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Ottawa, Ontario, October 5, 2009

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 are suing Novopharm for infringement of a patent for a medicine called olanzapine. Its brand name is Zyprexa. Olanzapine is regarded as a relatively safe, and often

effective, medicine for treating schizophrenia. Olanzapine is widely prescribed and is a commercial success. It is the subject of a Canadian patent (No. 2,041,113) that I will refer to as the '113 patent. I will refer to the plaintiffs collectively as "Lilly". Lilly applied for the '113 patent in 1991 and was granted it in 1998.

[2] Olanzapine was included within an earlier Lilly patent (No. 1,075,687) (the '687 patent). The main question before me is whether Lilly was entitled to a separate patent and a further monopoly on olanzapine.

[3] The '687 patent was a so-called "genus patent". It covered 15 trillion compounds all with a similar chemical structure – three-ring molecules called "thienobenzodiazapines". The '113 patent is a so-called "selection patent" which identifies an already-patented compound for separate patent protection based on the fact that it allegedly manifests unexpected, substantial and special properties in comparison with the other members of its chemical family.

[4] For ease of reference, I have set out relevant statutory provisions in Annex "A", a summary of expert witnesses' background and qualifications in Annex "B", and a glossary of terms in Annex "C".

II. Earlier Proceedings

[5] The ‘113 patent was litigated in two previous applications before the Federal Court under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/98-166, as amended SOR/93-113. 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 olanzapine (*Eli Lilly Canada Inc.* v. *Apotex Inc.*, 2007 FC 455). 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*, R.S.C. 1985, c. P-4. Justice Gauthier found that Apotex’s allegations were not justified. However, she also found that the question whether the ‘113 was 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: *Apotex Inc.* v. *Eli Lilly Canada Inc.*, 2008 FCA 44.

[6] In a separate proceeding under the *Patented Medicines (Notice of Compliance) Regulations*, involving, essentially, the same parties as are before me, Justice Roger Hughes found 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 an NOC to enter the olanzapine market (*Eli Lilly Canada Inc.* v. *Novopharm Limited*, 2007 FC 596). 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.

[7] Justice Hughes addressed the issue that was not before Justice Gauthier – whether the ‘113 is a valid selection patent; in particular, whether the ‘113 patent’s disclosure is 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. Before the Federal Court of 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 clearly stipulated that comparative data were required in selection patents.

[8] The essence of Justice Hughes’ decision is set out in his paragraph 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 says that 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.

[9] The compounds Justice Hughes was referring to in this passage (flumezapine and ethyl olanzapine) are other compounds from the ‘687 patent. His conclusion was 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. As will be seen below, I disagree with Justice Hughes’ conclusion that the ‘113 does not contain any comparisons between

olanzapine and the other ‘687 compounds. But I agree with him that the ‘113 patent does not adequately describe the alleged advantages of olanzapine. In fact, I conclude that in 1991 Lilly did not have evidence supporting the alleged advantages of olanzapine over the ‘687 compounds.

III. Issues

[10] The main issue before me is the validity of the ‘113 patent. Novopharm mounted its attack on numerous grounds, but I am persuaded that the main one – that the ‘113 is not a valid selection patent – is supported by the preponderance of evidence and, therefore, I deal with the others briefly at the end of my reasons. Novopharm’s other grounds for challenging the ‘113 patent included anticipation, double-patenting, wrong Inventorship, obviousness, s. 53 of the *Patent Act* (misrepresentation), and s. 73 of the *Patent Act* (deemed abandonment).

[11] There is no serious issue about infringement. Novopharm admits that, if the ‘113 patent is valid, it is infringing it by marketing a generic version of olanzapine.

[12] Lilly bears the burden of proof on a balance of probabilities on the infringement issue. Novopharm bears the burden of proof in respect of invalidity. In assessing whether it has met that burden, I must bear in mind that the Commissioner of Patents already concluded, by virtue of issuing the ‘113 patent to Lilly, that the patent is valid. The Commissioner’s conclusion is entitled to some deference; I can overturn it only if the evidence in Novopharm’s favour shows that it was unreasonable (*Apotex Inc*. v. *Wellcome Foundation Ltd*., 2002 SCC 77, at para. 41-44).

[13] I find, on a balance of probabilities, that the ‘113 patent is invalid and, therefore, not infringed.

IV. Treating Schizophrenia

[14] Schizophrenia is a 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.

[15] There is no known cure for schizophrenia. However, over the course of the past fifty or sixty years, scientists have found some drugs that mitigate some of the worst symptoms. The drug chlorpromazine was a breakthrough in the early 1950s. But the problem with chlorpromazine was that it came with 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.

[16] In time, scientists discovered a better drug, called clozapine, which 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.

[17] Once clozapine was off the market, many scientists, including those at Lilly, were looking 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.

[18] 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 promising 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).

V. The Story of Olanzapine

[19] The story of the development of olanzapine begins with a discussion of the family of compounds of which it is a member and the corresponding patent for that family – the ‘687 patent.

As described above, in the 1970s, the search was on for a safe clozapine. Lilly was exploring compounds that were chemically similar to clozapine as part of that quest.

[20] 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 issues encountered with clozapine. Dr. Chakrabarti suggested replacing one of clozapine's phenyl rings with a thiophene ring.

[21] 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.

[22] 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 "thienobenzodiazapines" 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).

[23] The focus of the ‘687 patent was clearly on the compounds themselves – their constituents, their structure and the processes by which they could be made. Still, the patent specifically asserted that the compounds’ utility 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 identified.

[24] 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 76 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).

[25] Lilly began tests on ethyl flumezapine, but this work was wound down 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.

[26] 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 the FDA who asked Lilly to discontinue treating patients with flumezapine.

[27] 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). Lilly could have changed the clinical trial protocols, for example, by reducing the maximum dose, or 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.

[28] 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, flumezapine was a tainted product.

[29] Dr. Pullar, who was the chairman of the flumezapine project team, described this as a "black time" at Erl Wood. Yet, the project 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 15-year existence that had actually made it to market.

