels in the female dogs receiving the highest dose of ethyl olanzapine. The study’s authors were surprised by the cholesterol results, but felt that they represented, on their own, an unexpected and substantial advantage that would provide a basis for a new patent for olanzapine. They concluded that this finding “had the greatest potential biological significance because of its early onset, persistence, and magnitude” (D-63, at p 13).

[190] Dr. Pullar agreed that the results of the comparative tests on ethyl flumezapine and flumezapine suggested that it was the presence of the ethyl group that was likely responsible for the neutropenias and thrombocytopenias discovered in dog studies with ethyl flumezapine. It was therefore expected that ethyl olanzapine would have the same effect. And it did. But what was surprising was that olanzapine did not perform much, if any, better.

[191] Dr. Paul Pentel described the Lilly dog study as being flawed because no serious attempt had been made to determine whether ethyl olanzapine and olanzapine were equally potent. Accordingly, he suggested that one cannot meaningfully compare the results for the two compounds. The fact that ethyl olanzapine caused elevated cholesterol in the female dogs on the highest dose, and olanzapine did not, may simply have meant that ethyl olanzapine was the more potent of the two compounds. It may have caused an effect that would also have been seen in olanzapine at a higher dose. No cholesterol elevations were seen in the ethyl olanzapine dogs given 4 mg/kg. A dose of 8 mg/kg may have been beyond the maximum tolerated dose for that compound. Dr. Pentel noted that the same design flaw was carried forward into subsequent studies comparing olanzapine with ethyl olanzapine, which found the same cholesterol effect. He also observed that there was some evidence that ethyl olanzapine was actually more potent than olanzapine (Pentel Expert Report, paras 44, 69).

[192] In studies with flumezapine, Lilly found that dogs did not tolerate doses above 4 mg/kg/day, whereas a dose of 1 mg/kg/day was considered “reasonably clear”. The same may have been true of ethyl olanzapine.

[193] Lilly felt that the toxicity of olanzapine in the dog was not a major concern because the dogs were dosed at levels far above what the therapeutic dose would be for humans. In response to queries from the Swedish Board of Health about olanzapine’s effects on blood cells and bone marrow, Lilly stated:

> [T]hese findings are believed not to have clinical relevance to humans since the effects occurred at large multiples of the clinical dose, were qualitatively and quantitatively different among these species, and, therefore, were not considered to result from a common mechanism. (D-247, at p 3).

[194] In summary, the dog study showed that olanzapine was just as toxic as ethyl olanzapine. The dog was a reasonably good model to predict effects in humans in areas other than cholesterol such as hematotoxicity, including cytopenias, red blood cell decreases and platelet decreases (Transcript, Vol 19, p 262, lines 12-20). Olanzapine did not show any advantage over ethyl olanzapine, except in respect of an irrelevant parameter – cholesterol.

(b) Olanzapine vs other antipsychotic agents

(i) High efficacy at low doses

[195] Most experts agreed that it does not particularly matter if a drug is dosed at 5 mg or 500 mg, so long as it is effective and, at that particular dosage, is relatively free of serious side-effects. If the effective dose is too large (e.g., 1000 mg), one may start to see problems with drug compliance – the pill will be too hard to swallow, or it might have to be taken twice or more a day. So, there may be a slight advantage for a drug with high efficacy at a low dose. Also, a potential benefit of a drug that shows high efficacy at a low dose is that it can be more easily administered by injection.

[196] Dr. Diamond's testimony in this area was shared by the other experts. He stated that "the dose is the dose, and I am not sure that it matters whether you need 10 or 100 milligrams of something (Transcript, Vol 10-A, p 62, lines 4-6). Dr. Young agreed, noting that, while olanzapine would likely be dosed at a lower concentration than other antipsychotics, "that's not really that important" (Transcript, Vol 30, pp 70-1, lines 25-1). Further, he stated that "where the decimal point

is really doesn't … matter" (Transcript, Vol 30, p 71, lines 8-9).

[197] Lilly certainly got some early positive signals from E001 but, as discussed above, the evidence of efficacy was thin and unreliable. As for relatively low doses, Lilly certainly found that the doses at which efficacy was detected were lower than expected from animal tests. Investigators adjusted the E001 study protocol accordingly. These early signals indicated a potential advantage, but only if the evidence of efficacy could be sustained over a longer term.

[198] I also note that investigators had also been impressed with flumezapine's efficacy (D-84, at p 2). Flumezapine was also a more potent compound. So, high activity at a low dose appears to have been a characteristic of both flumezapine and olanzapine.

[199] In sum, the evidence does not suggest any particular advantage for olanzapine in respect of its possible efficacy at low doses, either as compared to other antipsychotics or flumezapine.

(ii) Lower elevation of prolactin

[200] Dr. Goodwin explained that elevation of prolactin is a virtually inevitable result of blocking dopamine in the pathway to the pituitary gland. Therefore, drugs that block that pathway, as most antipsychotics do, will always elevate prolactin. Some elevation of prolactin is expected in patients taking antipsychotics. Dr. Healy agreed, noting that prolactin is rarely of any clinical concern.

[201] The early evidence about olanzapine suggested that prolactin increases were relatively mild, no more than double the normal range. Dr. Diamond felt that olanzapine's prolactin liability was comparable to flumezapine's. This evidence was favourable given that older drugs could elevate prolactin up to three times the normal range.

(iii) Lower EPS liability

[202] In 1991, psychiatrists were beginning to understand that the first-generation antipsychotics, such as haloperidol, were being dosed too high. That is part of the reason why those drugs had such a worrisome EPS liability. Still, there is no doubt that scientists were looking for compounds less likely to induce EPS. Certainly, any skilled reader would certainly have interpreted the '113 patent's assertion of "marked superiority" and a "better side effects profile" as including low EPS.

[203] Dr. Goodwin interpreted the "overall, therefore" statement in the '113 patent as an assertion by the inventors that "this is what we hope we will deliver and will find out more in time". Indeed, the inventors had little basis, given the small sample size and the short duration of the tests, for either asserting or predicting olanzapine's EPS liability. The preclinical tests suggested that olanzapine might have a low EPS liability, but human tests clearly were needed to confirm how the drug would perform in patients. As discussed above, there was little evidence available at the relevant time to support any advantage for olanzapine regarding EPS. In E001, some patients improved, some deteriorated and some stayed the same. Olanzapine (like flumezapine) appeared to have some EPS liability, possibly somewhat lower than conventional antipsychotics.

(iv) No alteration of white blood cell count

[204] The ‘113 patent makes a statement of fact that “no alteration of white blood cell count has been observed in clinical studies”. This statement was clearly intended to compare olanzapine with clozapine, whose major liability is its propensity to cause, in rare cases (1%), agranulocytosis.

[205] Dr. Rosenheck believed that the fact that there was no alteration of white blood cells in eight patients (E001), was not a basis to assert any kind of superiority or better side-effects profile for olanzapine (Transcript, Vol 18, pp 283-6). Dr. Goodwin testified that the chance of seeing a rare event like agranulocytosis in such a short trial as E001 would be very low (Transcript, Vol 37, p 207, lines 19-25). Even with clozapine, one would not see agranulocytosis in a short-term study.

[206] In truth, the evidence available to Lilly in 1991 about olanzapine’s efficacy and side-effects liability was scant. The human studies with olanzapine involved a small number of subjects over a short period of time. The fact that no alteration of white blood cell counts in those limited studies had been observed would not support an advantage for olanzapine over clozapine. While Lilly had been looking for a safe clozapine and appeared to assert in the “overall, therefore” statement – the promise of the patent – that it had found one, there was little foundation for that assertion. There was simply too little evidence of olanzapine’s side-effects profile to suggest any superiority over other known antipsychotics, particularly clozapine, in respect of white blood cells.

3. *Summary of the Factual Basis*

[207] I would summarize the factual basis for the ‘113 patent’s promise as follows:

- preclinical tests showed that olanzapine had antipsychotic potential and might have relatively low liability for some forms of EPS;
- olanzapine showed a liability to elevate liver enzymes, just as flumezapine had done;
- olanzapine’s tendency to raise CPK appeared to be similar to flumezapine’s at therapeutic doses;
- olanzapine’s EPS liability appeared to be comparable to flumezapine’s, perhaps somewhat lower than conventional antipsychotics;
- olanzapine’s prolactin liability appeared to be relatively mild;
- olanzapine was just as toxic as ethyl olanzapine except in respect of an irrelevant parameter – causing an elevation of cholesterol in female dogs;
- olanzapine appeared to have had some antipsychotic effect on some schizophrenia patients in a magnitude comparable to conventional antipsychotics;
- olanzapine’s therapeutic effect appeared at fairly low doses, but not lower than flumezapine’s;
- olanzapine did not affect white blood cells in the few human subjects who had taken olanzapine for a short period of time.

