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Ottawa, Ontario, October 11, 2012

PRESENT: The Honourable Mr. Justice O'Keefe

BETWEEN:

ASTRAZENECA CANADA INC. and ASTRAZENECA AB

Applicants

and

PHARMASCIENCE INC. and THE MINISTER OF HEALTH

Respondents

REASONS FOR JUDGMENT AND JUDGMENT

[1] In this application, the applicants, AstraZeneca Canada Inc. and AstraZeneca AB, collectively referred to as AstraZeneca, address allegations of patent invalidity made by the respondent, Pharmascience Inc. (Pharmascience) in its notice of allegation dated August 27, 2010 (the NOA). The NOA was filed pursuant to section 5 of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the NOC Regulations) for Canadian Patent No. 2,290,531 (the '531 Patent) and Canadian Patent No. 2,346,988 (the '988 Patent). In an order dated August 8,

2011, Prothonotary Mireille Tabib dismissed the application with respect to the '988 Patent. The scope of this application is therefore limited to the '531 Patent.

[2] AstraZeneca requests a declaration that the NOA is neither a valid notice of allegation nor a detailed statement as contemplated by the NOC Regulations. In the alternative, AstraZeneca requests an order prohibiting the Minister of Health (the Minister) from issuing a notice of compliance (NOC) to Pharmascience for its 20 and 40 mg dosage esomeprazole magnesium capsules (the Pharmascience capsules) until the expiry of the '531 Patent.

Background

[3] Pharmascience filed an Abbreviated New Drug Submission (ANDS) with the Minister seeking an NOC for its Pharmascience capsules. These capsules are intended to treat duodenal ulcer disease associated with Helicobacter pylori infection. In its ANDS, Pharmascience compared the Pharmascience capsules to AstraZeneca's 20 and 40 mg dosage capsules of NEXIUM to demonstrate bioequivalence under subsection 5(1) of the NOC Regulations.

[4] In its NOA, Pharmascience alleged that the claims made in the '531 Patent were irrelevant and/or invalid on the following grounds:

- Insufficient disclosure/lack of support;
- Claims broader than invention made or disclosed;
- Lack of novelty and anticipation by prior use;
- Double-patenting;

- Lack of inventive step/obviousness;
- Not an invention (under section 2 of the *Patent Act*, RSC, 1985, c P-4);
- Lack of sound prediction and lack of utility;
- Not a valid selection patent; and
- Fraud on the patent officer (under subsection 34(1) and section 53 of the *Patent Act*).

[5] The main polymer at issue is hydroxypropyl methylcellulose (HPMC). HPMC has different properties depending on its molecular weight. The molecular weight of HPMC is proportional to the viscosity of an aqueous solution of HPMC; thus, as the molecular weight of HPMC increases, so does the viscosity of an aqueous solution of HPMC. High molecular weight HPMC has a viscosity greater than 4,000 cps and dissolves slowly in water which makes it advantageous for controlled release formulations that require slow release of drugs. Conversely, low molecular weight HPMC has viscosity ranging from 5 to 15 cps and is often used in film coatings due to its faster dissolution in water.

‘531 Patent

[6] The ‘531 Patent, entitled *Pharmaceutical Formulation of Omeprazole*, issued on December 12, 2006 from an international patent application filed in Canada on May 18, 1998. The ‘531 Patent claimed priority from Swedish patent application No. 9702000-2 filed on May 28, 1997. The ‘531 Patent was published on December 3, 1998 and expires on May 18, 2018.

[7] The inventors of the '531 Patent are Magnus Erikson (Sweden) and Lars Josefsson (Sweden). The patent is owned by AstraZeneca AB and is listed on the Minister's Patent Register for AstraZeneca's NEXIUM brand of 20 and 40 mg esomeprazole magnesium trihydrate tablets.

[8] Specific terms are defined as follows in the '531 Patent:

> Omeprazole, an alkaline salt thereof, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole
>
> […]
>
> Cloud point is the temperature at which this polymer phase separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution.

[9] The '531 Patent is directed at the use of low viscosity HPMC of a specific quality (as reflected by its CP) in an enteric-coated omeprazole immediate release formulation. The enteric coating, an acid, is used to withstand the omeprazole, an acid labile compound, from the acidic conditions of the stomach. The HPMC layer serves as a binder and/or separating layer between the omeprazole-containing core and the enteric coating. The inventors stated that they surprisingly found that different batches of a single low viscosity HPMC product, as gauged by the cloud point (CP), may have different abilities to influence the rate of release of omeprazole from an enteric-coated formulation.

The "Claimed CP"

[10] The patent's claimed CP for low viscosity HPMC is as follows:

- CP of not less than 45.6˚C at 96% light transmission measured with a Mettler FP90/FP81C instrument, where the CP is determined by dissolving the HPMC in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 to 6.85; and

- CP of not less than 44.5˚C at 95% light transmission measured with a spectrophotometer, where the CP is determined by dissolving the low viscosity HPMC in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 to 6.85.

[11] The patent states that this claimed CP ensures sufficient drug release from the formulation. Thus, by following the '531 Patent, the amount of product discarded from insufficient release is reduced, which results in a significant advantage.

Claims

[12] The '531 Patent has 20 claims.

[13] The first claim is for an enteric coated oral pharmaceutical formulation comprising the following three layers:

1. Core material consisting of an active ingredient (omeprazole, as defined above, in admixture with one or more pharmaceutically accepted excipients and an optional binding agent) and optionally an alkaline reacting compound;

2. Separating layer on the core material; and

3. Enteric coating layer on the separating layer.

[14] The optional binding agent and/or constituent of the separating layer are comprised of low viscosity HPMC with at least the claimed CP.

[15] Claims 2 to 8 add the following specifications:

Claim 2: subset of Claim 1 where the constituent of the separating layer is low viscosity HPMC.

Claim 3: subset of Claim 2 where the enteric coating layer is methacrylic acid copolymer.

Claim 4: subset of Claim 1 where the binding agent is low viscosity HPMC.

Claim 5: subset of Claims 1 to 4 where the low viscosity HPMC has a viscosity of less than 7.2 cps in 2% aqueous solution.

Claim 6: subset of Claims 1 to 5 where the active ingredient is omeprazole.

Claim 7: subset of claims 1 to 5 where the active ingredient is magnesium salt of omeprazole.

Claim 8: subset of Claims 1 to 5 where the active ingredient is magnesium salt of the (-)-enantiomer of omeprazole.

[16] Claims 9 and 10 specify an enteric coated oral pharmaceutical formulation manufactured with an optional binding agent and a separating layer of low viscosity HPMC at the claimed CP of 45.6˚C and 44.5˚C, as described above, respectively. Similarly, Claims 11 and 12 specify an enteric coated oral pharmaceutical formulation that does not contain a separating layer but is manufactured with at least a binding agent of low viscosity HPMC at the claimed CP of 45.6˚C and 44.5˚C, as

described above, respectively. Claim 13 pertains to any of the Claims 9 to 12, wherein the low viscosity HPMC has a viscosity of less than 7.2 cps in 2% aqueous solution.

[17] Claims 14 to 17 describe the process for the manufacture of an enteric coated oral pharmaceutical formulation in accordance with Claims 9 to 12, respectively.

[18] Claims 18 and 19 describe the use of a pharmaceutical formulation as defined in any one of the Claims 1 to 8 for the manufacture of a medicament in the treatment of gastrointestinal diseases and in the treatment of gastrointestinal diseases, respectively.

[19] Finally, Claim 20 describes a commercial package comprising a pharmaceutical formulation as defined in any one of Claims 1 to 8, with instructions for the use thereof in the treatment of gastrointestinal diseases.

Experiments

[20] Three experiments (examples) were presented in the '531 Patent. Two different batches of low viscosity HPMC were tested in these experiments: Type A and Type B.

[21] Examples 1 and 2 tested the rate of release of omeprazole from omeprazole pellets layered with two different batches of low viscosity HPMC used as a constituent of the separating layer. The omeprazole pellets were prepared according to the description in EP 247 983. The test methodology was described as follows:

> The pellets were pre-exposed to simulated gastric fluid USP (without enzyme) at 37˚C for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of 100.0 parts of simulated gastric fluid USP (without enzyme) and 80.0 parts of 0.235 M disodium hydrogen phosphate solution, pH should be between 6.75 and 6.85. The simulated gastric fluid USP (without enzyme) was prepared by dissolving 2.0 g NaCl and 7.0 ml conc. HCl and add water to 1000 ml. The 0.235 M disodium hydrogen phosphate solution was prepared by dissolving 41.8 g $Na_2HPO_4.2H_20$) and add water to 1000 ml.

[22] The composition of the core material, separating layer and enteric coating layer of the tested omeprazole pellets was set out at pages 10 and 11 of the '531 Patent. The separating layer included Type A or Type B HPMC at 6 cps.

[23] The CP determinations were performed with two different apparatus: a commercial equipment from Mettler (example 1) and a spectrophotometer equipped with a heating coil and stirring function (example 2). The results were presented in a table on page 11 of the '531 Patent (the page 11 table), as follows:

Pellets containing HPMC	Cloud Point (˚C)		Release of omeprazole from enteric coated pellets [%]
	Ex. 1 (n=2)	Ex. 2 (n=1)	
Type A	44.4	42.5	69 (60-84)
Type B	47.5	47.2	93 (93-94)

[24] The results of examples 1 and 2 were depicted on figures 1 and 2, respectively. Compared to the marketing approval for the Losec® capsule formulation of at least 75% release of omeprazole within 30 minutes in a buffer solution (the marketing standard), the results on the tests on the Type

A and Type B separating layers showed, respectively, unacceptable (i.e., 69% below 75%) and acceptable (i.e., 93% above 75%) release of omeprazole for a pharmaceutical product.

[25] The patent also stated that:

> Results from a number of experiments with different batches of HPMC indicate that HPMC with a cloud point of at least 45.6˚C is desirable in fulfilling the regulatory requirements on rate of release of omeprazole, when the cloud point determination is performed in a commercial Mettler instrument. [emphasis added]

[26] Example 3 tested the two types of low viscosity HPMC when used as a binding agent in the preparation of core material for pellets. The pellets were not coated with a separating layer or an enteric coating layer. The core material was prepared by spray leaching omeprazole magnesium salt and HPMC on sugar spheres in a fluidized bed. The composition of the core material was indicated on page 13 of the '531 Patent. The prepared pellets were then tested to determine the rate of release of omeprazole in a buffer solution of pH 6.8 with identical composition as used in example 1 at 37˚C with a paddle speed of 100 rpm. The release of omeprazole was determined with a spectrophotometer.

[27] The results of example 3 were presented on figure 3. The graphs shows that the release of omeprazole was delayed for Type A compared with Type B.

Evidence

[28] The witnesses whose evidence is on the record are as follows:

For Pharmascience – Dr. Colombo, Dr. Miller, Dr. Desbrières, Mr. Alderman.

For AstraZeneca – Dr. Bodmeier.

Pharmascience's Experts

[29] Dr. Paolo Colombo is a professor in the Department of Pharmacy at the University of Parma, Italy. Dr. Colombo has worked in academia since receiving his Pharm. D. in 1968. Dr. Colombo has published extensively and has been involved in research related to cellulose polymers such as HPMC since 1983. Dr. Colombo was asked to provide background information on delayed release pharmaceutical dosage forms and the use of HPMC in delayed release formulations.

[30] Dr. Colombo provided a background on delayed release formulations, noting that the dosage form of a pharmaceutical product is chosen based on the intended site of administration and the time period over which a therapeutic agent is to be administered. A delayed release dosage form delivers the therapeutic agent in the gastrointestinal tract. Dr. Colombo explained that delayed release formulations typically contain an acid resistant outer layer, termed an enteric coating, to protect the drug. This layer dissolves in the neutral-to-basic conditions of the intestine such that the drug is immediately released when the dosage form enters the intestine. Some polymers conventionally used as enteric coatings contain acidic groups that can cause degradation of sensitive drugs and Dr. Colombo noted that he had encountered such problems with omeprazole tablets.

[31] Turning to HPMC, Dr. Colombo noted that this polymer has been widely employed as a thin film coating on conventional tablets since the 1980s. Low viscosity HPMC dissolve under both

acidic and basic conditions and are suitable for preparing films that dissolve rapidly at the target site. Dr. Colombo referred to an article by Rowe that indicated that the disintegration time of tablets coated in HPMC is directly related to the polymer molecular weight. At paragraphs 20 and 22 to 24 of his affidavit, Dr. Colombo discussed high molecular weight/high viscosity HPMC, which is commonly used to form controlled release matrixes that allow slow release of a drug.

[32] Based on his familiarity with formulations containing omeprazole and esomeprazole, Dr. Colombo reviewed Canadian Patent No. 1,292,693 and WO 95/01783 at paragraphs 26 to 38 of his affidavit.

[33] Canadian Patent No. 1,292,693 involved a separating layer, such as low viscosity HPMC, to protect omeprazole formulation discolouring arising from the interaction of the enteric coating and the active ingredient. The rate of drug release would be dictated by the type and thickness of the enteric coating and the amount and type of excipients used in the core, not the type of HPMC film used which Dr. Colombo stated only functions as a physical barrier between the omeprazole and the material of the enteric coating. Dr. Colombo noted that a person skilled in the art (PSA) would know that low viscosity HPMC would be required to fulfill this role of requiring quick dissolution in water.

[34] WO 95/01783 pertained to the same formulation as Patent No. 1,292,693, but focused on a novel physical form of omeprazole magnesium salt. Dr. Colombo noted that the reported rate of dissolution would be considered an immediate release (93% dissolution within 30 minutes) and this rate was not reduced by the thickness of the enteric coating.

[35] Turning to the ‘531 Patent, Dr. Colombo noted that the formulation described therein was the same as that described in the two patents discussed above. At paragraphs 39 to 44, Dr. Colombo summarized the information contained in the ‘531 Patent. Dr. Colombo noted that the different release profiles for two core pellets (one made of Type A and the other of Type B) depicted in figure 3 appeared to be by chance as the pellets were both manufactured by spray layering and both dissolved over 90% in 30 minutes. This was consistent with the fact that the amount of HPMC in the core would not affect the release rate. With regards to the experiment set out on pages 10 and 11 that suggested different release rates for Type A and Type B, Dr. Colombo noted that this difference could not be attributed to the low viscosity HPMC, which would dissolve immediately, unless there was a problem with the amount of polymer deposited on the pellet that was not directly controlled. Dr. Colombo stated that the difference would not be caused by a difference in CP.