[30] Within a few weeks of the discontinuation of flumezapine, Dr. Tupper and his colleague, Mr. Terrence Hotten, synthesized seven more 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, 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.

[31] So, by 1983, Lilly was satisfied 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.

[32] 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 its clinical trials. It had also concluded a six-month study in dogs. The patent mentions these studies and provides some general information about what they disclosed.

VI. The '113 Patent

[33] The '113 patent proclaims a number of advantageous qualities for olanzapine. These can be grouped into two main categories. First, the '113 patent identifies certain advantages of olanzapine over the other compounds from the '687 patent. Second, the '113 patent boasts the superiority of

olanzapine over other known antipsychotic drugs used in the treatment of schizophrenia and related conditions.

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

[34] The '113 patent says that olanzapine displays "surprising and unexpected properties" as compared to flumezapine and other related compounds. This broad statement involves a direct comparison between olanzapine and the other compounds of the '687 patent. There are four such comparisons in the patent.

[35] The patent notes that Lilly developed flumezapine to the point where it was administered to 17 patients. However, as mentioned above, due to an "unacceptably high incidence" of elevated liver enzymes (SGPT and SGOT), as well as creatine phosphokinase (CPK), Lilly discontinued clinical trials of flumezapine after discussions with the FDA. Later, the '113 patent states that patients treated with olanzapine experienced "a low incidence of only mild and transient elevation of liver enzymes", and CPK levels were lower than with flumezapine. In my view, the '113 patent asserts the superiority of olanzapine over flumezapine in respect of both liver enzymes and CPK levels in patients receiving therapeutic doses.

[36] 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, it states "[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." Taken together, I read these statements in the '113 patent as an assertion of the superiority of olanzapine over flumezapine with respect to its EPS liability.

[37] 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. To understand the scope and nature of this comparison, one must examine the dog study closely. Several experts gave testimony in this area. Their evidence is discussed in greater detail below. For present purposes, I interpret the statement in the '113 patent about cholesterol levels in dogs as an assertion of the superiority of olanzapine over ethyl olanzapine in terms of its liability for elevating cholesterol in humans. Ethyl olanzapine raises cholesterol; olanzapine does not.

[38] Therefore, the '113 patent declares olanzapine to be superior to the '687 compounds due to:

- 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

[39] The '113 patent describes olanzapine's function as an antagonist at various brain receptors (including dopamine at the D-1 and D-2 receptors, the 5HT-2 receptor and noradrenergic q-receptors). These characteristics suggest that olanzapine has potential as a drug with relaxant, anxiolytic or anti-emetic properties, and might be useful in treating psychotic conditions, including schizophrenia.

[40] In addition, the patent states that olanzapine shows "surprising and excellent results" in experimental screens and clinical trials. Further, 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 describes an open study in which six out of eight patients who had taken olanzapine for at least two weeks showed between 66% and 87% improvement on a well-recognized scale for measuring symptoms of schizophrenia (the BPRS scale). Further, preliminary results from three ongoing clinical trials confirmed a high level of efficacy at low doses (2.5 and 5.0 mg).

[41] These statements are followed by the broadest and stoutest assertion about olanzapine in the '113 patent:

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

[42] Because of its placement – just after a description of particular side effects and olanzapine's comparative advantages – and because of the introductory words of the sentence ("overall, therefore"), I interpret this assertion as being a general contention about the advantages of olanzapine in respect both of its efficacy and the particular side effects discussed in the preceding passages. It is not a statement asserting the superiority of olanzapine in respect of all possible side effects. In my view, a fair interpretation of the patent is that it asserts the superiority of olanzapine in respect of the side effects specifically identified in it, most importantly, the ones that presented the greatest concern to schizophrenia patients – EPS and agranulocytosis.

[43] However, I also believe that a skilled reader would infer from the broad declaration about olanzapine's superiority with respect to side effects that the inventors had conducted sufficient tests to be able to have a fair idea about what olanzapine's side effects liability was. 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, the treatment of schizophrenia with antipsychotic agents.

[44] Therefore, with that implied assertion in mind, in my interpretation of the '113 patent, the advantages coming within this broad statement of olanzapine's superiority over other antipsychotic drugs include:

- high level of efficacy at low doses;

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

[45] 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, when I analyze the '113 as a selection patent below, I will deal with the assertion about liver enzymes within the discussion of the comparison with the '687 compounds, given the direct comparison with flumezapine.

(c) The '113 patent's claims

[46] The claims in issue here 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.

VII. Is the ‘113 patent a valid selection patent?

(a) The requirements for a valid selection patent

[47] As discussed, the earlier ‘687 patent covered olanzapine, as well as a large number of other related compounds. By contrast, the ‘113 patent deals with olanzapine alone. In these circumstances, patent law considers the ‘113 to be a “selection patent”. A selection patent is valid if it discloses to the public something new and useful in exchange for a further monopoly on the already-patented compound. In other words, the question is whether the selected compound truly represents an invention that merits a separate and free-standing monopoly. An “invention” under s. 2 of the *Patent Act* is a “new and useful . . . composition of matter, or any new and useful improvement in any . . . composition of matter”. Just as with any other kind of patent, then, a selection patent must disclose an invention. What sets selection patents somewhat apart is that the inventor must disclose an invention over and above what was disclosed in the prior patent – the “genus” patent – covering the selected compound.

[48] Justice Marshall Rothstein recently summarized the requirements for selection patents in *Apotex Inc*. v. *Sanofi-Synthelabo Canada Inc*., 2008 SCC 61, [2008] 3 S.C.R. 265, relying on the well-known precedent of *Re I.G. Farbenindustrie A.G.'s Patents* (1930), 47 R.P.C. 289 (Ch. D.) where the following principles were set out:

> 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 a special character. (At para. 10.)

[49] Therefore, in order to uphold the '113 patent as a valid selection patent, I must be satisfied that olanzapine has an advantage over the other compounds of the '687 patent. Further, that advantage must be substantial and somewhat peculiar to olanzapine. Finally, the patent must clearly describe olanzapine'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" (at para. 114).