4. *Demonstrated Utility*

[208] Lilly maintains that the promise of the ‘113 patent (a relatively safe and effective antipsychotic) had been demonstrated at the filing date. It cites the following as grounds for that position:

- *In vitro* and animal tests showed that olanzapine had useful central nervous system activity;
- olanzapine was shown in pre-clinical studies to be an antagonist of dopamine, to have antimuscarinic and anticholineric properties, and to be an antagonist of activity at the 5HT-2

and noradrenergic receptors of the brain, and to block serotonin, demonstrating its potential use as a neuroleptic drug with reduced EPS liability;

- mouse studies showed that olanzapine inhibited apomorphine-induced climbing behaviour, and induced hypothermia; and
- clinical tests showed that olanzapine had antipsychotic activity, low EPS and, overall, a side-effect profile more favourable than conventional antipsychotics.

[209] If the utility of the invention in the ‘113 patent relates merely to a compound with potential antipsychotic properties that might have relatively low EPS liability, that utility had been demonstrated by the tests conducted prior to the filing date. However, I cannot accept that the ‘113’s promise was so small. As stated above, based on the wording of the ‘113 patent and the evidence, I find that the promise of the patent is that olanzapine treats schizophrenia patients in the clinic in a markedly superior fashion with a better side-effects profile than other known antipsychotics.

[210] As recently held by the Federal Court of Appeal, where a patented compound is claimed to be safe and effective in the treatment of a chronic condition, utility will be demonstrated if the patent discloses studies showing that the patented compound, when administered over a long term, meets that promise: *Pfizer Canada Inc v Canada (Minister of Health)*, 2011 FCA 236, para 30 [*Pfizer 2011*]. Clearly, schizophrenia is a chronic condition. In my view, the evidence available to Lilly in April 1991 did not demonstrate that olanzapine could meet the promise of the ‘113 patent that it would provide markedly superior clinical treatment of schizophrenia with a better side effects profile than other known antipsychotics.

[211] In terms of Lilly’s clinical studies, only one (E001) involved patients with schizophrenia. Lilly maintains that this short study showed that olanzapine had an antipsychotic effect, low EPS

liability, low prolactin effects, and high efficacy at low doses.

[212] Witnesses agreed that Lilly had some early positive signals about olanzapine's efficacy and safety but, as discussed above, not enough evidence to demonstrate those characteristics. As Dr. Goodwin stated. "You can't conclusively determine anything with a preliminary study. . . Certainly to prove the promise of the patent, you would certainly need to conduct [placebo-controlled clinical trials in sufficiently large groups of patients]" (Transcript, Vol 37, p 197, lines 14-22). Given the available evidence, he interpreted the assertions in the '113 patent as representing "a kind of hypothesis that olanzapine will have those advantages" (Transcript, Vol 37, pp 224-5, lines 25,1). Dr. Diamond's view was similar: "They had no control data, so they couldn't show anything. They had suggestions" (Transcript, Vol 11-AM, p 111, lines 23-24).

[213] In my view, Novopharm has shown that the evidence available to Lilly in 1991 was clearly insufficient to demonstrate olanzapine's capacity to treat schizophrenia patients in the clinic in a superior fashion and with fewer side effects than other known antipsychotics.

[214] The real question, as Justice Layden-Stevenson pointed out, is whether the factual basis available to Lilly in April 1991 and the promise of the '113 patent are linked by a sound line of reasoning.

### 5. *Are the Promise and the Factual Basis Linked by a Sound Line of Reasoning?*

[215] In my original decision, I found that the predictive value of the studies Lilly had conducted by the filing date was nil in respect of any advantageous properties of olanzapine. I agreed with Dr. Healy's summary of Lilly's evidence from its clinical trials of olanzapine:

> Of these five, . . . four were in healthy volunteers and only two were placebo controlled. The healthy volunteer studies were of extremely short duration. It appears that a total of 31 people had been exposed to olanzapine for not much more than one patient year of exposure. This extremely limited experience was the basis for all of Lilly's claims about olanzapine in the '113 patent. In my view, the design of these studies (being mainly healthy volunteer, mainly non-placebo controlled dose ranging and pharmacology studies in small populations over short durations) were not powered and could not have shown what Lilly was claiming in terms of superior efficacy or fewer side effects. Equally, in my view, the predictive value of these studies was nil. (D-104, at para 51)

[216] This was not to say, of course, that those studies were worthless. They supported the prediction of certain properties of olanzapine, but I concluded that they did not support a sound prediction of the stated utility of the '113 patent, the advantages over other compounds.

[217] Nevertheless, as Justice Layden-Stevenson points out, the proper question is whether the information available to the inventors at Lilly supported a *prima facie* reasonable inference of the patent's promise, which I had not explicitly considered in my earlier decision.

[218] In fact, I am satisfied that the information in Lilly's possession in April 1991 could support certain reasonable inferences about olanzapine's properties. In particular, a reasonable inference could be made that olanzapine had some antipsychotic properties, and had prolactin liability in a safe range. With regard to EPS, olanzapine appeared to have some liability, which might have been lower than that of conventional antipsychotics. On the other hand, one could not reasonably infer from the available evidence that olanzapine would treat schizophrenia patients in the clinic in a

markedly superior way. Its antipsychotic effect was, at best, comparable to that of conventional antipsychotics. Olanzapine's liver enzyme and CPK liabilities were a concern. Its effect on white blood cells could not be predicted, on the basis of the available evidence, nor could its overall side-effects liability.

[219] In short, as explained below, the evidence shows that the inventors could not draw a *prima facie* reasonable inference from the information available in April 1991 to the promise of the '113 patent that olanzapine could treat schizophrenia patients significantly better, and with fewer side-effects, than other known antipsychotic drugs.

[220] Like Dr. Goodwin, Dr. Leber felt that the stated promise of the '113 patent "could have been a reasonable hope that Lilly had, but there is no evidence or source of evidence that would speak to that. It's saying, 'we hope it will be like this'. But I didn't see any evidence of anything I looked at that would allow someone to conclude that this was true in human subjects" (Transcript, Vol 6, p 203, lines 6-13).

[221] Lilly points to a number of cases where courts found that the utility of an invention could be inferred from a weaker factual basis than existed for olanzapine:

- A sound prediction that sildenafil could be used to treat erectile dysfunction could be made on the basis of a study of 16 patients over six days [*Pfizer Canada Inc v Novopharm Ltd*, 2009 FC 638, aff'd 2010 FCA 242];

- A sound prediction that a trifluoromethyl compound could be used as an antipsychotic was recognized even though the compound had never been made or tested [*Olin Mathieson Chemical Corp v Biorex Laboratories Ltd*, [1970] RPC 157 (Eng Ch Div)];

- The activity in three compounds justified a sound prediction of the utility of 126 others that had not been tested [*Monsanto Co v Canada (Commissioner of Patents)*, [1979] 2 SCR 1108];

- The utility of AZT to treat HIV/AIDS in humans could be soundly predicted on the basis of *in vitro* studies in human cells [*AZT*];

- The capacity of untested compounds to inhibit ACE could be soundly predicted on the basis of the testing of others in the class (*Laboratoires Servier v Apotex Inc*, 2008 FC 825, aff'd 2009 FCA 222);

- A test on rodents which had shown citalopram to be a useful anti-depressant supported an inference that escitalopram could be put to the same use (*Lundbeck Canada Inc v Canada (Minister of Health)*, 2009 FC 146, aff'd 2010 FCA 320 [*Lundbeck*]).

[222] Lilly points to these cases and urges me to conclude that a reasonable inference links the factual basis it had assembled in 1991 and the promise set out in the '113 patent. Lilly also submits that the inventors of olanzapine had an articulable and sound line of reasoning linking the factual basis and the promise of the patent. Animal tests and *in vitro* studies indicated that olanzapine had potential as an antipsychotic agent with reduced side effects. As the '113 patent states, rodent studies showing olanzapine's CAR-CAT separation indicated "that the compound is less likely to induce extrapyramidal side effects in the clinic".

[223] In addition, Lilly points out that it had some early indications of olanzapine's safety and efficacy in its clinical trial and healthy volunteer studies. As mentioned, Lilly contends that olanzapine's inventors had more to go on than the inventors of AZT. Therefore, based on the existing factual information, Lilly was in a position to make a reasonable inference that olanzapine

was “a relatively safe and effective antipsychotic”.

[224] Lilly also relies on a judgment of mine in which I noted that there might be different levels of utility required for different claims: *Pfizer Canada Inc v Apotex Inc*, 2007 FC 26. In that case, the compound, sildenafil, had advantageous properties that could have been put to use in a variety of ways. Accordingly, with respect to a claim to the compound itself, demonstration or sound prediction of those properties would have persuaded me that the utility requirement had been met. On the other hand, with respect to a claim for the use of the compound to treat various conditions, additional evidence might be required.

[225] In this case, however, while there are different kinds of claims in issue (e.g., claims 3 and 6), the promise of the patent as construed above applies to all of them. Claim 3 relates to olanzapine itself and claim 6 relates to the use of olanzapine in the making of a drug to treat schizophrenia. However, the promise of the ‘113 patent is that olanzapine treats schizophrenia in the clinic in a markedly superior fashion, with a better side-effects profile than other antipsychotics. I see no basis for applying that promise differently to the claim for the compound, olanzapine (claim 3), and the claim for the therapeutic use of olanzapine (claim 6).

