Federal Court  Cour fédérale

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Docket: T-336-15

Citation: 2017 FC 142

Toronto, Ontario, February 07, 2017

PRESENT: The Honourable Mr. Justice Diner

BETWEEN:

ASTRAZENECA CANADA INC
AND
POZEN INC

Applicants

And

MYLAN PHARMACEUTICALS ULC
AND
THE MINISTER OF HEALTH

Respondents

JUDGMENT AND REASONS

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I. Introduction

[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 [*Regulations*], a Notice of Compliance [NOC] to the Respondent Mylan Pharmaceuticals ULC [Mylan] in respect of its generic naproxen-esomeprazole magnesium tablet product, until the expiry of Canadian Patent No. 2,449,098 [098 Patent].

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

II. Background

[3] Nonsteroidal anti-inflammatory drugs [NSAIDs] are commonly used to treat pain, fever, and inflammation through their analgesic (pain-killing), antipyretic (fever-reducing), and anti-inflammatory properties. They are used to treat inflammation and pain associated with chronic, incurable rheumatic and degenerative musculoskeletal disorders, including rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. NSAIDs are distinguished from acetaminophen (TYLENOL), steroidal anti-inflammatories (corticosteroids such as cortisone), and other drugs used to treat pain (such as opioids).

[4] NSAIDs are amongst the world's most widely used medications, having been used for over a century. They include drugs such as acetylsalicylic acid (ASPIRIN, BUFFERIN),

ibuprofen (ADVIL, MOTRIN, NUPRIN), diclofenac (VOLTAREN), and naproxen (ALEVE, NAPROSYN).

[5] Unfortunately, NSAIDs can cause gastrointestinal [GI] injuries, including ulcers in the interior surface (mucosa) of the upper GI tract – primarily the stomach and duodenum. Complications arising from ulcers include bleeding and perforations, resulting in thousands of deaths every year around the world including in North America. There currently are no means of entirely eliminating the risk of these side effects, but a number of drugs can help mitigate them.

[6] Approaches to mitigating the side effects have included taking co-therapy drugs such as misoprostol, H_2 receptor antagonists, and proton pump inhibitors [PPIs] with NSAIDs. By 2001, accepted risk-reduction therapies included using less injurious NSAIDs (at least with respect to GI injury) such as COX-2 specific inhibitors (CELEBREX), and a co-therapy drug such as misoprostol or a PPI. NSAID co-therapy with other drugs, including misoprostol, a prostaglandin analogue, remained risky due to the side effects of the chosen co-therapy drug.

[7] One of the issues with co-therapy, no matter which of the varieties it came in, was known to be patient non-compliance.

[8] In 2001, commercially available PPIs were formulated as oral solid dosage forms (for simplicity, and consistent with the claims asserted in this case, “Tablets”) with an enteric coating. The enteric coating delayed release of the PPI until the dosage form reached the small intestine, thus avoiding degradation by gastric acid.

[9] Tablets can be formulated for various internal impacts, which include: (a) immediate release in the stomach; (b) delayed release in the small intestine or further down the GI tract; or (c) sustained release through all or part of the GI tract.

[10] Nothing but abstinence from NSAID therapy will eliminate the risk of GI injury. NSAID toxicity may result from both local and systemic effects of the drug. Locally, the NSAID impacts the mucosa of the stomach lumen. Systemically, NSAIDs inhibit cyclooxygenase [COX] enzymes, thereby reducing prostaglandin synthesis throughout the body, including in the GI tract. Prostaglandins help to maintain the integrity of the mucosal lining of the stomach and duodenum, which provides a natural defence against the highly acidic conditions in those lumens. Specifically, prostaglandins inhibit acid secretion, stimulate mucous and bicarbonate secretion, and increase blood flow and healing. Therefore, systemic reduction of prostaglandin production caused by NSAIDs can cause ulcers and related GI damage.

[11] An advent to co-therapy came with the drug ARTHROTEC, first disclosed in 1992, and then launched commercially in 1998. It is a multilayer tablet containing a NSAID (diclofenac) with an enteric coating and immediate-release misoprostol.

[12] This application relates to a formulation of an immediate-release prophylactic (preventative) medication to address the deleterious effects of NSAIDs, namely VIMOVO, marketed by AstraZeneca Canada Inc. [AstraZeneca]. VIMOVO is the brand name of AstraZeneca’s patented naproxen-esomeprazole magnesium tablet, which pairs naproxen (a NSAID) with esomeprazole magnesium (a PPI).

[13] The 098 Patent is owned by Pozen Inc. and is listed on the Health Canada Patent Register against AstraZeneca's VIMOVO drug. It was filed in Canada on May 31, 2002 [the Filing Date], claiming priority to June 1, 2001 [the Claim Date], and was published on December 12, 2002. Unless found to be invalid, it will expire on May 31, 2022.

[14] The 098 Patent states that a new method of reducing GI risks would ensue from a single unit dosage form that provides a coordinated, sequential release of an acid inhibitor first, and a NSAID second.

[15] The patent provides examples: examples 5 through 8 contain enteric-coated naproxen and immediate release PPI, omeprazole or pantoprazole; examples 9 and 10 set out clinical studies examining the relationship of gastric pH to NSAID-induced gastric ulcers, and whether co-administration of an H_2 blocker (famotidine) with a NSAID (naproxen) reduces NSAID-related GI damage.

[16] Mylan filed an Abbreviated New Drug Submission with the Minister of Health for the issuance of a NOC with respect to a generic naproxen-esomeprazole magnesium tablet product. As required by section 5 of the *Regulations*, on January 20, 2015 Mylan served a Notice of Allegation [NOA] on AstraZeneca. The NOA claimed non-infringement of certain claims of the 098 Patent, as well as invalidity on a number of grounds.

[17] In response to the NOA, the Applicants initiated the present proceeding under subsection 6(1) of the *Regulations*, asserting claims 26 to 28, 34 to 38, and 39 to 44 where dependent on

claims 26 to 28 and 34 to 38 of the 098 Patent. For the purposes of these proceedings, Mylan relied on its allegations of invalidity, which focus primarily on obviousness, but in the alternative that the claims lack utility and are overbroad.

[18] In a pre-hearing conference, AstraZeneca advised that it was narrowing its claims from those asserted in its Application to claim 37 (itself dependent on claim 34, 35, and/or 36) and claims 38 to 44 where dependent on claim 37 [the Asserted Claims, reproduced in Annex A to these Reasons]. AstraZeneca stated that it was focusing its claims in this manner both (a) to reflect the commercial product (a tablet) and (b) because the case did not turn on some of the properties that were the focus of the other claims that had originally been asserted.

III. Expert Evidence

[19] The Applicants served affidavits from two expert witnesses:

- Dr. James Polli is a Professor of Pharmaceutical Sciences and the endowed chair in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy.
- Dr. David Armstrong, a gastroenterologist, is a Professor in the Gastroenterology Division of the Department of Medicine at McMaster University.

[20] Mylan served affidavits from three expert witnesses:

- Dr. Leah Appel, an industrial formulator, is a managing partner of Green Ridge Consulting, a company based in Oregon that provides formulation consulting services to the pharmaceutical industry.

- Dr. Ping Lee is a Professor in Pharmaceutics and Drug Delivery at the University of Toronto.
- Dr. Loren Laine, a gastroenterologist, is a Professor of Gastroenterology and Director of Clinical Research at the Yale School of Medicine.

IV. Issue

[21] The sole issue in this case is whether the Asserted Claims of the 098 Patent are invalid. The Respondent Mylan relies primarily on obviousness for its invalidity claim, although it raises lack of utility and overbreadth as alternate bases of invalidity. The Applicants strenuously refute all contentions of invalidity.

V. Burden of Proof

[22] In terms of the burden of proof for NOC proceedings under the *Regulations*, subsection 43(2) of the *Patent Act*, RSC, 1985, c P-4 [*Patent Act*] creates a presumption that a patent is valid. In order to rebut this presumption, Mylan bears the evidential burden of giving its allegations of invalidity an air of reality, thereby putting the issues in play. If Mylan is successful in doing so, AstraZeneca must establish, on a balance of probabilities, that Mylan's allegations of invalidity are unjustified (*Pfizer Canada Inc v Canada (Minister of Health)*, 2007 FCA 209 at paras 109-111; *Leo Pharma Inc v Teva Canada Ltd*, 2015 FC 1237 at paras 62-64).

[23] The bulk of the written and oral submissions in this matter revolved around the first and primary issue of obviousness. An overview of that area of the law follows the next section, which construes the claims at issue.

VI. Claim Construction

A. *The Law*

[24] Patents are to be construed purposively, having regard to the whole of the patent, in order to ascertain the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of the invention (*Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras 44-45 [*Whirlpool*]). The claims are to be construed as of the date of publication (*Whirlpool* at para 55).

[25] Claims are to be construed through the eyes of the notional person of ordinary skill in the art [POSITA] (*Whirlpool* at para 70, quoting Dickson J in *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504 at 523, 56 CPR (2d) 145 (SCC), in turn quoting HG Fox, *Canadian Law and Practice Relating to Letter Patent for Invention*, 4th ed (Toronto: Carswell, 1969) at 204:

> The persons to whom the specification is addressed are "ordinary workmen", ordinarily skilled in the art to which the invention relates and possessing the ordinary amount of knowledge incidental to that particular trade. The true interpretation of the patent is to be arrived at by a consideration of what a competent workman reading the specification at its date would have understood it to have disclosed and claimed.

