Federal Court  Cour fédérale

**Date: 20130307**

**Docket: T-1259-11**

**Citation:2013 FC 245**

**Ottawa, Ontario, March 7, 2013**

**PRESENT: The Honourable Mr. Justice Near**

**BETWEEN:**

**ASTRAZENECA CANADA INC. AND ASTRAZENECA UK LIMITED**

**Applicants**

**and**

**TEVA CANADA LIMITED AND THE MINISTER OF HEALTH**

**Respondents**

## REASONS FOR JUDGMENT AND JUDGMENT

[1] The Applicants seek an order prohibiting the Minister of Health from issuing, pursuant to the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [*NOC Regulations*], a Notice of Compliance [NOC] to the Respondent Teva Canada Limited [Teva] in respect of quietiapine fumarate extended release [XR] tablets until the expiry of Canadian Patent No. 2,251,944 ['944]. The Applicants have brought two parallel applications: one addressing Teva's Notice of Allegation [NOA] concerning 50 mg strength tablets (Court file no. T-1259-11),

and the other addressing Teva's NOA concerning 150, 200, 300 and 400 mg strength tablets (Court file no. T-1905-11).

[2] For the reasons that follow, the application is dismissed.

***Background***

[3] AstraZeneca Canada Inc. [AstraZeneca] markets the patented sustained release quetiapine tablets in Canada under the brand name SEROQUEL XR®. The drug is used to treat various psychiatric disorders, including schizophrenia, bipolar disorder and major depressive disorder.

[4] The patent, owned by AstraZeneca UK Limited, is listed on the Health Canada Patent Register. It was filed in Canada on May 27, 1997 [the filing date], claiming priority from a UK application dated May 31, 1996 [the claim date], and was issued on April 10, 2007. It expires on May 27, 2017.

[5] Teva filed Supplemental Abbreviated New Drug Submissions with the Minister of Health for the issuance of an NOC for its versions of 50 mg, and 150, 200, 300 and 400 mg strength extended release quetiapine fumarate, TEVA-QUETIAPINE XR. It delivered its NOAs for the 50 mg strength tablets and the 150, 200, 300 and 400 mg strength tablets to the Applicants on June 20, 2011 and October 14, 2011, respectively. The NOAs claim non-infringement of the '944 patent. They further posit that the '944 patent is invalid for a number of reasons, including

obviousness, inutility, insuffiency and ambiguity. Teva has since abandoned its claim of non-infringement, and has focused its invalidity arguments on (A) obviousness and (B) ambiguity.

***Expert Evidence***

[6] AstraZeneca served affidavits from five expert witnesses in these proceedings (credentials current as of the date of the cross-examination of each):

- Dr. Joseph Calabrese, a psychiatrist, directs the Mood Disorder Program in the Department of Psychiatry, University Hospitals of Cleveland, Case Western Reserve University. He also holds an endowed research chair in bipolar disorder, and is a Professor of Psychiatry at Case Western Reserve University School of Medicine.

- Dr. Philip Seeman, an antipsychotic drug researcher, is a Professor in the Departments of Pharmacology and Psychiatry at the University of Toronto.

- Dr. Christopher Moreton, a pharmaceutical formulator, is Vice President, Pharmaceutical Sciences of FinnBrit Consulting, a company based in Massachusetts that provides consulting and advisory services to the pharmaceutical industry.

- Dr. Robert Prud'homme, also a pharmaceutical formulator, is a Professor in the Department of Chemical and Biological Engineering and the Director of the Program in Engineering Biology at Princeton University.

- Jeffrey Hames is Senior Marketing Manager for Seroquel XR® at AstraZeneca.

[7] For its part, Teva served affidavits from four expert witnesses (credentials equally current as of the date of the cross-examination of each):

- Professor Paul Harrison, a psychiatrist, is a Professor of Psychiatry at Oxford University, an Honorary Consultant in General Adult Psychiatry at Oxford Health Foundation NHS Trust and a Governing Body Fellow of Wolfson College in Oxford.

- Dr. Joel Sadavoy, also a psychiatrist, is a Chair in Applied General Psychiatry at the University of Toronto and Mount Sinai Hospital, and is a Professor of Psychiatry at the University of Toronto. Among other positions he holds, he is also Head of the Geriatric Psychiatry and Community Psychiatry programs at Mount Sinai Hospital, a teaching hospital of the University of Toronto.

- Dr. Ping Lee, a pharmaceutical formulator, is a Professor and Chair in Pharmaceutics and Drug Delivery at the Leslie Dan Faculty of Pharmacy at the University of Toronto.

- Professor Lea Katsanis is a Professor in the Department of Marketing at the John Molson School of Business at Concordia University.

***Issues***

[8] At issue is whether the '944 patent is invalid on the basis of:

A. Obviousness; and/or

B. Ambiguity.

***Analysis***

Burden of Proof

[9] The burden of proof in cases of invalidity has been described in several cases of this Court (see *Pfizer Canada Inc v Apotex Inc*, 2007 FC 26, [2007] FCJ No 36 (aff'd 2007 FCA 195, leave to appeal refused [2007] SCCA No 371) at paras 9-12; *Pfizer Canada Inc v Mylan Pharmaceuticals ULC*, 2011 FC 547, [2011] FCJ No 686 (aff'd 2012 FCA 103) at para 188; *GlaxoSmithKline Inc v Pharmascience Inc*, 2011 FC 239, [2011] FCJ No 287 at para 43; *Allergan Inc v Canada (Minister of Health)*, 2012 FC 767, [2012] FCJ No 906 (aff'd 2012 FCA 308) at para 42). Teva bears the burden of giving its allegations of invalidity an air of reality. If it succeeds, the presumption of the patent's validity is rebutted, and AstraZeneca must establish, on a balance of probabilities, that Teva's allegations of invalidity are unjustified.