[226] Lilly also points out that olanzapine showed advantages over three members of the ‘687 class of compounds. Ethyl flumezapine caused neutropenia in dogs, raising concerns that it might cause agranulocytosis in humans. Results of a clinical study of flumezapine suggested a potentially worrisome rise in CPK levels and liver enzymes. Ethyl olanzapine appeared to have some impact on the cholesterol levels of female dogs. Obviously, Lilly says, olanzapine had a significant advantage

over the other ‘687 compounds because it went on to pass clinical tests, be approved for administration to patients, and enjoy commercial success.

[227] Justice Robert Barnes has noted that the Court should approach with caution the comparisons set out in a selection patent. He worried that inventors might choose unrepresentative compounds for comparison in order to accentuate the alleged unexpected and special advantages of the selected compound: *GlaxoSmithKline Inc v Pharmascience Inc*, 2008 FC 593, para 63 [*GlaxoSmithKline*]. There, the patentee had merely stated that one particular compound, valacyclovir, was better than two other members of the class. That was not enough, according to Justice Barnes, to establish an advantage over the whole class. He added that it would not be necessary to conduct tests of all members of the class, but there must be “sufficient representative testing that a person skilled in the art could soundly predict that the surprising characteristic would not be expected to be found in a large number of the other members of the genus” (para 70).

[228] The main problem, however, with Lilly’s submissions on sound prediction is that they are based on a reading-down of the promise of the ‘113 patent to the same utility that had been relied on for the ‘687 patent. This argument is not in keeping with the prevailing jurisprudence, including Justice Layden-Stevenson’s approach, which requires a selection patent to set out a specific promise of a substantial advantage over the genus compounds. As discussed above, on my reading of the patent, the specific promise is that olanzapine is substantially better (“marked superiority”) in the clinical treatment of schizophrenia (and related conditions) than other known antipsychotics, with a better side-effects profile, and a high level of activity at low doses.

[229] The question, therefore, is whether there is an articulable and sound line of reasoning connecting the factual information about olanzapine at the filing date and the ‘113’s promise as I construed it above. The cases referred to above that are relied on by Lilly involved different factual bases and different levels of promise. They are of little assistance in determining whether Lilly’s factual basis in 1991 was connected to the specific promise in the ‘113 patent by a *prima facie* reasonable inference. Sound prediction is a question of fact.

[230] Once again, as mentioned above, it is essential to recognize the chronic nature of schizophrenia. Therefore, the promise of the ‘113 patent that olanzapine is markedly superior to, and safer than, other known anti-psychotic agents in the clinical treatment of schizophrenia would be read by the skilled person as an assertion of its efficacy and safety over a reasonable time frame. Treatment of schizophrenia is not a short-term proposition.

[231] There was no dispute about this among the experts. Therefore, I need only refer to a sample of the evidence on this point:

- Even today, schizophrenia remains essentially incurable. While drug treatments can produce remarkable temporary effects in a certain proportion of patients, and while a small number of patients have achieved full recovery both before the discovery of the antipsychotics and since, for most schizophrenic patients the long-term clinical outlook is poor and the prospect of remaining on antipsychotic medication for an extended period of time is high. In general, the side-effects of the antipsychotic group of drugs and current treatment modalities are not benign. There is a marked fall in the life expectancy for schizophrenia patients not found in patients suffering from any other major disorder in the Western world. (Healy, D-104, at p 4)

- Unfortunately, schizophrenia is typical of severe mental illnesses with respect to chronicity and cost in that even though it can be defined and treated, it is a long-term condition that has numerous direct and indirect costs to the patients and society. These costs closely match the overall costs of medical conditions such as respiratory and cardiovascular disease. . . .

> Overall, the course of illness in patients with schizophrenia is generally chronic with highly variable patterns of exacerbation and remission. (Newcomer, D-187, at pp 11, 13)

- Schizophrenia: is a currently incurable mental illness that affects approximately 1% of people. It usually begins in late adolescence or early adulthood. The symptoms of schizophrenia are often classified into four categories: positive symptoms (which can include delusions and hallucinations), negative symptoms (which can include lack of energy and loss of interest in daily activities), cognitive symptoms (which can include poor concentration) and emotional symptoms (which can include depression). Most people with schizophrenia will need to take medication for life. (Rosenheck, D-191, at p 5)

[232] The chronic nature of the condition treated by a patented compound must be taken into account when determining whether the patent's promise has been demonstrated or can be soundly predicted. This is clear from the recent decision of the Federal Court of Appeal in *Pfizer 2011*, above. Justice Johanne Trudel concluded that the promise of a patent for a compound (latanoprost), which was claimed to be safe and effective in the treatment of glaucoma, a chronic condition, must be supported by a factual basis and line of reasoning consistent with the use of the compound over a long term.

[233] Justice Trudel explained that the doctrine of sound prediction comprises three mandatory components: a factual underpinning, an articulable and sound line of reasoning linking the facts and the desired result, and sufficient disclosure (para 34). In the case before her, the factual basis consisted of single-dose tests of the claimed compound in animals and humans. There was no line of reasoning set out in the patent linking the factual basis to chronic use of the compound in the treatment of glaucoma. In fact, the evidence suggested that single-dose studies could not predict long-term safety or efficacy.

[234] Similarly, Justice John Evans held in *Eli Lilly & Co v Teva Canada Ltd*, 2011 FCA 220, that the trial judge, Justice Robert Barnes, had been correct in concluding that the utility of a compound (atomoxetine), which was claimed to be useful in the treatment of ADHD, a chronic condition, could not be demonstrated on the basis of a short-term study. Justice Evans concluded that the meaning of the word "treatment" must be considered in the context of a patent for a compound claimed to be useful in addressing the symptoms of a chronic condition.

[235] The study in that case was a double-blind, placebo-controlled cross-over trial involving 21 adult patients over seven weeks. Eleven patients showed improvement. Justice Barnes concluded that the study had serious methodological shortcomings – small sample and short duration – that had been acknowledged by the authors themselves.

[236] Justice Barnes also found that the study showed promising results, but still did not demonstrate that the claimed compound would be an effective treatment for ADHD. With respect to sound prediction, he concluded that Lilly could not rely on this doctrine to support the patent because the study had not been disclosed in it. Justice Evans found no error in Justice Barnes's analysis.

[237] In my view, there is no evidence before me of a line of reasoning that would link the factual basis set out above with the specific promise of the '113 patent. To begin with, with regard to olanzapine's alleged superiority in the clinical treatment of schizophrenia, the factual basis consisted solely of the E001 study. The expert evidence consistently described that study as preliminary, hypothesis-generating and, at best, providing early, positive signals that would warrant further study

of olanzapine. None of the witnesses went so far as to suggest that the results of E001 would support a sound prediction that olanzapine would treat schizophrenia in a markedly superior manner to other known antipsychotics. In fact, the E001 investigators themselves thought olanzapine's effect might be comparable to that of conventional antipsychotics, but acknowledged that it was difficult to make any predictions based on such a short study with so few patients.

[238] Dr. Leber expressed the general view that the evidentiary basis for the superiority of olanzapine, particularly over flumezapine, was thin. He stated "It wasn't that you didn't have a hope. It is that you didn't have a basis to reach that conclusion. . . You may have had a hint that that is true, but you don't have probative evidence" (Transcript, Vol 6, pp 182-3, lines 10-12, 3-4).

[239] Dr. Young stated that, with respect to a study without a control group, one can "infer some limited degree of causation related to a study like that, but you've got to be very skeptical about it. . . They can be very valuable in giving you signals for future developments" (Transcript, Vol 30, p 231, lines 5-7, 19-20).

[240] The same is true, in my view, in respect of the promise that olanzapine had a better side-effects profile than other known antipsychotics, including in respect of the specific side effects mentioned in the '113 patent.

[241] With respect to the specific assertions of superiority in the '113 patent, there is no evidence of a line of reasoning that would sustain a sound prediction that olanzapine's liver enzyme liability was particularly advantageous. The evidence showed that olanzapine often raised liver enzymes. Its

liability was comparable to flumezapine's. A reasonable inference is that olanzapine would likely raise liver enzymes in some patients to a level comparable with known antipsychotics.

[242] Nor is there evidence of a chain of reasoning supporting a prediction that olanzapine's CPK liability was particularly advantageous. The factual evidence showed that olanzapine's CPK liability was probably comparable to flumezapine's at therapeutic doses.

[243] Further, I do not see a line of reasoning that would support the assertion that olanzapine had particularly low EPS liability. Lilly had good CAR-CAT data from animal tests and *in vitro* binding assays, but all witnesses agreed that the effect in humans could not be predicted until sufficient clinical testing had been done. Dr. Goodwin understood the '113 patent as expressing the inventors' hope that olanzapine would deliver a low EPS liability and that they would find out more in time. Their hope was based on the preclinical studies (Transcript, Vol 37, pp 258-9).