[26] In sum, a patent is to be construed through the eyes of the POSITA having a mind willing to understand the invention, and the claims are to be approached in a purposive manner and construed in light of both the disclosure and the claims (*Eli Lilly Canada Inc v Canada (Attorney General)*, 2015 FCA 166 at para 52; see also *ABB Technology AG v Hyundai Heavy Industries Co Ltd*, 2015 FCA 181 at para 36). That said, while it is permissible to read the disclosure in order to assist in understanding the terms used in the claims, the disclosure cannot be used to construe the claims more narrowly or widely than the text of the claims allows (*Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61 at para 77 [*Sanofi*]; see also *MediaTube Corp v Bell Canada*, 2017 FC 6 at paras 35-37).

[27] As the construction of claims precedes an evaluation of infringement or validity (*Whirlpool* at para 43), this is where my analysis begins.

B. *Analysis*

[28] As discussed, the claims asserted from the 098 Patent are claims 34 to 38, and 39 to 44 where dependent on claims 34 to 38 (see Annex A). The construction of the claims in this case proved to be straightforward, and was not a source of dispute between the parties. Nonetheless, in an effort to construe the claims purposively and contextually as instructed by the jurisprudence, including *Whirlpool*, a sequential examination of the Asserted Claims follows.

[29] Claim 34 is the relevant independent claim. Like other independent claims of the 098 Patent not asserted in this case, Claim 34 follows the general structure set out in Claim 1, which

does not specify any particular acid inhibitor or NSAID. Specifically, Claim 34 provides as follows:

> 34. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:
>
> (a) a pharmaceutically acceptable salt of esomeprazole, wherein at least a portion of said pharmaceutically acceptable salt of esomeprazole is not surrounded by an enteric coating; and
>
> (b) naproxen, wherein said naproxen is surrounded by a coating that inhibits its release from said dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;
>
> wherein said unit dosage form provides for release of said pharmaceutically acceptable salt of esomeprazole and said naproxen such that:
>
> i. upon introduction of said unit dosage form into a medium, at least a portion of said pharmaceutically acceptable salt of esomeprazole is released regardless of the pH of the medium; and
>
> ii. said naproxen is released when the pH of said medium is 3.5 or higher. [Emphasis added.]

[30] In light of the whole of the 098 Patent, I construe claim 34 as comprising a pharmaceutical formulation of a PPI (esomeprazole) and a NSAID (naproxen), such that there is a coordinated release of at least a portion of the PPI regardless of the pH of the medium, and a delay of all of the NSAID until the pH of the medium is at least 3.5.

[31] Claims 35 to 38 are cascading dependent claims.

[32] Claim 35 provides an alternative pharmaceutical composition of claim 34 wherein none of the pharmaceutically acceptable salt of esomeprazole is surrounded by an enteric coating, such that upon introduction into a medium, essentially all of it would be immediately released.

[33] In other words, claim 35 limits the pharmaceutical composition in claim 34 such that none of the esomeprazole (the PPI) is surrounded by an enteric coating, as distinct from claim 34, which as I have construed above, instructs that 'at least a portion of the PPI' not be enteric coated. This means that whereas in claim 34 anywhere from 1% through 99% of the PPI would have no enteric coating, in claim 35 none (0%) of the PPI would be coated.

[34] Claim 36 provides that the naproxen be present in an amount between 250 and 500 mg. Claim 37 provides that the unit dosage form be a tablet. Claim 38 provides that the pharmaceutically acceptable salt be the magnesium salt of esomeprazole.

[35] Claims 39 to 44 are usage claims. The claimed uses of the pharmaceutical composition include treating a patient for pain or inflammation (claim 39), or in the manufacture of a medicament to treat the same (claim 40), and in particular for use where the said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis (claim 41). Similarly, the other claimed uses include treating osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis (claim 42), or in the manufacture of a medicament to treat the same (claim 43), and in particular for use in patients at risk of developing NSAID associated gastric ulcers (claim 44).

VII. Obviousness

A. *The Law*

[36] Section 28.3 of the *Patent Act* provides that the subject-matter defined by a claim of a patent must not have been obvious to the skilled person, having regard to the information that was publicly available as of the claim date or one year before the Canadian filing date:

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 the public in Canada or elsewhere; and	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 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.
[Emphasis added.]	[Non souligné dans l'original.]

[37] In what remains the leading case on obviousness almost a decade later, *Sanofi*, the Supreme Court of Canada adopted a four-step analytical framework for assessing a claim of obviousness, which culminates in whether the differences between the state of the art and the inventive concept constitute steps that would have been obvious to the POSITA (para 67):

> [67] It will be useful in an obviousness inquiry to follow the four-step approach first outlined by Oliver L.J. in *Windsurfing International Inc. v. Tabur Marine (Great Britain) Ltd*., [1985] R.P.C. 59 (C.A.). This approach should bring better structure to the obviousness inquiry and more objectivity and clarity to the analysis. The Windsurfing approach was recently updated by Jacob L.J. in *Pozzoli SPA v. BDMO SA*, [2007] F.S.R. 37 (p. 872), [2007] EWCA Civ 588, at para. 23:
>
> In the result I would restate the Windsurfing questions thus:
>
> (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? [Emphasis added.]
>
> It will be at the fourth step of the *Windsurfing/Pozzoli* approach to obviousness that the issue of "obvious to try" will arise.

[38] In *Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289, [1986] FCJ No 87 (Fed CA) [*Beloit*], Justice Hugessen provided this classic description of the technically knowledgeable yet uninventive POSITA:

> The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. The question to be asked is whether this mythical creature (the man in the Clapham omnibus of patent law) would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.

[39] While still good law, the Supreme Court cautioned that the *Beloit* test must neither be treated as a statutory prescription, nor applied in an acontextual manner (*Sanofi* at paras 61-62).

[40] The Supreme Court also provided that, as part of the fourth step of the obviousness analysis, the "obvious to try" test may be applied to assess obviousness in circumstances such as these (*Sanofi* at para 68):

> i. When Is the "Obvious to Try" Test Appropriate?
>
> [68] In areas of endeavour where advances are often won by experimentation, an "obvious to try" test might be appropriate. In such areas, there may be numerous interrelated variables with which to experiment. For example, some inventions in the pharmaceutical industry might warrant an "obvious to try" test since there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances.

[41] 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", but "[m]ere possibility that something might turn up is not enough" (*Sanofi* at para 66). In *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8 at paras 28-29, the Federal Court of Appeal

clarified that the “obvious to try” test is not a “worth a try” test and provided the following guidance:

> The test recognized is "obvious to try" where the word "obvious" means "very plain". According to this test, an invention is not made obvious because the prior art would have alerted the person skilled in the art to the possibility that something might be worth trying. The invention must be more or less self-evident.
>
> The factors to consider when assessing whether an invention was “obvious to try” include the following (*Sanofi* at paras 69-70):
>
> 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?

[42] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.

[43] The Supreme Court stipulated in *Sanofi* that the obvious to try factors enumerated above are not exhaustive, but rather must be (a) applied in accordance with the facts of each case (para 69), and (b) approached cautiously as one consideration in the broader obviousness inquiry, not as a “panacea for alleged infringers” (para 64).

[44] As specified in the *Patent Act*, the obviousness test is to be considered based on information that was available to the public before the claims date, which is June 1, 2001 in this case (see *Mediatube Corp v Bell Canada*, 2017 FC 6 at para 119, commenting on s. 28.3 of the *Patent Act*).

B. *Expert Evidence*

(1) Summary of the Experts Affidavits

(a) *Dr. Polli (Applicants' Pharmaceutical Expert)*

[45] Dr. Polli provided an in-depth analysis of the 098 Patent, reviewing the available treatment options and co-therapies listed, considering its examples, and interpreting its claims. Dr. Polli noted the harmful side effects of NSAIDs on the GI system, and approaches to mitigating this, including combining NSAIDs with a cytoprotective prostaglandin, such as misoprostol, in ARTHROTEC.

[46] After examining the prior art listed by Mylan in its NOA, Dr. Polli stated that it showed that PPIs were well known to be sensitive to acid, and it was clear in teaching that PPIs had to be protected from acids in the abdomen. PPIs were therefore, at the time, always enteric coated.

[47] Dr. Polli wrote that the skilled person would only have been led to the inventive concept with the benefit of the 098 Patent's teachings and a hindsight analysis, given that the prior art taught away from – and indeed provided absolutely no suggestion of – a coordinated dosage unit

containing a PPI and NSAID where the PPI or a portion thereof would be released immediately followed by a delayed NSAID release.

[48] Dr. Polli rejected the obvious to try assertions of Mylan in maintaining that despite significant academic and industry interest in developing alternative co-therapies to traditional NSAID formulations, the skilled person would not have been thinking about trying an oral solid dosage form in which all or a portion of the PPI was not enteric coated or otherwise unprotected from gastric acid. With respect to ARTHROTEC, Dr. Polli concluded that the skilled person would not think that an uncoated PPI could simply be substituted for the misoprostol with immediate release in the stomach.