[10] If the evidence is "evenly balanced (a rare event), the applicant (first person) will have failed to prove that the allegation of invalidity is not justified and will not be entitled to the order of prohibition" (*Eli Lilly Canada Inc v Apotex Inc*, 2009 FC 320, [2009] FCJ No 413 at para 38).

Construction of the Claims

[11] Claim construction precedes an evaluation of infringement or validity (*Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] SCJ No 68 [*Whirlpool*] at para 43; *Laboratoires Servier v Apotex Inc*, 2009 FCA 222, [2009] FCJ No 821 (leave to appeal refused [2009] SCCA No 403) [*Servier*] at para 58). Patents are to be construed purposively, having regard to the whole of the patent – i.e. the description and the claims – in order to ascertain the nature of the invention (*Servier*, above, at para 58).

[12] In the case at hand, the construction of the claims is not contested. The parties agree that the '944 patent claims a sustained release formulation of quetiapine, made up of: (i) the particular gelling agent hydroxypropyl methylcellulose [HPMC]; (ii) the hemifumarate salt of quetiapine; and (iii) one or more pharmaceutically acceptable excipients. The claims at issue in these proceedings are reproduced in Annex A.

[13] Despite AstraZeneca's protestations, this is not always the end of the analysis (see *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] SCJ No 63 [*Sanofi*] at para 77). Where, as in this case, the inventive concept of the claims is not discernible from the claims themselves because they present a bare chemical formula, the Court is directed to read the specification in the patent to determine the inventive concept of the claims (*Sanofi*, above, at para 77; *Servier*, above, at para 58; *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60, [2012] SCJ No 60 [*Teva v Pfizer*] at para 50). The Supreme Court and the Federal Court of Appeal both recently reiterated the principle that "the entire specification, including the claims, must be considered in determining the

nature of the invention" (*Teva v Pfizer*, above, at para 50; *Allergan Inc v Canada (Minister of Health)*, 2012 FCA 308, [2012] FCJ No 1467 at para 73). However, this does not give the Court free rein to construe the claims as broadly or as narrowly as it wishes. The patentee is "entitled to have the question of obviousness determined by reference to his claim and not to some vague paraphrase based upon the extent of his disclosure in the description" (*Servier*, above, at para 69; *Angiotech Pharmaceuticals Inc v Conor Medsystems Inc*, [2008] UKHL 49 at para 19).

[14] Accordingly, the '944 patent specifies the following:

> It is desirable in the treatment of a number of diseases, both therapeutically and prophylactically, to provide the active pharmaceutical ingredient in a sustained release form. Desirably the sustained release provides a generally uniform and constant rate of release over an extended period of time which achieves a stable and desired blood (plasma) level of the active ingredient without the need for frequent administration of the medicament.
>
> While there are numerous sustained release formulations known in the art which utilize gelling agents, such as hydroxypropyl methylcelluloses, it has been found to be difficult to formulate sustained release formulations of soluble medicaments and gelling agents, such as hydroxypropyl methylcellulose, for several reasons. First of all, active ingredients which are soluble in water tend to generate a sustained release product which is susceptible to a phenomenon known as dose dumping. That is, release of the active ingredient is delayed for a time but once release begins to occur the rate of release is very high. Moreover, fluctuations tend to occur in the plasma concentrations of the active ingredient which increases the likelihood of toxicity. Further, some degree of diurnal variation in plasma concentration of the active ingredient has also been observed. Finally, it has been found to be difficult to achieve the desired dissolution profiles or to control the rate of release of the soluble medicament.
>
> Accordingly, a need exists for sustained release formulations of soluble medicaments, such as [quetiapine] or a pharmaceutically acceptable salt, which overcome, or at least alleviate, one or more of the above described difficulties and which further provide the advantageous property of allowing the active medicament to be

> administered less frequently, e.g. once a day, while achieving blood (plasma) levels similar to those attained by administering smaller doses of the medicament more frequently, e.g. two or more times daily.
>
> [Emphasis added]

[15] A purposive and complete reading of the patent leads the Court to conclude that a decreased occurrence of dose dumping and a less frequent dosing regimen are key elements of the inventive concept claimed by the '944 patent.

A. *Obviousness*

General Principles

[16] Section 28.3 of the *Patent Act*, RSC, 1985, c P-4 states that the subject-matter of a patent must not be obvious:

| Invention must not be obvious | Objet non évident |
|---|---|
| **28.3** The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to | **28.3** L'objet que définit la revendication d'une demande de brevet ne doit pas, à la date de la revendication, être évident pour une personne versée dans l'art ou la science dont relève l'objet, eu égard à toute communication : |
| (*a*) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to | *a*) qui a été faite, plus d'un an avant la date de dépôt de la demande, par le demandeur ou un tiers ayant obtenu de lui l'information à cet égard de façon directe ou autrement, de manière telle qu'elle est devenue accessible au public au |

| | |
|---|---|
| the public in Canada or elsewhere; and | Canada ou ailleurs; |
| (*b*) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere. | *b*) qui a été faite par toute autre personne avant la date de la revendication de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs. |

[17] As set out in *Beloit Canada Ltd v Valmet Oy,* 8 CPR (3d) 289 (FCA), [1986] FCJ No 87 at p 294, "[t]he classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination." In updating the Canadian approach to obviousness in *Sanofi,* the Supreme Court adopted a four-step guide for analysis with a view to inserting more flexibility into this aspect of Canadian patent law (see *Sanofi,* above, at para 67):

> [67] […]
>
> […]
>
> (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 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?