[244] Further, as Dr. Healy noted, animal tests are good for predicting some forms of EPS (i.e., Parkinsonism) but not others (i.e., akathesia). Some EPS effects are seen relatively soon after starting treatment; however, with more prolonged exposure, other EPS effects, such as tardive dyskinesia, can be detected. These are relatively common in patients treated with antipsychotics over the long term (Transcript, Vol 37, p 18, lines 18-24; see also Goodwin Expert Report, paras 51, 148). Lilly's tests were brief, and the results obtained for EPS were somewhat equivocal – some patients improved, some deteriorated and some remained constant. A reasonable inference from the factual basis is that olanzapine had some EPS liability, similar to flumezapine's, but perhaps

somewhat better than conventional antipsychotics.

[245] There was early evidence showing that olanzapine's prolactin liability was fairly low. However, there was little basis for determining what its effect on prolactin would be over a longer term. A reasonable inference is that olanzapine's prolactin liability would likely be comparable to that of other antipsychotics, and would be of little clinical concern.

[246] There was no way of knowing what olanzapine's long-term or overall effect would be on the white blood cells of patients. Dr. Rosenheck pointed out that the fact that Lilly did not detect any alteration of white blood cell counts during brief studies in healthy volunteers and a handful of schizophrenia patients would not have provided grounds on which to predict that olanzapine had no liability for agranulocytosis, or that it had any kind of superiority or a better side-effects profile than other antipsychotics (Transcript, Vol 18, pp 283-6). Dr. Goodwin agreed. The chance of seeing a rare event like agranulocytosis in a short trial would be very low. Even with clozapine, you would not expect to see agranulocytosis in a short-term study (Transcript, Vol 37, pp 207-8, lines 19-25, 6-8). Longer studies were needed. Therefore, there appeared to be no grounds to assert an advantage over clozapine. A reasonable inference from the factual basis is that olanzapine's effect on white blood cells was unknown.

[247] Regarding efficacy at low doses, an early signal of efficacy at a low dose in the E001 study could not support a prediction that olanzapine would be effective at that dose across a broader range of patients over a longer period of time. The summary of the E001 trial stated "[i]t is difficult to make conclusions on the efficacy of [olanzapine] on the basis of an open study with so small a

sample of patients. However, the results of this study appear to indicate that [olanzapine] has overall efficacy similar to that of conventional antipsychotic drugs" (E001 Clinical Study Report, p 114). In my view, a reasonable inference from the factual basis is that olanzapine had a moderate therapeutic effect at relatively low doses.

[248] Returning to the overall promise of the '113 patent, Dr. Newcomer's view was that "[p]rior to 1991, there was effectively no evidence upon which the inventors of the '113 Patent (or anyone else) could have based the statements in the '113 Patent. . . At that time, these statements would have been entirely speculative, as the sorts of trials required to provide the minimum level of clinical evidence to support such statements had not even begun, much less been completed or analyzed" (D-187, at p 65). With respect to the promise of the patent, he stated "I thought that was sticking their neck out awfully far in the absence of credible evidence or inability to even predict" – "It was a very hopeful statement, I thought, but I couldn't understand the basis on what such great hopes would be based" (Transcript, Vol 26-A, p 94, lines 7-13). Further, "I couldn't understand how that claim could be made and a statement about a better side effect profile than prior known antipsychotic agents. In 1991, there was virtually no evidence on which such a claim could be made" (Transcript, Vol 26-A, p 83, lines 13-17). As mentioned, Dr. Newcomer's view was that the open-label study would serve only to detect large safety signals; "[y]ou might get some initial kind of feel for whether or not the compound has got any activity at all" (Transcripts, Vol 27-A, p 28, lines 20-22).

[249] Dr. Rosenheck's view was that the references in the '113 patent to olanzapine's advantages do not "in any way support the claim of marked superior(ity) and better side effect profile than prior

known antipsychotic agents. You just can't get from what's gone before with animals and activity levels and no white cell dyscrasia in ten people, you can't get from that to marked superiority – from the perspective of someone expert in the art, you can't get from that to marked superiority than prior-known antipsychotic agents" (Transcript, Vol 18, p 289, lines 1-10).

[250] On the other hand, Dr. Nichols' opinion appears to favour Lilly's position:

> Therefore, if I am looking for a compound that would have an atypical profile and that would not adversely impact on white blood cell count, based on what is disclosed in the '113 patent, I could soundly predict that there was a basis for believing that olanzapine would be an improvement over the typicals and clozapine in terms of the ability of olanzapine to treat psychosis with a lower rate of EPS than the typicals and a safer profile with respect to white blood cell production than clozapine". (P-191, at p 66)

[251] However, I note that Dr. Nichols was careful to say that he could soundly predict only the existence of "a basis for believing" olanzapine would meet the promise of the patent. I read his opinion as setting out a much more tentative conclusion than saying that he could infer that olanzapine actually possessed the promised characteristics. He was saying, in effect, that he could predict that Lilly would, in time, assemble the evidence that would support a sound prediction of the patent's promise, not that Lilly had that evidence at the relevant time.

[252] In support of the '113 patent's validity, Lilly relies heavily on the fact that the Supreme Court of Canada upheld a patent based on sound prediction founded solely on an *in vitro* test, with no testing in humans (*AZT*, above). Lilly says the case for the '113 patent's validity is stronger because at least some testing in humans had been carried out.

[253] In AZT, the patent involved the use of a drug in the treatment of HIV/AIDS. The Supreme Court of Canada upheld the patent under the doctrine of sound prediction. The trial judge had concluded that the inventors had both a factual basis for their prediction that AZT would work in human patients and a sound line of reasoning linking those facts to the desired outcome. In particular, having already achieved positive results from *in vitro* tests of mouse cells, the inventors went on to conduct *in vitro* tests in a human cell line. Positive results from the latter supported their theory (called the "chain terminator effect") that AZT would be useful both in HIV/AIDS treatment and prophylaxis. Justice Binnie, speaking for the full Court, noted that the trial judge had found "that the inventors possessed and disclosed in the patent both the factual data on which to base a prediction, and a line of reasoning (chain terminator effect) to enable them to make a sound prediction at the time they applied for the patent" (para 75).

[254] Justice Binnie made clear that it would be sufficient if the inventors "disclosed in the patent a rational basis for making a sound prediction that AZT would prove useful in the treatment and prophylaxis of AIDS, which it did (para 3). It was not possible to predict from mouse cells alone "how a drug would work, if at all, in humans" (para 12). However, by the filing date, the patent holder had tested AZT *in vitro* against HIV-infected human cells. That information provided a sound basis to predict the effect of the drug in humans.

[255] That is not the situation before me. While the '113 patent contains some information about the testing of olanzapine, it does not set out a line of reasoning to support its alleged clinical superiority in the treatment of schizophrenia and better side effects profile. It does set out a rational basis for making a sound prediction that olanzapine would be useful in the treatment of

schizophrenia, but not grounds for a sound prediction that olanzapine would treat schizophrenia in a markedly superior fashion, with a better side-effects profile than other known antipsychotics.

[256] As for the implied assertion mentioned above – that the inventors had a sufficient basis for the statement that olanzapine had a superior side-effects profile – it is clear that there was little foundation for it. Novopharm presented a significant amount of evidence about olanzapine's tendency to cause a range of metabolic effects: weight gain, hyperlipidemia, high cholesterol, diabetes, and hyperglycemia. In particular, Dr. Newcomer gave extensive testimony in this area. I concur with Dr. Goodwin's assessment of Dr. Newcomer's evidence:

> I think Dr. Newcomer gave a very scholarly presentation to the Court. I think it would be extremely useful as an understanding of what we currently know about the risks of weight gain in the population in general and in psychiatric patients in particular.
>
> The fact that this is a growing worry as the whole population gains weight, and it is certainly true that what we have to do now when we prescribe antipsychotics to patients, because in a sense we are less concerned about extrapyramidal side effects, we think those are something we no longer have to worry about, our focus is in a sense on the next challenge, which is to avoid making things worse for our patients metabolically, and that Dr. Newcomer is very right to emphasize that as a major challenge for 2009 (Transcript, Vol 37, p 54, lines 6-23).

[257] I do not find it necessary or appropriate to go into this evidence in any detail. As discussed above, I read the '113 patent as asserting specific advantages over the '687 compounds and other antipsychotic agents in respect of efficacy and the side-effects mentioned in the patent and which were known at the relevant time to be of clinical concern. The patent also implies knowledge of olanzapine's overall side-effect profile. The extensive evidence I heard about olanzapine's metabolic effects underscores the fact that Lilly really had very little evidence in 1991 of what olanzapine's impact on patients experiencing a chronic mental illness like schizophrenia was likely

to be.