(b) *Dr. Armstrong (Applicants' Expert Clinician)*

[49] Dr. Armstrong provided a comprehensive review of the human body's defences to stomach acids, and the grave dangers of ulcers, lesions and other GI injuries. He examined the least harmful NSAIDs (such as COX-2 selective, and nitrous oxide NSAIDs), along with the various co-therapies available by 2001.

[50] Considering the prior art, Dr. Armstrong found that agents that raised gastric PH, including antacids (such as MAALOX), H_2 blockers (such as ranitidine in ZANTAC or famotidine in PEPCID), and PPIs (such as omeprazole in LOSEC), to be the most effective NSAID co-therapies at the relevant time. However, he found that the accepted wisdom was that PPIs required an enteric coat to be effective.

[51] Dr. Armstrong also considered exogenous prostaglandins, such as misoprostol in ARTHROTEC, as an existing co-therapy with NSAIDS in 2001. However, Dr. Armstrong wrote that a skilled clinician would not consider misoprostol and PPIs to be interchangeable, as they are different types of drugs, and have different mechanisms to reduce the risk of NSAID-induced GI injury (i.e., that misoprostol was known to have protective effects on the gastroduodenal mucosa that went beyond inhibition of gastric acid secretion).

[52] Dr. Armstrong concluded in his Affidavit that to the skilled clinician, the 098 Patent provided a novel and rationally-based approach to managing the risk of NSAID-induced GI disorders, as it was contrary to the conventional wisdom that PPIs had to be enteric coated.

(c) *Dr. Lane (Respondents' Expert Clinician)*

[53] Dr. Laine asserted that because physicians commonly recommended co-administration of a PPI with a NSAID to reduce gastric injury, a skilled person would have found the claimed formulation (such that the PPI would release initially, followed by the NSAID when the pH was 3.5 or higher) obvious in light of the common general knowledge at the time.

[54] Dr. Laine found that the 098 Patent's "sequential release" approach had already successfully been used for other agents including misoprostol in preventing GI tract injury, and oral formulations of uncoated PPIs in solid dosage forms were in use by the year 2000. He cited various prior art for these conclusions, including MD30 and MD10 (ARTHROTEC), MD7 (PPI/NSAID combination), and MD13 (oral formulation of non-enteric coated PPI).

[55] Dr. Laine, like Dr. Armstrong, identified various approaches to co-therapy, namely, protective agents, agents that raise gastric pH, and exogenous prostaglandins. However, according to Dr. Laine, the fact that PPIs have a different mechanism of action than other agents would not have deterred persons skilled in the art from pursuing the sequential-release approach of the 098 Patent, which he found at the relevant time would have been obvious to an ordinary clinician, and not involved any degree of inventiveness. Dr. Laine also wrote that sequentially releasing the PPI before the NSAID did not provide for any benefit over existing strategies. Dr. Laine noted the shortcomings of the examples used in the 098 Patent (based on the fact that the evidence relied upon did not provide any novel information), and that the patent did not provide any testing results for the claimed formulation.

[56] Ultimately, although acknowledging his expertise as a clinician rather than a formulator, Dr. Laine rejected the claims of Drs. Armstrong and Polli that the skilled person would only have considered enteric coating PPIs. Instead, he opined that there would have been a strong motivation to combine NSAIDs with PPIs in a single dosage form due to (i) co-administration of a NSAID with a PPI being a "standard of care" to reduce NSAID-associated GI injury; (ii) a concern about improving compliance for patients at risk of this type of injury; and (iii) existing and widely-used products that provided NSAID benefit and GI protection in a single dosage form.

(d) *Dr. Appel (Respondents' Pharmaceutical Formulator Expert)*

[57] Dr. Appel wrote that designing "a specific mechanism of release" and "a specific architecture" are distinct parts in the formulation process. She concluded, after considering the

prior art and claimed invention, that the asserted claims would have been obvious to a skilled formulator, as the architecture had been used previously in combination formulations containing NSAIDs and gastroprotective drugs, such as ARTHROTEC.

[58] Dr. Appel found that the architecture described in the 098 Patent could have been used for any combination of NSAID and PPI (i.e. not only naproxen and esomeprazole). She noted in any event that the combination of NSAID and PPI had previously been formulated in prior art. She disagreed with her counterpart expert for the Applicants, Dr. Polli, who opined that the prior art taught away from the patent. Rather, Dr. Appel posited that a formulator would have considered a broader range of approaches than had Dr. Polli, and would have been motivated to arrive at the claimed formulation. Indeed, the prior art demonstrated that there were multiple formulation approaches possible, including a sequential release profile.

[59] Dr. Appel outlined three types of strategies to counter NSAID degradation caused by its acid lability (sensitivity) and provided examples of each of them in the prior art: (i) enteric coating (MD7); (2) time-release coating (MD9 and MD33); and (3) an alkalizing agent (MD13 and MD14). Dr. Appel characterized enteric coating the PPI as one option, but not the only one. Furthermore, Dr. Appel noted that ARTHROTEC has the same formulation strategy and architecture as the proposed invention, namely the sequential release of an acid inhibitor and a NSAID from a unit dosage form.

[60] Dr. Appel concluded that the prior art indicated a consistent motivation to come up with new formulations and products in the area. Indeed, the patent itself covers numerous drugs with

different mechanisms, including PPIs and H_2 inhibitors. With "acid inhibitors" being broadly defined, there is no reason that misoprostol would not be included, as it had been shown to inhibit gastric acid secretion and raise pH levels.

(e) *Dr. Lee (Respondents' Pharmaceutical Formulator Expert)*

[61] Dr. Lee concluded that a skilled formulator at the relevant date would have seen the approach set out in the asserted claims as having been similarly pursued previously. He based this on various NOA materials, observing that the prior art showed that the sequential release approach in the asserted claims had been successfully applied to several other products co-formulated with a NSAID for the same GI-protective purpose, such as in ARTHROTEC.

[62] Dr. Lee disagreed with Dr. Polli, who wrote that the inventive concept was to delay the NSAID release until GI acid levels were reduced to non-toxic levels. Rather, Dr. Lee interpreted the claims as simply stipulating the NSAID release would occur in a medium with pH levels above 3.5, regardless of how the PPI behaves. Dr. Lee further opined that the claims in issue do not specify that the PPI (esomeprazole or its pharmaceutically acceptable salt) must achieve any minimum level of acid inhibition. In short, Dr. Lee found that the difference between the state of the art and the inventive concept of the asserted claims appeared to be choosing, in a single dosage form, to sequentially release a PPI – as opposed to another protective agent – prior to a NSAID.

[63] According to Dr. Lee, arriving at this NSAID-PPI tablet with its particular sequential release formulation was not inventive given the prior art, and would have been obvious to try

through minimal and routine experimentation. Of the four available formulation options he noted, Dr. Lee explained that the 098 Patent's 'tablet-in-tablet' approach required only a routine formulation exercise using the prior art, which included ARTHROTEC and which did not teach away from the claimed invention. A skilled formulator would have been motivated to (a) combine these agents in a single pill, given the finite number of combinations, and (b) consider a co-formulation that replaced misoprostol with a more efficient (or potent) acid inhibitor. He also critiqued the lack of clinical studies or results provided in the 098 Patent. Dr. Lee pointed to numerous sources where the PPI was not enteric-coated or otherwise protected.

(2) Challenges to Expert Evidence and Credibility

[64] Having seen the main thrust of the experts' evidence, this section will briefly summarize the primary attacks on the experts, and any conclusions drawn.

(a) *Partiality*

[65] Both sides impugned the partiality of the experts.

[66] AstraZeneca made claims impugning the impartiality of Mylan's experts given certain ties (financial and otherwise). For the reasons below, I reject those arguments.

[67] Mylan's argument that AstraZeneca's experts exhibited an unjustified bias towards enteric coating was equally unpersuasive: this was simply a point of disagreement in the interpretation of the prior art, rather than any demonstration of bias in the legal sense.

[68] The Supreme Court of Canada recently revisited the inadmissibility of expert evidence for partiality in *White Burgess Langille Inman v Abbott and Haliburton Co*, 2015 SCC 23 [*White Burgess*]. In *White Burgess*, the Supreme Court found that experts have a duty to the court to provide "fair, objective and non-partisan" assistance (at para 46), and are required to certify that they are aware of and will comply with this duty (at paras 28-29; see also *Federal Courts Rules*, SOR/98-106, Rule 52.2(1)(c)).

[69] The party opposing the admission of the evidence must show "a realistic concern that the expert's evidence should not be received because the expert is unable and/or unwilling to comply with that duty" (*White Burgess* at para 48). If successful, the burden switches back to the party supporting the expert to establish, on a balance of probabilities, that the evidence is admissible – a threshold that the Supreme Court states is "not particularly onerous". The following discussion and scenario provided is illustrative of the relatively low threshold to admit expert evidence (*White Burgess* at para 49):

> The trial judge must determine, having regard to both the particular circumstances of the proposed expert and the substance of the proposed evidence, whether the expert is able and willing to carry out his or her primary duty to the court. For example, it is the nature and extent of the interest or connection with the litigation or a party thereto which matters, not the mere fact of the interest or connection; the existence of some interest or a relationship does not automatically render the evidence of the proposed expert inadmissible. In most cases, a mere employment relationship with the party calling the evidence will be insufficient to do so. On the other hand, a direct financial interest in the outcome of the litigation will be of more concern… I emphasize that exclusion at the threshold stage of the analysis should occur only in very clear cases in which the proposed expert is unable or unwilling to provide the court with fair, objective and non-partisan evidence. Anything less than clear unwillingness or inability to do so should not lead to exclusion, but be taken into account in the overall weighing of costs and benefits of receiving the evidence.