[36] In addressing whether there was enough information in the ‘531 Patent for the PSA to understand the nature of the invention and how it works, Dr. Colombo noted the naming of HPMC used in the patent as “Type A” and “Type B”. As commercially available HPMC is well characterized in terms of viscosity and levels of methoxyl and hydroxypropyl substitution, Dr. Colombo found this naming approach questionable. To reproduce the formulation and understand whether there was actually a difference between the two types of HPMC, Dr. Colombo stated that a PSA would require more detailed information on the types of HPMC tested.

[37] Dr. Colombo also stated that the data did not support a finding that there was an actual difference between the two types of HPMC used. Rather than showing replicated results (typically 12 tests), there was only one acceptable value provided in the page 11 table for the Type A sample.

Dr. Colombo concluded that without a strict characterization of the film applied, it was not possible to assign an effect on drug dissolution to the small difference measured in CP of the two batches of HPMC having nominally the same viscosity.

[38] With regards to whether the invention would achieve what the patent promised, Dr. Colombo noted that the thickness of the film deposited remained unspecified.

[39] Dr. Colombo noted that the low viscosity (7.2 cps or lower) HPMC separating layer described in the '531 Patent was neither intended to exert control over the rate of drug release, nor capable of exerting such control. To exert any control over the rate of drug release, high viscosity (greater than 4,000 cps) HPMC that leads to strong polymer gel formation would need to be employed. Dr. Colombo stated that it is well known to formulators that low viscosity HPMC is most suitable for preparing thin films that dissolve rapidly and completely.

[40] At paragraph 56 of his affidavit, Dr. Colombo explained that another critical parameter to determining whether any control over the rate of drug release could be achieved was the thickness of the coating layer surrounding the core unit. In light of existing test results and the general knowledge of a PSA, Dr. Colombo stated that the low viscosity HPMC described in the '531 Patent was too thin to exert any control over the rate of drug release. After reviewing the formulations described in pages 10 and 11 of the patent, Dr. Colombo found at paragraph 59 of his affidavit that the amount of low viscosity HPMC polymer described in the '531 Patent could not function to control the rate of drug release from the omeprazole containing core units described therein.

[41] At paragraphs 60 to 67, Dr. Colombo highlighted information missing in the patent, including:

- the dosage form tested;
- the strength of the final dosage form;
- the conditions under which the dissolution studies were carried out;
- which apparatus was used for conducting dissolution testing;
- number of samples tested; and
- the thickness or uniformity of the separating layer produced with the two types of HPMC.

[42] Dr. Colombo commented that the most glaring oversight of the numbers reported on page 11 was the assertion that they represented a release of omeprazole from a formulation because rather than representing a release, these numbers represented dissolution of omeprazole in the buffer solution at a particular time.

[43] At paragraphs 69 to 73, Dr. Colombo also criticized the dissolution testing reported in Figure 3 of the '531 Patent, stating that when used as a binding agent, HPMC cannot exert control over the rate of drug release.

[44] Finally, Dr. Colombo considered whether a PSA would consider that the '531 Patent disclosed an invention. Dr. Colombo highlighted that the prior art disclosed the identical formulation to that found in the '531 Patent, including the use of low viscosity HPMC for the film separating layer. Dr. Colombo noted that:

> 80. […] The addition of an irrelevant parameter, namely Cloud Point, does not create a difference between the formulations of the '531 Patent and those of the prior art.
>
> 81. Low viscosity HPMC (having a viscosity lower than 7.2 cps) applied as a thin separating layer or as binder cannot control the rate of release of omeprazole. The bioavailability of omeprazole will be determined by the rate of dissolution of omeprazole within the gastrointestinal tract. This is independent of the cloud point of low viscosity HPMC.

[45] For these reasons, Dr. Colombo concluded that the '531 Patent cannot be considered an invention.

[46] Dr. Robert Miller is the president of MPD Consulting, a consulting company to the pharmaceutical industry in the areas of dosage form formulation and manufacturing process design. Dr. Miller received his Ph.D. in Pharmaceutics in 1977. He was employed in the pharmaceutical industry from 1978 to 1994. From 1994 to 2002, Dr. Miller was employed as an assistant professor and also provided technical pharmaceutical services to private industry.

[47] At paragraphs 15 to 22 of his affidavit, Dr. Miller provided a background summary on the use of HPMC in pharmaceutical formulations. Dr. Miller noted that no specifications for CP were provided in the 1995 edition of the United States Pharmacopeia (USP) for low viscosity HPMC. CP was not something that a pharmaceutical formulator would consider when designing a formulation in 1997 or today; rather, the primary governing factors are molecular weight and viscosity. Dr. Miller noted that a low molecular weight HPMC would provided an immediate release. As well, when used as a binder in a formulation, HPMC would not impact the release rate of the formulation.

[48] At paragraphs 23 to 63 of his affidavit, Dr. Miller considered the following prior art patents on omeprazole: Canadian Patent No. 2,025,668; Canadian Patent No. 1,292,693; Canadian Patent No. 1,302,891; WO 94/27988; WO 95/01783; WO 96/01623; Canadian Patent No. 2,184,842; and Canadian Patent No. 2,184,037.

[49] From this review, Dr. Miller listed various factors that the PSA would learn from formulations of benzimidazoles such as omeprazole and esomeprazole at paragraph 64 of his affidavit. These findings included the following:

> HPMC is recommended as a separating layer to be used in between the active and the enteric coating; and the recommended thickness of the separating layer is 2-4 µm (which would be a thin film coating)
>
> […]
>
> the separating coating must be water soluble or in water rapidly disintegrating – which would mean a low viscosity/low molecular weight HPMC as this type of HPMC will dissolve in water; …

[50] A PSA would take these factors into account and use a grade of HPMC as a binder or separating layer that would not impact the release rate of the formulation. The delayed release of the active ingredient would be determined by the enteric coating, which would withstand the stomach acid but dissolve immediately in the alkaline intestine.

[51] Dr. Miller then considered the ‘531 Patent at paragraph 66 of his affidavit. Dr. Miller noted that the testing reported in the patent and the clinical use of the capsules was at 37˚C. This was below the claimed CP of both types of HPMC referred to in the patent. Dr. Miller also noted that the following information was missing on the tests reported in the patent: the specific grade of HPMC,

the number of hydroxypropyl groups, the number of methoxy groups and which specific HPMC was tested. Dr. Miller found that prior art provided teachings on the appropriate thickness and weight of the HPMC layer to ensure an acceptable release rate.

[52] With regards to whether there was sufficient information for a PSA to understand the invention and how it works, Dr. Miller noted that the patent did not disclose sufficient information on what Type A and Type B HPMC was; thus, key information was missing to allow the PSA to obtain the correct quality of HPMC. In addition, Dr. Miller stated that the testing in the '531 Patent did not show that the CP of HPMC affects drug release. Based on his own experience, Dr. Miller was skeptical that CP in and of itself has any effect on release. Dr. Miller noted that no information was provided on the coating amounts on the spheres or the size of the spheres; differences in the amount of coating could account for the numbers provided in the page 11 table. Dr. Miller found that a PSA could not put the invention into practice without difficulty in light of the lack of information on what type of HPMC to purchase.

[53] With regards to the patent's suggestion that different batches of HPMC may differ in their abilities to influence the rate of release of omeprazole in simulated intestinal fluid, Dr. Miller noted that, in his experience, there were no obvious differences in 1997 in different batches of a particular grade of HPMC. The overall characteristics of a certain grade of HPMC are and were the same from batch to batch. At paragraph 93 of his affidavit, Dr. Miller also noted that the differences in release rates reported in the testing of HPMC as a separating layer could not be attributed to CP because that temperature was not reached in the course of the testing (which was done at 37˚C). In conclusion, Dr. Miller found that "[t]here is no invention in adding parameters to the specifications

for HPMC – i.e. cloud point, particularly when the parameters are irrelevant to the use of the formulation in the body".

[54] Dr. Jacques Desbrières is a professor at the University of Pau, France. Dr. Desbrières obtained a degree in chemical engineering in 1980. He worked as a research engineer and project leader at a pharmaceutical company between 1981 and 1988. In 1990, he entered academia where he remains today. Dr. Desbrières has published extensively and teaches in the areas of physical chemistry and polymer science.

[55] At paragraphs 15 to 24 of his affidavit, Dr. Desbrières provided a summary on HPMC polymers and their physical properties, including thermal gelation and CP. Dr. Desbrières highlighted the findings of a study published by Sarkar in 1979. In this study, the thermal gelation temperatures and CPs of numerous HPMC polymers produced by Dow Chemical Corporation (Dow) under the trade-mark METHOCEL were determined experimentally. A significant finding in this study was that the thermal gelation temperatures and CPs are predominantly determined by the percentage of methoxyl groups present on the polymer. However, where methoxyl groups and hydroxypropyl groups were similar, the CP was found to be within a narrow range for HPMC polymers having vastly different molecular weights.

[56] At paragraphs 25 to 31 of his affidavit, Dr. Desbrières discussed his experiments on low viscosity HPMC to determine CPs. He conducted these tests on samples of METHOCEL E5, E6 and E15 from Dow and on Pharmacoat 603 and 606 from Shin-Etsu Chemical Corporation (Shin-Etsu). In Table 1 of his affidavit, Dr. Desbrières presented the results of his experiments as follows:

Sample	IPT* buffer C=1%	CP* buffer CP=1%	%** Methoxyl	%** Hydroxypropyl	Viscosity (cP)**	M_n* (g/mol)	M_w* (g/mol)
Pharmacoat 603	47.8	49.2	28.9	9.1	3.09	12100	15600
Pharmacoat 606	45.8	47	28.7	9.0	5.96	19100	24600
Dow E5	47.7	49.3	28.5	8.9	4.4	15900	19000
Dow E6	46.6	48	29.5	8.0	5.6	18600	22700
Dow E15	45.2	46.2	28.7	9.1	15	30300	38200

* = Determined Experimentally

** = Provided by Manufacturer

[57] The first column, entitled IPT, provides the results that correspond with the CP as defined in the '531 Patent (i.e., the temperature where light transmission is reduced to 95% when measured using a spectrophotometer with an ultraviolet detector). The second column, entitled CP, provides the results that correspond with the temperature at which light transmission was reduced to 50% (i.e., the true CP; namely the definition that Dr. Desbrières stated is prevalent in the literature and understood by a PSA). Dr. Desbrières noted that for polymers having viscosities below 7.2 cps, both these data returned narrow temperature ranges. In tests on buffer solutions containing phosphate salts, results of which were presented in Table 2 of his affidavit (not reproduced here), the IPTs and CPs were depressed and remained within narrow temperature ranges for polymers of low viscosity.

[58] Dr. Desbrières considered the '531 Patent at paragraphs 33 to 37 of his affidavit. He noted that CP values obtained using a Mettler FP90/FP81C instrument would be slightly higher than values obtained using a spectrophotometer, which explained why the curves in Figures 1 and 2 were

slightly different. In addition, Dr. Desbrières noted that these figures showed that the two types of HPMC used in the patent would be fully dissolved at body temperature.

[59] In considering whether a PSA would understand the nature of the invention and how it works, Dr. Desbrières stated that "claiming a low viscosity HPMC with a specific cloud point appears to be an indirect way of claiming a low viscosity HPMC with a certain degree of methoxyl groups and hydroxypropyl groups" (at paragraph 38). Thus, to put the invention into practice without difficulty, Dr. Desbrières noted that the patent should have specified the degree of substitution for the methoxyl groups and the molar substitution for hydroxypropyl groups; information provided by manufactures on their certificates of analysis.

[60] Finally, Dr. Desbrières noted that he did not see a scientific reason for choosing HPMC at the claimed CP because, when used as an excipient in a pharmaceutical formulation, HPMC would not be exposed to temperatures above body temperature (37˚C). Thus, the CP would not affect the polymer's solubility under physiological conditions.

[61] Mr. Daniel Alderman obtained a chemical engineering degree in 1975. From graduation through to 2000, Mr. Alderman held increasingly senior positions at Dow in the areas of emulsion polymers and cellulose ethers. Between 2000 and 2002, Mr. Alderman worked in the Dow automobile division. Between 2002 and his retirement in 2008, Mr. Alderman was the corporate research and new business development intellectual asset manager at Dow.

[62] At paragraphs 11 to 20 of his affidavit, Mr. Alderman provided a background on the HPMC products sold by Dow. Dow's HPMC products for pharmaceutical application as film formers were

the low viscosity METHOCEL E5 Premium and E6 Premium. These were designed to dissolve quickly in water or gastric fluids. They were not designed to nor did they affect the performance or release of the active ingredients in the tablet. Mr. Alderman noted that when used as a film former, it is important that the low viscosity HPMC be applied in a continuous film, without holes or cracks. Mr. Alderman stated that, to the best of his recollection, Dow did not receive any complaints from their customers (including AstraZeneca) on batch-to-batch performance variation of their low viscosity HPMC products. Mr. Alderman also remarked that the HPMC products produced by Dow under the trade-mark METHOCEL in 1997 and 1998 are the same HPMC polymers produced today.

[63] At paragraphs 14 to 17 of his affidavit, Mr. Alderman explained the chemical structure of Dow's METHOCEL HPMC polymers. Mr. Alderman also explained that Dow has developed innovative processes to prepare HPMC polymers with controlled physical properties. The HPMC monograph in the USP was created according to Dow's specifications. The USP specifications relating to methoxyl content and hydroxypropyl content have not changed in the last 25 years. In addition, methods for testing HPMC polymers were developed by Dow and the American Standards Association for Testing and Materials.

[64] Mr. Alderman considered the '531 Patent at paragraphs 21 to 25 of his affidavit. He noted that although it is highly unlikely that significant differences exist between different lots of HPMC, a reason for such differences could relate to differences in the continuity of the separating layers formed by the Type A and Type B HPMC described in the patent. Mr. Alderman observed that the formulation described on page 11 for the separating layer did not contain a plasticizer. Plasticizers

are important for creating defect-free continuous films. This is particularly true for very thin films, where cracks or imperfections would have a greater deleterious effect and for films made of low viscosity polymers that tend to be more brittle and prone to cracking.