[258] Lilly presented evidence showing that in a series of studies olanzapine was shown to be superior to other antipsychotic drugs on a measure referred to as “time to discontinuation for any cause” (see especially the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study – P-41). In essence, this means that patients taking olanzapine tended to stay on their medication longer, implying that the drug was effective, well-tolerated and tended not to cause serious side effects. This measure is controversial. Many experts disputed the significance of it. Again, I do not find it necessary to go into the details of these studies. At best, they would show that olanzapine has been shown in some recent studies (well after the filing date) to have a potential advantage over some other antipsychotic agents. However, that advantage, if it exists, is in respect of a measure that could not have been contemplated by the inventors of olanzapine or other skilled persons. It does not fall within the ‘113 patent’s promise that olanzapine is markedly superior and has a better side-effects profile than other drugs. Accordingly, I need say no more about it.

[259] In sum, the evidence before me simply does not support a *prima facie* reasonable inference that olanzapine would treat schizophrenia in a markedly superior manner with a better side-effects profile than other antipsychotics.

[260] More particularly, the evidence does not support a prediction that the alleged advantages of olanzapine over two ‘687 compounds, flumezapine and ethyl olanzapine, are substantial. To the extent they existed at all, their magnitude was insignificant. In addition, there is no evidence that olanzapine was superior to any other compounds in the ‘687 class in respect of the characteristics

described in the ‘113 patent. The comparisons did not relate to the class as a whole and I have no evidence that any advantage was peculiar to olanzapine.

[261] None of the comparisons in the ‘113 patent was supported by evidence suggesting that olanzapine was a peculiar or special member of the ‘687 class. I have no information about any of the other ‘687 members’ properties in respect of efficacy, liver enzymes, CPK, cholesterol, or anything else. I do not know flumezapine’s tendency, if any, to raise cholesterol or ethyl olanzapine’s liability, if any, in respect of liver enzymes or CPK. There is no evidence before me indicating whether only a small number of unselected compounds possess the same alleged advantages as olanzapine, or whether a larger number of them does.

[262] The assertion that olanzapine was markedly superior to, and had a better side-effects profile than, the other antipsychotic agents on the market in 1991 would certainly have constituted a substantial advantage setting olanzapine apart from the other ‘687 compounds, only one of which had made it into human testing (flumezapine). In 1991, a markedly superior antipsychotic drug with an enhanced side-effect profile would have been highly effective, had little or no EPS liability, and would not cause agranulocytosis (as clozapine did). In addition, by implication, it would not have any other major adverse side-effect. The evidence did not support a reasonable inference that olanzapine had those properties. As Dr. Rosenheck stated, the references to olanzapine’s advantages in the ‘113 patent do not “support the claim of marked superior(ity) and better side effect profile than prior known antipsychotic agents. You just can’t get from what’s gone before with animal and activity levels and no white cell dyscrasia in ten people, you can’t get from that to marked superiority – from the perspective of someone expert in the art, you can’t get from that to marked

superiority than prior-known antipsychotic agents" (Transcript, Vol 18, p 289, lines 1-10).

[263] In sound prediction cases, there will often arise a question whether the patent was filed before the necessary factual basis had been established. It is important that the Court remain vigilant about the requirements of a factual basis, sound line of reasoning and proper disclosure in the patent. As Justice Binnie noted (*AZT*, above, para 46):

> A policy of patent first and litigate later unfairly puts the onus of proof on the attackers to prove *invalidity*, without the patent owner's ever being put in a position to establish validity. Unless the inventor is in a position to establish utility as of the time the patent is applied for, on the basis of either demonstration or sound prediction, the Commissioner 'by law' is required to refuse the patent (*Patent Act*, s 40)

[264] The evidence before me suggests that Lilly filed the '113 patent before it had a basis on which to found a sound prediction of olanzapine's advantages, if any, over the '687 compounds or other antipsychotics. In circumstances where the patent-holder has not established "utility by tests or sound prediction at the time it applied for its patent, then it was offering nothing to the public but wishful thinking in exchange for locking up potentially valuable research turf for (then) 17 years" (*AZT*, para 52).

[265] In sum, at the time the patent was filed in April 1991, Lilly had not found any special qualities of olanzapine that would justify a fresh monopoly. Lilly had carried out routine testing of olanzapine's properties. It had some early signals of safety and efficacy in a few small studies of healthy volunteers and patients. While Lilly scientists showed persistence, diligence and sound science in getting olanzapine that far, that is not necessarily enough for a patent. There must be an invention. And, in the context of a selection patent, the invention is the discovery of a substantial

advantage over the genus compounds.

[266] I note that Justice Binnie in *AZT* was careful to note that the doctrine of sound prediction should be circumscribed, lest it be abused:

> There is no doubt that care must be taken that the doctrine is not abused, and that sound prediction is not diluted to include a lucky guess or mere speculation. The public is entitled to obtain a solid teaching in exchange for the patent rights. (Para 69)

[267] Olanzapine was a compound that showed promise and, later, some of the early positive indications were borne out. Lilly received some early signals of potential safety and efficacy, but there is no sound and articulable line of reasoning, or a *prima facie* reasonable inference, that would have led the inventors from the evidence available at the relevant time to the explicit promise of the substantial advantage set out in the '113 patent relating to clinical-superiority and a better side-effects profile. At best, the evidence supported a working hypothesis that olanzapine had some antipsychotic effect and a manageable safety profile.

[268] In my view, the preponderance of the evidence does not support a sound prediction of the '113 patent's promise. Therefore, the '113 is not a valid patent.

## VII. Issue Two – Sufficiency?

[269] Novopharm argues that s 27(3) of the *Patent Act* requires Lilly to disclose in clear terms the substantial advantages of olanzapine over the '687 genus. They must be "plainly and fully set out in

sufficient detail so as to enable a person skilled in the art to know and appreciate what they are" (citing *Lilly (2)*, above, para 139).

[270] A selection patent must set out clearly what is better and different about the selected compound as compared to the genus from which it derives. The patent must give enough detail that a person skilled in the art would know what the advantages of the selected compound are: *Lilly (2)*, above, para 139. Justice Rothstein endorsed this view of the sufficiency requirement for selection patents, stating that "it is necessary that the specification of the selection patent define in clear terms the nature of the characteristic which the patentee alleges to be possessed by the selection for which he claims a monopoly (*Sanofi-Synthelabo*, above, para 114, citing the *Farbenindustrie* case). Not only must the selected compound have special advantages, those advantages must be spelled out with adequate precision in the patent.

[271] Lilly maintains that to meet the requirements of s 27(3) of the *Patent Act* it must simply state in the patent what the invention is and how it works. The '113 patent makes clear, Lilly says, that the invention is olanzapine, an antipsychotic with particular advantages, and there is no evidence that skilled persons would be unable to put it into practice. Therefore, Lilly met the requirements of s 27(3).

[272] I believe Lilly's position is supported by Justice Layden-Stevenson's discussion of sufficiency, as well as *Pfizer Canada Inc v Canada (Minister of Health)*, 2008 FCA 108. In my earlier judgment, I had interpreted the obligation to describe the invention and how it works as including, in the case of an invention based on an alleged sound prediction of utility, the duty to set out the factual basis and line of reasoning supporting that prediction. Clearly, Justice Layden-

Stevenson concluded otherwise and I am bound by her approach. The ‘113 patent describes the compound of the invention, its advantages, how to make it, and the range within which it can be dosed. To require more – such as disclosure of the basis for the assertion that olanzapine has certain advantages – would lead me to repeat the error in my original judgment identified by Justice Layden-Stevenson. I must conclude, therefore, that Novopharm’s attack on the sufficiency of the ‘113 patent fails.

## VIII. Conclusion and Disposition

[273] Lilly had a patent for olanzapine (the ‘687) that lasted from 1980 to 1997. But as the ‘687 patent neared expiry, it became important to Lilly to try to extend the patent protection for olanzapine. The ‘113 patent was clearly drafted with a view to justifying a fresh patent. But the evidence just was not there in 1991, when the patent was filed. Novopharm has established that the patent’s promise had not been demonstrated and could not have been soundly predicted on the basis of the evidence available to the inventors in 1991. Accordingly, I must conclude that the ‘113 is not a valid selection patent. The claims set out above are invalid. Lilly’s action for patent infringement is dismissed, with costs.