[70] The Supreme Court went on to further explain that the high threshold is breached when the expert is actually unable or unwilling to fulfil this duty to the court, not by a perceived lack of independence (at para 50):

> When looking at an expert's interest or relationship with a party, the question is not whether a reasonable observer would think that the expert is not independent. The question is whether the relationship or interest results in the expert being unable or unwilling to carry out his or her primary duty to the court to provide fair, non-partisan and objective assistance.

[71] Of course, prior inconsistent statements or implausible positions may also lead one to question the credibility of that expert. However, there would need to be evidence of such statements and positions (see, for instance, *Allergan Inc v Canada (Minister of Health)*, 2011 FC 1316 at para 32). I find no such evidence in this case.

[72] The Court finds, after having listened to the submissions about the experts, insufficient evidence to sustain any credible presumption of bias. Suffice it to say that pharmaceutical experts often appear before the Court for the same party, and may have even been previously employed by that party. But this does not mean that they lack independence, and it certainly does not mean they are not impartial: to suggest that their opinions have been tainted by prior work or affiliations can only hold water with compelling evidence of the same.

[73] This is far from a clear case where any of the experts were unable or unwilling to provide fair, objective and non-partisan input; no evidence of same was furnished. As a result, none of the five experts who gave evidence for this litigation will be rejected on the basis of bias or credibility. That the experts evidently disagreed on their interpretation of certain aspects of the

prior art, common general knowledge, and resulting obviousness conclusions, is common in pharmaceutical litigation. Certain experts' observations and conclusions are more compelling than others, and as a result, the Court places more weight and greater reliance on some experts' evidence than others.

(b) *Blinding*

[74] AstraZeneca claims that the Mylan's experts simply responded to Dr. Polli's opinions without reviewing the NOA, and that Dr. Polli was the only expert who expressly addressed the allegations raised in the NOA. Mylan's experts, on the other hand, relied on new factual bases outside of the NOA. Furthermore, Mylan failed to blind their experts to the patent. AstraZeneca's experts, on the other hand, gave their opinions based on their review of the common general knowledge and prior art, ensuring they had open minds.

[75] Mylan deflected AstraZeneca's criticisms of the experts, arguing that the latter's approach was worse, namely blinding to any alternative to enteric coating for PPIs. Mylan also noted that while AstraZeneca's experts were blinded to the patent, they were given an inventive concept and asked to evaluate it, which is tantamount to receiving the patent without the ability to independently assess it.

[76] For its part, Mylan argued that its experts were respectful of their roles within a clinician-formulator team, correctly instructed on the law, told to avoid using hindsight, and not provided with a copy of the NOA (which would have revealed Mylan's position).

[77] Blinding experts does not necessarily produce a more reliable outcome. As Justice Locke recently held in *Shire Canada Inc v Apotex Inc*, 2016 FC 382 at paras 45-46:

> 45 …I am mainly interested in the substance of an expert's opinion and the reasoning that led to that opinion. If it is well-reasoned, there may be no reason for concern about whether the witness was blinded to certain facts when giving the opinion. A concern may arise where the expert's opinion seems tortured or less well-reasoned.
>
> 46 I am also conscious that the blinding of witnesses is no guarantee that the expert evidence before the Court is reliable. It would not be difficult (though it would be expensive) for an unscrupulous party to seek opinions from a number of experts, keeping them all blind to unnecessary information. If one of those many experts provided the opinion that the party sought and all of the others concluded otherwise, the party would be able to retain the outlier and present him or her as a blinded (and therefore reliable) witness.

[78] In this case, the approach of both sides in the preparation of their witnesses was acceptable, and as a result neither warrants exclusion or less weight. Rather, my analysis turns on which of the experts provided the most compelling evaluations of the common general knowledge held by the POSITA, the state of the art, and other factors in the obviousness analysis.

C. *Obviousness Analysis*

(1) The State of the Art

(a) *The POSITA*

[79] The parties and the expert witnesses agree that the notional POSITA would include a skilled pharmaceutical formulator with relevant education and experience, working in

collaboration with a drug development and formulation team that includes at least a skilled medical clinician.

(b) *Common General Knowledge*

[80] The parties differ on their positions with respect to the common general knowledge at the relevant time.

[81] In short, AstraZeneca posits that the common general knowledge would have led the POSITA to conclude that a PPI, when co-administered with a NSAID, had to be protected by an enteric coating in order to avoid being immediately released. Immediate release would have failed to protect the PPI from the acidic conditions of the stomach. Mylan refutes this argument, contending that the skilled person would have known not only of NSAID-PPI combination formulations and of co-formulations of a NSAID with other gastroprotective drugs with a sequential release profile, but also of non-enteric coated PPIs.

[82] The Court's task at this stage is simply to determine the common general knowledge of the POSITA at the relevant date, as opposed to what the POSITA might have been expected to find and consider from researching the relevant prior art.

[83] As discussed in the facts section above, as of the relevant date the skilled person knew, as common general knowledge, that alternative treatments to the 098 Patent's co-therapy of a NSAID with an uncoated PPI included: (a) less injurious NSAIDs, such as COX-2 specific inhibitors (CELEBREX); and (b) NSAID co-therapy with drugs such as H2 blockers (e.g. MD8),

misoprostol (as in ARTHROTEC), or enteric coated PPIs (e.g. MD7). While some of these alternatives were less desirable and prescribed than others, they were all commonly known. Indeed, the 098 Patent itself mentions these treatment options.

[84] Of particular note here is that PPI and NSAID combinations were well known. Indeed, as Dr. Laine pointed out in his affidavit, the 1998 American College of Gastroenterology guidelines on the treatment and prevention of NSAID-induced ulcers, which remained current in 2001, recommended preventative co-therapy with either misoprostol or PPIs (Dr. Laine Affidavit at para 56). The specific choice of naproxen and esomeprazole for a NSAID-PPI combination was also not novel (e.g. MD7).

[85] Further, enteric coated NSAIDs were widely used; even enteric coated naproxen specifically was commercially available (MD24; Dr. Laine Affidavit at para 144).

[86] Finally, there were three other pieces of prior art that were the focus of significant debate in the obviousness issue: (i) MD52: a 1985 journal article which AstraZeneca argued 'taught away' from non-enteric coated PPIs; (ii) MD13: a May 2000 patent application for a medication combining a PPI with a bicarbonate salt; and (iii) ARTHROTEC, e.g. MD30: a 1992 journal article discussing ARTHROTEC, the co-formulation of misoprostol and a NSAID in a multi-layer tablet, with the immediate release of misoprostol followed by a delayed release of the NSAID.

(i) Non-enteric Coated PPIs (MD52, MD13 and MD14)

[87] According to AstraZeneca, MD52 shows that the prior art ‘taught away’ from not fully enteric coating a PPI. AstraZeneca argued that despite being from 1985, this prior art was not outdated as of the relevant date, and that the prior art relied upon by Mylan is not relevant. For example, MD7, which was published many years later in 1997, is consistent with MD52.

[88] Nevertheless, I agree with Mylan that MD52 is dated art. Mylan’s experts (Drs. Laine and Appel) addressed it, and I agree with them that subsequent art, including MD13, superseded it.

[89] According to Dr. Laine, by the relevant date, the administration of PPIs without enteric coating was not merely theoretical; it was well-described and used in clinical practice (Dr. Laine Affidavit at para 185). MD13, which was released in 2000 (15 years after MD52), is a patent directed to the treatment of gastric disorders by administering a pharmaceutical composition of a PPI with a bicarbonate salt in a dry solid formulation, prior to dissolution. MD13 acknowledged challenges with existing PPI-sodium bicarbonate formulations, but taught that the invention therein overcame these. In particular, its inventors claimed a solid oral pharmaceutical composition containing a PPI and bicarbonate salt wherein the dosage form, such as a tablet or capsule, is not enteric coated or time released (claims 5 and 8 of MD13).

[90] In reply, AstraZeneca argues that this prior art is directed only to the administration of PPIs as suspensions or solutions, not solid dosage forms, and so it is not relevant. In particular, it was for those who cannot swallow. The solid form is simply for storage.

[91] These objections are noted. However, it is also noted that MD13 teaches that the dry formulation need not necessarily be mixed with water prior to ingestion; it may simply be ingested and then acted upon by the water utilized to swallow the solid formulation (MD13 at 27).

[92] Moreover, MD14 is another patent from 2000 directed to a non-enteric coated PPI, and it was published by AstraZeneca. Of particular note is the comment of its inventors regarding their dosage form without an enteric coating "which previously [has] been almost an axiom for dosage forms containing omeprazole or any other proton pump inhibitor compounds" (MD14 at 2-3). According to the MD14 inventors, any 'teaching away' was now in the past. Further, MD14 taught that the alkalizing agent in the core would neutralize the absorbed acidic fluid and protect the active ingredient against degradation.

[93] As a result of the above, I find that the common general knowledge included several approaches to formulating acid-sensitive compounds such as PPIs, including the use of an alkalizing agent to reduce degradation by acid in the stomach.