[65] At paragraphs 29 to 30 of his affidavit, Mr. Alderman explained the HPMC manufacturing process. Mr. Alderman noted that it is known that the apparent viscosity of an aqueous solution of a HPMC polymer is proportional to its molecular weight. Similarly, it is known that the dissolution of HPMC varies directly with the molecular weight. Mr. Alderman explained that the viscosity of HPMC polymers produced by Dow is controlled through the manufacturing process.

[66] At paragraphs 34 to 38, Mr. Alderman described the results of studies on the thermal gelation and CP temperatures of HPMC polymers. He explained that HPMC polymers possess a unique property of decreased solubility in water above a critical temperature; thus, where a solution of HPMC is dissolved in water and heated above that critical temperature, the decreasing solubility of HPMC is manifested as an increase in viscosity and an onset of cloudiness or turbidity of the solution. The temperature at which the amount of light transmitted through the solution is reduced to 50% is termed the CP temperature and is dependent on the percentage of methoxyl groups present in the polymer. The molecular weight and viscosity of a polymer has a very small effect on the CP. The process of increasing cloudiness or turbidity is reversible by cooling the solution. At paragraph 35 of his affidavit, Mr. Alderman explained that this phenomenon has been attributed to an association of methoxyl groups along the same polymer chain and the association of methoxyl groups on different polymer chains.

[67] At paragraph 43 of his affidavit, Mr. Alderman noted the following regarding the CP of a solution of HPMC:

> The cloud point of a solution of a given HPMC is a property of the polymer that arises from its physical properties, in particular, the percentage of methoxyl groups present on the polymer chain. If the physical properties of a given HPMC polymer are known, such as percentage methoxyl groups, the cloud point of an aqueous solution of the polymer can be predicted within a very narrow temperature range. Methocel E5 and E6 have had the same percentage of methoxyl groups (and viscosity/molecular weight) since at least 1997 to today.

[68] At paragraphs 47 to 49 of his affidavit, Mr. Alderman considered the claims contained in the '531 Patent and whether the alleged invention would have been obvious to a PSA. As low viscosity HPMC having a specific CP was essentially a claim to an inherent property of a known material, Mr. Alderman concluded that the '531 Patent would be obvious to a PSA.

[69] Finally, Mr. Alderman considered whether there was sufficient information in the '531 Patent for a PSA to understand the nature of the invention and how it works. However, as the patent did not disclose information that would have been found in HPMC specifications in 1998, namely, the percentage of methoxyl groups or the molecular weight, Mr. Alderman concluded that a PSA would not be able to choose the correct HPMC with the specified cloud point. Thus, the results in the patent would not be reproducible by a PSA and could not be relied on for practical applications.

AstraZeneca's Expert

[70] Dr. Roland Bodmeier is a professor at the Institute für Pharmazie Freie Universität Berlin, Germany. Dr. Bodmeier obtained his Ph.D. in pharmaceutics in 1986 and a post-doctorate degree in 1993. Since 1994, he has been employed in his current position. Dr. Bodmeier has published extensively and consulted to the pharmaceutical industry in the areas of drug dosage forms and controlled drug delivery systems.

[71] At paragraphs 11 and 12, Dr. Bodmeier provided a background on the terminology of HPMC and CP. Dr. Bodmeier noted that there is no generally accepted level of light transmission that defines a CP; a percentage between 50 and 97.5 is typically chosen.

[72] Turning to the '531 Patent, Dr. Bodmeier noted that in December 1998, the inventors' finding that different batches of low viscosity HPMC differ in their ability to influence the rate of release of omeprazole from an enteric coated formulation; a difference that can be gauged by reference to the CP and would have been surprising to a PSA for two reasons.

[73] First, the use of low viscosity HPMC in a pharmaceutical formulation was not generally known to be capable of influencing release rate. The opposite would have been believed because low viscosity HPMC dissolves quickly in water. Thus, if a PSA saw that their omeprazole enteric formulations were being released at different rates, the PSA would have considered other process or formulation parameters rather than investigating variability of different batches of subtypes of a specific product family of HPMC. As such, Mr. Alderman's statement that he did not recall

receiving any complaints on batch-to-batch variation from customers was not surprising. Dr. Bodmeier also highlighted that a PSA would have understood that the reference to different batches in the patent is a reference to different batches of one subtype of HPMC, not different batches of different subtypes. Second, CP was not a factor considered in selecting a low viscosity HPMC for use as a binder and/or separating layer.

[74] Dr. Bodmeier further noted that CP of low viscosity HPMC is primarily affected by the level of methoxyl and hydroxypropyl substitution of a given HPMC polymer. As categories of HPMC are defined in the USP by reference to specific ranges of percent methoxyl and hydroxypropyl substitution, there are an infinite number of possible combinations, each of which will affect CP. Dr. Bodmeier noted that CP is also affected by other variables, such as the nature of substitution along a given cellulose backbone and molecular weight/viscosity of the polymer. Further, as HPMC polymers consist of dozens to hundreds of repeating glucose units, the assigned percent methoxyl and hydroxypropyl substitution is simply an average of the substitution of all glucose units in the polymer. Thus, even when batches have identical viscosity and methoxyl and hydroxypropyl content, the pattern of substitution and distribution can vary which will affect CP.

[75] As it is highly improbable that different lots will have identical substitution patterns because the number of substitution sites on the polymer chain far exceeds the number of possible substituents, the CP of an HPMC batch can only be obtained from direct measurement. Dr. Bodmeier further highlighted that the allowable ranges for viscosity and percentage substitution of methoxyl and hydroxypropyl, as indicated in Dow's certificate of analysis for METHOCEL E5, highlights the infinite number of variations of HPMC for one subtype. This can be further

complicated by the distribution of substituted groups along the polymer chain and on individual glucose units. By characterizing HPMC by reference to its CP, Dr. Bodmeier explained that the inventors of the '531 Patent provided an elegant and objective proxy to assess the sum effect of the infinite combination of these variables. Concurrently, the inventors determined that when the CP exceeded a certain value when measured with a specific instrument, there was greater release of omeprazole within 30 minutes.

[76] At paragraphs 35 to 50 of his affidavit, Dr. Bodmeier provided a summary of the claims contained in the '531 Patent. In the remainder of his affidavit, Dr. Bodmeier responded to the affidavits of Pharmascience's experts.

[77] At paragraphs 51 to 55 of his affidavit, Dr. Bodmeier responded to Dr. Desbrières' affidavit. Dr. Bodmeier disagreed with Dr. Desbrières' characterization of CP as the temperature at which light transmission is reduced to 50%. Rather, Dr. Bodmeier stated that there was and is no common understanding as to what light reduction level defines a CP. Dr. Bodmeier stated that the testing reported in Dr. Desbrières' affidavit was premised on an incorrect understanding of the invention of the '531 Patent. Rather than comparing batches of a single low viscosity HPMC subtype, Dr. Desbrières' testing compared different subtypes of HPMC products. Dr. Desbrières' testing results are thus not informative.

[78] Dr. Bodmeier also stated that even though HPMC is expected to be fully dissolved at 37˚C, this does not mean that all HPMC batches dissolve at the same rate. Dr. Bodmeier states that Dr. Desbrières ignored the date in the table at page 11 of the '531 Patent that explicitly shows that when

tested in simulated gastric conditions at 37˚C, two batches of HPMC resulted in different average omeprazole release rates; one within the marketing standard and one that was not. Thus, different batches of one subtype of HPMC interact differently with water, which results in the release of omeprazole at different rates.

[79] At paragraphs 56 to 68 of his affidavit, Dr. Bodmeier responded to Mr. Alderman's affidavit. At the outset, Dr. Bodmeier noted that Dr. Desbrières, Dr. Miller, Dr. Colombo and Mr. Alderman provided several of the same statements. Where that was the case, his comments on one affidavit applied equally to the others.

[80] Dr. Bodmeier noted Mr. Alderman's suggestion that low viscosity HPMC would not affect the release of the active ingredient in the tablet. However, Dr. Bodmeier noted that Mr. Alderman concurrently contradicted that statement by noting that HPMC dissolution varies with molecular weight and that there is a clear correlation between increasing viscosity and increasing time of disintegration. Based on the data on viscosity and tablet disintegration time presented in the Rowe study and the range for viscosity stated in the certificate of analysis for METHOCEL E5 (4.0 to 6.0 mPas), Dr. Bodmeier showed that batch-to-batch variation in viscosity for METHOCEL E5 correlated with an approximately 30 second difference in disintegration times between batches. Thus, Dr. Bodmeier stated that Mr. Alderman's statement that HPMC would not affect release rate of the active ingredient was incorrect.

[81] In response to Mr. Alderman's suggestion that a possible reason for the difference in release rates between different batches of HPMC (as reported in the page 11 table) could be imperfections

in the film from lack of plasticizer use, Dr. Bodmeier noted that this appeared to merely be an unfounded guess. In addition, neither batches included a plasticizer.

[82] Dr. Bodmeier also noted that Mr. Alderman incorrectly stated that methoxyl groups, rather than hydroxypropyl groups, are responsible for turbidity. The Sarkar article clearly showed that both groups are responsible for the turbidity caused by phase transition. In addition, Dr. Bodmeier disagreed with Mr. Alderman's statement that if the physical properties of a given HPMC polymer were known, the CP of an aqueous solution of the polymer could be predicted within a very narrow range. Rather, CP is influenced by the nature of the substitution and distribution of both methoxyl and hydroxypropyl along the polymer chain and on the individual glucose units and by the molecular weight/viscosity of the polymer.

[83] Turning to the sufficiency of disclosure, Dr. Bodmeier disagreed with Mr. Alderman's statement that a PSA would not be able to choose the correct HPMC with the specified CP without having the percentage of methoxyl groups provided. Dr. Bodmeier noted that methoxyl groups are not the only determinant of CP. In addition, this statement ignored the invention of the '531 Patent, which improved on prior art omeprazole formulations by providing a means (HPMC at the claimed CP) to avoid having to know physical properties of a given batch of HPMC in selecting an HPMC batch that would result in the required levels of omeprazole release within 30 minutes. Thus, the '531 Patent clearly teaches a PSA how to select a specific quality of HPMC for omeprazole enteric formulation.

[84] At paragraphs 69 to 76 of his affidavit, Dr. Bodmeier responded to Dr. Miller's affidavit. Dr. Bodmeier noted that none of the patents cited by Dr. Miller as prior art discussed concerns with batch-to-batch variation in HPMC, nor did they direct the PSA towards selecting an HPMC above the claimed CP. The invention of the '531 Patent was not obvious in light of any or all the prior art cited. Dr. Bodmeier noted that Dr. Miller's critique on the absence of information on the specific grade of HPMC being tested and the coating amounts of HPMC on the spheres or size of the spheres missed the point of the invention. Based on the '531 Patent, the PSA would understand that any suitable grade or coating amount of low viscosity HPMC could be used to prepare an enteric omeprazole formulation as long as it meets the claimed CP.

[85] Dr. Miller's observation that the release for Type A HPMC was acceptable for at least one of the coated pellet batches because the range of release reached 84% also missed the point. What the patent teaches is a means of selecting a specific quality HPMC to avoid variation. In addition, Dr. Bodmeier disagreed with Dr. Miller's statement that the dissolution results for the two cores in Type A and Type B listed in Figure 3 do not vary greatly. Rather, there is a difference of approximately six minutes between the two profiles, which is equivalent to approximately 20% of the total release time of approximately 30 minutes; a significant difference for immediate release, uncoated pellet cores.

[86] In addition, contrary to Dr. Miller's statement that the '531 Patent does not indicate what type of HPMC a PSA should purchase, Dr. Bodmeier stated that the patent clearly provides that the PSA should purchase a low viscosity HPMC at the claimed CP. Where the HPMC is selected at the claimed CP, the patent teaches that all batches will sufficiently release 75% of the active ingredient

in 30 minutes (in accordance with the marketing standard), thereby reducing product discard due to failed formulations.

[87] Finally, at paragraphs 77 to 88 of his affidavit, Dr. Bodmeier responded to Dr. Colombo's affidavit. Dr. Bodmeier noted Dr. Colombo's statement that the amount of HPMC in the core would be less than 3% thereby not affecting the release rate. However, Dr. Bodmeier stated that this calculation was incorrect. Rather, there is approximately 15% HPMC which is a significant amount in the drug and would be expected to affect the drug release rate. In addition, although low viscosity HPMC is commonly understood to dissolve quickly, there are differences in the dissolution rates of HPMC and low viscosity HPMC used as a coating does affect the rate of immediate release of the active ingredient.

[88] Dr. Bodmeier also noted that Dr. Colombo's statement that dissolution tests require 12 replicate dissolutions was incorrect. Rather, as per scientific literature, a maximum of three to six replicates are generally used. Dr. Bodmeier highlighted that the patent indicates that the findings are based on a "number of experiments". Dr. Bodmeier critiqued several of Dr. Colombo's claims on the basis that they pertained to controlled release formulations and not to immediate release formulations, the subject matter of the '531 Patent.

[89] Dr. Bodmeier further noted Dr. Colombo's statement that the '531 Patent did not specifically state what final dosage form and strength was tested which would cause the PSA to not know which USP standards to compare the tests to and what apparatus was used for conducting the dissolution testing. However, Dr. Bodmeier stated that the PSA, on reading the patent as a whole,

would clearly understand that the tests should be compared to 75% release in 30 minutes (the marketing standard) and that the apparatus used was the Dissolution Apparatus 2 (paddle). Dr. Bodmeier also stated that Dr. Colombo's critique of the word "release" as opposed to "dissolve" was incorrect and stemmed from confusion between controlled release and immediate release. Dr. Bodmeier finally stated that Dr. Colombo's calculation of the similarity factors between the two release profiles for the core pellets shown in Figure 3 of the '531 Patent was error prone and unfounded.

Issues

[90] AstraZeneca submits the following point at issue:

Are Pharmascience's allegations of invalidity of the '531 Patent justified?

[91] Pharmascience submits the following points at issue:

1. Is the patent invalid for inutility?
2. Does the patent meet the requirements of sufficiency?
3. Is the claimed invention obvious?

[92] I would rephrase the issues as follows:

1. Is the '531 Patent not an invention as defined in section 2 of the *Patent Act* because it merely ascertains the properties of a known substance?
2. Does the '531 Patent meet the validity requirements for utility?
3. Does the '531 Patent meet the validity requirements of sufficient disclosure?