[18] Further analysis may be required at the fourth step, namely the "obvious to try" test. In order to find that an invention was "obvious to try," there must be "evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough" (*Sanofi*, above, at para 66). The word "obvious" has been defined as "very plain" (*Sanofi*, above, at para 66).

[19] The factors to take into account when assessing whether an invention was "obvious to try" include (see *Sanofi*, above, at paras 69):

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

[20] The Court may also consider the actual course of conduct which culminated in the making of the invention, particularly in cases where the skill level of the inventors is the same as that of the hypothetical person skilled in the art (*Sanofi*, above, at para 70). The Supreme Court was clear in *Sanofi* that these factors are not exhaustive, are to be applied in accordance with the facts of each

case (para 69), and are to be approached cautiously, as one part to assist in the obviousness inquiry (para 64).

[21] As the *Patent Act* sets out, the relevant time for the obviousness test is the claim date – here, May 31, 1996 – having regard to the information available a year prior to the Canadian filing date – here, May 27, 1996.

Application to the Facts

(1) The State of the Art

(a) The Person Skilled in the Art

[22] The parties and the expert witnesses agree that the notional person skilled in the art would include both (i) a person with education and experience relevant to formulation [the formulator]; and (ii) either a clinician with relevant experience with respect to antipsychotic drugs or a researcher familiar with antipsychotic drugs and how they are used and work to treat psychotic disorders [the clinician] (see Memorandum of Fact and Law of AstraZeneca Canada Inc [AstraZeneca's Memo] at para 31).

(b) Common General Knowledge

*Schizophrenia and Antipsychotics*

[23] The person skilled in the art knew, at the relevant time, that schizophrenia is a type of psychosis, a severe psychiatric disorder. It causes both positive and negative symptoms. While the

exact cause of schizophrenia is unknown, the prevailing theory in 1996 was the dopamine theory, under which it is posited that the disorder is associated with excessive levels of the neurotransmitter dopamine released in certain areas of the brain. While there were competing theories in the course of development in 1996 -- for instance, the 5HT2 receptor occupancy theory -- the experts agree that it is generally accepted that in order to have antipsychotic effect, a drug must interfere to some extent with dopamine neurotransmission. I find that this is a sufficient factual finding for the purposes of this decision, and thus do not find it necessary to pronounce on the discrepancy in the evidence provided by Professor Harrison and Dr. Seeman on the specifics of the dopamine receptor occupancy required for antipsychotic efficacy.

[24] The first generation of antipsychotic drugs was developed in the early 1950s. These antipsychotics are known as "typical" antipsychotics. They were not effective in all patients, however, and caused debilitating motor and other neurological side effects called extrapyramidal symptoms [EPS]. Such symptoms include tremors, slowness of movements, twisting of the neck, arching of the back, involuntary movements of the tongue, head or limbs, and chronic distortions of posture (see Memorandum of Fact and Law of Teva Canada Limited [Teva's Memo] at para 9). Not surprisingly, such side effects frequently led to non-compliance with a patient's prescribed course of treatment.

[25] The development and introduction of the second generation of antipsychotics began in the 1960s. The first "atypical" antipsychotic -- named as such because of the absence of EPS -- was clozapine. However, this drug often caused agranulocytosis, a potentially fatal blood disorder.

As of May 1996, only clozapine and another atypical, risperidone, were available on the market, and the typical antipsychotics remained the most commonly prescribed of such drugs.

[26] In certain cases of schizophrenia, a rapid titration method of administering antipsychotics was used. Otherwise known as the "sledgehammer approach", this method consisted of administering a certain dose of the drug, then increasing it rapidly to achieve a high peak plasma level as quickly as possible, sedating the patient. This treatment was applied in narrow circumstances, namely to those patients in a specific subset of the acute phase of the disorder in which violence was displayed.

[27] The notional skilled person further knew that, in the chronic phase of the disorder, sedation is not a priority. Rather, maintenance and long-term efficacy and tolerability are the focus (see Application Record [AR] Vol 18, Tab 26, Affidavit of Professor Harrison at paras 77-78).

[28] The prior art discloses that many antipsychotics had a recommended dosing frequency of two or more times per day. However, it also indicates that many antipsychotics could be dosed once a day in certain circumstances, given the long half-life of most of the available immediate release antipsychotic drugs. Professor Harrison stated in his cross-examination that, all other things being equal, the notional skilled person would use the recommended dosing regimen in deciding what to prescribe. In many cases, this was twice or more times per day.

*Quetiapine*

[29] The person skilled in the art knew that, as of May 1996, the immediate release version of quetiapine had been studied in phase II and phase III clinical trials. It was generally understood that quetiapine had antipsychotic properties with a reduced tendency to cause EPS. The prior art further discloses the following properties of quetiapine:

(*i*) *Effective dose size* – Quetiapine had been studied at doses of 300 to 750 mg/day, and was found to have antipsychotic efficacy at those levels. While AstraZeneca points out that none of the studies conducted up to the relevant date had determined the optimal dose of quetiapine, the evidence is clear – and AstraZeneca states itself – that the drug was effective at doses as low as 300 mg/day (see AstraZeneca's Memo at paras 17, 44).