[94] I further find that at the relevant date the common general knowledge was that there were alternatives to enteric coating a PPI. Stated conversely, it was not common general knowledge that one must enteric coat a PPI.

(ii) ARTHROTEC (MD10, MD11, and MD30)

[95] AstraZeneca argued that ARTHROTEC should not figure into the obviousness analysis because misoprostol acts differently than a PPI; it is not an "acid inhibitor". This is because it has a different protective mechanism than PPIs: misoprostol is a prostaglandin analogue, supplementing prostaglandins (which help to protect the stomach lining). Therefore, the administration of misoprostol is sometimes referred to as "replacement therapy." Misoprostol inhibits prostaglandins throughout the body, rather than targeting just the stomach lining, which can be contrasted with PPIs, which solely inhibit acid by inactivating proton pumps (which secrete acid) within the parietal cells of the stomach lining. Dr. Laine lists the various defensive mechanisms of prostaglandins as follows:

(a) inhibition of acid secretion;

(b) stimulation of mucus (which covers the lining of the stomach) and bicarbonate (alkaline molecule which counteracts/neutralizes acid;

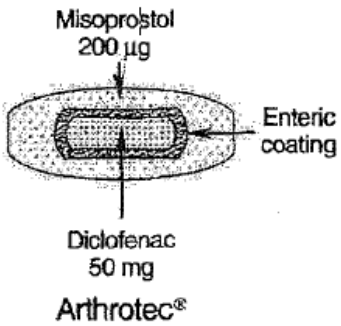
(c) increased blood flow in the stomach lining;

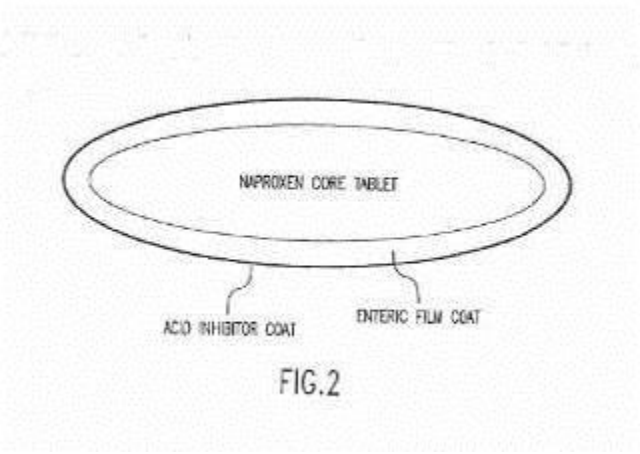
(d) accelerated restoration and healing of the stomach lining; and

(e) prevention of blood cells from sticking to the walls of blood vessels.

[96] Mylan argues that while misoprostol may not work in exactly the same way as other acid inhibitors such as PPIs, and may have different side effects, arguing that it is not an acid inhibitor equates to saying a Swiss Army Knife is not a knife. ARTHROTEC was the only commercially-available fixed dose NSAID co-therapy drug to mitigate GI side-effects at the relevant time. AstraZeneca's own expert Dr. Armstrong appeared to accept this (Dr. Armstrong Cross-Examination at 71:14-22) and generally noted that misoprostol reduced gastric acid secretion and NSAID-induced ulcers (Dr. Armstrong Affidavit at para 74).

[97] MD30, a journal article about ARTHROTEC published in 1992, showed not only that fixed-dose combinations of NSAIDs and other gastroprotective drugs were well-known, but also showed that a sequential-release formulation was commercially available for such combinations. It depicted ARTHROTEC's formulation (left), which can be compared to the 098 Patent's Fig. 2 (right), below.





[98] Both diagrams depict a NSAID core, immediately surrounded by an enteric coating, with an outer layer of a gastroprotective drug (misoprostol on the left, and an acid inhibitor – being a PPI in the Asserted Claims – on the right). Dr. Appel addressed the architectural similarities at length, which I find to be persuasive evidence.

[99] After considering the arguments from both parties, I do not find it necessary to decide whether misoprostol is properly labeled as an "acid inhibitor", due to the fact that I find that misoprostol has a similar purpose and ultimate effect as PPIs within their respective formulations (ARTHROTEC and the 098 Patent).

[100] I find the distinction made among the two types of effects – systemic and local – is of no consequence for the purposes of this proceeding, as ultimately both act on the same receptors and have the same net effect of limiting GI injury resulting from NSAID use.

[101] The fact that, as conceded by Mylan, misoprostol was not as desirable a NSAID co-therapy option as PPIs due to its side-effects does not eliminate it from the state of the art. That art, including MD10, MD11, and MD30, clearly shows that as part of a multi-layer tablet, misoprostol was co-formulated using similar architecture to that depicted in the 098 Patent.

[102] Despite the disagreement over misoprostol's proper classification, it is not disputed that misoprostol has the effect of inhibiting acid. Further, there is uncontradicted evidence that misoprostol and PPIs were generally recommended co-therapy agents to protect against NSAID-associated injury at the relevant date. For example, as discussed in paragraph 84, the 1998 American College of Gastroenterology guidelines on the treatment and prevention of NSAID-induced ulcers, which remained current in 2001, identified misoprostol and PPIs as the acceptable co-therapy agents (Dr. Laine Affidavit at para 56).

[103] In short, it is unnecessary to determine whether misoprostol is properly classified as an "acid inhibitor" because what ultimately impacts the obviousness analysis is whether misoprostol would have been considered by the POSITA. While misoprostol might not be "interchangeable" with PPIs *per se*, I find that the skilled person would have considered it as part of the relevant prior art as one of the other generally recommended NSAID co-therapy agents.

(2) The Inventive Concept

[104] As discussed in Section II (“Background”) above, for the purposes of these proceedings, the Applicants asserted claim 37 (itself dependent on claim 34, 35, or 36) and claims 38 to 44 where dependent on claim 37.

[105] According to AstraZeneca, the inventive concept could be described, consistent with the experts evidence, as follows: a solid dosage form (such as a tablet) that provides for the immediate release of at least a portion (or all) of the esomeprazole regardless of the pH of the medium, and for the delayed release of all of the naproxen. AstraZeneca claimed that what made the 098 Patent inventive was that it offered “a new method of reducing the risk of GI side effects in people taking NSAIDs: a single tablet or capsule that provides for a coordinated (i.e., sequential) release of acid inhibitor first and NSAID second” (Applicants’ Memorandum at para 17).

[106] According to Mylan, the inventive concept is the use of a coordinated, sequential-release formulation architecture for a formulation containing a NSAID and a PPI. Mylan goes on to argue that the inventive concept neither includes the decision to combine a NSAID and a PPI, nor the specific choice of naproxen or esomeprazole as the NSAID and PPI in the formulation.

[107] In other words, the parties and their experts were in large measure agreed as to the inventive concept. However, in light of my findings with respect to the common general knowledge, as set out above, I agree with Mylan that there was nothing novel or inventive about combining a NSAID and a PPI, nor the specific type of each used in the Asserted Claims. Therefore, I find the inventive concept to be a Tablet formulated for immediate release of a

portion, or all, of the PPI regardless of the pH of the medium, with a delayed release of the NSAID until the pH of the medium is at least 3.5.

(3) Differences Between the State of the Art and Inventive Concept

[108] The third determination considers the difference, or delta, between the state of the art and the inventive concept. It is that delta on which the obviousness determination will hinge.

[109] A substantial difference between what was known in the art and what was represented in the 098 Patent normally would not have been obvious to the POSITA. A small delta, by contrast, might have been relatively easy to bridge and therefore may satisfy the difficult obviousness threshold – although a mere scintilla of inventiveness is always sufficient to put the difference beyond what would have been obvious to the POSITA.

[110] As a result, in an obviousness challenge to a patent's validity, determining the knowledge delta is a key inquiry.

[111] The parties differed in describing the delta between the state of the art and inventive concept. According to AstraZeneca, the major difference between the inventive concept and the state of the art includes the sequential release of a PPI followed by a NSAID. AstraZeneca contends that this constituted a major difference that would not, without the patent, have been self-evident to the POSITA, because the prior art taught away from the invention.

[112] Mylan disagreed, contending that the difference between the inventive concept and the state of the art is the application of the well-known sequential release architecture to the well-known NSAID-PPI combination, using routine means, to achieve a well-known advantage: reduction of GI side effects in NSAID co-therapy. In other words, the inventive concept is simply a combination of the prior art – a minor difference.

[113] Despite Mylan's ostensible disagreement, I do not believe the parties are, in substance, far apart on this point. Both focus on the formulation's sequential release profile.

[114] As discussed, a NSAID-PPI co-formulation for this purpose was not new, and neither was the concept of sequential release when co-formulating a PPI with a gastroprotective drug. What was indeed novel, however, was the application of this sequential release profile in a NSAID-PPI co-formulation. Therefore, I find that the difference between the state of the art and the inventive concept lies in the sequential release profile, which is achieved by the decision not to fully enteric coat the PPI.

[115] In my view, the divergence between the parties' position, as outlined above, properly goes to the fourth step, and so is further considered in the analysis section below.

(4) Whether Those Differences Constitute Obvious Steps

[116] The fourth and final section of the obviousness analysis involves a determination of the steps that the POSITA would have required to bridge the gap between the state of the art and the inventive concept. The key question to be answered in this final stage of *Sanofi*'s four part test is

whether the bridging of this gap required steps which would have been obvious to the POSITA. Otherwise stated, did the steps require any degree of invention? In my view, they did not.