[50] Justice Rothstein described a selection patent as containing "only a bit of the subject matter of the original genus patent because that bit does something better than and different from what was

claimed in the genus patent" (at para. 100). Does olanzapine do something better than and different from its '687 classmates?

(b) Analysis of the '113 patent as a selection patent

[51] In interpreting 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. 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.

[52] As mentioned, there is a general assertion in the '113 patent that olanzapine is superior to the class of compounds covered by the '687 patent. It says that olanzapine displays "surprising and unexpected properties" as compared to flumezapine and other related compounds. As mentioned, there are four examples of superiority provided in the patent, 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;

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

[53] As direct comparisons with members of the ‘687 patent, these assertions are obviously relevant to the determination whether the ‘113 is a valid selection patent. However, in my view, the comparisons in the ‘113 patent between olanzapine and “prior known antipsychotic agents” are also relevant here. In my view, 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. The ‘113 patent refers to two of the ‘687 compounds and discusses their disadvantages. But 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. As discussed above, the comparisons with other antipsychotic agents are:

(i) high level of efficacy at low doses;

(ii) lower elevation of prolactin;

(iii) lower EPS liability; and

(iv) no alteration of white blood cell count.

[54] According to Dr. Guy Goodwin, in addition to clozapine, the relevant drugs for these comparisons in 1991 would include chlorpromazine, haloperidol, flupenthixol, and perphenazine. In his view, these drugs provided choices but they presented similar side effects, most particularly EPS. Elevated prolactin was sometimes an issue, as well, but in Dr. Goodwin’s view, this rarely caused acute problems.

[55] Therefore, the first step I must take is to decide whether one or more of the asserted advantages of olanzapine was known to exist, or was soundly predicted, at the time the ‘113 patent was filed in 1991. Second, I must decide whether at least one of them could be considered a substantial advantage over the ‘687 compounds and somewhat peculiar to olanzapine. And, if so, the third question is whether the disclosure of that substantial and special advantage in the ‘113 patent was adequate. If I decide any one of them in the negative, I must find the ‘113 patent to be invalid.

(c) Were the alleged advantages of olanzapine known or soundly predicted in 1991?

[56] To understand whether the alleged advantages of olanzapine over the ‘687 class of compounds were known or soundly predicted, one must appreciate what was known about each of flumezapine, ethyl olanzapine and olanzapine in respect of the four relevant parameters at the time the ‘113 patent was filed in April 1991. 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.

[57] For olanzapine, results of a four-week, open-label clinical trial (called E001) involving ten patients were available prior to the filing of the ‘113 patent. In addition, four studies of olanzapine in healthy volunteers had been completed. In three of them, 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. The ‘113 patent refers to preliminary results from other clinical trials that were ongoing in 1991, but I heard little evidence about what, if any, advantages over the ‘687 compounds could be gleaned from those trials. There were some early indications of olanzapine’s efficacy, but that is not one of the alleged advantages over the ‘687 class that was set out in the ‘113 patent.

[58] To repeat, a selected compound is an invention, and separately patentable, if the patentee can establish that, as of the filing date, the selection had a substantial and peculiar advantage over the previously-patented family of compounds, or if that advantage could be soundly predicted.

[59] A sound prediction must meet four criteria. First, there must be a factual basis for the prediction. Second, the inventor must have an articulable and sound line of reasoning from the factual basis to the desired outcome. Third, the inventor must set out in the patent the factual basis and the line of reasoning he or she was applying. Fourth, of course, the predicted outcome must be borne out by subsequent testing. An incorrect prediction cannot be a sound one. (See *Apotex* v. *Wellcome*, above, at para. 70, 76.)

(i) Olanzapine vs. flumezapine – liver enzymes

[60] 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 drug. The project team characterized the liver enzyme rises as “mild”.

[61] 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. Some subjects were withdrawn from studies on that basis. 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 any of 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 wide-spread use.

[62] 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. However, he did not make any comparison to the flumezapine data. In fact, Lilly was aware, based on the healthy volunteer studies, that “both flumezapine and [olanzapine] have illustrated a propensity to cause elevations of liver enzymes” (D-435, p. 15).

[63] The evidence shows that olanzapine was not known in 1991 to have any superiority over flumezapine with respect to liver enzymes; nor was there a factual basis for a prediction that olanzapine would possess an advantage in that respect. Further, there is no evidence of a line of reasoning that would sustain a sound prediction that olanzapine's liver enzyme liability would be lower than flumezapine's. Neither a factual basis nor a line of reasoning appears in the '113 patent. We now know that olanzapine has a certain liability to raise liver enzymes. The olanzapine product monograph states that, in clinical trials, olanzapine "was associated with elevation of hepatic transaminases, primarily ALT (SGPT)". However, none "manifested clinical symptomatology associated with liver impairment". In other words, elevations of liver enzymes are generally not a health concern.

(ii) Olanzapine vs. flumezapine – CPK

[64] 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. As a muscle enzyme, CPK can be a harbinger of serious conditions such as neuroleptic malignant (NMS) or rhabdomyolysis.

[65] 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 were more a product of the site where the elevations were seen than a consequence of administering flumezapine. 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:

- 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.

- 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.

- 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 ten days later.

- 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).

[66] 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.

[67] At Lilly's request, an external physician reviewed the flumezapine data. He concluded that the CPK results were "not well explained". In other words, there was no clear connection to flumezapine. 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.

[68] 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 show 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.

[69] 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 they 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".

[70] 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". 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.

[71] In 1991, there was evidence that olanzapine also had some liability to elevate CPK based on the results of its first clinical trial. 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 have avoided the problems encountered in the flumezapine trial.