4. Does the ‘531 Patent meet the validity requirements for obviousness?

AstraZeneca’s Written Submissions

Evidence

[93] AstraZeneca submits that Pharmascience is strictly limited to making submissions on those invalidity allegations for which it filed evidence, namely: obviousness, insufficiency and lack of demonstrated utility. Thus, Pharmascience cannot rely on its other allegations of invalidity that it did not address in its evidence, namely: lack of novelty, claims broader, double patenting, lack of sound prediction, not a valid selection patent and fraud on the Patent Office.

[94] AstraZeneca also notes that the order of evidence was reversed by Prothonotary Tabib’s order dated February 15, 2011. A reversal of evidence is intended to define more narrowly the allegations of invalidity that will be argued by the generic company, thereby limiting the issues at play.

Patent Construction

[95] AstraZeneca submits that when the ‘531 Patent was published in December 1998, the inventors’ discovery that different batches of low viscosity HPMC, as reflected by their CP, may have different abilities to influence the rate of release of omeprazole from an enteric coated formulation would have been very surprising to a PSA. This was because the use of low viscosity

HPMC in a pharmaceutical formulation was not generally known to be capable of influencing release rate. Moreover, a PSA would actually have believed the opposite to be true because low viscosity HPMC is a polymer that dissolves quickly in water. AstraZeneca also notes that the reference to different batches in the patent would be clearly understood by a PSA to mean different batches of the same subtype of low viscosity HPMC.

[96] AstraZeneca notes that experts for both sides agreed that in December 1998, a PSA would not have referred to or categorized HPMC by reference to its CP. However, on reading the patent, it would have become apparent to a PSA that by selecting low viscosity HPMC in accordance with its CP, the inventors had provided a proxy by which to assess the sum effect of the infinite combinations of different variables that were understood to affect the CP and the release rate of omeprazole.

[97] AstraZeneca highlights the statement in the patent that an upper limit for the CP is not critical and must therefore not be specified. From this, a PSA would understand that when selecting a low viscosity HPMC, the upper limit is not important as long as the requirements defined in phamacopoeial monographs and the claimed CP are fulfilled. As a higher CP reflects higher water solubility, it would not be expected to decrease the rate of release of omeprazole. Thus, it is the specification for the lower limit, not the upper limit, that is critical to achieving the desired rate of release.

[98] In addition, the inventors stated in the patent that the reduction of product discard was a real economic advantage resulting from selecting a low viscosity HPMC in accordance with the claimed

CP. On following the patent, a PSA would also learn how to reduce unpredictable variations in release rates between different batches of formulations, further reducing product discard.

[99] Finally, AstraZeneca notes that none of Pharmascience's experts provided a discussion on the understanding of the PSA of the batch-to-batch variation described in the '531 Patent. This is fundamental to an understanding of the patent invention. Although the experts stated their general disbelief that differences in low viscosity HPMC as gauged by reference to the CP can affect the release of a drug, they did not provide evidence disproving the correlation or any credible basis for their disbeliefs.

Invention under Section 2 of the *Patent Act*

[100] AstraZeneca submits that Pharmascience's allegation that the '531 Patent is not an invention is fundamentally flawed as it is premised on an incorrect construction of the patent. When properly construed, the patent does not merely contribute a verification of the CP but also teaches that by selecting low viscosity HPMC above the claimed CP, a pharmaceutical formulator can reduce the amount of product discard that does not meet omeprazole release specifications. This was a surprising and unexpected teaching offering a substantial advantage.

[101] Furthermore, Pharmascience's evidence that the '531 Patent claims an inherent property of a known compound is flawed as it is premised on testing that purportedly indicates that low viscosity HPMC in 1998 and today would have a CP above the claimed CP. This testing failed to consider the

batch-to-batch variation in CPs. Concurrently, it provided a clear admission that the CP of some batches of the same low viscosity HPMC product can in fact be below the claimed CP.

Utility

[102] AstraZeneca submits that the patent's inventors demonstrated that by selecting low viscosity HPMC at the claimed CP for use in the omeprazole enteric formulation, at least 75% of the omeprazole would be released in a buffer solution in the first 30 minutes (as per the marketing standard). In reading this in the context of the whole patent, a PSA would clearly understand that different batches of a subtype of HPMC can differ in CPs. This difference can result in one batch with a certain CP releasing omeprazole within the prescribed 30 minutes while another batch with a different CP does not.

[103] AstraZeneca notes that the Federal Court of Appeal has explicitly rejected the notion that utility must be demonstrated in the patent disclosure. Nevertheless, AstraZeneca highlights the patent's reference to results from a number of experiments. These experiments demonstrated that selecting a batch of HPMC with at least the claimed CP is desirable for achieving the marketing standard.

[104] AstraZeneca submits that the Pharmascience experts' disbelief, which relies on Dr. Desbrières' testing, is pure conjecture and is not based on evidence. In support, AstraZeneca notes that Dr. Desbrières' testing does not address the invention of the '531 Patent and whether there is batch-to-batch variation of CPs in a given subtype of low viscosity HPMC. Moreover, these

experts' disbelief is directly contradicted by actual data in the '531 Patent and in a table produced by Pharmascience at page 60 of its allegation.

[105] AstraZeneca notes that Pharmascience did not share this information with its witnesses, including Dr. Desbrières, before he conducted the testing described in his affidavit. After considering this information, AstraZeneca submits that Dr. Desbrières admitted in cross-examination that test results showed some batches of low viscosity HPMC with a CP below 44.5˚C. This contradicted his affidavit evidence that all HPMC would have a CP above the claimed CP. Similarly, AstraZeneca notes Mr. Alderman's affidavit evidence that, based on Dr. Desbrières' testing, the CP of METHOCEL E5 in 1996 and today would have exceeded 45˚C. However, on cross-examination, Mr. Alderman admitted that he had not seen the data from Dr. Desbrières' testing when he provided his opinion, nor did he write that particular sentence in his affidavit.

[106] AstraZeneca also notes that Pharmascience's experts agree that within a subtype of low viscosity HPMC, there are allowable ranges of methoxyl and hydroxypropyl content and that both of these have an effect on CP. In addition, when a particular HPMC subtype is manufactured, it is highly improbable that one lot will have an identical distribution of substitutes as another because the number of sites on the polymer chain where the substitution occurs far exceeds the number of possible substituents. Dr. Desbrières admitted that in a heterogenous industrial process, the distribution of substituents of the HPMC will vary from batch to batch. Dr. Desbrières' evidence also shows that the distribution of substituents can affect gelation temperature, which can lead to differences of at least 20˚C for CP.

[107] AstraZeneca further notes that the experts agree that within a given subtype of low viscosity HPMC, there are allowable ranges of molecular weight and viscosity. Albeit to a lesser extent, CP is also affected by the molecular weight or viscosity of the polymer. These unpredictable differences will affect the CP and AstraZeneca notes that it is unchallenged that the CP of a low viscosity HPMC batch can only be obtained from direct measurement.

[108] AstraZeneca highlights that Pharmascience directed Dr. Desbrières to conduct testing on certain HPMC samples in support of its invalidity allegations. Dr. Desbrières admitted that he did not compare the CP of different batches of a given subtype of HPMC, rather, he compared the CP of different subtypes. As Dr. Desbrières' testing did not address the batch-to-batch variation addressed by the patent and is premised on a fundamentally incorrect understanding of the patent, AstraZeneca submits that his test results are not informative.

[109] AstraZeneca also submits that Dr. Desbrières's testing should be disregarded as he was unaware of the chain of custody of some of the HPMC samples he tested, particularly with what happened to the samples between the time they were shipped from Dow to his counsel and ultimately to him. AstraZeneca also notes the following in support of its submission that Dr. Desbrières' evidence should be treated with circumspection. Dr. Desbrières:

1. is not an expert in the formulation of enteric coatings and has never conducted a gastric acid release test;

2. gave an opinion that the differences in release rates disclosed in the gastric acid release tests in the '531 Patent could be erroneous even though he did not know the margin of error of these tests and has never conducted such a test;

3. suggested that the claimed CP was not a true CP because it was not designated as the temperature at which light transmission is reduced to 50%. However, he later admitted that CP does not have a fixed definition and gave no explanation as to why he defined CP at 95% in a 1997 publication;

4. gave affidavit evidence that low viscosity HPMC would have a minimum CP of 44.5˚C. However, he later admitted that he had no data as to whether the CP of multiple batches of one subtype of HPMC would fall below this temperature and admitted that the data provided by Pharmascience in its NOA shows several batches of the same subtype of HPMC with CPs below this temperature; and

5. approached the '531 Patent improperly as he applied all his knowledge gained up until drafting his affidavit rather than focusing on the understanding of a PSA reading the patent at the publication date.

[110] AstraZeneca also notes that although Pharmascience's experts provided affidavit evidence that CP does not affect release rate, Dr. Desbrières admitted that gelation properties (related to CP) have an effect on release and the heterogeneity of substitution provides a poor predictability of release. On Mr. Alderman's suggestion that a possible reason for the difference in release rates could be imperfections in the film caused by a lack of use of plasticizer, AstraZeneca notes that this appears to be a guess without basis. In addition, Mr. Alderman's experience with pharmaceutical formulations pertains to controlled release formulations rather than immediate release formulations and Mr. Alderman has also not been actively engaged in the field of controlled release since about 1988.

[111] AstraZeneca submits that Dr. Miller's statement that the release for Type A HPMC was acceptable for at least one of the coated pellet batches misses the point. The fact that one example has a release rate within the required limits is irrelevant. The patent teaches that the variation in release rates can be avoided by selecting an HPMC exceeding the claimed CP.

[112] In response to Dr. Colombo's statement that differences in the release rates for different types of HPMC cannot be attributed to differences in CPs because the HPMC would dissolve immediately, AstraZeneca notes that low viscosity HPMC are commonly understood to dissolve quickly. However, it is not true that there are no differences in the dissolution rates of HPMC or that low viscosity HPMC, when used as a coating, does not affect the rate of release of the active ingredient. Rather, prior to the release of the '531 Patent, a PSA would have generally believed that there were no relevant differences in the release characteristics of low viscosity HPMC designed for immediate release.

[113] The '531 Patent surprisingly and clearly shows that differences in low viscosity HPMC, as gauged by reference to the CP, do result in difference in release rate of omeprazole. Thus, selecting batches of low viscosity HPMC that exceed the claimed CP ensures that omeprazole release is consistently within the marketing standard. AstraZeneca submits that Dr. Colombo's statement on the quick dissolution of low viscosity HPMC and that is not used in preparing controlled release formulations confuses the matter because neither of these situations are taught in the '531 Patent. The '531 Patent pertains to avoidance of variations in immediate release formulations.

[114] With regards to Example 3, where low viscosity HPMC was used as a binder rather than a separating layer, AstraZeneca notes that in stating that the dissolution rates for the two cores did not vary greatly, Dr. Miller ignored that this test pertained to the release from uncoated pellet cores, for which there is a significant difference in immediate release. In addition, in his calculation of the similarity factor between the two release profiles, Dr. Colombo did not have the necessary information from the patent, nor did he indicate what assumptions he made in his calculation. Nevertheless, the figure that Dr. Colombo's calculation was based on (Figure 3) was developed from an experiment related to the use of low viscosity HPMC as a binder. The low viscosity HPMC was not exposed to gastric acid in that experiment as would have been the case for enteric formulation with the separating layer containing the low viscosity HPMC.

[115] AstraZeneca highlights that Pharmascience's own evidence shows that the least important cause of differences in CP, namely viscosity, also has an effect on the release. This data indicates that batch-to-batch variation in viscosity for METHOCEL E5 correlates with an approximately 30 second difference in disintegration times between batches at either end of the allowable range.

[116] Finally, AstraZeneca notes that although HPMC is expected to be fully dissolved at 37˚C, this does not mean that HPMC batches dissolved at the same rate. In fact, as admitted by Dr. Miller, different batches of HPMC dissolve at different rates and these rates are important to the release from a dosage form. AstraZeneca submits that Pharmascience's argument on body temperature also considers HPMC solubility in isolation. This is not the subject of the '531 Patent which is directed to the effect of HPMC on the release of the active ingredient. In fact, the data in the patent shows that when tested in simulated gastric conditions at 37˚C, two batches of HPMC resulted in different

average omeprazole release rates, only one of which met the marketing standard. This shows that different batches of one subtype of HPMC in formulations that are otherwise identical interact differently with water, resulting in the release of omeprazole at different rates.

Sufficiency

[117] AstraZeneca notes that an attack on the basis of insufficiency is a technical attack and will only succeed where the PSA, equipped with common general knowledge, could not put the invention into practice. Here, AstraZeneca submits that all the allegedly missing information would be clearly known to a PSA on reading the patent as a whole. Thus, the allegations of insufficiency are not justified.

[118] AstraZeneca notes that Pharmascience's evidence acknowledges that use of low viscosity HPMC in a separating layer and as a binding agent was well known at the date of publication. The '531 Patent adds to this prior art by teaching that the CP of HPMC should be above a certain limit (the claimed CP) to ensure desirable release characteristics. As there is no question that CP as defined in the patent is understood and can be determined, there is no insufficiency of disclosure.

[119] With regards to the statement by Pharmascience's experts that the '531 Patent does not indicate what type of HPMC a formulator should choose or purchase, AstraZeneca notes that the patent, on its face, could not be clearer. AstraZeneca submits that a PSA would understand that any suitable grade of low viscosity HPMC can be used to prepare an enteric omeprazole formulation, as

long as it exceeds the claimed CP. The patent also clearly explains how to determine the CP. Thus, a PSA could put the invention into practice by testing that it exceeds the claimed CP.

[120] AstraZeneca further submits that contrary to the evidence from Dr. Colombo, a dissolution test need not be run in replicates of 12. Rather, in scientific literature, three to six replicates is the standard. Thus, it is not credible for Dr. Colombo to suggest a lack of understanding of the patent data based on the number of replicates run.

[121] In response to Dr. Colombo's statement that the apparatus used for conducting dissolution testing was not disclosed in the patent, AstraZeneca states that a PSA, upon seeing the reference to the requirement of 75% release in 30 minutes (the marketing standard) and the reference to the use of a paddle in the patent, would clearly know that the inventors used the Dissolution Apparatus 2 (paddles). The patent also clearly states that enteric pellets were used in the testing. AstraZeneca notes that Dr. Colombo resiled from this position on cross-examination.