[117] AstraZeneca argued that the differences would not have been obvious to the POSITA at the relevant time: coordinated release, with the PPI releasing immediately (at least in part) in the stomach followed by a delayed release of the NSAID in the small intestine, was inventive "because PPIs were known to be acid sensitive and should not be immediately released in the acidic stomach from a solid dosage form" (Applicants' Memorandum at para 2). AstraZeneca maintained that "all commercial PPI products were delayed release formulations", as "[o]nly a delayed release PPI, when used with NSAID therapy, had been shown to effectively reduce the risks of NSAID-induced GI injury" (Applicants' Memorandum at para 2).

[118] According to Mylan, while the 098 Patent's coordinated release may not have been previously suggested in the exact combination proposed (i.e. NSAID-PPI), it was consistent with the common general knowledge at the relevant time and represented an obvious step.

[119] The obvious to try considerations are examined in a separate section below. Before looking at those factors, I will address some of the key elements explaining why bridging the gap between the state of the art and the inventive concept would have been self-evident to the POSITA at the relevant time.

[120] As discussed, a NSAID-PPI combination was part of the common general knowledge, as was the sequential delivery profile for combinations with other co-therapy agents.

[121] All of Mylan's experts provided compelling evidence that, although the combination had not yet been tried, applying the sequential release profile to a NSAID-PPI combination was obvious to try for a tablet-in-tablet formulation (e.g. Dr. Lee Affidavit at para 158).

[122] Even AstraZeneca's experts, when pressed, generally agreed that ARTHROTEC served a similar purpose in that misoprostol is used to help protect against the negative GI effects of NSAIDs. The fact that the side effects from misoprostol could be more severe than those from a PPI, making it a less desirable medication for many, does not detract from the fact that it served as (a) an option to address the nefarious effects of GI injury, along with some of the other co-therapies and anti-acidic agents paired with NSAIDs, and (b) a reason (or motivation) for inventors to try other formulations, including that set out (but not tested) in the 098 Patent. As already explained, I cannot support AstraZeneca's refusal to characterize misoprostol as an acid inhibitor, despite the acknowledgement that it inhibits acid and addressed the same problem as the 098 Patent.

[123] The prior art included formulations without an enteric coating, such as a PPI and bicarbonate where, like with the 098 Patent, there was no enteric coating or time-release (MD13). Further, the architecture was known in the context of another NSAID co-agent, misoprostol, and its commercial co-formulation ARTROTEC. What was <u>not</u> known was using a (non-enteric coated) PPI instead of misoprostol for the outer layer in this architecture, such that the PPI was subject to immediate release in the stomach, followed by the delayed release of the NSAID. However, I find this sequential release (via not enteric coating the PPI) to have been obvious, due in part to the prior art (such as MD7, MD10, MD13, and MD30). Given the highly

competitive nature of the pharmaceutical market, my conclusion is further supported by the "obvious to try" test, discussed below.

[124] Before proceeding with the obvious to try analysis, I wish to note that it, and indeed all facets underpinning the obviousness analysis, is focused on claim 37 as dependent on the other Asserted Claims, as the Applicant asserted. I have nevertheless considered all of the Asserted Claims individually, as first addressed in Section VI above. Limited attention has been expressly given to a number of the individual claims within the Asserted Claims simply because there was no genuine dispute regarding them in the context of the obviousness allegation.

[125] For instance, the composition specified in claim 35, as varied from that in claim 34, did not change the inventive concept for the purposes of the obviousness analysis. Further, I find that there was nothing inventive – nor was there any suggestion that there was anything inventive – regarding the following:

a. specifying that the dosage amount of naproxen in the composition be between 250 and 500 mg (claim 36);
b. specifying that the unit dosage form outlined in claim 34 (or claims 35 or 36) be a tablet (claim 37); or
c. using the pharmaceutical composition for any of the purposes set out in the usage claims (claims 39 to 44), which are consistent with the existing alternative products already discussed.

[126] Therefore, as with the rest of my analysis, the obvious to try considerations below will focus on crux of this matter: the application of the sequential release profile in a NSAID-PPI co-formulation, which was achieved by not fully enteric coating the PPI – whether it be partially enteric coated (claim 34), or not at all (claim 35).

(5) Obvious To Try Consideration

[127] The final point to canvass, as an adjunct to the fourth *Sanofi* criterion, is the "obvious to try" test. As is often the case in pharmaceutical patent disputes (*Sanofi* at para 68), the "obvious to try" test is warranted here. I have concluded that the inventive concept in this case was indeed obvious to try because: (i) there were a limited number of predictable solutions in managing GI injury that would have been more or less self-evident to work, (ii) the invention did not involve an undue amount of effort to achieve, and (iii) there was a strong motive to combine a NSAID with a PPI in a single dosage combination with the sequential release profile.

(a) *Is it More or Less Self-Evident That What is Being Tried Ought to Work?*

[128] Here, Mylan's experts found that there were indeed a limited number of identified predictable solutions known to the POSITA. Clearly, the options were limited as to what agents could be used in combination with a NSAID to lessen the risk of GI injury (see said options above). PPIs were commonly known to be one of those options, even if they had not been brought to market in a tablet form with sequential release. PPIs had been brought to market in other forms (such as co-administered for intravenous, immediate release).

[129] In light of the expert evidence, and given the common general knowledge as set out above, including the understanding that PPI's did not necessarily have to be enteric coated, I find it would have been self-evident to the POSITA that an ARTHROTEC-type of architecture could be successfully applied to a NSAID-PPI formulation.

[130] Therefore, it would have been more or less self-evident to the POSITA that the sequential release profile in the Asserted Claims, achieved in part by the decision not to fully enteric coat the PPI, would work.

(b) *What is the Extent, Nature, and Amount of Effort Required to Achieve the Invention?*

[131] Dr. Appel described the work that would have gone into the formulation of the 098 Patent as routine and noted the inventor's own observation in the 098 Patent that the invention "can be made in accordance with methods that are standard in the art" (098 Patent at p 10, lines 21-22).

[132] Drs. Appel, Laine, and Lee also found that the patent provided incomplete clinical testing data in its examples, with no testing of any NSAID-PPI formulation (rather, there were only limited trials conducted on other agents). AstraZeneca's experts did not counter these observations in their written testimony, and indeed, under cross-examination Dr. Polli agreed that the patent did not provide for any testing of the non-enteric coated PPI formulation in the patent.

[133] On this factor of effort, I am persuaded by Mylan's conclusion that only a limited amount of effort was required to achieve the inventive concept. The only evidence of any trials was of limited use because they were for other agents (Examples 8 and 9 of the 098 Patent). Nor is there any evidence from the inventor, apart from what has been set out in the patent which, as mentioned, is not very much. The fact that there was no evidence of any trials, nor any evidence of the knowledge of the inventors relative to the notional skilled person, can also be a relevant factor in considering the actual course of conduct (*AstraZeneca Canada Inc v Teva Canada Ltd*, 2013 FC 245 at para 64).

[134] Furthermore, neither the fact that (i) no one knew whether the claimed invention would provide any additional benefit (i.e. the non-enteric coated PPI), nor that (ii) there were other options amongst gastroprotective agents apart from PPIs, render the claims non-obvious. The following words of Justice Barnes in *Janssen Inc v Teva Canada Limited*, 2015 FC 184 at para 113, are apposite:

> …The fact that the formulator had a few choices to make and would need to test the formulation to ensure its efficacy does not render this exercise non-obvious. Here I adopt the point made by Justice Roger Hughes in *Shire Biochem Inc. v. Canada (Minister of Health)*, 2008 FC 538 (F.C.) at para 80, [2008] F.C.J. No. 690 (F.C.), that the existence of number of possible routes to solve a problem does not mean that the route taken was not obvious. In *Brugger v. Medicaid Ltd. (No. 2)*, [1996] R.P.C. 635 (England P.C.) at p 661, the same point was stated in the following way:
>
> > First a route may still be an obvious one to try even if it is not possible to be sure that taking it will produce success, or sufficient success to make it commercially worthwhile. ... Secondly, if a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well. If a number of obvious routes exist it is more

> or less inevitable that a skilled worker will try some before others.

(c) *Is There a Motive From the Prior Art to Find the Solution That the Patent Addressed?*

[135] The parties spent a significant amount of time putting forward their positions on specific versus general motivation, and whether the former alone could satisfy the "obvious to try" test.

[136] AstraZeneca argued that specific motivation – rather than simply a general motivation – must be present to satisfy *Sanofi*'s "obvious to try" test in this case. Here, there must have been a reason why a skilled person would have tried to specifically combine a PPI and NSAID with the uncoated PPI released first and the NSAID second. Otherwise stated, the motivation must be specific to the inventive concept.

[137] AstraZeneca claimed that Mylan's experts' evidence on whether it was obvious to try was (a) inconsistent, and (b) failed to establish any specific motivation to try. Drs. Appel and Lee, Mylan's expert formulators, stated that skilled clinicians would need to direct a particular release profile of a NSAID-PPI, and they provided inconsistent testimony as to what a skilled formulator would have done.