[72] In my view, given the factors described above, and the difficulty in comparing the results of separate trials of different drugs at various doses in diverse populations of patients, the evidence does not support an advantage for olanzapine over flumezapine regarding CPK. As Dr. Diamond stated:

> Much of the data on flumezapine was at a much higher level of medication. Some of the people were given it for much longer periods of time. So you are comparing different kinds of patients with different kinds of co-morbid medical problems with different compounds, with different doses, for different periods of time. And it makes any kind of strong comparison impossible. The most you can do is look at patterns and see if they look similar or different.

[73] 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."

[74] At best, there was some evidence available in 1991 that olanzapine's CPK liability might be lower than flumezapine's. But there is no evidence of a chain of reasoning that would suggest that such a prediction would bear out. There was some speculation within Lilly that the clinical problems with flumezapine and ethyl flumezapine were caused by their fluorine elements. Yet, other scientists thought that fluorine was the element responsible for efficacy and, without it, olanzapine would not be an effective antipsychotic. In any case, the '113 patent sets out neither a factual basis nor any line of reasoning supporting a prediction that olanzapine would have less CPK liability than flumezapine. The product monograph notes that olanzapine can raise CPK levels and, very rarely, can cause NMS.

(iii) Olanzapine vs. flumezapine – EPS

[75] Two patients allegedly 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.

[76] In the only study of schizophrenia patients completed before filing the ‘113 patent, eight out of ten patients on olanzapine showed improvement or no change in extrapyramidal symptoms. Two of the ten patients deteriorated. The investigators concluded from these results that olanzapine may cause EPS less frequently than conventional antipsychotic treatment. We do not know what, if any, preliminary results on EPS Lilly had received from its ongoing clinical trials of olanzapine at the time the ‘113 patent was filed (April 1991).

[77] In my view, the evidence does not support any advantage for olanzapine, and no factual basis on which to found a sound prediction of an advantage over flumezapine, with respect to EPS. Lilly did not present a line of reasoning that would support such a prediction, other than the CAR-CAT data from animal tests and *in vitro* binding assays. All witnesses agreed that the effect in humans could not be predicted until sufficient clinical testing had been done. Further, as Dr. Healy noted, animal tests are good for screening some forms of EPS (*i.e.*, Parkinsonism) but not others (*i.e.*, akathisia).

[78] There is certainly no disclosure in the ‘113 patent of a factual basis or line of reasoning suggesting olanzapine might be less likely than flumezapine to cause EPS in patients, as the patent asserts. As it turns out, olanzapine does have some dose-dependent EPS liability.

(iv) Olanzapine vs. ethyl olanzapine – cholesterol

[79] 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 the subject of discussion by many expert witnesses.

[80] Novopharm contested on numerous grounds the assertion in the ‘113 patent about olanzapine’s advantage with respect to cholesterol. It challenged the *bona fides* of the dog study on the basis that the comparison with ethyl olanzapine was contrived and not based on a genuine effort to compare olanzapine with a representative compound from the ‘687. In addition, Novopharm challenged the study’s methodology and results.

[81] I find that Lilly’s comparison of olanzapine with ethyl olanzapine was conducted in a good faith effort to show a difference between olanzapine and its closest relative from the ‘687 family of compounds. Dr. Tupper acknowledged that the closest prior art to olanzapine was ethyl olanzapine and Lilly needed to find a basis for showing the superiority of olanzapine over it. I also find that the study’s methodology was sound and the results reliable.

[82] However, in my view, the comparison, while valid, is meaningless. It does not support any advantage for olanzapine.

[83] 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. 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. The purpose was clearly patent-driven. Lilly expected ethyl olanzapine to cause agranulocytosis in the dog, just as ethyl flumezapine had done, and expected olanzapine to demonstrate a clear advantage by not causing serious blood problems.

[84] Overall, the study showed that the two compounds caused similar toxic effects in the dogs. The only area where there seemed to be a difference was in respect of cholesterol and, even then, only in the females 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".

[85] 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.

[86] Dr. 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 of 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. Therefore, 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 more potent than olanzapine.

[87] 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.

[88] Many expert witnesses suggested that the dog is not a good model for predicting a cholesterol effect in humans. Dr. Deborah Greco made the point that it is difficult to translate

cholesterol results in dogs to humans unless one knows the particular mechanism of action of the drug in question. For example, statin drugs, which lower cholesterol, have been tested effectively in dogs because we know that dogs and humans possess the same enzyme for synthesizing cholesterol in the liver. However, in respect of ethyl olanzapine, we do not know the mechanism that caused a cholesterol rise in dogs and, therefore, cannot make any conclusions about what the effect might be in humans. Dr. Greco was one of the witnesses who questioned the study's methodology. However, Dr. Ronald Thisted found that the results would not have been affected had the study been carried out according to Dr. Greco's methodology. Further, the dog study results were confirmed in two subsequent studies (the MPI and Calvert studies).

[89] The only witness who felt the dog was a good model for predicting cholesterol effects in humans was Dr. John Bauer. His view is that, while humans partition cholesterol differently from dogs (that is, as between high-density and low-density lipoproteins), that difference does not mean that their overall cholesterol metabolism is different or that cholesterol effects in dogs will not translate to humans. Accordingly, he believes that the elevation of cholesterol in ethyl-olanzapine-treated dogs would predict a similar effect in humans. The absence of a cholesterol effect in olanzapine-treated dogs shows an advantage of that compound over ethyl olanzapine.

[90] Dr. Bauer's theory was developed in the early to mid-1990s, after the '113 patent was filed. He agreed that the prevailing view in 1991 was that the dog was not a good model for cholesterol studies. In the circumstances, a skilled reader would expect to see in the patent some basis for believing that the results of the dog study pointed to an advantage for olanzapine in the treatment of

humans. I note that, in similar circumstances, the Federal Court of Appeal found that a patent's disclosure was insufficient when it referred only to a study in rats and omitted reference to a study showing a similar effect in humans (*Eli Lilly Canada Inc.* v. *Apotex Inc.*, 2009 FCA 97, at para 15).

[91] In any case, even accepting the dog study at face value, what does it tell us about olanzapine's advantage over the '687 class?