AstraZeneca relies primarily on the studies conducted by Wetzel and Fabre to support its argument about the large dose size that quetiapine demands (see AstraZeneca's Memo at para 17). Wetzel, in particular, suggested that doses upwards of 750 mg ought to be tested. However, Wetzel's study was very small, and he stated in his own paper that definitive conclusions with respect to the antipsychotic efficacy of quetiapine could not be drawn. Dr. Calabrese agreed that the person skilled in the art would not view Wetzel as a study to draw definitive conclusions (see Compendium (Volume 2) of Teva Canada Limited, Tab 42, Cross-Examination of Dr. Calabrese at question 367).

I find the studies relied on by Teva more compelling. First, both Borison studies and the Link study were much larger than Wetzel. No expert disagreed that larger studies were generally better regarded than smaller studies. Second, while AstraZeneca argues that the Borison studies were not designed to test the optimal dose of quetiapine, quetiapine was nonetheless found to be effective at doses as low as 250 or 300 mg. As AstraZeneca admits as much in its memorandum, I am satisfied that this is as far as our inquiry on this point must go.

*(ii)* *Metabolism* – Quetiapine had been found to be extensively metabolized, meaning that it was rapidly cleared by the body.

(*iii*) *Partition coefficient* – The partition coefficient of a drug describes whether it is more soluble in water or in an oil phase. This particular characteristic of quetiapine had not been disclosed in the prior art as of the relevant date.

(*iv*) *Duration of action* – Quetiapine was known to have a short half-life of between 3 and 6 hours. Other antipsychotics commonly prescribed in 1996 had comparatively longer half-lives.

(*v*) *Solubility* – As with partition coefficient, the prior art did not disclose the solubility of quetiapine.

*Other General Knowledge*

[30] The notional skilled person further knew that less frequent dosing generally leads to better compliance with a prescribed drug regimen. While the parties dispute the statistical significance of the difference between the benefits of once-a-day (QD) and twice-a-day (BID) dosing in the prior art, the Court is satisfied that the evidence shows a significant difference between three- and four-times-a-day (TID and QID, respectively) dosing on the one hand, and BID or QD dosing on the other. Indeed, the Greenberg paper referred to by both parties reports a rising compliance rate from 42% (QID) to 52% (TID) to 70% (BID) to 73% (QD). I do not find it necessary to decide on the significance of the difference between BID and QD dosing.

[31] Finally, the person skilled in the art would have been aware that, while there were many gelling agent options to choose from when making a sustained release formulation with a hydrophilic matrix, HPMC was commonly used. As the Court stated in *Apotex Inc v Syntex Pharmaceuticals International Ltd*, [1999] FCJ No 548 at para 64, HPMC was, at the relevant date – which in that case was 1983 – "one of the most popular and widely used mechanisms to control the release of the active ingredient in tablet formulations." The Dow brochure disclosed the same, and further taught that there are several grades of HPMC available. Dr. Moreton identified that the skilled person would have known that changing the viscosity or grade of the gelling agent, such as HPMC, would adjust the dissolution rate of a sustained release formulation (see AR Vol 26, Tab 34, Cross-Examination of Dr. Richard Moreton at question 667). It was also generally known that

formulation of sustained release tablets was dependent on the particular properties of the drug in question (see Applicants' Hearing Compendium Part 2C: Invention Not Self-Evident, Tab 2, excerpt from *Remington: The Science and Practice of Pharmacy, Volume II*).

(2) The Inventive Concept

[32] As outlined above, the invention is a sustained release formulation of quetiapine hemifumarate, made with HPMC as the gelling agent and one or more excipients, with a view to decreasing the occurrence of dose dumping and to enabling a less frequent dosing regimen.

(3) Differences between (1) & (2)

[33] The difference between the prior art and the inventive concept is a sustained release formulation for the specific drug quetiapine.

(4) Obvious Steps?

[34] The determinative issue in this case is whether it was more or less self-evident that if the skilled person combined quetiapine with a known sustained release formulation, the result would be a sustained release formulation of quetiapine. As Justice Judith Snider stated in *Laboratoires Servier v Apotex Inc*, 2008 FC 825, [2008] FCJ No 1094 (aff'd 2009 FCA 222, above) [*Servier* (FC)] at para 254 (see also *Biovail Corporation v Canada (Minister of Health)*, 2010 FC 46, [2010]

FCJ No 46 at para 84):

> [254] […] a mosaic of prior art may be assembled in order to render a claim obvious. Even uninventive skilled technicians would be presumed to read a number of professional journals, attend different conferences and apply the learnings from one source to another setting or even combine the sources. However, in doing so, the party claiming obviousness must be able to demonstrate not only that the prior art exists but how the person of ordinary skill in the art would have been led to combine the relevant components from the mosaic of prior art. […]

[35] To this effect, the parties agree that this is a case in which the "obvious to try" test is appropriate. The Court is of the same mind.

[36] The parties are, however, divided about the parameters of the "obvious to try" test. AstraZeneca focuses on the results of experimentation, maintaining that it must be obvious that successful results will be achieved before any experimentation is carried out. Teva, for its part, offers a less stringent proposition, contending that a patent will be obvious if it was more or less self-evident, in the words of *Sanofi*, to "try to obtain the invention" or, in Teva's words, to conduct routine experimentation with a fair expectation of success.