## JUDGMENT

**THIS COURT'S JUDGMENT is that** :

1. The claims of the '113 patent in issue are invalid;

2. Lilly's action for patent infringement is dismissed with costs.

"James W. O'Reilly"
Judge

Annex “A”

| *Patent Act*, R.S.C. 1985, c. P-4 | *Loi sur les brevets*, L.R.C. 1985, ch. P-4 |
|---|---|
| Definitions | Définitions |
| **2.** In this Act, except as otherwise provided, | **2.** Sauf disposition contraire, les définitions qui suivent s’appliquent à la présente loi. |
| “invention” means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter; | « invention » Toute réalisation, tout procédé, toute machine, fabrication ou composition de matières, ainsi que tout perfectionnement de l’un d’eux, présentant le caractère de la nouveauté et de l’utilité. |
| 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. |
| … | […] |
| Specification | Mémoire descriptif |
| (3) The specification of an invention must | (3) Le mémoire descriptif doit : |
| (*a*) correctly and fully describe the invention and its operation or use as contemplated by the inventor; | *a*) décrire d’une façon exacte et complète l’invention et son application ou exploitation, telles que les a conçues son inventeur; |
| (*b*) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it; | *b*) exposer clairement les diverses phases d’un procédé, ou le mode de construction, de confection, de composition ou d’utilisation d’une machine, d’un objet manufacturé ou d’un composé de matières, dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l’art ou la science dont relève l’invention, ou dans l’art ou la science qui s’en rapproche le plus, de confectionner, |

construire, composer ou utiliser l'invention;

(*c*) in the case of a machine, explain the principle of the machine and the best mode in which the inventor has contemplated the application of that principle; and

*c*) s'il s'agit d'une machine, en expliquer clairement le principe et la meilleure manière dont son inventeur en a conçu l'application;

(*d*) in the case of a process, explain the necessary sequence, if any, of the various steps, so as to distinguish the invention from other inventions.

*d*) s'il s'agit d'un procédé, expliquer la suite nécessaire, le cas échéant, des diverses phases du procédé, de façon à distinguer l'invention en cause d'autres inventions.

Void in certain cases, or valid only for parts

**53.** (1) A patent is void if any material allegation in the petition of the applicant in respect of the patent is untrue, or if the specification and drawings contain more or less than is necessary for obtaining the end for which they purport to be made, and the omission or addition is wilfully made for the purpose of misleading.

Nul en certains cas, ou valide en partie seulement

**53.** (1) Le brevet est nul si la pétition du demandeur, relative à ce brevet, contient quelque allégation importante qui n'est pas conforme à la vérité, ou si le mémoire descriptif et les dessins contiennent plus ou moins qu'il n'est nécessaire pour démontrer ce qu'ils sont censés démontrer, et si l'omission ou l'addition est volontairement faite pour induire en erreur.

Exception

(2) Where it appears to a court that the omission or addition referred to in subsection (1) was an involuntary error and it is proved that the patentee is entitled to the remainder of his patent, the court shall render a judgment in accordance with the facts, and shall determine the costs, and the patent shall be held valid for that part of the invention described to which the patentee is so found to be entitled.

Exception

(2) S'il apparaît au tribunal que pareille omission ou addition est le résultat d'une erreur involontaire, et s'il est prouvé que le breveté a droit au reste de son brevet, le tribunal rend jugement selon les faits et statue sur les frais. Le brevet est réputé valide quant à la partie de l'invention décrite à laquelle le breveté est reconnu avoir droit.

Copies of judgment

(3) Two office copies of the judgment rendered under subsection (1) shall be furnished to the Patent Office by the patentee, one of which shall be registered and remain of record in the Office and the other attached to the patent and made a part of it by a reference thereto.

Copies du jugement

(3) Le breveté transmet au Bureau des brevets deux copies authentiques de ce jugement. Une copie en est enregistrée et conservée dans les archives du Bureau, et l'autre est jointe au brevet et y est incorporée au moyen d'un renvoi.

Annex "B" - Expert Witnesses

Dr. Jeffery B. Press (Defendant's witness)

Dr. Press received a BSc *cum laude* in 1969 from Bucknell University. He received a PhD in organic chemistry from Ohio State University in 1973 and completed a postdoctoral study in 1975 at Harvard University with Nobel Prize-winning scientist Dr. Robert Woodward. Dr. Press worked for 25 years in the pharmaceutical and biopharmaceutical industry as a research chemist and director. He has received grants from the National Institutes of Health, sits on the editorial board of a book series (*Organic Reactions*), and has sat on the editorial board of two other journals (*Analgesia* and *Expert Opinion on Therapeutic Patents*). He has published widely in well-respected journals and is the named inventor on more than 50 patents in the area of central nervous system, cardiovascular and gastrointestinal applications.

Dr. Press was accepted as being qualified to give expert opinion evidence in the fields of organic and medicinal chemistry and in the application of organic and medicinal chemistry, and drug discovery and development in the pharmaceutical industry.

Dr. Paul Leber (Defendant's witness)

Dr. Leber received a BA from Hamilton College in 1958. He received a doctor of medicine degree from New York University in 1963 and interned at John Hopkins. Dr. Leber completed a residency in internal medicine in New York and then entered the field of academic pathology at New York University and Harvard University for several years, during which he researched and taught pathology to medical students. Dr. Leber then re-trained in the field of psychiatry through Cornell University. He is board certified in both general psychology and anatomical and clinical pathology, and holds an active medical license in the State of Maryland. Dr. Leber worked for the United States Food and Drug Administration (FDA) from 1978 to 1999. During that time he held positions that oversaw the application process for the approval of new drugs, specifically in the area of neuropharmacology. This included reviewing clinical trials and the data from clinical trials for regulatory and scientific validity. He also received two awards of merit from the FDA during his tenure there. Dr. Leber has published widely on the subject of regulatory and scientific considerations in the process of evaluating drug products. Dr. Leber is a member of the American College of Neuropsychopharmacology and the American Neurological Association. He is currently the director of a consultancy practice, the Neuro-Pharm Group, that offers opinions to clients on important elements for the submission of applications related to drug approvals.

Dr. Leber was accepted as being qualified to give expert opinion evidence on drug regulation in the United States, and on the design, conduct, and interpretation of clinical trials of drugs for the treatment of neurological and psychiatric disorders.

Dr. Ronald Diamond (Defendant's witness)

Dr. Diamond joined the University of Wisconsin as a post-doctoral fellow in 1977. He is currently a professor of psychiatry at the University of Wisconsin, medical director of the Mental Health Centre of Dane County, and consultant to the Wisconsin Bureau of Mental Health and

Substance Abuse. He teaches and lectures widely on the topics of community-based medicine and psychopharmacology. He also has a small practice in which he sees patients and oversees the work of other clinical psychiatrists. In that capacity, he regularly reviews test results, including liver enzyme levels and CPK. Dr. Diamond's clinical and academic focus is community-based treatment of persons with schizophrenia and other serious mental illness, which includes interpreting research studies and translating existing research into medical practice. He has published books, chapters, and journal articles on psychopharmacology in well-respected journals, and is frequently invited to speak internationally. Dr. Diamond has previously been qualified several times as an expert witness on general psychiatry, and once specifically in clinical psychiatry, psychopharmacology and test analysis, always in other jurisdictions.

Dr. Diamond was accepted as being qualified to give expert opinion evidence in the areas of clinical psychiatry and psychopharmacology, including the analysis of liver and muscle data tests.

Dr. Paul Pentel (Defendant's witness)

Dr. Pentel received a doctor of medicine degree from Stanford Medical School in 1975. He completed his internship and residency at the University of Minnesota, and a fellowship in clinical pharmacology at the University of California, San Francisco. Dr. Pentel is currently certified by the American Board of Medical Specialties in the areas of internal medicine and medical toxicology. Dr. Pentel is currently the chief of the clinical pharmacology division, director of the tobacco dependence clinic, and chair of the pharmacy and therapeutics committee at the Hennepin County Medical Centre in Minneapolis, Minnesota. He is also the president of the Minneapolis Medical Research Foundation and past president of the American College of Medical Toxicology. He has conducted research over the past 30 years on the toxicity of antidepressant drugs and anorectic drugs, immunotherapy of drug overdose, drug pharmacokinetics, medication development for drug addiction, and nicotine and tobacco pharmacology. Dr. Pentel has published in the areas of both animal and human drug studies, including toxicity studies. He has previously been qualified several times as an expert in toxicology and clinical pharmacology for litigation in other jurisdictions.

Dr. Pentel was accepted as being qualified to give expert opinion evidence in the areas of toxicology and clinical pharmacology.

Dr. Michael Escobar (Defendant's witness)

Dr. Escobar received a PhD in statistics from Yale University in 1988, and was a member of the Yale University Department of Epidemiology and Public Health from 1988 to 1990. He has also been on faculty at Carnegie Mellon University and the University of Pittsburgh, and is currently a professor at the Dalla Lana School of Public Health in the Department of Statistics for the University of Toronto, a department he joined in 1993. He has served as associate editor of the *Journal of the American Statistical Association* and president of the Biostatistics Section of the Canadian Statistical Society, and has published many refereed publications on topics that include statistical methodology and applied statistics. Dr. Escobar also gained experience in analyzing data and reviewing study protocol as an instructor and member of the review board for a clinical resource centre.

Dr. Escobar was accepted as being qualified to give expert opinion evidence in the areas of statistics, biostatistics, and statistical and biostatistical analysis.