[138] AstraZeneca argued at the hearing that the evidence of Mylan's experts showed that there was no motivation to try the claimed sequential release formulation. AstraZeneca's argument in this regard was based primarily on the testimony of Dr. Laine, Mylan's expert gastroenterologist (clinician), whose evidence supposedly raised two bases for showing a lack of motivation.

(i) Alleged lack of motivation on part of clinician to instruct the formulation

[139] Normally, in the pharmaceutical team process which represents the POSITA in this case, the clinician's role is to direct the formulator. Simply put, the clinician generally identifies a clinical problem and may suggest approaches to solve it, while the formulator would generally develop the new drug or formulation that achieves that need, is stable, and can be reliably manufactured. The clinician directs and the formulator executes in the drug's design.

[140] In AstraZeneca's view, Dr. Laine (as clinician) would not have directed the formulator to design the sequential-release tablet described in the disputed claim. Specifically, AstraZeneca points to Dr. Laine's evidence that it was not clear that the sequential release of the PPI followed by the NSAID provides any additional benefit as compared to a formulation not designed to provide sequential release. This statement, AstraZeneca posits, is tantamount to admitting that there was no impetus to direct the formulators to come up with the inventive concept; and therefore there was no motivation to try.

[141] I do not accept this argument. The comment in question arises from a portion of Dr. Laine's Affidavit in which he is supporting his opinion that the sequential release formulation – the concept of having a protective agent (in the 098 Patent, the PPI) release before the NSAID – was well-known in clinical practice, in the medical literature, and in patents.

[142] In particular, just before the impugned comment, Dr. Laine stated that the knowledge that misoprostol, H_2s, and other similar NSAID co-therapy agents were released before the NSAID

with the goal of providing more effective protection against NSAID-induced GI injury in other formulations, would "certainly have suggested to the skilled clinician that he/she could pursue a similar approach with PPI protective therapy" (Dr. Laine Affidavit at para 204).

[143] While Dr. Laine indeed goes on to say that there is no evidence that the sequential release provides additional benefits in a NSAID-PPI combination, he was pointing out the 098 Patent's lack of evidence to support any additional benefits, and that it did not provide any inventive advantage, concluding at paragraph 223 of his Affidavit that:

> … sequential-release formulation could have produced an inventive advantage if the inventor has documented or taught that sequential release provided greater reduction of NSAID-associated GI injury, such as ulcers, than coadministration of PPI and NSAID or a combination formulation without the specified sequential-release pattern. However, this was not the case.

(ii) Alleged lack of known benefit

[144] Furthermore, I do not agree with the implicit argument that if there is no known inventive benefit to something, there would be no reason to try it. Such a reading would also be inconsistent with the context provided by the rest of Dr. Laine's opinion, namely that the existing sequential release co-formulations of NSAIDs with other gastroprotective agents would suggest to the skilled clinician that a similar approach could be taken with PPI protective therapy, and his ultimate conclusion that it was indeed obvious to try. Dr. Laine acknowledged that not enteric coating the PPI in such a combination had not previously been formulated, but it was nonetheless obvious. In other words, just because an idea is new, does not mean it cannot also be obvious. Mylan pointed to several classic cases that stood for this basic principle in patent law (e.g. *Actavis UK Ltd v Novartis AG*, [2010] EWCA Civ 82 (UK CA) at paras 36-38).

[145] Mylan argued that the skilled clinician would have had the required motivation to develop a sequential-released NSAID-PPI tablet formulation, and that the law does not require that motivation to be so specific as to be the singular pursuit of the exact invention claimed when there were many good options available. To require otherwise would mean protecting claims without any inventive step.

[146] I do not read Dr. Laine's testimony as stating that skilled formulators would have lacked any motivation. After emphasizing that he was not a formulator (Dr. Laine Affidavit at para 213), Dr. Laine nonetheless went on to explain why the inventive concept, and in particular the formulation of sequential release NSAID with non-enteric coated PPI, was neither novel (paras 213-220) nor advantageous (paras 221-227). Dr. Laine went on to explain immediately after, "[i]n my view, there was a motive to combine an NSAID with a PPI in a single dosage combination, because co-administration of an NSAID with a PPI was a standard of care to reduce NSAID-associated GI injury such as ulcers…" (para 229).

[147] Dr. Armstrong acknowledged under cross-examination that a NSAID-PPI combination would have been of strong interest in 2001 to the clinician, as an improvement over ARTHROTEC. As discussed, misoprostol has undesirable side-effects.

(iii) General vs Specific Motivation

[148] Returning to the basic principles on motivation (general or specific), *Sanofi* requires that a contextual analysis be conducted: it teaches that the importance of motivation as a factor depends wholly on the facts.

[149] Among other cases, Mylan relied on *Janssen-Ortho Inc v Novopharm Ltd*, 2007 FCA 217 [*Janssen-Ortho*] at subpara 25(5) (quoting from Justice Hughes's trial judgment below):

> "Motivation" in this context may mean the reason why the claimed inventor made the claimed invention, or it may mean the reason why one might reasonably expect the hypothetical person of ordinary skill in the art to combine elements of the prior art to come up with the claimed invention. If within the relevant field there is a specific problem that everyone in the field is trying to solve (a general motivation), it may be more likely that the solution, once found, required inventive ingenuity. On the other hand, if there is a problem that only the claimed inventor is trying to solve (a unique or personal motivation), and no one else has a reason to address that problem, it may be more likely that the solution required inventive ingenuity. However, if commonplace thought and techniques can come up with a solution, there may be a reduced possibility that the solution required inventive ingenuity.

[150] Mylan argues that specific motivation is not be required in order to find that it was "obvious". While acknowledging that *Janssen-Ortho* pre-dates *Sanofi*, Mylan posits this statement is entirely consistent with *Sanofi*'s contextual approach to motivation, and remains consistent with the current state of the law. I agree.

[151] In *Sanofi*, the Supreme Court recognized specific motivation as the third of three factors, rather than as an independent requirement. Its relative importance will depend on the context and factual backdrop of each case. Other factors may weigh equally or even more so on the outcome of the "obvious to try" test, since *Sanofi*'s three enumerated factors are neither determinative, nor exhaustive. When taking into account the third factor, a general motivation to search for new and improved medications is generally a given in the intensely competitive pharmaceutical industry (*Sanofi* at para 90). The parties discussed several individual cases at length on this point, with Mylan first contending they were examples where obviousness had been made out despite only

general motivation being found, while AstraZeneca then countered that in all of those cases specific motivation had actually been found – even if only implicitly (*Ratiopharm Inc v Pfizer Ltd*, 2009 FC 711, aff'd 2010 FCA 204; *Janssen-Ortho Inc v Novopharm Ltd*, 2007 FCA 217; *AstraZeneca Canada Inc v Teva Canada Ltd*, 2013 FC 245; *Gilead Sciences Inc v Canada (Health)*, 2016 FC 856 [*Gilead*]; *Bristol-Myers Squibb Canada Co v Teva Canada Ltd*, 2016 FC 580). In my view, the difficulty here arises from the jurisprudence generally describing motivation as falling on either side of a dichotomy: general or specific.

[152] It is unclear to me that the Supreme Court, when articulating the *Sanofi* test, intended that motivation fall wholly on one side or the other. In many cases, one could compellingly argue either side of this "motivation" coin. After all, motivation is an intrinsically difficult measure to take, and even more so when it comes to the notional POSITA. In short, a "general" versus "specific" motivation distinction, which consumed a great deal of energy in these proceedings, may be a false dichotomy.

[153] Rather, the measure to be taken is one of difference or degree, not kind. Like with many subjective measures, the notional skilled person's motivation would at best be identified as somewhere along a spectrum. It is a given that the drive to modernize results in an innate motivation to innovate; science will always strive to search for new and improved formulations, including with medications.

[154] Some of the submissions on motivation, which tended to frame motivation as being an independent requirement – and therefore requiring a binary determination from the court – only exacerbated the potential for confusion here.

[155] This is not to say that there will not be cases where motivation clearly falls on the side of specificity: in certain cases, motivation may clearly be specific to the invention ultimately claimed.

[156] However, when that motivation falls short of being so specific to the exact invention, instead falling somewhere in the middle, identifying it categorically as being general or specific may be an entirely subjective exercise, akin to evaluating modern art. What one person characterizes as general motivation could reasonably be described as specific motivation by another, while in many cases the truth lies somewhere in the gray – between the black of general motivation, and the white of specific motivation.

[157] The recent decision in *Gilead* – one of the cases upon which the parties to this proceeding disagreed on regarding whether general or specific motivation had been found – provides a useful illustration of what I have described as the false dichotomy of the motivational split. Justice Brown put the debate thus in *Gilead* (at para 119):

> Gilead asks the Court to consider whether there was specific motivation to co-formulate Coviracil and VIREAD®, and suggests that where these drugs were not yet widely used or prescribed together, there would not have been a motive for the co-formulation of the claimed invention. I disagree that this level of specificity was required in the motivation analysis. I find that the Conference Call establishes general motivation to develop a single-dose, once-daily co-formulation of VIREAD® and FTC. This was

> enough for the skilled formulator to turn his or her attention to the co-formulation of TDF and FTC. [Emphasis added.]