[37] I find that Teva's interpretation is more apt on the facts of this case. Lord Justice Lewison recently remarked that in many "obvious to try" cases, it is the idea of trying that constitutes the inventive step (*Medimmune Ltd v Novartis Pharmaceuticals UK Ltd & Ors* [2012] EWCA Civ 1234 at para 184, cited with approval in *Pfizer Canada Inc v Pharmascience Inc*, 2013 FC 120, [2013] FCJ No 111 at para 189). AstraZeneca's point might have been better received were the invention in this case the idea of trying to obtain a sustained release formulation of quetiapine. However, as already established, the inventive concept in our case is the end product – a physical

sustained release formulation of quetiapine. Lord Justice Lewison approved of the notion that "obviousness connotes something which would at once *occur* to a person skilled in the art who was desirous of accomplishing the end" (*Medimmune*, above, at para 184, emphasis Lord Justice Lewison's). I find that this is entirely in accord with the Canadian elaboration in *Sanofi* that a patent may be found obvious if it is more or less self-evident to try to obtain the invention (*Sanofi*, above, at para 66). Of course, the jurisprudence is wary of the expansion of this notion, and thus narrowed the scope of cases that might fall into this category by enumerating the non-exhaustive factors of the "obvious to try" test, to which I now turn. In my view, motivation is the key factor in this case.

1. Self-Evident?

[38] AstraZeneca lists a number of characteristics of quetiapine that made it a "poor candidate" for a sustained release formulation, arguing that the prior art taught away from such a formulation. Furthermore, AstraZeneca argues that there were a number of possible formulations that could have been chosen. Thus, the choice of HPMC as a gelling agent would not have been self-evident.

[39] For its part, Teva submits that these factors relied on by AstraZeneca are better suited to the discussion about motivation. I agree. The question of whether certain pharmacokinetic properties of the drug would have de-motivated the notional skilled person will thus be addressed in the motivation section below.

[40] Teva offers an alternative proposition for the "self-evident" analysis. Looking to *Sanofi*, it posits that two issues are raised in areas in which advances are won by experimentation, as in the

pharmaceutical industry: First, the question is whether the experimentation conducted is routine; and second, whether there is a fair expectation of success. I find this characterization to be an apt and helpful description of the law, though the question about the routine nature of the experimentation will be addressed in the next section.

[41] *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8, [2009] FCJ No 66 [*Pfizer v Apotex*] intends that "fair expectation of success" is the standard to be adopted by the Court. The Federal Court of Appeal, at para 44, described that "predictable", and therefore obvious, solutions are equivalent to "solutions that provide 'a fair expectation of success'" (*Pfizer v Apotex*, above). This Court has also adopted this standard. In *Pfizer Canada Inc v Ratiopharm Inc*, 2010 FC 612, [2010] FCJ No 748, for example, the Court decided that it was self-evident or plain that the drug in that particular case had a fair expectation of success based on the prior art to achieve the solution the patent addressed (see para 171).

[42] In the case at hand, I find the following evidence given by Dr. Lee compelling:

> 153. As set out above, a gelling agent, and in particular HPMC, in the quantities claimed, would have been the first choice for a sustained release formulation of quetiapine, and the PSA would have had a high expectation of achieving success. The use of such gelling agents in sustained release formulations which provided the claimed sustained release characteristics was known and conventional at the relevant date.
>
> [Emphasis added]

[43] While AstraZeneca argues, as one example, that the person skilled in the art "would not be able to predict with any certainty the precise amounts and grades of HPMC to be used" (AstraZeneca's Memo at para 75), the correct standard against which to assess obviousness is not

"predict with certainty," but rather "fair expectation of success." Based on the evidence, I thus conclude that it was self-evident or plain that there was a fair expectation that a sustained release formulation of quetiapine using HPMC would be successful.

2. Extent, Nature and Effort Required to Achieve Invention

[44] The *Sanofi* test suggests that, where the experimentation is "prolonged and arduous" and thus not routine, it is less likely that the invention will be obvious to try (see *Sanofi*, above, at para 69). Conversely, if the experimentation is routine, it is more likely that an invention will be obvious to try.

[45] It is worth noting that there was no evidence submitted specifically on the point of how arduous the testing was for the sustained release formulation of quetiapine. It is, however, settled law that there is no invention in discovering properties of known substances (*Biovail*, above, at para 85; *Pfizer Canada Inc v Canada (Minister of Health)*, 2006 FCA 214, [2006] FCJ No 894 (leave to appeal refused [2006] SCCA No 335) at para 24).

[46] AstraZeneca notes that at least two properties of quetiapine were unknown at the relevant time, namely its partition coefficient and solubility, particularly its pH-related solubility. It argues that the experimentation connected with determining these properties of quetiapine was not merely routine. For its part, Teva argues that these two particular properties would be easily discovered by the skilled person through routine experimentation. I am satisfied with the evidence submitted by Teva on this point, and find that such testing would have been routine for the notional skilled

person. Even were the experimentation with respect to these properties not routine, this alone would not be determinative, given the principle stated in *Biovail*, above.

[47] This prong of the "obvious to try" test thus turns more centrally on whether the choice of HPMC would have been the product of routine or prolonged and arduous experimentation. AstraZeneca argues that this process is difficult and complex, and that the person skilled in the art would not be able to "predict with any certainty" the precise amounts and grades of HPMC to be used (AstraZeneca's Memo at para 75). Teva argues that it was straightforward and routine, made using commonly available equipment.

[48] Dr. Lee described that making choices such as which type of formulation to use, the type of gelling agent and the amount and grade of HPMC to use in a sustained release formulation was a "routine exercise" for the person skilled in the art (see AR Vol 21, Second Tab 30, Affidavit of Dr. Ping Lee at para 38). On cross-examination, Dr. Moreton corroborated this statement, conceding that manufacturing hydrophilic matrix devices was "straightforward. The processing was known. It didn't require expensive investment" (see Compendium (Volume 3) of Teva Canada Limited, Tab 97, Cross-Examination of Dr. Richard Moreton at question 651). When combined with the already-established fact that the person skilled in the art would have known that changing the viscosity or grade of the gelling agent, such as HPMC, would adjust the dissolution rate of a sustained release formulation, I am satisfied that the choice of HPMC and its specific grades would have been the product of routine experimentation.