[122] With regards to Dr. Miller's statement that there is no information in the patent on the coating amounts of HPMC on the spheres or the size of the spheres, AstraZeneca submits that a PSA would understand that any suitable amount of coating of low viscosity HPMC can be used to prepare an enteric omeprazole formulation as long as it exceeds the claimed CP.

[123] AstraZeneca further submits that the allegation by Pharmascience's witnesses that a PSA would not be able to choose the correct HPMC without knowing the percentage of methoxyl groups highlights their misunderstanding or mischaracterization of the '531 Patent. This patent improves on

prior art omeprazole formulations by ensuring adequate release without having to know or determine specific physical properties of a given batch of low viscosity HPMC. Moreover, as admitted by Pharmascience's experts, certain characteristics cannot be readily determined. Thus, the patent provides an elegant means for incorporating all the various physical properties of low viscosity HPMC that affect release by reference to CP as a proxy.

[124] Finally, AstraZeneca notes that Dr. Colombo alone took issue with the fact that the '531 Patent does not specifically state which final dosage form and strength was tested in the release studies. Dr. Colombo alleged that as a result, a PSA would not know to which USP-stipulated standards to compare the release tests of the patent. However, AstraZeneca submits that a PSA, having read the patent and seen the numerous references to USP and Losec®, would have understood that the release tests should be compared to 75% release in 30 minutes (the marketing standard). AstraZeneca highlights that Dr. Colombo also resiled from this evidence on cross-examination.

Obviousness

[125] AstraZeneca notes Pharmascience's reference to other patents as indicative of prior art. However, AstraZeneca highlights that none of these patents discuss the concerns with batch-to-batch variations in HPMC. In addition, the other patents do not direct a PSA towards selecting and using HPMC above a particular CP to reduce product discard during manufacturing.

[126] AstraZeneca submits that the invention of the '531 Patent would not be obvious from all or any of the prior art cited. In fact, prior to 1998, a PSA would not have considered the low viscosity HPMC on seeing that omeprazole enteric formulations were being released at different rates. Rather, a PSA might have considered other formulation or process parameters to solve his or her problems.

[127] All experts also agreed that CP was not a factor considered in selecting low viscosity HPMC for use as a binder and/or separating layer. In fact, this information was not included in low viscosity HPMC sold commercially in December 1998 nor was it considered by PSAs in their selection or design of a formulation. The nexus between the CP of low viscosity HPMC and release rate was an important and counter-intuitive innovation born out of the differential release data in the '531 Patent.

[128] In conclusion, AstraZeneca submits that Pharmascience's invalidity allegations are not justified. AstraZeneca therefore requests that this Court prohibit the Minister from issuing a NOC for the Pharmascience capsules until the expiry of the '531 Patent.

Pharmascience's Written Submissions

[129] Pharmascience submits that the '531 Patent does not disclose an invention or a useful contribution to the science of formulations. Rather, a clear reading of the '531 Patent indicates that there is no invention at all.

Evidence

[130] Pharmascience notes that it is settled law that the ultimate burden of proof rests on AstraZeneca to disprove Pharmascience's allegations of invalidity on a balance of probabilities. Conversely, Pharmascience merely has an evidentiary burden to present sufficient evidence to give its allegations of invalidity an air of reality.

[131] Pharmascience highlights that it provided evidence from four separate experts, all of whom were straightforward in giving their evidence. Conversely, AstraZeneca only filed evidence from one expert (Dr. Bodmeier) and none from the patent inventors. In giving his evidence, Dr. Bodmeier acted as an advocate for AstraZeneca. Pharmascience therefore submits that, to the extent that there is any conflict between the evidence from the two parties, the evidence from their witnesses must be preferred.

[132] Pharmascience notes that the viscosity of HPMC is controlled through the manufacturing process. Pharmascience submits that the article by Rowe shows that the disintegration time of tablets coated with HPMC is directly related to the molecular weight. The sole batch-to-batch variation that AstraZeneca's expert identified from this article was a 30 second variation for METHOCEL E5.

[133] Further, a paper by Sangalli shows that a coating of METHOCEL E5 is not thick enough to induce control over the rate of drug release. Notably, the coating of METHOCEL E5 in that testing was 30 times greater than the thickness of the separating layer used in the '531 Patent.

[134] Thus, Pharmascience submits that the literature supports a finding that low viscosity HPMC, when used as a binder or as a separating layer in a pharmaceutical formulation, does not delay the release of the drug. Pharmascience notes that AstraZeneca has not provided any scientific literature that indicates that low viscosity HPMC will impact drug release. In addition, Dr. Bodmeier either did not report any effect of HPMC on the release of the drug or in fact reported that low viscosity HPMC increased the release rate of drugs in the papers he authored.

Prior Art Patents

[135] Pharmascience submits that prior art patents on formulations of omeprazole have consistently disclosed the following three layer formulation:

1. Core with omeprazole and an alkaline compound or an alkaline salt of omeprazole;
2. Coating layer that is soluble in water or rapidly disintegrating in water and that consists of non-acidic inert substances such as HPMC; and
3. Enteric coating.

[136] Pharmascience submits that a PSA would understand that the HPMC used as a binder in the core and in the coating layer would be a low viscosity HPMC. In addition, most prior art patents disclose that rapid dissolution of the formulation in the intestine is needed and the formulation that provides such dissolution is this three layer formulation. This is the formulation described in the '531 Patent.

[137] Pharmascience summarizes the basic teaching of prior art patents as follows:

- Omeprazole is susceptible to degradation in acid reacting and neutral media;

- A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal;

- Omeprazole must be protected from the acidic juice of the stomach by enteric coating;

- Enteric coatings are made of acidic compounds and if applied directly to omeprazole, the omeprazole will become badly discoloured; and

- The three layer formulation is used to protect omeprazole with the separating layer protecting omeprazole from the enteric coating.

[138] Pharmascience submits that the teaching of prior art patents is to use the three layer formulation when formulating benzimidazoles such as omeprazole and esomeprazole and that HPMC is used in the separating layer as part of a rapidly dissolving formulation. A skilled formulator would know that low viscosity HPMC used as a separating layer or as a binder would not impact on the release rate of the formulation. Further, no problems with the dissolution of HPMC were indicated in the prior art patents and no problems with batch-to-batch variation were reported by AstraZeneca to its supplier, Dow. Pharmascience submits that the CP of HPMC would not be considered when designing a formulation either in 1997 or today. Rather, the primary governing factors are molecular weight and viscosity.

Cloud Point (CP)

[139] Pharmascience submits that the two main manufacturers of HPMC (Dow and Shin-Etsu) manufacture HPMC using the same technology and their products meet the same pharmacopeial

specifications. The HPMC polymers that were commercially available in 1997 are the same HPMC polymers that are available today. These are: METHOCEL E3, E5 and E15 and Pharmacoat 603, 606 and 615.

[140] Pharmascience submits that the CP of a solution of HPMC is an inherent property of the polymer that arises from its physical properties. In particular, the percentage of methozyl groups present on the polymer chain. This percentage is determined through the manufacturing process. As METHOCEL E5 and E6 have had the same percentage of methozyl groups, they would have CPs within a narrow range. Further, the specifications of METHOCEL E6 and Pharmacoat 606 are identical and they can therefore be considered two batches of the same subtype. Pharmascience notes that the CPs for Pharmacoat 606, METHOCEL E6 and METHOCEL E5 range from 45.8˚C to 47.7˚C, all of which exceed the claimed CP.

[141] In response to AstraZeneca's attack on the chain of title for the samples sent to Dr. Desbrières, Pharmascience notes that the samples came either from counsel or directly from the manufacturer, both of which are reliable sources.

[142] Further, although AstraZeneca submits that the differences in the substitution of methoxyl and hydroxypropyl groups along the backbone of HPMC has significant effects on the CP, these submissions were unsupported by scientific evidence. In addition, although AstraZeneca seeks to rely on the gelation properties of HPMC and their correlation to the release of the drug, these were not covered by the '531 Patent.

Patent Construction

[143] Pharmascience highlights that the '531 Patent admits that extensive information about the ingredients at issue therein was already known. The main qualification that this patent adds pertains to the CP of HPMC.

[144] Contrary to AstraZeneca's assertion that the formulation is an immediate release formulation, Pharmascience submits that it is a delayed release formulation since the drug is not released until the formulation travels through the stomach and into the intestine.

[145] Pharmascience submits that the patent does not present any tests or supporting evidence as to why the claimed CPs were selected. As such, they are arbitrary choices. Further, Pharmascience notes that the '531 Patent does not disclose that the CP of HPMC has any effect on drug release. Rather, it discloses the opposite as the tests included therein pertained to only one batch of low viscosity HPMC at the claimed CP. These tests can therefore not show batch-to-batch variation. In addition, Pharmascience notes that the three tests in the '531 Patent purport to compare two unidentified types of HPMC, one above and one below the claimed CP. As AstraZeneca admits that these two types are equivalent, Pharmascience notes that they could be one batch of METHOCEL E6 and one batch of Pharmacoat 606.

[146] Pharmascience further notes that Figures 1 and 2 in the '531 Patent indicate full dissolution of both types of HPMC at body temperature. Thus, the patent does not teach anything on a cause and effect relationship between the CP of the HPMC and the release of the drug at body

temperatures. In addition, contrary to AstraZeneca's submissions, Dr. Miller did not agree that different batches of HPMC dissolve at different rates. Rather, Dr. Miller stated that low viscosity HPMC would provide an immediate release while high viscosity HPMC would not dissolve as fast.

[147] With regards to the test results depicted in Figure 3 of the '531 Patent, Pharmascience notes that HPMC was used as a binder in that experiment and there was no confounding factor such as an enteric coating. The results of this testing indicated that both types of HPMC meet the dissolution specification for omeprazole and that, when used as a binder, HPMC cannot exert control over the rate of drug release.

[148] Pharmascience further notes that AstraZeneca attempts to dismiss its own patent tests on the basis that the HPMC is not exposed to gastric acid in the experiment, as would be the case for enteric formulation. However, Pharmascience submits that this argument overlooks the fact that the enteric coating is expected to withstand the gastric juices and dissolve at the higher pH of the intestine. Only then will the HPMC layer dissolve. This is the clear teaching provided by AstraZeneca's patents on the three layer formulation.

[149] Pharmascience also notes that significant data is missing from the enteric coated pellet test reported in the '531 Patent; including: number of pellets made and tested; whether the pellets were tested separately or as part of a capsule or tablet formulation; dosage form tested (pellets, capsules or tablets); strength of the final dosage form; thickness of the enteric coating; quantity of omeprazole in the pellets when they were placed in the buffer solution; whether the same conditions were employed for the pellets containing Type A and Type B HPMC; number of dissolution studies

performed for the pellets containing the different types of HPMC; and information on any statistical analysis conducted.

[150] Pharmascience notes that, contrary to AstraZeneca's allegation, some of the Type A batch did release within the 30 minute time frame. Further, as there was only one batch of HPMC Type A, the differences in the dissolution were not due to the nature and properties of the HPMC. In addition, given that the pellets made with Type A HPMC worked, there was nothing to indicate that the HPMC affected the dissolution. Finally, Pharmascience notes that the pharmacopeial specifications for omeprazole allow for the dissolution of 70% in 30 minutes for 40 mg capsules. At that dose, all the Type A and Type B pellets met the specifications.

[151] Pharmascience highlights that the '531 Patent does not show that the HPMC is the rate controlling step in the dissolution of the drug. Rather, the difference reported in the '531 Patent is more likely attributed to something in the enteric coating than in the sub-coat. Further, if one wants to determine if HPMC is affecting the release of a coated pellet, the pellet should be tested both with and without HPMC. This test was not conducted in the '531 Patent. With no direct cause and effect between the HPMC and the dissolution of the drug shown in the '531 Patent, Pharmascience submits that it is clear that another explanation accounts for the dissolution. Possible alternate explanations include:

1. Release may be affected by the thickness of the polymer and by the types and amounts of plasticizers in the polymer enteric coating;

2. Aggregates can form during the coating process that might create a thicker layer on some spheres rather than others;

3. Excipients in the core can have an effect on the release of omeprazole;

4. Thickness or uniformity of the separating layer produced with the two types of HPMC may be different and a very thin separating layer would reduce the integrity of the layer making it susceptive to cracks, holes and deformation;

5. Spraying the HPMC too quickly could cause the pellets to stick together, thereby impacting the integrity of the film; and

6. There could have been a loss of omeprazole (which was not measured) at the first stage of the test in the acidic conditions.

[152] Pharmascience notes that before December 1988, a PSA would have investigated the other parameters that can cause delay in release, such as spray rate, product temperature and air flow. Pharmascience also notes that there is not a single specification for HPMC after the '531 Patent publishing date that contains a CP measurement. Meanwhile, pharmaceutical formulators before and after that date continue to consider factors such as viscosity and molecular weight.

Invention under Section 2 of the *Patent Act*

[153] Pharmascience submits that in May 1998, it was already well known that low viscosity HPMC dissolved in aqueous solutions under both basic (intestinal) and acidic (stomach) conditions. This renders it suitable for preparing films that dissolve rapidly at the target site. In addition, when used as a thin coating on the outside of tablets or as a separating layer, it provides immediate release and does not exert any control over the rate of dissolution or drug release.

[154] Pharmascience thus submits that no invention was provided in the ‘531 Patent. Prior art patents disclosed the three layer formulation made with low viscosity HPMC both as a binder and as a separating layer. HPMC becomes cloudy and viscosity increases at 41˚C. However, this is not relevant to the formulation because it must dissolve at 37˚C (body temperature).

[155] Even if this Court finds that CP is relevant, Pharmascience notes that it is a factor determined primarily by the percentage of methoxyl groups in the HPMC. Pharmascience highlights that the uncontradicted testing evidence shows that low viscosity HPMC with the methoxyl content used for over thirty years will have CPs within the claimed CP.

Utility

[156] Pharmascience submits that the ‘531 Patent does not meet the requirement of utility. It is insufficient to state that the tests were run. Once challenged, the patentee must file evidence of those tests. Here, AstraZeneca has not filed evidence of utility and Pharmascience submits that utility is not demonstrated in the ‘531 Patent. Pharmascience also submits that where a patent had made a promise of commercial utility, the patentee must be held to that standard. Here, AstraZeneca has failed to meet that standard. Thus, the patent offers nothing beyond the prior art three layer formulation.