Dr. David Healy (Defendant's witness)

Dr. Healy completed medical training at the University College in Dublin, Ireland. He received an MD degree in the United Kingdom (the equivalent of a PhD in North America). He began research in the area of neuropharmacology and neuropsychopharmacology in Ireland, and continued this research when he moved to Cambridge, England in the mid-1980s. In 1990 Dr. Healy took a position at Cardiff University, where he continues to hold a position made up of teaching, research, and publicly-funded clinical practice in which he sees patients with schizophrenia, mood disorders, or similar conditions. Dr. Healy has extensive experience consulting in the pharmaceutical field to help design clinical trial protocols for new drug studies, and has also run clinical trials of antipsychotics and antidepressants in both healthy volunteers and patients. His research also includes work on the history of the development of antidepressant and antipsychotic drugs. Dr. Healy is a fellow of the Royal College of Psychiatrists, a member of the British Association for Psychopharmacology, and a member of other societies involved in the issue of the role drugs play in modern clinical practice. He has been an invited international lecturer on mood disorders and their treatment; has authored, co-authored and published multiple books, chapters, and peer-reviewed articles; and is a reviewer for dozens of journals. Dr. Healy has previously been qualified several times as an expert in the area of psychiatry for litigation carried out in other jurisdictions.

Dr. Healy was accepted as being qualified to give expert opinion evidence in the areas of clinical psychiatry, neuropharmacology, neuropsychopharmacology, and psychiatric history.

Dr. John Newcomer (Defendant's witness)

Dr. Newcomer received a bachelor's degree from Brown University in 1981 and a medical degree from Wayne State University in 1985. He received residency training in general psychiatry and completed postdoctoral research in psychopharmacology and clinical phenomenology from 1986 to 1990 at the Stanford University School of Medicine. In 1990, he joined the faculty of Washington University in St. Louis, in the Department of Psychiatry in the School of Medicine. Dr. Newcomer is a professor in that department and also continues his clinical work by running an in-patient unit that treats patients who have been predominantly diagnosed with schizophrenia, bipolar disorder, or severe forms of major depressive disorder. Dr. Newcomer is also the medical director of the Centre for Clinical Studies for Washington University and co-director of the Clinical Trials Unit, Institute for Clinical and Translational Science. Dr. Newcomer is a member of several research grant review committees for existing and developing medications, for which he evaluates proposed studies for their goals and objectives, and whether the proposed methodology will achieve those objectives. He also chairs the Drug Utilization Review Board for Medicaid for the state of Missouri, which sets formulary policy for the state, and sits on data safety monitoring committees for clinical trials.

Dr. Newcomer was accepted as being qualified to give expert opinion evidence in the areas of clinical psychiatry, with particular focus on four areas: development, evaluation and administration of antipsychotic medicines; the design, conduct and analysis of clinical trials of

antipsychotic medicines; the effects and side effects of antipsychotic medicines; and specifically the metabolic side effects of antipsychotic medicines.

Dr. Robert Rosenheck (Defendant's witness)

Dr. Rosenheck completed an MD degree at the University of Pennsylvania in 1973 and subsequently completed a chief residency in psychiatry at Yale Psychiatric Institute in 1977. He is board certified in psychiatry and is licensed to practice medicine in the state of Connecticut. Dr. Rosenheck is currently a professor of psychiatry, epidemiology and public health at the Yale University School of Medicine, where he has taught since 1977. From 1977 to 1988, Dr. Rosenheck was the director of general psychiatry services and associate director of education at West Haven Veteran Affairs Hospital. Since 1987, Dr. Rosenheck has been the director of the Department of Veterans Affairs Northeast Program Evaluation Centre, which is responsible for monitoring and evaluating specialized mental health programs for Veterans Affairs nationally. Of the 5 million patients, approximately 1 million have psychiatric disorders, and 100,000 have schizophrenia. Dr. Rosenheck has published over 450 academic papers and over 100 government reports on the subject of evaluating mental health interventions for severely mentally ill patients, with a special interest in mental health services research. He has also been a reviewer on numerous well-respected journals, and has had extensive involvement in analyzing the cost-effectiveness of mental health programs, including drug delivery. Dr. Rosenheck gained experience in the design, conduct and analysis of clinical trials through his involvement in several studies completed through the Veterans Affairs Cooperative Studies Program. Within the general field of epidemiology, Dr. Rosenheck has a specific research and practice interest in pharmacoepidemiology, observing the pattern with which medications are used in practice.

Dr. Rosenheck was accepted as being qualified to give expert opinion evidence in the areas of psychiatry; mental health services research; design, conduct, and analysis of clinical trials, including trials examining the effectiveness of antipsychotics, especially in patients with schizophrenia; epidemiology and mental health care in the public health context; and marketing of antipsychotic medications.

Dr. Deborah Greco (Defendant's witness)

Dr. Greco received a bachelor of animal science from California State Polytechnic University in 1978 and a doctor of veterinary medicine from University of California (Davis) in 1982. She has been practicing veterinary medicine since then. Dr. Greco received board certification in internal medicine from the American College of Veterinary Internal Medicine in 1986, and, subsequently, a master of science in veterinary medicine and surgery and a PhD in veterinary physiology and pharmacology from Texas A&M. From 1990 to 2002, Dr. Greco was a professor at Colorado State University in the Department of Clinical Sciences in the College of Veterinary Medicine and Biomedical Science. During that time she taught veterinary students (including PhD and postdoctoral students), residents, and interns; she also maintained clinical and research activities, with a focus on dogs and cats, and was involved in several drug trials. From 2002 to 2006, Dr. Greco was a staff internist and endocrinologist at the Animal Medical Center in New York City. From 2006 to the present, Dr. Greco has been a senior research scientist at Nestle Purina. In this capacity she delivers lectures internationally on animal endocrinology and

nutrition and designs studies for product development. She also sits on the Canine Health Foundation board, and reviews grant applications, including evaluating the design of proposed trials. She is involved with various organizations (e.g., Society for Theriogenology, American Association of Feline Practitioners, American College of Veterinary Internal Medicine, American Diabetes Association, American Animal Hospital Association, American Veterinary Hospital Association), and was the president of the Society of Comparative Endocrinology from 1995-1997. She is widely published in her areas of research, and has served on the editorial boards of several journals in the veterinary area.

Dr. Greco was accepted as being qualified to give expert opinion evidence in veterinary medicine, including veterinary pharmacology and endocrinology, and as an expert in the design, conduct and analysis of animal studies in dogs.

Mr. Keith L. Altman (Defendant's witness)

Mr. Altman has a BSc in astronomy and physics from the State University of New York and a JD from Concord Law School. Mr. Altman has 20 years' experience analyzing complex databases; 11 of those years dealt directly with pharmaceutical adverse event databases, including the Food and Drug Administration database. For the past five years, Mr. Altman has been the director of adverse events analysis for Finkelstein & Partners, working in the field of drug development and conducting safety analyses for new drug applications to be submitted to the Food and Drug Administration in the United States. He has worked on a wide variety of drugs, including several central nervous system drugs. He has previously been qualified to give expert evidence in the areas of pharmacovigilance and adverse event reporting systems in other jurisdictions, and has been involved in drug litigation as a consultant to coordinate electronic discovery demands. Mr. Altman is a member of the International Society of Pharmacoepidemiology and the Drug Information Association, and is the co-chair of the Electronic Discovery Litigation Group of the American Association for Justice.
Mr. Altman was accepted as being qualified to give expert opinion evidence in the analysis of adverse events databases, including adverse events reporting and pharmacovigilance.

Mr. Tom Brogan (Plaintiffs' witness)

Mr. Brogan received an honours bachelor of arts from the University of Windsor, and graduate training in economics and econometrics from the University of Western Ontario. After a period of working for the New Brunswick provincial government as a labour market economist and New Brunswick Telephone Company as an economist, he entered the federal civil service in 1977. He first set up an unemployment insurance database, and subsequently reviewed the compulsory licensing of pharmaceuticals and developed the Patented Medicines Prices Review Board. In 1989, Mr. Brogan started a company (Brogan Inc.) with a view to improving communication between the regulatory bodies and the private sector. Specifically, the company collects data from provincial governments and private drug plans on the medications patients take over a period of time, and from Canadian pharmacies to measure volumes of sales and rates of prescription. Clients include provincial and federal governments, pharmaceutical companies, and pharmacies.

Mr. Brogan was accepted as being qualified to give expert opinion evidence in the pharmaceutical industry from the commercial side, particularly with respect to sales, marketing, government policy, economics, measurement of commercial actions, reimbursement, and the collection and interpretation of data in respect of pharmaceutical companies in Canada.

Dr. Allan H. Young (Plaintiffs' witness)

Dr. Young completed a medical degree at the University of Edinburgh in 1984, and was certified in psychiatry in 1988. He earned a Master's degree and a PhD at the University of Oxford, where he also lectured for three years. He lectured at Newcastle-upon-Tyne for 10 years before moving to his current position at the University of British Columbia in 2005. His early research focused on schizophrenia, which later broadened to include mood disorders. Dr. Young has been awarded various research grants to study central nervous system agents, and has also published analyses of clinical trials that he designed. Dr. Young has also been involved in several Cochrane reviews, appraising evidence at the high standards required by the Cochrane collaboration.

Dr. Young was accepted as a psychiatrist qualified to give expert opinion evidence on the design, conduct, and analysis of clinical trials of central nervous system agents.