[92] Had ethyl olanzapine been a candidate for development, the dog study would have justified concern about taking it into human trials. Given its potency and the high dose at which it produced the cholesterol effect, ethyl olanzapine might still have been taken forward, all else being equal, but its impact on cholesterol in humans would surely have been closely monitored. Lilly itself 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, p. 3.)

[93] Yet, the reference in the '113 patent to the dog study and the cholesterol findings implies a concern about the potential effect in humans. Since the cholesterol elevations were only seen in the highest doses of ethyl olanzapine, presumably there should have been little concern about a potential effect in patients consuming therapeutic doses.

[94] Further, the dog study would not have provided a basis for believing that olanzapine would not cause a cholesterol effect in humans. There was no basis for believing that a cholesterol effect in female dogs would indicate anything about what would happen in female or male humans. It is clear now that the dog model does not work – olanzapine *does* have a cholesterol effect in humans. If the dog had actually been a good model for studying cholesterol effects in humans, one should have seen that olanzapine had that effect in the dog.

[95] In summary, the dog study showed that olanzapine was just as toxic as ethyl olanzapine except in relation to cholesterol. Its putative advantage is that it did not cause a rise in the cholesterol of female dogs at the highest dose, far beyond the therapeutic range. I cannot regard this as advantage over the ‘687 class – it is not even a clear advantage over ethyl olanzapine in terms of olanzapine’s potential use in the treatment of human disease.

(v) Olanzapine vs. other antipsychotic agents - high efficacy at low doses

[96] 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.

[97] The only clinical trial of olanzapine in patients with schizophrenia that had been concluded by 1991 was the E001 study in ten in-patients at St. Mary's Hospital in London, England. This was an open-label study and, as many witnesses commented, 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". 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".

[98] As mentioned, it is not clear what was known in April 1991 about Lilly's ongoing clinical trials. However, a memorandum dated May 2, 1991 (D-346) summarized some early results. An open-label study in Finland (E004) found improvement in four out of five patients. An open-label study in Denmark (E005) also found improvement in the first three patients. An open-label study in South Africa (E006) found improvement in two of four olanzapine patients and two of four haloperidol patients. A large study in 450 patients was scheduled to begin in September 1991.

[99] From my review of the evidence, there was very little factual foundation for the '113 patent's assertions of high efficacy at low doses. Lilly certainly was getting some early positive signals, but the evidence of efficacy was thin. As for relatively low doses, Lilly certainly found that

the doses at which efficacy was detected were lower than were 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 was reliable and could be sustained over a longer term. An early signal of efficacy at a low dose in an open-label trial could not support a prediction that olanzapine would be effective at that dose across a broad range of patients over a longer period of time.

[100] I am not satisfied that the evidence was sufficient to support an assertion about olanzapine's efficacy at low doses. Nor do I think there was a sufficient factual basis for a sound prediction. Furthermore, there was no disclosure of the underlying facts or a line of reasoning that would permit a skilled reader to appreciate what olanzapine's alleged advantage was.

(vi) Olanzapine vs. other antipsychotic agents - lower elevation of prolactin

[101] Dr. Goodwin explained that elevation of prolactin is an inevitable result of blocking dopamine in the pathway to the pituitary gland. Therefore, drugs that block that pathway, as most antipsychotics do, will elevate prolactin. Some elevation of prolactin is expected in patients taking antipsychotics.

[102] Dr. Healy agreed, noting that prolactin is rarely of any clinical concern:

> In clinical practice, very few clinicians see people where adverse prolactin levels caused by the drugs are leading their patients to have problems that would lead me to say, for instance, you have to halt this drug. I can think of one or two in my

> clinical career. Because of this there is no need, for instance, in routine clinical practice, to measure prolactin levels. We just don't do it. (D-104, para. 60, 299)

[103] The early evidence about olanzapine showed that prolactin increases were mild, no more than double the normal range. This evidence was relatively favourable given that older drugs could elevate prolactin up to three times the normal range. But the early tests of olanzapine were of very short duration. There was too little evidence to determine what olanzapine's effect would be over a longer term or even to support a sound prediction of lower elevations than were associated with other antipsychotics. The basis for the assertion of superiority on this measure is not set out in the patent, nor is there a line of reasoning that would permit the reader to understand the inventors' assertion of superiority. The olanzapine product monograph confirms that olanzapine generally causes mild elevations of prolactin.

(vii) Olanzapine vs other antipsychotic agents – lower EPS liability

[104] In 1991, psychiatrists were beginning to understand that 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 have interpreted the '113 patent's assertion of "marked superiority" and a "better side effects profile" as including low EPS.

[105] Dr. Goodwin interpreted the '113 patent as a statement 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 at the date

of filing for either asserting or predicting olanzapine's EPS liability. As discussed above, the evidence available at the time did not support any advantage for olanzapine, and no factual basis on which to found a sound prediction of an advantage. Further, there is certainly no disclosure in the patent of either a factual basis or line of reasoning suggesting olanzapine might be less likely than other antipsychotics to cause EPS in patients. And we now know that olanzapine does have some dose-dependent EPS liability.

(viii) Olanzapine vs. other antipsychotic agents - no alteration of white blood cell count

[106] The '113 patent makes a statement of fact that "no alteration of white blood cell count has been observed in clinical studies". This statement is clearly intended to compare olanzapine with clozapine, whose major liability is its propensity to cause, in rare cases, agranulocytosis.

[107] The evidence available to Lilly in 1991 about olanzapine was scant. The inventors would have had no way of knowing what its effect would be on the white blood cells of patients. The fact that they did not detect any alteration of white blood cell counts during brief studies in healthy volunteers and a handful of patients would not have provided grounds on which to predict that olanzapine had an advantage over clozapine. It might actually have been worse. Again, no basis for the assertion or a line of reasoning is set out in the patent. The product monograph confirms that olanzapine is not associated with alterations of white blood cell counts. There are no reported cases of agranulocytosis among olanzapine patients.