[157] Pharmascience notes that a sole data point cannot demonstrate consistency throughout a range. Thus, a single batch cannot evidence batch-to-batch variation. Where the claimed invention

does not have the promised utility, such as better dissolution and elimination of batch-to-batch variation, then an attack of invalidity is justified.

[158] Where a PSA can come to no meaningful conclusion based on the information in the patent, the Court will find inutility. Here, two of the three tests clearly show that there is no difference in the dissolution of the two types of HPMC. In the third test, some of the units tested worked fine so there is no demonstration that the CP of the HPMC was the cause of any dissolution problems. Thus, the patent does not show the utility of HPMC of a certain CP. In addition, Pharmascience submits that the basis of the patent is not shown in the patent or in the evidence. Thus, the '531 Patent is invalid for lack of utility.

Sufficiency

[159] Pharmascience submits that the '531 Patent fails to provide the public with any meaningful new information on the making of a three layer tablet that they did not already know. The patent also lacks sufficiency because the underlying data demonstrates that the result is much less than promised.

Obviousness

[160] Finally, Pharmascience submits that there is nothing inventive in finding a solution to a problem that never existed. Here, AstraZeneca never complained to its HPMC supplier about batch-

to-batch variation. As CP is an irrelevant parameter, Pharmascience submits that there are no differences between the three layer formulation in the prior art and that claimed in the '531 Patent.

[161] Even if this Court were to accept that the claimed CP has some meaning, it is an inherent property of low viscosity HPMC that was used in the prior art patents. It was thus a known and measurable parameter. There is also no suggestion that measuring CP is inventive. Finally, Pharmascience notes that a claim based on HPMC with a certain CP is indirectly a claim based on the percentage of methozyl groups in the HPMC, something that was already well known.

[162] For these collective reasons, Pharmascience requests that this application be dismissed.

Analysis and Decision

Preliminary Determinations

[163] The respondents submitted that Dr. Bodmeier acted as an advocate and accordingly, if there was a conflict between the evidence of the respondents' experts and that of Dr. Bodmeier, the evidence of the respondents' experts should be preferred. I have reviewed the evidence of Dr. Bodmeier and I do not agree that he was acting as an advocate. He was elaborating on his answers.

[164] I would also note that I accept Dr. Bodmeier's evidence that the '531 Patent refers to different batches of the same HPMC product. He stated at paragraph 19 of his affidavit (hearing

compendium of AstraZeneca Canada Inc., part 1, tab 5, volume 6, page 2224 of the application record):

> It should be noted that when the 531 patent makes reference to "different batches" it would be understood as a reference to different batches of the same HPMC product, for example, a specific subtype of HPMC. It was known that the quality of excipients, including HPMC, may differ depending on the subtype and it would be contrary to accepted practice to use different HPMC subtypes in commercial manufacture of pharmaceutical formulations since consistency is critical. A skilled person would understand that a specific HPMC subtype will have been selected for use in the final manufacturing formulation and that batch to batch variations therefore refer to different batches of that subtype. For example, Dow Chemical makes several product families of HPMC, including METHOCEL A, E, F, J and K. Within METHOCEL E, there are several subtypes such as E5, E6, and E15. Therefore when the patent refers to different batches, it is a reference to different batches of one subtype of HPMC listed above, for example, different batches of METHOCEL E5. Commercial vendors will identify different batches of an HPMC subtype by batch number.

[165] The evidence shows that Dr. Desbrières' tests deal with five different subtypes of low-viscosity HPMC rather than tests of different batches of the same subtype.

[166] At the outset, the regulatory process at issue here is worth noting. The Federal Court of Appeal described this process succinctly in *Pfizer Canada Inc v Mylan Pharmaceuticals ULC*, 2012 FCA 103, [2012] FCJ No 386 as follows:

> 4 In order to sell a new drug in Canada, an innovator must obtain regulatory approval from the Minister of Health under Division 8 of Part C of the *Food and Drug Regulations*, C.R.C. c. 870. This approval is by way of a notice of compliance, which may be issued only following a submission containing sufficient information and material enabling the Minister to assess the safety and effectiveness of the drug, including detailed reports of the tests made to establish its safety for the purpose and under the conditions of use recommended, and substantial evidence of its clinical effectiveness.

5 If a generic manufacturer then wishes to market a generic version of that drug, it must file a submission (designated as an abbreviated new drug submission) with the Minister of Health in which it makes specified comparisons between its generic drug and the innovator drug for the purpose of satisfactorily meeting the conditions set out in Division 8 of Part C of the *Food and Drug Regulations* in order to obtain a notice of compliance for the generic drug.

6 The *NOC Regulations*, adopted pursuant to section 55.2 of the *Patent Act*, R.S.C. 1985, c. P-4, allow an innovator who files a new drug submission to also submit to the Minister of Health a patent list relating to the submission. A patent on this list may then be added to a register of patents maintained by that Minister.

7 A generic drug manufacturer who seeks a notice of compliance in respect of a drug and which compares that drug with another drug marketed in Canada under a notice of compliance must, with respect to each patent listed on the register for that other drug, either accept that it will not obtain the Minister's approval until the patent expires, or allege (through what is known as a "Notice of Allegation") that the patent is not valid or would not be infringed, and include a detailed statement of the legal and factual basis for the allegation: section 5 of the *NOC Regulations*.

8 An innovator that is served with such a Notice of Allegation may apply to the Federal Court for an order prohibiting the Minister of Health from issuing a notice of compliance to the generic manufacturer until after the expiration of its patent. The court must make such an order if it finds that the allegations relating to that patent and contained in the Notice of Allegation are not justified: section 6 of the *NOC Regulations*.

9 The Supreme Court of Canada and our Court have determined that such an application is a highly fact specific summary proceeding, the sole object of which is to prohibit the issuance of a notice of compliance under the *Food and Drug Regulations*. Consequently, issues of patent infringement or validity cannot be finally determined in such a proceeding: *Eli Lilly & Co. v. Novopharm Ltd.*, [1998] 2 S.C.R. 129 at paras. 95-96; *Merck Frost Canada Inc. v. Canada (Minister of Health and Welfare)* (1994), 55 C.P.R. (3d) 302 (F.C.A.) at pp. 319-20; *David Bull Laboratories (Canada) Inc. v. Pharmacia Inc.*, [1995] 1 F.C. 588 (C.A.) at p. 600.

10 If the innovator is successful in the proceeding, the Minister of Health is prohibited from issuing to the generic a notice of

> compliance for its generic drug until the relevant patent has expired. If the generic is successful, the Minister may issue a notice of compliance for its generic version of the drug. Whatever the outcome of the proceeding under the *NOC Regulations*, patent validity and patent infringement proceedings under the Patent Act may be initiated or continued by the parties before any competent court. [emphasis added]

[167] The notice of allegation frames the proceeding under the NOC Regulations. Thus, any allegation not included therein cannot be addressed in the proceeding (see *Pfizer Canada (2012)* above, at paragraph 29).

[168] Guiding principles on notice of allegations were summarized by Mr. Justice Roger Hughes in *GlaxoSmithKline Inc v Pharmascience Inc*, 2011 FC 239, [2011] FCJ No 287, as follows:

> 40 Without comment as to whether they are right or wrong as a matter of "fairness", certain principles have emerged as a result of judicial interpretation as to an NOA, including:
>
> i. The NOA cannot be amended once legal proceedings have commenced except that certain allegations made can be omitted or no longer relied upon (e.g. *Hoffmann-La Roche Ltd v. Canada (Minister of National Health and Welfare)* (1996), 70 C.P.R. (3d) 1, (FCA); *Bayer A/G v. Novopharm Ltd.* (2006), 48 C.P.R. (4th) 46 (FC) at paras 72 to 84).
>
> ii. The Notice of Allegation must be sufficient so as to make the "first person" fully aware of the grounds raised as to invalidity or non-infringement (*Mayne Pharma (Canada) Inc. v. Aventis Pharma Inc. (*2005), 38 C.P.R. (4th) 1 (FCA) at paras. 19-21).
>
> iii. A second person cannot, in proceedings taken in Court, present argument and evidence relating to an issue that is outside the scope of its NOA (e.g. *Ratiopharm Inc. v. Canada (Minister of Health)* (2007), 58 C.P.R. (4th) 97 (FCA) at para. 25.
>
> iv. The second party may not shift ground or raise a new ground during the legal proceedings that has not been raised in its NOA

> (*Pfizer Canada Inc. v. Canada (Minister of Health)* (2006), 54 C.P.R. (4th) 279 (FC) at paras 70 - 71).
>
> 41 In the Court proceedings, a first person is required to demonstrate, in accordance with subsection 6(2) of the NOC Regulations, that "none of those allegations is justified". Thus, the object of the proceedings is to look at the allegations, consider the evidence, apply the law, and determine whether an allegation made in the NOA is justified. Such a determination, for instance, whether an allegation as to invalidity is justified or not, does not preclude that issue from being litigated in an ordinary action respecting the patent, in other words, there is no *res judicata* (*Aventis Pharma Inc. v. Apotex Inc.* (2006), 46 C.P.R. (4th) 401 (FCA) at para. 7). [emphasis added]

[169] In this case, AstraZeneca requests a declaration that the NOA is neither a valid notice of allegation nor a detailed statement as contemplated by the NOC Regulations. The sufficiency of a notice of allegation is a question of mixed fact and law (see *Pfizer Canada (2012)* above, at paragraph 30).

[170] In *Pfizer Canada Inc v Apotex Inc*, 2007 FC 26, 59 CPR (4th) 183 (aff'd 2007 FCA 195, leave to appeal refused [2007] SCCA No 371), Mr. Justice James O'Reilly described the burden of proof in an NOC proceeding (at paragraph 12):

> To summarize, Pfizer bears the legal burden of proving on a balance of probabilities that Apotex's allegations of invalidity are unjustified. Apotex merely has an evidentiary burden to put its case "into play" by presenting sufficient evidence to give its allegations of invalidity an air of reality. If it meets that burden, then it has rebutted the presumption of validity. I must then determine whether Pfizer has established that Apotex's allegations of invalidity are unjustified. If Apotex does not meet its evidential burden, then Pfizer can simply rely on the presumption of validity to obtain its prohibition order.

[171] On review of the NOA at issue here, I find that Pharmascience has provided a sufficiently detailed statement of the legal and factual basis for its allegations, as required under subparagraph 5(3)(b)(ii) of the NOC Regulations. As mentioned above, Pharmascience provided extensive submissions on the following grounds of invalidity in its NOA:

1. Insufficient disclosure/lack of support;
2. Claims broader than invention made or disclosed;
3. Lack of novelty and anticipation by prior use;
4. Double-patenting;
5. Lack of inventive step/obviousness; not an invention (under section 2 of the *Patent Act*);
6. Lack of sound prediction and lack of utility;
7. Not a valid selection patent; and
8. Fraud on the patent officer (under subsection 34(1) and section 53 of the *Patent Act*).

[172] In this proceeding, Pharmascience limited its submissions to the grounds of: not an invention (#6), lack of utility (#7), insufficient disclosure (#1) and lack of inventive step/obviousness (#5). As all these grounds were adequately raised by Pharmascience in the NOA, I find that Pharmascience has met its evidentiary burden of putting its case into play. Thus, pursuant to subsection 6(2) of the NOC Regulations, the burden of proof now rests on AstraZeneca to establish that Pharmascience's allegations on these issues are not justified. In rendering its decision, this Court must "look at the allegations, consider the evidence, apply the law, and determine whether an allegation made in the NOA is justified" (see *GlaxoSmithKline* above, at paragraph 41).

[173] **Issue 1**

Is the '531 Patent not an invention as defined in section 2 of the *Patent Act* because it merely ascertains the properties of a known substance?

Pharmascience submits that no invention was provided in the '531 Patent because it only pertains to the CP of low viscosity HPMC, which is an inherent physiochemical property that is primarily determined by the percentage of methoxyl groups in the HPMC. In support, Pharmascience submitted test results of experiments conducted by Dr. Desbrières. The low viscosity HPMC products that Dr. Desbrières tested each had different contents of methoxyl and hydroxypropyl. Dr. Desbrières' test results for CP, determined in accordance with the methodology presented in the '531 Patent, exceeded the claimed CP for each type of low viscosity (less than 7.2 cps) HPMC tested, thereby suggesting that the low viscosity HPMC products commonly sold on the market are already manufactured to the claimed CP.

[174] Pharmascience also notes that prior art patents have disclosed the three layer formulation made with low viscosity HPMC both as a binder and as a separating layer. In addition, Pharmascience states that the claimed CP is irrelevant to the formulation because, in application, it must dissolve at the lower temperature of 37˚C (i.e., body temperature). Pharmascience also submits that when used as a thin coating on the outside of tablets or as a separating layer, low viscosity HPMC provides immediate release and does not exert any control over the rate of dissolution or release of the active ingredient.

[175] Conversely, AstraZeneca submits that Pharmascience's allegation is fundamentally flawed as it is premised on an incorrect construction of the '531 Patent. A correct construction provides the

surprising teaching that the amount of product discard can be reduced by only selecting those batches of a low viscosity HPMC product that exceed the claimed CP. AstraZeneca claims that this advantage stems from the patent's finding that the rate of release of omeprazole from an enteric coated formulation is affected by a variation in CP between different batches of the same low viscosity HPMC product. AstraZeneca submits that this teaching was clearly provided in the page 11 table of the patent, which showed one batch exceeding the marketing standard while another batch of the same low viscosity HPMC did not. As a result of a number of experiments, the patent inventors identified the claimed CP that would ensure consistent release of 75% of omeprazole within 30 minutes (i.e., at the marketing standard). Thus, AstraZeneca submits that the patent teaches that the selection of a batch of low viscosity HPMC in accordance with the claimed CP ensures the marketing standard is consistently met, which reduces the product discard associated with a failure to meet prescribed drug release requirements.

[176] On review of the evidence and the '531 Patent, I agree with AstraZeneca that the patent provides more information than merely identifying inherent physiochemical properties of a known substance. Rather, as submitted by AstraZeneca, the patent delves into batch-to-batch variations of a single low viscosity HPMC product and a property that can be tested to ensure consistent release of omeprazole in accordance with the marketing standard.

[177] The first two experiments described in the patent show that the use of different batches of one type of low viscosity HPMC product can result in different release rates of omeprazole from enteric coated pellets. Notably, the third experiment does show the release of omeprazole meeting the marketing standard for both batches. However, that experiment was not conducted on enteric

coated pellets and the pertinent finding from that test is instead that the different batches exhibit different release rates of omeprazole.