### 3. Motivation

[49] Motivation is relevant in "determining whether the skilled person has good reason to pursue 'predictable' solutions or solutions that provide 'a fair expectation of success'" (*Pfizer v Apotex*, above, at para 44).

[50] The parties' first point of contention pertains to the identity of the skilled person for the purposes of motivation. AstraZeneca asserts that the Court should focus on the clinician as the skilled person for the purposes of motivation, whereas the formulator should be the focus of the self-evidence of the invention criterion. I cannot accept this argument. While it is true that the clinician and the formulator are both part of the "team" that comprises the notional person skilled in the art in this case, it is *a* notional skilled *person* upon whom the characteristics of the real-life team are layered, and not a notional skilled *team*. As such, both clinician and formulator are equal participants in each step of the "obvious to try" test.

[51] The crux of the parties' disagreement about obviousness, however, is whether the prior art disclosed a motive to create a sustained release formulation of quetiapine. Teva argues (i) that there was a motive in the prior art to decrease the dosing frequency of quetiapine. For its part, AstraZeneca focuses its motivation submissions on two main components: (ii) first, it argues that the prior art revealed that a number of quetiapine's characteristics made it a "poor candidate" for a sustained release formulation, thus teaching away from the invention; and (iii) second, it posits that there were a number of possible formulations that could have been chosen and that the skilled

person would not have been specifically motivated to choose HPMC as a gelling agent.

(i) Frequency of Dosing

[52] Teva submits that both a general and specific motive existed in the prior art to create a sustained release formulation, namely to reduce dosing frequency. The Court has already found that the skilled person would know that less frequent dosing – meaning BID or QD over TID or QID – was beneficial for compliance. Teva relies on the Gefvert article to show that there was a specific motive to decrease the dosing frequency of quetiapine: "Given the importance of compliance with medication in schizophrenics, a more convenient dose regimen would be beneficial" (see Applicants' Hearing Compendium Part 2B: No Motivation, Tab 48). I find this evidence compelling.

[53] In its oral reply submissions, AstraZeneca challenged Teva's reliance on Gefvert to point to a specific motivation to dose quetiapine less frequently because (i) the article was not relied on in Teva's NOA, and (ii) the argument was not raised in its memorandum. It is well-established that a second person (i.e. Teva) "cannot, in proceedings taken in Court, present argument and evidence relating to an issue that is outside the scope of its NOA" (*GlaxoSmithKline Inc v Pharmascience Inc*, 2011 FC 239, [2011] FCJ No 287 [*GlaxoSmithKline*] at para 40; *Abbott Laboratories v Canada (Minister of Health)*, 2007 FCA 83, [2007] FCJ No 270 at para 25). Furthermore, the second party may not "shift ground or raise a new ground during the legal proceedings that has not been raised in its NOA" (*GlaxoSmithKline*, above, at para 40; *Pfizer Canada Inc v Canada (Minister of Health)*, 2006 FC 1471, [2006] FCJ No 1848 at paras 70-71).

[54] I am satisfied, after reviewing the NOAs, that the issue of a specific motive to create a sustained release version of quetiapine was squarely raised in the NOAs (see AR Vol 3, Tab 3 at p 706 and Tab 4 at p 772; *Pfizer Canada Inc v Novopharm Ltd*, 2009 FC 638, [2009] FCJ No 688 (aff'd 2010 FCA 242, reversed 2012 SCC 60 on other grounds) [*Novopharm*] at para 95). Furthermore, it is settled law that a second person may respond to matters raised by an applicant in NOC proceedings (*AstraZeneca AB v Apotex Inc*, 2004 FC 313, [2004] FCJ No 386, [*Apotex*] at para 48; *Novopharm*, above, at paras 95-96). Such a response does not constitute an expansion of the legal and factual basis of the NOA (*Apotex*, above, at para 48). I note that Dr. Seeman, one of AstraZeneca's witnesses, referred to the Gefvert paper in his affidavit (see Applicants' Hearing Compendium Part 2B: No Motivation, Tab 49, Affidavit of Philip Seeman, M.D., Ph.D.). Teva was thus well within its rights to respond to Gefvert in its submissions.

[55] Finally, I cannot accept AstraZeneca's argument that Teva raised this argument for the first time in its oral argument. The issue of less frequent dosing as a motive was indeed canvassed in Teva's written submissions at paragraphs 67 through 76. While Teva does not appear to have relied on Gefvert for this specific proposition, the rules about raising new arguments pertain to shifting or raising new grounds for relief, and not to relying on evidence which is already in the record to support a ground that is already in issue.

### (ii) Quetiapine's Pharmacokinetic Properties

[56] In its effort to demonstrate that Teva's allegations of invalidity are not justified, AstraZeneca points to five characteristics of quetiapine that would have de-motivated the person skilled in the art from trying a sustained release formulation of the drug: (a) large dose size; (b) solubility; (c) partition coefficient; (d) extent of metabolism; and (e) duration of action. I am not convinced that any of these properties taught away from a sustained release formulation. The person skilled in the art would not have viewed them as "lions in the path", but rather as paper tigers, to use the language of Lord Justice Jacob in *Pozzoli SPA v BDMO SA*, [2007] EWCA Civ 588 at para 126, and echoed by Justice Arnold in *Teva UK Ltd & Ors v AstraZeneca AB*, [2012] EWHC 655 (Pat).