(d) Conclusion

[108] The evidence shows no advantage for olanzapine over flumezapine or ethyl olanzapine. Nor does it provide a factual basis for a prediction that olanzapine would have the asserted advantages over those compounds, or a line of reasoning that would support a sound prediction. Finally, there is no disclosure in the patent of any factual basis or line of reasoning that would permit a person skilled in the art to appreciate what the alleged invention in the ‘113 patent – a superior compound to the ‘687 class – actually was.

[109] In addition, the evidence shows no advantage, and no factual basis for a sound prediction, for olanzapine in comparison with other antipsychotic agents. There is no evidence of a sound line of reasoning leading to a conclusion that olanzapine would display superiority over other drugs. Nor is there any disclosure in the patent of facts or reasoning that would support olanzapine’s superiority.

[110] Witnesses agreed that Lilly had early positive signals about olanzapine’s efficacy and safety. But it had no proof of anything. 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”. He interpreted the assertions in the ‘113 patent as representing “a kind of hypothesis that olanzapine will have those advantages”.

[111] I agree with Dr. Healy's summary of Lilly's evidence from its trials of olanzapine in 1991:

> 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, para. 51)

[112] Overall, there was an insufficient basis for the '113 patent's assertion of an advantage for olanzapine over the '687 compounds and other antipsychotic agents.

[113] In support of the patent's validity, Lilly suggests that the Supreme Court of Canada has upheld a patent based on sound prediction when it was founded solely on an *in vitro* test, with no testing in humans (*Apotex Inc.* v. *Wellcome Foundation Ltd.*, above). Lilly says the case for the '113 patent's validity is stronger because at least some testing in humans had been carried out.

[114] *Apotex Inc.* v. *Wellcome Foundation Ltd.* involved a patent for the use of a drug called AZT 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" (at para. 75). That is not the situation before me. The '113 patent contains little information about the testing of olanzapine. It does not set out a line of reasoning to support its alleged superiority. And I have little evidence before me in respect of either of those legal requirements.

[115] As for the implied assertion mentioned above – that the inventors had a sufficient basis for the statement that olanzapine had a favourable 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.

[116] 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 the side effects mentioned in the patent and which were known at the relevant time to be of clinical concern. However, the patent also implies knowledge of olanzapine's overall side-effect profile. The evidence about olanzapine's metabolic effects underscores the fact that Lilly really had very little idea in 1991 about what olanzapine's effect on patients was likely to be.

[117] On the other hand, 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 dispute 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 to have an 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. It does not fall within the '113 patent's assertion that olanzapine is markedly superior and has a better side-effects profile than other drugs. Accordingly, I need say no more about it.

(a) Are the alleged advantages of olanzapine “substantial” and “peculiar”?

[118] Even if olanzapine does have advantages, those advantages must be substantial and somewhat peculiar to it in order to sustain a separate and subsequent patent.

[119] Clearly, it is not enough for a selected compound merely 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 that they are belonging to a class specified by an earlier invention” (*PfizerCanada Inc.* v. *Canada* (*Minister of Health*), 2006FCA 214, at para. 22, citing *Dreyfus and Other Applications* (1945), 62 R.C.P. 125 at 133). In other words, it would not be enough for Lilly to maintain that the substantial and special advantage of olanzapine is that it actually does what the ‘687 patent said that all members of that class did, or had the potential of doing -- that is, to treat schizophrenia and other psychoses. The advantage must be something better and different than what the general class is supposed to be able to do.

[120] 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 at para. 63. 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 member 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. 67).

[121] Lilly argues that recent Supreme Court of Canada jurisprudence makes clear that a selection patent will be valid if the selected compound has 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 selection patent where the selected compound had only one advantage over a compound falling within the genus. I do not read the *Sanofi-Synthelabo* case in the same manner as Lilly.

[122] In *Sanofi-Synthelabo*, 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 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.

[123] 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 the selected compound only has one advantage over one 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 isomer had all of the activity and little of the toxicity of the racemate. The 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, at para. 22)

[124] 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.

[125] 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 other compounds of the ‘687 patent.

[126] Can the ‘113 patent’s assertions that olanzapine is superior to flumezapine, ethyl olanzapine and other antipsychotic agents be considered substantial and peculiar advantages over the ‘687 compounds?

[127] In my view, the alleged advantages of olanzapine over flumezapine and ethyl olanzapine are not substantial. To the extent they existed at all, their magnitude was insignificant. Further, 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.

[128] The ‘113 patent merely asserts that olanzapine’s liability to elevate liver enzymes and CPK is not as great as flumezapine’s. At best, it is a slight advantage over flumezapine in respect of those specific parameters. Olanzapine is, at most, only somewhat better, not substantially better.

[129] Olanzapine’s alleged superiority over ethyl olanzapine is based on a study in dogs, not humans. Ethyl olanzapine caused a significant rise in cholesterol in four female dogs out of a total of eight dogs dosed at 8 mg/kg, whereas olanzapine did not. Leaving aside for a moment the issue whether this is an accurate summary of the study and whether it tells us anything about olanzapine’s potential effect on humans, the comparison is ambiguous. One does not know whether the rise was statistically significant or biologically significant. The effect was seen at a dosage level that was far beyond any dose contemplated for humans (the equivalent dose would be 560 mg for a 70 kg person; the ‘113 patent refers to a dosage range for olanzapine of 2.5 to 5 mg). Again, if this is an advantage, it does not appear to be substantial.

[130] Olanzapine’s advantage over ethyl olanzapine, a compound whose potential as an antipsychotic is entirely unknown (but doubtful), in respect of a single measurement in a dog study

(of questionable application to humans), cannot be a substantial advantage. And I have no evidence that this putative advantage was peculiar to olanzapine.

[131] None of these comparisons shows olanzapine to be a peculiar or special member of the ‘687 class. We have no information about any of the other members’ properties in respect of liver enzymes, CPK, cholesterol, or anything else. We 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. And both of the comparisons in the ‘113 patent are to failed compounds.