[178] Finally, although Dr. Desbrières' test results suggest that low viscosity HPMC products already exceed the claimed CP, I note that he did not provide any results on tests conducted on different batches of the same type of low viscosity HPMC. I therefore do not find that his results are sufficient to render the findings presented in the '531 Patent merely inherent physiochemical properties of a known substance.

[179] **Issue 2**

Does the '531 Patent meet the validity requirements for utility?

The requirement that an invention have "utility" has statutory grounding in section 2 of the *Patent Act*, which defines an invention as something that is "new and useful". At the outset, it is notable that utility does not depend on marketability. As stated by Madam Justice Judith Snider in *Sanofi-Aventis Canada Inc v Apotex Inc*, 2009 FC 676, [2009] FCJ No 986 at paragraph 145:

> … assessing whether an invention has utility, the issue is not whether the invention is sufficiently useful as to be able to support commercialization, unless commercial utility is specifically promised; …

[180] Utility must be demonstrated or soundly predicted based on the information and science available at the time of the prediction, as of the relevant date (see *Sanofi-Aventis* above, at paragraph 143). The relevant date is the date of filing of the Canadian patent application (see *Sanofi-Aventis* above, at paragraph 145).

[181] Demonstrating or soundly predicting that an invention will produce at least one useful result, or "a "mere scintilla" of utility" is sufficient where no particular result has been promised (see *Sanofi-Aventis* above, at paragraph 145). However, where a particular result has been promised in the patent specification, the claims must demonstrate or soundly predict that result or promise (see *Sanofi-Aventis* above, at paragraph 145).

[182] In construing the specification of a patent, "the promise should be properly defined, within the context of the patent as a whole, through the eyes of the [PSA], in relation to the science and information available at the time of filing" (see *Eli Lilly Canada Inc v Novopharm Limited*, 2010 FCA 197, [2010] FCJ No 951, leave to appeal refused in [2010] SCCA No 377 at paragraph 80). Thus, while determining the promise (or lack thereof) of a patent is a question of law, the assistance of experts is useful in this assessment.

[183] In *GlaxoSmithKline* above, Mr. Justice Roger Hughes explained the general manner in which a patent specification should be read:

> 84 The Supreme Court of Canada has set out the approach to construction of the specification of a patent in *Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Limited*, [1981] 1 S.C.R. 504 at pages 520 - 521:
>
> > We must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance, (*Noranda Mines Limited v. Minerals Separation North American Corporation* [1950] S.C.R. 36]), being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public. There is no occasion for being too astute or technical in the matter of objections to either title or specification for, as Duff C.J.C. said, giving the judgment of the Court in *Western Electric Company, Incorporated, and*

> *Northern Electric Company v. Baldwin International Radio of Canada* [1934] S.C.R. 570], at p. 574, "where the language of the specification, upon a reasonable view of it, can be so read as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction". Sir George Jessel spoke to like effect at a much earlier date in *Hinks & Son v. Safety Lighting Company* [(1876), 4 Ch. D. 607]. He said the patent should be approached "with a judicial anxiety to support a really useful invention".

[…]

89 The late Dr. Harold Fox in his book "The Canadian Law and Practice Relating to Letters Patent for Invention", 4th ed., 1969, Carswell, Toronto (Fox on Patents) provided a useful insight into this issue at pages 208 - 209 (omitting footnotes):

> IMPARTIAL CONSTRUCTION
>
> Originally patents were regarded with disfavour as being in the nature of monopolies and there existed a great tendency to be unnecessarily strict in construing patents against the patentee. The tendency then swung to the other extreme and courts were often found construing a patent most benevolently in favour of the patentee who had introduced a new manufacture. It should not be necessary to observe that a construction that is, even in the slightest degree, either too strict or too benevolent, ceases to be an impartial construction and is, therefore, improper. A patent specification is subject to the same impartial canons of construction as ordinarily apply to written documents generally. As Chitty J. observed in Lister v. Norton. "It certainly ought not to be construed malevolently; I will not say it ought to be construed benevolently; I do say it ought to be construed fairly. It must be read by a mind willing to understand, not by a mind desirous of misunderstanding."
>
> ...
>
> The court should, therefore, in construing a specification, be the fair and impartial arbitrator

> between the patentee and the public. The construction must be reasonable, fair and logical, in accordance with the manner of construction of all written documents according to the true intent. Nothing should be presumed in favour of the patentee or an alleged infringer, although it is proper for the court to endeavour to support a patent if it can be done honestly and fairly and without improper construction, for it is a reasonable presumption that a patentee would not claim anything that would render his patent void. [emphasis added]

[184] As noted above, if the utility of an invention has not been demonstrated as of the relevant date, an inventor can still rely on the doctrine of sound prediction to justify his or her patent claims. The purpose of this doctrine was explained by Mr. Justice Ian Binnie in *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77, [2002] 4 SCR 153 (at paragraph 66):

> The doctrine of "sound prediction" balances the public interest in early disclosure of new and useful inventions, even before their utility has been verified by tests (which in the case of pharmaceutical products may take years) and the public interest in avoiding cluttering the public domain with useless patents, and granting monopoly rights in exchange for misinformation.

[185] The test for determining whether a utility has been soundly predicted was also set out in *Apotex* above:

> 70 The doctrine of sound prediction has three components. Firstly, as here, there must be a factual basis for the prediction. In *Monsanto* and *Burton Parsons*, the factual basis was supplied by the tested compounds, but other factual underpinnings, depending on the nature of the invention, may suffice. Secondly, the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis. In *Monsanto* and *Burton Parsons*, the line of reasoning was grounded in the known "architecture of chemical compounds" (*Monsanto*, at p. 1119), but other lines of reasoning, again depending on the subject matter, may be legitimate. Thirdly,

> there must be proper disclosure. Normally, it is sufficient if the specification provides a full, clear and exact description of the nature of the invention and the manner in which it can be practised: H. G. Fox, *The Canadian Law and Practice Relating to Letters Patent for Inventions* (4th ed. 1969), at p. 167. It is generally not necessary for an inventor to provide a theory of *why* the invention works. Practical readers merely want to know that it does work and how to work it. In this sort of case, however, the sound prediction is to some extent the *quid pro quo* the applicant offers in exchange for the patent monopoly. Precise disclosure requirements in this regard do not arise for decision in this case because both the underlying facts (the test data) and the line of reasoning (the chain terminator effect) were in fact disclosed, and disclosure in this respect did not become an issue between the parties. I therefore say no more about it.
>
> 71 It bears repetition that the soundness (or otherwise) of the prediction is a question of fact. Evidence must be led about what was known or not known at the priority date, as was done here. Each case will turn on the particularities of the discipline to which it relates. In this case, the findings of fact necessary for the application of "sound prediction" were made and the appellants have not, in my view, demonstrated any overriding or palpable error.

[186] More recently, Madam Justice Snider succinctly set out this three-step test as follows (see *Sanofi-Aventis* above, at paragraph 146):

> 1. There must be a factual basis for the prediction;
>
> 2. The inventor must have an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and
>
> 3. There must be proper disclosure.

[187] Madam Justice Snider added that to be sound, a prediction does not need to amount to a certainty, as it does not exclude the risk that some compounds within the area claimed may, at some later time, prove to be devoid of utility (see *Sanofi-Aventis* above, at paragraph 147).

[188] In determining the type of evidence that would satisfy the three-step test for a sound prediction, the Federal Court of Appeal noted in *Eli Lilly* above:

> 84 *AZT* does not define the threshold required for sound prediction. However, Binnie J. states that more than mere speculation is required (para. 69). He also provides the following indicia:
>
> * the requirement is that the claims be fairly based on the patent disclosure (para. 59);
>
> * it must be *prima facie* reasonable that the patentee should have a claim (para. 60);
>
> * it cannot mean a certainty (para. 62);
>
> * the desired result must be able to be inferred from the factual basis (para. 70).
>
> 85 In my view, these indicia signify that a sound prediction requires a *prima facie* reasonable inference of utility. Notably, in *AZT*, the factual basis for the sound prediction of a new use compound rested upon the results of an *in vitro* test of AZT against the HIV in a human cell line along with Glaxo's data on AZT, including animal tests (para. 72). The line of reasoning was found to be Glaxo's knowledge of the mechanism for reproduction of a retrovirus.

[189] In this case, Pharmascience submits that the '531 Patent did not indicate that any tests were performed to demonstrate that the low viscosity HPMC actually possessed the claimed utility and no substantive data was provided to demonstrate the promised utility. Once utility is challenged, Pharmascience submits that it is insufficient to state that tests were run; evidence must be filed of those tests. In addition, as AstraZeneca promised commercial utility, the patent must be held to that standard, a burden that Pharmascience submits AstraZeneca has failed to meet. Thus, Pharmascience submits that the '531 Patent offers nothing over the prior art three layer formulation.

[190] AstraZeneca submits that the Federal Court of Appeal has explicitly rejected the notion that utility must be demonstrated in the patent disclosure. It relies in support on *Pfizer Canada Inc v Novopharm Ltd*, 2010 FCA 242, [2010] FCJ No 1200 (leave to appeal granted in [2010] SCCA No 443, currently on reserve), which states:

> 87 Although there is no jurisprudence dictating whether or not utility need be demonstrated in the patent disclosure, I am of the view that the answer is that it need not be demonstrated in the patent disclosure. First, there is nothing in the Act which leads one to conclude that such a demonstration is necessary. Second, there is no *a priori* reason to think that the patent disclosure should contain proof of all the elements required to obtain the patent. *Hughes &Woodley, supra*, describe the goal of the disclosure as follows at s. 25:
>
> > The description of the invention ... is to give the public adequate details as will enable a workman skilled in the art to which the invention relates to construct or use that invention when the period of the monopoly has expired. In essence what is called for in the specification (including both disclosure and claims) is a description of the invention and the method of producing and constructing it, coupled with a claim or claims which state those novel features in which the applicant wants the exclusive right; the specification must define the precise and exact extent of the exclusive property and privilege claimed.
>
> 88 In other words, the disclosure provides direction, not proof: it tells practitioners how to practice the invention. It does not prove to them its utility, though they can require proof through invalidity proceedings.
>
> 89 Indeed, the Supreme Court's most recent decision on utility, *Wellcome* (SCC), *supra*, makes no mention of any requirement to prove utility in the disclosure. At paragraph 56 of his Reasons, Binnie J. wrote as follows:
>
> > [56] Where the new use is the *gravamen* of the invention, the utility required for patentability (s. 2) must, as of the priority date, either be demonstrated or be a sound prediction based on the information and

> expertise available. If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, *per* Pigeon J. in *Monsanto Co. v. Commissioner of Patents*, [1979] 2 S.C.R. 1108, at p. 1117, the prediction at the date of the application was not sound, or, irrespective of the soundness of the prediction, "[t]here is evidence of lack of utility in respect of some of the area covered."
>
> 90 The appellant's argument that Pfizer was required to include evidence of demonstrated utility in the patent disclosure is without merit. The requirements for demonstrated utility can be provided in evidence during invalidity proceedings as opposed to in the patent itself. So long as the disclosure makes reference to a study demonstrating utility, there do not appear to be any other requirements to fulfil section 2. [emphasis added]

[191] AstraZeneca submits that it demonstrated utility in the statement at page 12 of the '531 Patent that: "[r]esults from a number of experiments with different batches of HPMC indicate that HPMC with a cloud point of at least 45.6˚C is desirable in fulfilling the regulatory requirements on rate of release of omeprazole". AstraZeneca submits that this is sufficient to meet its burden for proving utility. Although this evidence is relatively non-descriptive, I do not find that the law requires that AstraZeneca meet a higher burden.

[192] AstraZeneca also submits that Pharmascience's expert's disbelief that the CP of low viscosity varies such that it falls below the claimed CP is directly contradicted by data included in the NOA. Specifically, AstraZeneca highlights the table at the bottom of page 60 of the NOA. This table shows different CPs for different batches of the same subtype of HPMC. Three of these samples have CPs below the claimed CP. AstraZeneca questioned Dr. Desbrières about these results on cross-examination. However, Dr. Desbrières highlighted that those samples that had CPs below

the claimed CP were described in a column on the table as "non-approved". Although Dr. Desbrières was unable to provide greater detail on the meaning of such non-approval, I find that the classification of those batch samples as "non-approved" undermines AstraZeneca's reliance on them as evidence of batches of low viscosity HPMC having CPs below the claimed CP.

[193] Nevertheless, I do not find that Dr. Desbrières' own test results lend support to Pharmascience's position. All Dr. Desbrières' tests were conducted on different subtypes of low viscosity HPMC. Although these all had CPs above the claimed CP, Dr. Desbrières did not test different batches of the same low viscosity HPMC product. I therefore do not find that his test results sufficiently undermine the results from the "number of experiments" relied on in the '531 Patent. The risk of variability between different batches of the same subtype is accentuated by the number of factors that can affect the CP that were highlighted by Dr. Bodmeier in his affidavit.

[194] Finally, I note Pharmascience's submission that AstraZeneca was required to establish commercial utility. On review of the '531 Patent, I find that the relevant "promise" of such utility is as follows (at page 4):

> From an economic aspect it is advantageous to specify and check the HPMC quality and keep the discard of produced pharmaceutical product low.

[195] As mentioned above, there is no requirement to show marketability to establish utility. However, where a promise is made, it must be upheld. I do not find that this statement clearly promises commercial utility. Rather, it promises that by following the patent, the discard of produced pharmaceutical product will be kept low. The patent does teach that predetermining the

CP of a particular batch of low viscosity HPMC and limiting selection for use in enteric coated oral pharmaceutical formulations to those batches with CPs that exceed the claimed CP, will ensure that the release rate of omeprazole will meet the marketing standard. Without this teaching, some batches of low viscosity HPMC may be used in the manufacture of enteric coated oral pharmaceutical formulations; formulations that must later be discarded for failure to adequately release omeprazole. Thus, I find that the patent adequately upholds this promise.

[196] In summary, I find that Pharmascience has failed to demonstrate "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do" (see *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504; and *Eli Lilly* above, at paragraph 75).

[197] **Issue 3**

Does the '531 Patent meet the validity requirements of sufficient disclosure?

The specification in a patent must disclose sufficient information to enable a PSA to make and use the claimed invention. Sufficiency is a question of fact, determined as of the date of publication. The sufficiency requirement is mandated under subsection 27(3) of the *Patent Act*.