#### (a) *Dose Size*

[57] AstraZeneca argues that, because quetiapine was a "weak antipsychotic", a large dose size would necessitate a large and uncomfortable-to-swallow tablet. Its argument is based on the assumption that a dose closer to 750 mg would be necessary in order for the tablet to exhibit antipsychotic efficacy. However, as already established, quetiapine was shown to be effective at doses as low as 300 mg. I am further convinced that, even were a 750 mg dose required, the person skilled in the art would have been motivated to split the dose into two smaller tablets to be taken at once. At the very least, this would not have constituted a lion in the path of the skilled person.

(b) *pH Solubility*

[58] The arguments with respect to quetiapine's solubility are related to its pH profile. AstraZeneca maintains that neither of these was a known property at the relevant time, and that the person skilled in the art would have been de-motivated by this want of knowledge. As already established, determining these properties would have been routine. Furthermore, the Dow brochure revealed that: "The viscosity of the gel which forms on the tablet surface and the rate of hydration are relatively independent of the pH environment. Release rates of drugs will not be affected by pH unless drug solubility varies greatly over the normal pH range" (see Compendium (Volume 3) of Teva Canada Limited, Tab 85, Affidavit of Dr. Ping Lee at para 171). Dr. Prud'homme confirmed in his cross-examination that the skilled person would have been using the Dow brochures, reference being made to them even in patents filed at the time (see Compendium (Volume 3) of Teva Canada Limited, Tab 85, Cross-Examination of Dr. Robert Prud'homme at question 1024). I am thus not satisfied that the pH solubility of quetiapine would have de-motivated the skilled person from pursuing a sustained release formulation of the drug.

(c) *Partition Coefficient*

[59] The partition coefficient of quetiapine was also unknown at the relevant time. I am again satisfied that determining this particular property of the drug would have been a matter of routine experimentation and would thus not have dissuaded the person skilled in the art from pursuing a sustained release formulation, particularly since it did not appear to cause any problems for the immediate release version of the drug.

(d) *Metabolism*

[60] AstraZeneca argues that quetiapine's extensive metabolism suggested at the relevant time that it may be a poor candidate for a sustained release formulation. This is because the faster a drug is processed by the body, the more of it is needed to achieve the therapeutic blood concentration (see AstraZeneca's Memo at para 66). Despite these concerns, and as previously determined, quetiapine was found to be therapeutically effective in doses around 300 mg. Dr. Prud'homme further confirmed this in his cross-examination (see Compendium (Volume 3) of Teva Canada Limited, Tab 89, Cross-Examination of Dr. Robert Prud'homme at question 717). Dr. Lee noted that, if the extensive metabolism of quetiapine was not problematic for the immediate release version, that it would not have been expected to cause a problem in the sustained release version (see Compendium (Volume 3) of Teva Canada Limited, Tab 88, Affidavit of Dr. Ping Lee at para 200). I find this to be a rational characterization, and determine that quetiapine's extensive metabolism would not deter the person skilled in the art from formulating a sustained release version of the drug.

(e) *Duration of Action*

[61] AstraZeneca argues that a drug with both a large dose and a short half-life would not be well-suited for a sustained release formulation. Its argument on this point is a variation on its large dose size argument, which I have already rejected (see AstraZeneca's Memo at para 67). Furthermore, the fact that quetiapine had a short half-life actually indicated that there would be a

motive to make a sustained release formulation (see Compendium (Volume3) of Teva Canada Limited, Tab 90, Affidavit of Dr. Ping Lee at paras 195, 228).

(iii) Other Formulations

[62] The fact that there may have been a number of possible formulations, as posited by AstraZeneca, does not mean that the alleged invention is not obvious (*Biovail*, above, at para 100; *Shire Biochem Inc v Canada (Minister of Health)*, 2008 FC 538, [2008] FCJ No 690 at para 79). HPMC was one of the most commonly used gelling agents. This prior art knowledge combined with the relative straightforward manner in which HPMC could be manufactured, discussed above, point to a motive to choose HPMC.

4. Actual Course of Conduct

[63] Additionally, *Sanofi* instructs that the Court may look, in certain cases, to the actual course of conduct followed by the inventors: "For example, if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that may be evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person" (*Sanofi*, above, at para 71).

[64] While not central to my findings on obviousness, I find it telling that AstraZeneca did not lead any evidence with respect to the length or difficulty of the trials conducted, or with respect to

whether their inventors possessed a knowledge base that was above that which should be attributed to the skilled person in this case. Satisfied as I am that Teva has given its allegations of invalidity an air of reality, I draw an adverse inference from AstraZeneca's failure to provide evidence on these points.

*Conclusions on Obviousness*

[65] "[O]bviousness connotes something which would at once occur to a person skilled in the art who was desirous of accomplishing the end" (*Medimmune*, above, at para 184). The end, or the inventive concept, here is a sustained release formulation of quetiapine with a view to minimizing dose dumping and decreasing dosing frequency. The skilled person would have been led to combine the elements of the prior art to accomplish this end in the following manner: First, the prior art – particularly Gefvert – motivated the skilled person to find the solution the patent addresses (see *Sanofi*), which is to decrease dosing frequency and avoiding dose dumping. Second, the prior art clearly taught that sustained release formulations were commonly used to achieve this purpose, HPMC being the most commonly used gelling agent in such formulations, in part because of the relatively straightforward manner in which it could be manufactured. The choice of a sustained release formulation using HPMC would thus have been obvious steps to accomplish the claimed end for quetiapine.