[158] Despite this pronouncement, *Gilead* serves as a good example of the uncertainty caused by the motivational dichotomy in the present proceeding. Mylan, in its written submissions and then at the hearing, relied on *Gilead* (citing paras 117-122) as an example of where general motivation satisfied the obvious to try test. AstraZeneca, for its part, acknowledged that general motivation was indeed expressly recognized in paragraph 119 (see extract above), but nevertheless argued that Justice Brown then went further in the subsequent paragraphs, adding more specificity, which was tantamount to a finding of specific motivation (citing the remainder of para 119 and para 120). This debate occurred despite Justice Brown's statement in paragraph 119 (above) that "I disagree that this level of specificity was required in the motivation analysis."

[159] Finally, specific motivation arguably cuts both ways. It could be said that its existence indicates that it was likely obvious that someone would eventually get there, without inventiveness. On the other hand, it could be said that the existence of specific motivation before the claimed invention was patented only reinforces *Beloit*'s classic question (at para 21): if it was obvious – and there was specific motivation to try it – why didn't you?

[160] The third factor in the "obvious to try" test asks, "is there a motive provided in the prior art to find the solution the patent addresses?" (*Sanofi* at para 69). This does not prescribe the exact nature or degree of the motive needed. The key question is thus, assuming there is a motive provided in the prior art, "how specific" to the claim was the motivation. The more specific to the claim, the more weight motivation may have as a factor in determining whether the claim

was obvious to try. Here, I find, like in *Gilead*, that the prior art provided to the skilled person the motive to develop the claimed invention.

[161] It is also important to keep in mind that neither this motivation factor, nor the larger obvious to try consideration, determines obviousness. Rather, both are considerations in the decisive obviousness question set out as the fourth step in the framework: "viewed without any knowledge of the alleged invention as claimed, do those differences [between the state of the art and the inventive concept] constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention" (*Sanofi* at para 68).

[162] Viewed as a whole, I agree with the Respondent's position on motivation. Mylan's experts were consistent in their observations – albeit based on their individual analyses – of a strong and documented motivation to improve outcomes for GI injury, which included NSAIDs and PPIs in different formulations. ARTHROTEC provided the same architecture in the same tablet format. In arriving at their conclusions, the Mylan experts each conducted individualized studies of the prior art, and backed their conclusions with compelling reference sources contained in the NOA, and in particular, MD7, MD8, MD10, MD12, MD13, MD18, and MD30.

(d) *Conclusion on Obvious to Try Considerations*

[163] Even if the prior art would have alerted a skilled person that something might be "worth trying", that remains insufficient to make it obvious to try unless the invention was more or less self-evident: *Alcon Canada Inc v Cobalt Pharmaceuticals Co*, 2014 FC 462 at para 129, aff'd 2015 FCA 191. The test is not whether the skilled person had good reason to pursue solutions

that provide a "fair expectation of success": *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FCA 286 at para 4.

[164] In sum, I find that the inventive concept in the Asserted Claims was obvious to try, given the (a) finite number of identified predictable solutions known to the POSITA, (b) minimal amount of effort apparently required to achieve the invention, and (c) strong motivation to arrive at better outcomes for NSAID-related GI injury and in particular to try the claimed formulation. It would have been more or less self-evident to the POSITA to try to obtain the sequential release formulation addressed in the Asserted Claims, and that such a formulation would work.

(6) Reliance on Mosaics

[165] AstraZeneca criticized Mylan's alleged reliance on mosaics to arrive at its conclusions of obviousness – that is, relying on a series of prior art that in combination led to the 098 Patent's invention. Citing *Bridgeview Manufacturing Inc v 931409 Alberta Ltd*, 2010 FCA 188 at para 51 [*Bridgeview*], AstraZeneca stressed that just because each piece of prior art may have been known or even in the realm of common general knowledge, does not mean that the combination is obvious: the mere idea to combine those independent parts can be inventive, and was in this case. Specifically, the Court of Appeal stated the following in *Bridgeview* (at para 51):

> It is not fair to a person claiming to have invented a combination invention to break the combination down into its parts and find that, because each part is well known, the combination is necessarily obvious…

[166] Overall on the issue of combinations, AstraZeneca contended that Mylan's obviousness arguments consisted of pointing to small excerpts from a number of pieces of prior art.

AstraZeneca argued this was indicative of hindsight, and that it lacked any specific motivation to combine the art.

[167] In response, Mylan acknowledged that the NOA indeed contained several mosaics, but asserted that they are all very similar. For instance, the Mylan pointed to NOA Mosaic 7.2.3.1 in its NOA, which sets out the following breakdown of prior art:

- MD18: PPI-NSAID combination;
- MD07: Esomeprazole-Naproxen combination specifically;
- MD65: Esomeprazole is no better than any other PPI;
- MD10: ARTHROTEC architecture; and
- MD13: Non-enteric coated PPI.

[168] Of these pieces of prior art, only MD10 (ARTHROTEC) and MD13 (non-enteric coated PPI) are disputed, according to Mylan.

[169] I agree with Mylan that this combination was an example of illustrating the prior art. Mylan also gave another example at footnote 140 of its Memorandum (albeit in response to criticisms that its experts had relied upon art outside of the NOA):

> The crux of the analysis is that a well-known formulation architecture in the prior art (*e.g.*, in MD10/MD30) is adapted for use with a PPI (known to be effective, *e.g.* in MD18, and formulated in combination, *e.g.* in MD7/MD12), with no difficulty in formulating the PPI for immediate release (*e.g.*, as taught in MD13).

[170] All of the pieces of prior art relied upon in this decision were asserted in the NOA. Further, for reasons already explained, I have found that all of the underlying points asserted in the above examples were indeed common general knowledge at the relevant date.

[171] I am persuaded by Mylan's arguments. Therefore, consistent with my obvious to try findings in the section immediately above, I find that it would have been self-evident to the POSITA to combine the ample common general knowledge known at the relevant time, with a limited amount of prior art, to arrive at the inventive concept, expecting it to work.

VIII. Utility and Overbroadness

[172] Given my obviousness findings, there is no need to address the alternative issues raised by the Respondent.

IX. Conclusion

[173] For the reasons set out above, I find that Mylan's allegations that it was obvious to try to obtain a sequential release of a NSAID-PPI formulation in a single oral dosage combination has an air of reality. AstraZeneca failed to convince the Court that Mylan's allegations of invalidity on the basis of obviousness are unjustified. The application for an order of prohibition is dismissed.

[174] AstraZeneca's application for an order pursuant to section 6 of the *Regulations* prohibiting the Minister of Health from issuing a Notice of Compliance to Mylan for a generic

naproxen-esomeprazole magnesium tablet is dismissed. The Minister of Health may therefore issue a Notice of Compliance to Mylan for the contested product forthwith.

X. Costs

[175] There was a brief discussion on costs during the Case Management Conference of October 18, 2016, wherein the parties agreed that they would attempt to come to an agreement on costs, and report back to the Court on the outcome of those discussions, within 15 days of receiving the judgment.

[176] If unable to arrive at a mutually agreeable costs order, the parties will have ten days to provide submissions, of no longer than five pages each, setting out their positions on costs.

JUDGMENT

THIS COURT'S JUDGMENT is that

1. AstraZeneca's application for an order pursuant to section 6 of the *Regulations* prohibiting the Minister of Health from issuing a Notice of Compliance to Mylan is dismissed.
2. Costs to the Respondent, per Section X of the Judgment.

"Alan S. Diner"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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ANNEX A

Claims of Canadian Patent 2,449,098

[…]

34. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:

    (a) a pharmaceutically acceptable salt of esomeprazole, wherein at least a portion of said pharmaceutically acceptable salt of esomeprazole is not surrounded by an enteric coating; and
    (b) naproxen, wherein said naproxen is surrounded by a coating that inhibits its release from said dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;

    wherein said unit dosage form provides for release of said pharmaceutically acceptable salt of esomeprazole and said naproxen such that:

        i) upon introduction of said unit dosage form into a medium, at least a portion of said pharmaceutically acceptable salt of esomeprazole is released regardless of the pH of the medium; and
        ii) said naproxen is released when the pH of said medium is 3.5 or higher.

35. The pharmaceutical composition of claim 34, wherein none of said pharmaceutically acceptable salt of esomeprazole in said unit dosage form is surrounded by an enteric coating and wherein, upon introduction of said unit dosage form into a medium, essentially all of said pharmaceutically acceptable salt of esomeprazole is released, regardless of the pH of the medium.

36. The pharmaceutical composition of claim 34 or 35 wherein said naproxen is present in an amount of between 250 and 500 mg.

37. The pharmaceutical composition of any one of claims 34 to 36 wherein said unit dosage form is a tablet.

38. The pharmaceutical composition of any one of claims 34 to 37 wherein the pharmaceutically acceptable salt is the magnesium salt of esomeprazole.

39. Use of the pharmaceutical composition of any one of claims [34 to 38] for treating a patient for pain or inflammation.

40. Use of the pharmaceutical composition of any one of claims [34 to 38] for the manufacture of a medicament for treating a patient for pain or inflammation.

41. The use of claim 39 or 40, wherein the pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

42. Use of the pharmaceutical composition of any one of claims [34 to 38] for the treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

43. Use of the pharmaceutical composition of any one of claims [34 to 38] in the manufacture of a medicament for the treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

44. The use according to claim 42 or 43 in patients at risk of developing NSAID associated gastric ulcers.