[198] The test for sufficient disclosure was set out in *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at paragraph 27:

> […] The applicant must disclose everything that is essential for the invention to function properly. To be complete, it must meet two conditions: it must describe the invention and define the way it is produced or built (Thorson P. in *Minerals Separation North American Corp. v. Noranda Mines Ltd.*, [1947] Ex. C.R. 306, at p. 316). The applicant must define the nature of the invention and

> describe how it is put into operation. A failure to meet the first condition would invalidate the application for ambiguity, while a failure to meet the second invalidates it for insufficiency. The description must be such as to enable a person skilled in the art or the field of the invention to produce it using only the instructions contained in the disclosure (Pigeon J. in *Burton Parsons Chemicals Inc. v. Hewlett-Packard (Canada) Ltd.*, [1976] 1 S.C.R. 555, at p. 563; *Monsanto Co. v. Commissioner of Patents*, [1979] 2 S.C.R. 1108, at p. 1113) and once the monopoly period is over, to use the invention as successfully as the inventor could at the time of his application (*Minerals Separation*, *supra*, at p. 316). [emphasis added]

[199] More recently, in *Eli Lilly* above, the Federal Court of Appeal explained the requirement of sufficient disclosure (at paragraph 113):

> In addition to meeting the tests for patentability, an invention must also be sufficiently disclosed. The specification represents the bargain between the Crown on behalf of the public and the inventor (*Consolboard*). Accordingly, the patent must contain enough information to allow a [PSA] to make the invention. The claims must be precisely laid out, without being overbroad. If the disclosure requirements are not met, the patent will be invalid even if it is new, useful and not obvious. These requirements for a patent specification are set out in subsections 27(3) and 27(4) of the Act. [emphasis added]

[200] In this case, Pharmascience submits that the '531 Patent inadequately describes the invention and does not provide the public with any meaningful or new information on the making of a three layer tablet. The patent also fails to indicate the specific type of low viscosity HPMC used in the experiments. Thus, the patent provides insufficient disclosure of the alleged invention.

[201] Conversely, AstraZeneca submits that the allegations of insufficiency are unjustified because all the allegedly missing information would be clearly known to a PSA on a thorough reading of the patent. AstraZeneca notes that the use of low viscosity HPMC in a separating layer

and as a binding agent was well known at the date of publication. In addition, there was no question that CP as defined in the patent could be understood and determined as per the instructions provided therein.

[202] In response to Pharmascience's allegation that the patent did not indicate what type of HPMC to use, AstraZeneca submits that a PSA would easily understand that any suitable grade of low viscosity HPMC can be used to prepare an enteric omeprazole formulation, as long as it exceeds the claimed CP. The patent clearly referred to HPMC having a viscosity of 6 cps. Similarly, AstraZeneca submits that on seeing the reference to the marketing standard and the reference to the use of a paddle, a PSA would understand that the inventors used the Dissolution Apparatus 2.

[203] Further, AstraZeneca submits that a PSA would also understand from the patent that any suitable amount of coating of low viscosity HPMC can be used to prepare an enteric omeprazole formulation as long as it exceeds the claimed CP.

[204] On reading the '531 Patent, I would agree with AstraZeneca's characterization of the sufficiency of the disclosure provided therein. I note that AstraZeneca's last point on the amount of coating is somewhat troublesome in light of the evidence from Pharmascience's experts on the importance of an adequate layer. However, I also note that those experts did not offer any concrete evidence to show that the thickness of the coating caused the variability presented in the patent and therefore do not find it determinative.

[205] I would also note that the '531 Patent does not explicitly state the temperature of the buffer solution in which the omeprazole release was measured. However, at page 10, the '531 Patent does state that: testing was conducted in accordance with marketing approval for the Losec® capsule formulation; "[t]he pellets were pre-exposed to simulated gastric fluid USP (without enzyme) at 37˚C for 2 hours"; and the buffer solution comprised "simulated gastric fluid USP (without enzyme)". This suggests that the testing was done at 37˚C (i.e., body temperature). I note that the later reference to temperature ranges from 35˚C to 50˚C (at page 12 of the patent) pertained to the CP determination of the two different batches (Type A and Type B) of the same low viscosity HPMC. Thus, those temperatures clearly do not pertain to the measurements of the release of omeprazole in the buffer solution.

[206] In summary, I find that the '531 Patent sufficiently defines the nature of the invention and describes how it is put into operation. Based on the description provided, I find that a PSA could learn the teaching provided therein and select an appropriate batch of low viscosity HPMC for use in an enteric coated oral pharmaceutical formulation as contemplated in the '531 Patent.

[207] **Issue 4**

Does the '531 Patent meet the validity requirements for obviousness?

To be valid, a patent must not be obvious, it must have an inventive step. This requirement is mandated under section 28.3 of the *Patent Act*.

[208] In *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] 3 SCR 265, the Supreme Court of Canada adopted a four-step approach to the inquiry into obviousness. Writing for the Court, Mr. Justice Marshall Rothstein explained:

> 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.
>
> 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.
>
> ii. "Obvious to Try" Considerations
>
> 69 If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> 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?
>
> 70 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.

[209] In this case, Pharmascience submits that there is nothing inventive in finding a solution to a problem that never existed. As CP is an irrelevant parameter, there is nothing inventive presented in the patent that was not already known in the prior art. Notably, CP is indirectly based on the percentage of methozyl groups in the HPMC, a fact that was already well known.

[210] Conversely, AstraZeneca notes that none of the prior art considered batch-to-batch variation in one subtype of low viscosity HPMC, nor did any of it direct PSAs to select batches that had CPs exceeding the claimed CP to reduce product discard. In fact, prior to 1998, a PSA would not have considered the low viscosity HPMC on seeing that omeprazole enteric formulations were being released at different rates. It was thus not surprising that Mr. Alderman did not recall receiving any complaints on batch-to-batch variability and the effect thereof on the release of omeprazole.

[211] To evaluate this claim, it is necessary to consider the four-step approach adopted in *Sanofi-Synthelabo* above.

[212] The first step entails identifying the PSA and that person's common general knowledge. In their submissions, the parties offer similar descriptions of the PSA as follows. AstraZeneca, "Pharmaceutical formulator with knowledge of HPMC used in pharmaceutical formulations." And Pharmascience, "pharmaceutical formulator, a polymer chemist or chemical engineer with a PhD or with a Bachelors or Masters Degree and relevant experience in polymer chemistry." This person would be "familiar with low viscosity HPMC used as a thin coating or as a binder that would readily dissolve in water" and "would be familiar with omeprazole formulations using a separating layer between the core material and the enteric coating."

[213] Drawing from these definitions, I find that the appropriate PSA here is a pharmaceutical formulator, polymer chemist or chemical engineer with experience in polymer chemistry and knowledge of low viscosity HPMC and omeprazole formulations.

[214] The second step entails identifying or construing the inventive concept of the claim. Here, the inventive concept is that there is batch-to-batch variation in low viscosity HPMC products used as a binding agent and/or a constituent of a separating layer in an enteric coated oral pharmaceutical formulation. This variation may affect the release rate of omeprazole from the formulation, resulting in failures to achieve marketing standards. However, these standards can consistently be achieved when the formulation is only manufactured of batches of low viscosity HPMC with CPs exceeding the claimed CP.

[215] The third step entails identifying what, if any, differences exist between the prior art and the inventive concept identified in the second step. Pharmascience's experts provided an extensive review of the prior art. The knowledge contained therein can be summarized as follows:

- omeprazole is susceptible to degradation in acid reacting and neutral media;

- a fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal;

- omeprazole must be protected from the acidic juice of the stomach by enteric coating;

- enteric coatings are made of acidic compounds and if applied directly to omeprazole, the omeprazole will become badly discoloured; and

- the three layer formulation is used to protect omeprazole with the separating layer protecting omeprazole from the enteric coating.

[216] There are clear differences in the inventive concept of the '531 Patent, as described in the second step above and in this prior art. As indicated, the prior art does not delve into batch-to-batch

variations of a low viscosity HPMC product. Nor does it provide information on CPs, or on the claimed CPs described in the '531 Patent.

[217] Finally, the fourth step evaluates whether these differences would have been obvious to the PSA or whether they required a degree of invention. Based on the evidence on the record, I find that these differences required a degree of invention and would not have been obvious to the PSA. The fact that CP of low viscosity HPMC could be determined may have been obvious to a PSA, but I do not find that the relevance of this property to the rate of release of omeprazole, or the actual claimed CP above which variations in the release of omeprazole between batches of the same product would be minimized, would be obvious to the PSA. I therefore find that the '531 Patent was not obvious on the claim date.

[218] As I have found that AstraZeneca has discharged its burden of proving that the allegations raised by Pharmascience in its NOA and relied upon at the hearing are not justified, an order prohibiting the Minister from issuing a notice of compliance to Pharmascience for its 20 mg and 40 mg esomeprazole magnesium capsules will issue.

[219] **JUDGMENT**

THIS COURT'S JUDGMENT is that:

1. The Minister of Health is prohibited from issuing a notice of compliance to Pharmascience for its 20 and 40 mg esomeprazole magnesium capsules until after the expiration of Canadian Patent No. 2,290,531.

2. AstraZeneca shall have its costs of the application.

"John A. O'Keefe"

Judge

ANNEX

Relevant Statutory Provisions

***Patent Act*, RSC, 1985, c P-4**

2. In this Act, except as otherwise provided,	2. Sauf disposition contraire, les définitions qui suivent s'appliquent à la présente loi.
. . .	. . .
"invention" means any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter;	« invention » Toute réalisation, tout procédé, toute machine, fabrication ou composition de matières, ainsi que tout perfectionnement de l'un d'eux, présentant le caractère de la nouveauté et de l'utilité.
27. The specification of an invention must	27. Le mémoire descriptif doit :
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	a) décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
27. (3) The specification of an invention must	27. (3) Le mémoire descriptif doit :
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	a) décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
(b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;	b) exposer clairement les diverses phases d'un procédé, ou le mode de construction, de confection, de composition ou d'utilisation d'une machine, d'un objet manufacturé ou d'un composé de matières, dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l'art ou la science dont relève l'invention, ou dans l'art ou la science qui s'en rapproche le plus, de confectionner, construire, composer ou utiliser l'invention;
(c) in the case of a machine, explain the	c) s'il s'agit d'une machine, en expliquer

principle of the machine and the best mode in which the inventor has contemplated the application of that principle; and

clairement le principe et la meilleure manière dont son inventeur en a conçu l'application;

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

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

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.

***Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133**

5. (1) If a second person files a submission for a notice of compliance in respect of a drug and the submission directly or indirectly compares the drug with, or makes reference to, another drug marketed in Canada under a notice of compliance issued to a first person and in respect of which a patent list has been submitted, the second person shall, in the submission, with respect to each patent on the register in respect of the other drug,

5. (1) Dans le cas où la seconde personne dépose une présentation pour un avis de conformité à l'égard d'une drogue, laquelle présentation, directement ou indirectement, compare celle-ci à une autre drogue commercialisée sur le marché canadien aux termes d'un avis de conformité délivré à la première personne et à l'égard de laquelle une liste de brevets a été présentée — ou y fait renvoi —, cette seconde personne doit, à l'égard de chaque brevet ajouté au registre pour cette autre drogue, inclure dans sa présentation :

(a) state that the second person accepts that the notice of compliance will not issue until the patent expires; or

a) soit une déclaration portant qu'elle accepte que l'avis de conformité ne sera pas délivré avant l'expiration du brevet;

(b) allege that

b) soit une allégation portant que, selon le cas :

(i) the statement made by the first person under paragraph 4(4)(d) is false,

(i) la déclaration présentée par la première personne aux termes de l'alinéa 4(4)d) est fausse,

(ii) the patent has expired,

(ii) le brevet est expiré,

(iii) the patent is not valid, or

(iii) le brevet n'est pas valide,

(iv) no claim for the medicinal ingredient, no claim for the formulation, no claim for the dosage form and no claim for the use of the medicinal ingredient would be infringed by the second person making, constructing, using or selling the drug for which the submission is filed.

(iv) elle ne contreferait aucune revendication de l'ingrédient médicinal, revendication de la formulation, revendication de la forme posologique ni revendication de l'utilisation de l'ingrédient médicinal en fabriquant, construisant, utilisant ou vendant la drogue pour laquelle la présentation est déposée.

. . .

. . .

(3) A second person who makes an allegation under paragraph (1)(b) or (2)(b) shall

(3) La seconde personne qui inclut l'allégation visée à l'alinéa (1)b) ou (2)b) doit prendre les mesures suivantes :

(a) serve on the first person a notice of allegation relating to the submission or supplement filed under subsection (1) or (2) on or after its date of filing;

a) signifier à la première personne un avis de l'allégation à l'égard de la présentation ou du supplément déposé en vertu des paragraphes (1) ou (2), à la date de son dépôt ou à toute date postérieure;

(b) include in the notice of allegation

b) insérer dans l'avis de l'allégation :

(i) a description of the medicinal ingredient, dosage form, strength, route of administration and use of the drug in respect of which the submission or supplement has been filed, and

(i) une description de l'ingrédient médicinal, de la forme posologique, de la concentration, de la voie d'administration et de l'utilisation de la drogue visée par la présentation ou le supplément,

(ii) a detailed statement of the legal and factual basis for the allegation;

(ii) un énoncé détaillé du fondement juridique et factuel de l'allégation;

(c) include in the material served a certification by the Minister of the date of filing of the submission or supplement; and

(d) serve proof of service of the documents and information referred to in paragraphs (a) to (c) on the Minister. . . .

c) joindre à la signification une attestation par le ministre de la date du dépôt de la présentation ou du supplément;

d) signifier au ministre la preuve de toute signification des documents et renseignements visés aux alinéas a) à c).
. . .

FEDERAL COURT

SOLICITORS OF RECORD

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STYLE OF CAUSE:	ASTRAZENECA CANADA INC. and ASTRAZENECA AB - and - PHARMASCIENCE INC. and THE MINISTER OF HEALTH
PLACE OF HEARING:	Toronto, Ontario
DATE OF HEARING:	June 4, 2012
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APPEARANCES:

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Carol Hitchman Rosamaria Longo	FOR THE RESPONDENT PHARMASCIENCE INC.
No One Appearing	FOR THE RESPONDENT THE MINISTER OF HEALTH

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