[66] I conclude that it was more or less self-evident to try to obtain a sustained release formulation of quetiapine using HPMC, and that the person skilled in the art would have had a fair expectation of success. Given my conclusion with respect to the main factors listed in *Sanofi*, I find

it unnecessary to address the parties' arguments with respect to secondary considerations (i.e. commercial success and unexpected benefits).

B. *Ambiguity*

[67] Further given my conclusions with respect to obviousness, it is not necessary to explore the limited argument and evidence put forward by Teva with respect to ambiguity. It is important to note the comments made by Justice Roger Hughes in *Pfizer Canada Inc v Canada (Minister of Health)*, 2005 FC 1725, [2005] FCJ No 2155 that it is difficult to find a patent invalid for ambiguity: "In short, ambiguity is truly a last resort, rarely, if ever, to be used" (para 53; see also paras 51-52). In my view, these comments are particularly apt in this matter.

***Conclusion and Costs***

[68] I find that Teva's allegations that it was more or less self-evident to try to obtain a sustained release formulation of quetiapine have an air of reality. AstraZeneca has failed to establish that Teva's allegations of invalidity are unjustified, and, as a result, its application for an order of prohibition is dismissed.

[69] Costs are awarded to Teva at the usual level for these types of proceedings, viz. the middle of Column IV of Tariff B.

## JUDGMENT

**THIS COURT'S JUDGMENT is that** the application is dismissed. Costs are awarded to Teva at the middle of Column IV of Tariff B.

" D. G. Near "
Judge

ANNEX "A"

Claims of Canadian Patent 2,251,944

1. A sustained release formulation comprising a gelling agent and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients.

2. The sustained release formulation according to claim 1, wherein the 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof is released from the formulation in a controlled fashion over a period of between 8 and 24 hours where the at least 60% of the 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof has been released at the end of the period.

3. The sustained release formulation according to claim 1 or 2 wherein the gelling agent is a hydroxypropyl methylcellulose.

4. The sustained release formulation according to claim 3, comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof.

5. The sustained release formulation according to claim 3, comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about

19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof; with the proviso that if the formulation contains a hydroxypropyl methylcellulose defined under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

6. The sustained release formulation according to claim 4 or 5, comprising about 5 to 40% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a), (b), (c), (d) and mixtures thereof.

7. The sustained release formulation according to claim 6, comprising about 8 to 35% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a), (b), (c), (d) and mixtures thereof.

8. The sustained release formulation according to claim 7, comprising about 10 to 30% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a), (b), (c), (d) and mixtures thereof.

9. The sustained release formulation according to claim 8, comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a), (b), (c), (d) and mixtures thereof.

10. The sustained release formulation according to any one of claims 1 to 9, wherein the 11-[4-[2-(2-hydroxy-ethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof is present in about 35 to 65% by weight.

[…]

13. The sustained release formulation according to any one of claims 1 to 10, wherein one of the one or more pharmaceutically acceptable excipients is a pH modifier.

14. The sustained release formulation according to claim 13, wherein the pH modifier is sodium citrate.

15. The sustained release formulation according to any one of claims 1 to 14, wherein the 11-[4-[2-(2-hydroxy-ethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine is in the form of a hemifumarate salt.

16. The sustained release formulation according to any one of claims 1 to 15, wherein the formulation is coated.

17. The sustained release formulation according to claim 1 or 2, wherein the gelling agent is hydrophilic.

[…]

20. The sustained release formulation according to any one of claims 1 to 19, in a unit dosage form comprising 50 mg, 200 mg, 300 mg or 400 mg of said 11-[4-[2-(2-hydroxy-ethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or pharmaceutically acceptable salt thereof.

21. The sustained release formulation according to any one of claims 1 to 20 in the form of a tablet.

22. Use of a sustained release formulation according to any one of claims 1 to 21 for treating psychotic states in a warm-blooded animal.

[…]

24. Use of a sustained release formulation according to any one of claims 1 to 19 for preparing a medicament for treating psychotic states in a warm-blooded animal.

[…]

26. The use according to any one of claims 22 to 25 wherein said warm-blooded animal is human.

**FEDERAL COURT**

**SOLICITORS OF RECORD**

| | |
|---|---|
| **DOCKET:** | T-1259-11 |
| **STYLE OF CAUSE:** | ASTRAZENECA CANADA INC. ET AL v TEVA CANADA LIMITED ET AL |
| **PLACE OF HEARING:** | Toronto |
| **DATE OF HEARING:** | January 21-23, 2013 |
| **REASONS FOR JUDGMENT AND JUDGMENT:** | NEAR J. |
| **DATED:** | March 7, 2013 |

**APPEARANCES:**

| | |
|---|---|
| Yoon Kang<br>Colin B. Ingram<br>Andrew Mandlsohn | FOR THE APPLICANTS |
| David W. Aitken<br>Marcus Klee | FOR THE RESPONDENT<br>TEVA CANADA LIMITED |
| No appearance | FOR THE RESPONDENT,<br>THE MINISTER OF HEALTH |

**SOLICITORS OF RECORD:**

| | |
|---|---|
| Smart & Biggar<br>Barristers & Solicitors<br>Toronto, Ontario | FOR THE APPLICANTS |
| Osler, Hoskin & Harcourt LLP<br>Barristers & Solicitors<br>Ottawa, Ontario | FOR THE RESPONDENT,<br>TEVA CANADA LIMITED |
| William F. Pentney<br>Deputy Attorney General of Canada<br>Toronto, Ontario | FOR THE RESPONDENT,<br>THE MINISTER OF HEALTH |