[132] On the other hand, olanzapine’s alleged superiority to other antipsychotic drugs on the market would certainly amount to a substantial advantage over the ‘687 class of compounds. The invention described in the ‘687 patent was 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 is a drug that is 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, as outlined above, the broad assertion in the ‘113 patent was unsupportable at the time Lilly applied for it.

[133] 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.

[134] The specific benefits over other antipsychotics cited in the ‘113 patent – high activity at low dose, prolactin sparing, low EPS, and no lowering of white blood cells – would, if they had been known to be real or soundly predictable, have amounted to a substantial advantage over the ‘687 compounds, so long as olanzapine did not bring with it any other major disadvantage. Otherwise, flumezapine might actually have been the superior compound. And we know little or nothing about the billions of other compounds of the ‘687 class that might have been equal to or better than olanzapine.

[135] I cannot conclude from the evidence that olanzapine had substantial and special advantages over the other ‘687 compounds.

(b) Is the disclosure of the ‘113 patent adequate?

[136] There are two intersecting disclosure obligations on Lilly that I must consider. The first is the duty to set out the basis on which olanzapine is believed to have a substantial and peculiar

advantage over the ‘687 compounds. The second is the duty to set out the basis for the sound prediction for that advantage. As Justice Barnes stated:

> [W]hen a patentee is attempting to establish the utility of a selection by relying upon evidence of sound prediction, there may be an obligation to disclose in the patent the underlying facts and the line of reasoning which support the prediction . . . It seems to me that if a patentee is relying on sound prediction to establish that its selection has some unexpected advantage over the genus, it does have a heightened obligation to disclose in the patent its line of reasoning because that is part of the *quid pro quo* for the claimed monopoly over the selection. (*GlaxoSmithKline Inc.*, above, at para. 71.)

[137] 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: *Eli Lilly Canada Inc*. v. *Novopharm Ltd*., 2007 FC 596 at 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 (at 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.

[138] In my view, the two disclosure requirements are, in a case like this, coextensive. That is, if the disclosure requirements for sound prediction had been met, so would the disclosure requirements for a selection patent. If the patent had set out the factual basis and line of reasoning on which the assertions of substantial and special advantages were based, then the disclosure

requirements for a valid selection patent would have been satisfied. I have already concluded, therefore, that the ‘113 patent’s disclosure was insufficient.

(c) Conclusion – the ‘113 patent is not a valid selection patent

[139] The ‘113 patent does not describe an invention over and above what was disclosed in the ‘687 patent. Therefore, the ‘113 is not a valid selection patent.

VIII. Anticipation, Double-patenting, Wrong Inventorship and Obviousness

[140] Given my finding that the ‘113 does not describe an invention, most of Novopharm’s other grounds of attack on the ‘113 patent become superfluous. If there is no invention, there is no need to analyze whether the “invention” was anticipated by prior art, whether it was double-patented, or whether the proper “inventors” were named. In this case, by definition, the ‘113 patent was anticipated by the ‘687 patent. Olanzapine was double-patented by the ‘687 and the ‘113 patents. There are no “inventors”of olanzapine.

[141] However, the issue of obviousness is somewhat distinct. Justice Rothstein made clear the current law on obviousness in *Apotex* v. *Sanofi-Synthelabo*, above. The test includes consideration whether the subject-matter of the patent was “obvious to try” in light of what was previously known. Justice Rothstein stated that the “obvious to try” test will apply “only where it is very plain or . . . more or less self-evident that what is being tested ought to work” (para. 65). A “mere possibility that something might turn up is not enough” (para. 66).

[142] Justice Rothstein also noted that the "obvious to try" test may apply in circumstances where "there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances" (para. 68). That is very clearly the situation before me. The compounds of the '687 patent clearly were chemically similar to one another, but those that were made and tested produced very different biological responses.

[143] He set out the steps of the analysis as follows:

> (1) (a) Identify the notional "person skilled in the art";
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention? (para. 67)

[144] The "obvious to try" issue arises in the fourth step. Within that step, Justice Rothstein set out three factors to take into account:

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

[145] It is clear that this test assumes an inventive step in arriving at the subject-matter of the patent in issue. As will be clear from the discussion above, I cannot find an inventive step in Lilly's decision to develop olanzapine. In effect, Lilly was working its own patent, the '687, trying to find a compound that could be safely administered to humans and achieve the purpose underlying the '687 patent itself – good antipsychotic activity and low EPS.

[146] By the time the patent was filed in April 1991, Lilly had not found any unexpected, substantial or special qualities for olanzapine that would justify a fresh monopoly. Lilly had merely 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. Lilly scientists showed persistence, diligence and sound science in getting olanzapine that far. New methods of synthesis had to be worked out (after an explosion in the lab during synthesis of flumezapine). But that is not enough for a patent. There must be an invention. And, in the context of a selection patent, the invention is the discovery of unexpected, substantial and special advantages.

[147] I would not conclude that the selection of olanzapine as a development compound was an obvious choice. It made sense to try a non-ethyl, non-fluorol compound given the problems with earlier compounds. But olanzapine was not the only candidate under consideration, and did not even appear to be particularly active. It was not "more or less self-evident" that olanzapine would work.

[148] I think the best way to characterize olanzapine in 1991 is that it was an "almost invention" to use Justice Binnie's term (*Apotex Inc*. v. *Welcome Foundation Ltd.*, above, at para. 84). It was

neither obvious nor a genuine invention. It was a compound that showed promise and, later, some of the early positive indications were borne out. Lilly received some early signals of safety and efficacy, but nothing that would support an assertion of surprising and unexpected properties, and nothing that would set olanzapine apart from the other ‘687 compounds.

[149] I find that the development of olanzapine was neither obvious nor an invention. However, I must emphasize that I am using the term “invention” strictly in the legal sense, as the law applies to selection patents. Scientists, whether at Lilly or elsewhere, may well regard olanzapine as an invention, perhaps even a remarkable one. But that is not the question before me.