Dr. Ronald Thisted (Plaintiffs' witness)

Dr. Thisted earned an undergraduate degree in mathematics and philosophy from Pomona University. He subsequently studied statistics and biostatistics at Stanford University, and was granted a Master's degree in 1973 and a PhD in 1977. He is currently a professor in and chair of the Health Studies Department and professor in the Department of Statistics at the University of Chicago, as well as the Director of the Biostatistics Consulting Facility of the University of Chicago Cancer Center. Dr. Thisted's research focus is on statistical analysis of data and methods for designing and executing clinical and preclinical investigations, and he has worked with both pharmaceutical companies and colleagues at the University of Chicago in designing clinical trials and animal trials. He has also received several grants from the National Institute of Health, and has published on statistics and adverse events reported in clinical trials. Dr. Thisted was qualified as a biostatistician and epidemiologist with experience in clinical epidemiology, the design and analysis of preclinical and clinical studies, and spontaneous adverse events reporting and analysis.

Dr. Joseph McEvoy (Plaintiffs' witness)

Dr. McEvoy graduated with a BA from Manhattan College in 1969, and an MD from Vanderbilt Medical School in 1973. He completed a residency in psychiatry in 1978. He held the position of assistant professor at Vanderbilt University in the Department of Psychiatry until 1981, and as assistant and associate professor at the University of Pittsburgh's Department of Psychiatry until 1988. Since 1989, he has been associate professor in the Department of Psychiatry of Duke University Medical Center as well as the Deputy Clinical Director of the John Umstead Hospital. Dr. McEvoy has published widely and has received honours related to his area of expertise (e.g., Distinguished Fellow, American Psychiatric Association (2003), Eugene A. Hargrove Mental Health Research Award (2002)).

Dr. McEvoy was accepted as a psychiatrist with experience in the design, conduct and analysis of clinical trials for central nervous system agents, with a particular expertise in the CATIE study.

Dr. Karl A. Traul (Plaintiffs' witness)

Dr. Traul received a BSc in biology and chemistry from the University of Akron in 1963, a master's (microbiology, immunology and immunochemistry) in 1965 and a PhD (immunology and immunochemistry) in 1969, both from Iowa State University. Dr. Traul worked for Pfizer, Exxon, and American Cyanamid in research, toxicology, new drug development, and regulatory compliance roles. Since 1995, he has been president of K.A. Traul Pharmaceutical Consulting, advising clients on the development of non-clinical studies (i.e., to identify toxicologic and pharmaceutical effects). This includes suggesting studies that should be conducted, setting up and supervising studies, writing reports, and presenting the data to regulatory authorities. Since 1995 he has been involved in the development of 75-100 pharmaceutical agents.

Dr. Traul was qualified as a toxicologist with experience in the design, conduct, and analysis of toxicology studies for drug regulatory and non-regulatory purposes.

Dr. David Nichols (Plaintiffs' witness)

Dr. Nichols received a bachelor's degree in chemistry in 1969, and a PhD in medicinal chemistry from the University of Iowa in 1973. He completed post-doctoral work at the University of Iowa for two years, and then moved to Purdue University, where he is currently the Robert C. and Charlotte P. Anderson Distinguished Chair in Pharmacology. His research in two areas (drugs that modify consciousness and dopamine) has led him to gain expertise in the study of small molecules that have an effect on the central nervous system. He has previously been accepted in the United Kingdom and the United States as qualified to give expert opinion in areas of chemistry and pharmacology.

Dr. Nichols was qualified as a medicinal and organic chemist with experience in drug discovery and drug development, including biological testing used in developing structure-activity relationship (i.e., the mechanism of action of CNS agents).

Dr. John B. Bauer (Plaintiffs' witness)

Dr. Bauer received a BSc in chemistry with high honours from the University of Kentucky. He earned an MSc in nutritional sciences in 1975, a doctor of Veterinary Medicine degree in 1979, and a PhD in nutritional biochemistry in 1980, all from the University of Illinois. Dr. Bauer spent 12 years as a professor and researcher at the University of Florida, where he was also the head of the clinical chemistry laboratory. He is currently the Mark L. Morris Professor of Clinical Nutrition in the Department of Small Animal Medicine and Surgery at Texas A&M University. He has been certified as a specialist in the American College of Veterinary Nutrition. His research is concentrated on lipid nutrition, biochemistry and cholesterol metabolism in animals, and how this compares to humans. He has taught students in areas of veterinary animal nutrition as well as those who earn designations in human nutrition.

Dr. Bauer was accepted as an expert in veterinary medicine, animal nutrition, and comparative clinical pathology with specialized expertise in cholesterol, including animal models for cholesterol-related diseases in humans.

Dr. Guy Goodwin (Plaintiffs' witness)

Dr. Goodwin is currently a professor of psychiatry and head of the Department of Psychiatry at Oxford University. This involves both research and clinical activity. He has conducted research in neuroscience and neuropsychopharmacology, and his current clinical research focus is on the areas of bipolar disorder, particularly mania and depression. Dr. Goodwin has published widely in his research areas, and has helped develop evidence-based guidelines for the treatment of bipolar disorders through the British Association for Psychopharmacology and the World Federation of Societies of Biological Psychiatry. From 2002 to 2004, Dr. Goodwin was president of the British Association for Psychopharmacology, an organization devoted to collaborations in the development and evaluation of medicines for the treatment of psychiatric conditions. Since 2005 he has been on the executive council of the European College of Neuropsychopharmacology. Dr. Goodwin has also consulted for and received grants from pharmaceutical companies for the development of trials and medications within his research areas. He has previously been accepted as an expert in other jurisdictions.

Dr. Goodwin was accepted as a psychiatrist with experience in the design, conduct and analysis of clinical trials for CNS agents, spontaneous adverse event reporting, and the utilization of CNS agents.

Dr. John Lehmann (Plaintiffs' witness)

Dr. Lehmann received a PhD in Neuroscience from the University of British Columbia in 1980. He has served as a professor at the Johns Hopkins University School of Medicine, the MCP-Hahnemann University School of Medicine, and Queens University. In addition he has worked in the pharmaceutical industry at CIBA-GEIGY Corporation, Fondax-Groupe de Recherche Servier, LifeSpan BioTechnology Medical Devices, GB Therapeutics Inc., and Layton BioScience. He is currently President and Founder of Pharmikos Inc. Dr. Lehmann was qualified as a pharmacologist with a particular emphasis on neuropharmacology, and with experience in drug discovery and the design, conduct, and analysis of *in vitro* and *ex vivo* preclinical trials, as well as the conduct and analysis of clinical studies for CNS agents.

Dr. Alexander Giaquinto (Plaintiffs' witness)

Dr. Giaquinto graduated in 1966 with a BSc in Pharmacy from St. John's University, and in 1972 with a PhD in Pharmaceutics from the University of Connecticut. Dr. Giaquinto has over 30 years' experience working in the pharmaceutical industry. His early roles included development and clinical manufacturing, and process and packaging development. For over 20 years, Dr. Giaquinto was employed in the regulatory affairs area at Schering-Plough. In that capacity he was exposed to and directed drug development processes and decisions. In 1990, Dr. Giaquinto became the U.S. industry representative to the International Conference on Harmonisation (of which Canada was a member), which developed guidelines for the development of new pharmaceuticals for use in Europe, Japan and the United States. Since

2003, Dr. Giaquinto has been consulting part-time, and is also now Senior Vice-President of Regulatory Affairs and Quality Assurance for Regado Biosciences Inc. He is a member of several professional societies, committees, boards, and advisory boards related to the pharmaceutical industry.

Dr. Giaquinto was qualified as a pharmaceutical scientist with experience in drug development and drug regulatory approval.

FEDERAL COURT

**SOLICITORS OF RECORD**

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| **DOCKET:** | T-1048-07 |
| **STYLE OF CAUSE:** | ELI LILLY CANADA INC., ET AL v NOVOPHARM LIMITED |
| **PLACE OF HEARING:** | Toronto, Ontario |
| **DATE OF HEARING:** | January 19-21, 2011 |
| **REASONS FOR JUDGMENT AND JUDGMENT:** | O'REILLY J. |
| **DATED:** | November 10, 2011 |

**APPEARANCES:**

| | |
|---|---|
| Mr. Anthony G. Creber<br>Ms. Cristin Wagner<br>Dr. John Norman | FOR THE PLAINTIFFS<br>(Defendants by Counterclaim) |
| Mr. Jonathan Stainsby<br>Mr. Andrew Skodyn<br>Mr. Andrew Radhakant<br>Mr. Neil Fineberg | FOR THE DEFENDANT<br>(Plaintiff by Counterclaim) |

**SOLICITORS OF RECORD:**

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| GOWLING LAFLEUR HENDERSON LLP<br>Ottawa, ON. | FOR THE PLAINTIFFS<br>(Defendants by Counterclaim) |
| HEENAN BLAIKIE LLP<br>Toronto, ON | FOR THE DEFENDANT<br>(Plaintiff by Counterclaim) |