IX. Patent Act, sections 53 and 73

[150] Novopharm argues that the ‘113 patent is invalid because Lilly wilfully made a misleading, material allegation in its patent application (s. 53(1)). Alternatively, if the misrepresentation was involuntary (not wilful), then the parts of the patent containing false statements should be severed off from the remainder (s. 53(2)).

[151] Despite my findings that the ‘113 patent is not valid, it does not necessarily follow that Lilly intended to mislead anyone. Novopharm has not presented any evidence to that effect. Nor do I have before me sufficient evidence from which to infer that intention. As for unintentional misstatements or omissions, Novopharm has not persuaded me that Lilly made any false statements. Novopharm relies on a recent decision of Justice Hughes in *Ratiopharm Inc*. v. *Pfizer Ltd*., 2009 FC

711. But there, Justice Hughes found that some of the statements in the patent were wrong. The evidence before me is not that clear.

[152] In addition, Novopharm argues that Lilly should be deemed to have abandoned its patent application because it failed to respond in good faith, and within six months, to a requisition by the patent examiner (s. 73(a)). Here again, I do not have sufficient evidence supporting Novopharm's position. Mr. Frank Pole, the patent agent who prosecuted the '113, now retired, testified that Lilly's communication with the patent examiner was intended to be a good faith response to the examiner's queries. The patent examiner accepted them as such. That conclusion merits some deference on my part.

[153] As I have found above, some of the assertions in the '113 were hopeful. They were based on too little evidence to be factual contentions or even sound predictions of olanzapine's alleged advantages. But, to my mind, that does not mean that they were misleading or made in bad faith. I find no basis under s. 53 or s. 73 to invalidate the '113 patent, or any part of it.

X. Conclusion and Disposition

[154] One does not have to discredit a product or those who make it in order to invalidate its patent. I am satisfied that olanzapine is a useful drug for the treatment of schizophrenia. However, Lilly had a patent for it that lasted from 1980 to 1997. It sought a separate and supplementary patent for it, no doubt, to try to recuperate some of its corporate investment in its neuroleptic programme. It had not sought a separate patent for flumezapine, presumably because at the time that compound

was in clinical trials there was ample time left in its monopoly. But as the sun began to set on the ‘687 patent, it became important to try to extend the patent protection for olanzapine. The ‘113 patent was clearly drafted with a view of justifying a fresh patent. But the evidence just was not there, yet. Accordingly, I must conclude that the ‘113 is not a valid selection patent. The claims set out above are invalid. Novopharm is entitled to relief under s. 8 of the *Patented Medicines (Notice of Compliance) Regulations*, to be determined in a separate proceeding, and to its 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;

3. Novopharm is entitled to relief under s. 8 of the Patented Medicines (Notice of Compliance) Regulations to be determined in a separate proceeding, and to its costs.

"James W. O'Reilly"
Judge

Annex “A”

Patent Act, R.S.C. 1985, c. P-4

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.

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.

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.

Deemed abandonment of applications

73. (1) An application for a patent in Canada shall be deemed to be abandoned if the applicant does not

(*a*) reply in good faith to any requisition

Loi sur les brevets, L.R.C. 1985, ch. P-4

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) 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 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.

Abandon

73. (1) La demande de brevet est considérée comme abandonnée si le demandeur omet, selon le cas :

a) de répondre de bonne foi, dans le cadre

made by an examiner in connection with an examination, within six months after the requisition is made or within any shorter period established by the Commissioner;

(*b*) comply with a notice given pursuant to subsection 27(6);

(*c*) pay the fees payable under section 27.1, within the time provided by the regulations;

(*d*) make a request for examination or pay the prescribed fee under subsection 35(1) within the time provided by the regulations;

(*e*) comply with a notice given under subsection 35(2); or

(*f*) pay the prescribed fees stated to be payable in a notice of allowance of patent within six months after the date of the notice.

d'un examen, à toute demande de l'examinateur, dans les six mois suivant cette demande ou dans le délai plus court déterminé par le commissaire;

b) de se conformer à l'avis mentionné au paragraphe 27(6);

c) de payer, dans le délai réglementaire, les taxes visées à l'article 27.1;

d) de présenter la requête visée au paragraphe 35(1) ou de payer la taxe réglementaire dans le délai réglementaire;

e) de se conformer à l'avis mentionné au paragraphe 35(2);

f) de payer les taxes réglementaires mentionnées dans l'avis d'acceptation de la demande de brevet dans les six mois suivant celui-ci.

Annex " B"

Expert Witnesses

Qualification of 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 Neuropscyhopharmacology and the American Neurological Association. He currently is 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 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's 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. Newcomber 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 focuses 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 the 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 as 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 with 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 analysing 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 of 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 Ph.D. and post-doctoral 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. 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 joined entered the federal civil service in 1977. He first set up a 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 the pharmaceutical company 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 was 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, and the Director of the Biostatistics Consulting Facility of the University of Chicago Cancer Centre. 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 Institutes 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 and 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, analysis of clinical trials for central nervous system agents, and, a particular expertise on 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, and 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 into two areas (drugs that modify

consciousness, and dopamine) has led him to attain 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 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 Professorship 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 and 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, 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 research focus is on clinical research in 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 Ph.D 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, and 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 a PhD in Pharmaceutics in 1972 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 of 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, and 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.

Annex "C"
Glossary

Agranulocytosis: Rare but serious blood disorder characterized by a drastic, and sometimes fatal, reduction in the production of white blood cells.
Akathisia: An internal sense of restlessness often manifest as an inability to be still.
CAR: conditioned avoidance response
CAT (catalepsy): Condition characterized by muscle rigidity and fixed posture regardless of external stimuli.
CPK: creatin phosphokinase, a liver enzyme
EPS: extra pyramidal symptoms
Neutropenia: A blood disorder characterized by abnormally low levels of neutrophils, a type of white blood cell. Severe neutropenia is also known as agranulocytosis.
NMS: neuroleptic malignant syndrome
Thrombocytopenia: a lowering of blood platelets
Zyprexa: Eli Lilly's brand name for olanzapine

FEDERAL COURT

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