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Ottawa, Ontario, March 16, 2015

PRESENT: The Honourable Mr. Justice Barnes

Docket: T-1409-04

BETWEEN:

ASTRAZENECA CANADA INC. AND AKTIEBOLAGET HÄSSLE

Plaintiffs

and

APOTEX INC.

Defendant

Docket: T-1890-11

AND BETWEEN:

ASTRAZENECA AB AND AKTIEBOLAGET HÄSSLE

Plaintiffs

and

APOTEX INC.

Defendant

JUDGMENT AND REASONS

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I. The Patent

[1] In these proceedings AstraZeneca Canada Inc., Aktiebolaget Hässle and AstraZeneca AB assert that Apotex Inc. [Apotex] has infringed Canadian Letters Patent 1,292,693 [the 693 Patent] – in which they all claim an interest. Except where otherwise expressly or contextually indicated, any reference to AstraZeneca in these reasons will apply collectively to the Plaintiffs.

[2] The proceedings have been bifurcated so that this decision concerns only the issue of liability.

[3] The 693 Patent sets out 19 claims pertaining to a formulation for omeprazole but only Claims 1, 5, 6, 13 and 19 are in issue. Apotex challenges the validity of the 693 Patent on several grounds. It also argues that its omeprazole formulation does not infringe any of the asserted claims. Much of its infringement defence is built around the construction of the language of Claim 1 with a view to establishing essential differences with its omeprazole formulation.

[4] The 693 Patent describes the field of the invention as the discovery of a new stable pharmaceutical preparation containing omeprazole for oral use and a method for its manufacture. This formulation has been successfully marketed by AstraZeneca under the trade name LOSEC.

[5] In the Background of the Invention, the inventors describe what was generally known about omeprazole. Omeprazole had been shown to be a powerful inhibitor of gastric acid

secretion and was useful to treat gastric and duodenal ulcers. The 693 Patent cites Pilbrant and Cederberg Scand. J. Gastroenterology 1985; 20 (suppl. 108) p 113-120 [hereafter referred to as the Pilbrant reference] for the knowledge that omeprazole is susceptible to degradation in acid reacting and neutral media and can be stabilized in solution in the presence of higher pH values. Pilbrant is also cited for the proposition that a conventional enteric coat doseage form of omeprazole had been shown to provide sufficient stability for clinical studies. This approach was, however, later found to provide inadequate stability in long term storage. Following the Pilbrant citation, the inventors state "the stability profile [of omeprazole] is similar in solid phase".

[6] The stability problem associated with conventional enterically coated omeprazole formulations is described in the 693 Patent as follows:

> In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.
>
> In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

[7] At page 4 of the 693 Patent, the object of the invention is said to be the development of an omeprazole formulation which provides acceptable gastric acid resistance that dissolves rapidly in neutral to alkaline media (ie. the intestine), and that has good stability during long term storage. This object is said to be fulfilled with a new doseage form made up of three structural elements:

a. Cores of neutral or alkaline salts of omeprazole optionally mixed with alkaline compounds;

b. A separating sublayer coating or coatings soluble or rapidly disintegrating in water consisting of non-acidic, otherwise inert pharmaceutically acceptable substances; and

c. An outer layer consisting of an enteric coating.

The final doseage form is then treated in a suitable way to reduce the water content to a very low level in order to obtain good stability during long term storage.

[8] In the Detailed Description of the Invention, the omeprazole cores are further described. Gelatine capsules are said to be "used as cores for further processing". The separating layer and its purpose are described in detail in the following way:

> The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of coated articles. The pH-buffering properties of the separating layer can be further

> strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, [examples omitted] or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.
>
> The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.
>
> The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyvinyl acetal diethyl-aminoacetate or the like. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.
>
> In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.
>
> In case of gelatin capsules the gelatin capsule itself serves as separating layer.

[9] Much of the expert evidence presented in this case was concerned with the language of Claim 1. At the heart of the infringement dispute is whether Claim 1, properly construed, has been infringed by the manufacture and sale of Apotex's omeprazole formulation, Apo-Omeprazole. A key aspect of the dispute is whether Apo-Omeprazole contains a subcoating

layer meeting the criteria described in Claim 1. Apotex's challenges to the validity of the 693 Patent were similarly directed at Claim 1. Among other issues, Apotex and its experts maintain that the formulation described in Claim 1, however construed, was anticipated, obvious and overbroad.

[10] Claim 1 of the 693 Patent describes the formulation in the following terms:

> 1. An oral pharmaceutical preparation comprising: (a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone; (b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of material selected from among tablet excipients and polymeric film forming compounds; and (c) an outer layer disposed on said subcoating comprising an enteric coating.

[11] Claims 5, 6 and 13 are all directly or indirectly dependant on Claim 1. Claim 19 covers the use of the formulation according to any of the Claims 1 to 16 for the treatment of gastrointestinal diseases.

[12] The 693 Patent has a priority date of April 30, 1986, a Canadian filing date of April 29, 1987 and a date of issuance of December 3, 1991. It is common ground that the relevant date for construing the patent claims is December 3, 1991 and the relevant date for assessing obviousness is April 30, 1986.

II. The Expert Evidence

[13] In order to more fully understand the construction, validity and infringement issues arising in these proceedings, it is helpful to first consider the scientific evidence presented by the expert witnesses and, in particular, the few points where they agreed and the many where they disagreed.

[14] AstraZeneca's case was advanced by Dr. Martyn Davies and Dr. Roland Bodmeier. Apotex led evidence from Dr. Peter Griffiths, Dr. William Amos, Dr. Frank Bright and Dr. Arthur Kibbe.

[15] I accept that all of these witnesses were appropriately qualified. My assessments of their credibility and the weight I have attributed to their evidence are set out later in these reasons.

A. Dr. Martyn Davies

[16] Dr. Davies has a record of extensive work, research and professional recognition in the areas of pharmaceutical testing analysis and characterization of drug formulations. He has widely employed advanced analytical techniques in his work. He has been qualified to testify as an expert witness on 12 occasions and, in particular, his evidence was accepted in the United States patent infringement proceedings involving the equivalent to the 693 Patent. He was qualified as an expert in pharmaceutical formulation, particularly the formulation of coated oral doseage forms, including enteric coatings.

[17] Dr. Davies was retained by AstraZeneca to ascertain the composition of the Apotex omeprazole pellets. His precise mandate is set out at paragraph 23 of his initial report. He had previously been retained by AstraZeneca in the United States in connection with patent infringement litigation between AstraZeneca and a number of competitors, including Apotex.

[18] Dr. Davies subjected the Apotex pellets to a number of tests including various forms of microscopy, infrared spectroscopy, visual inspection, video micro-imaging, pH measurement, and water content analysis. Some of his testing was conducted in 2004 in support of his opinions in the United States' litigation concerning the equivalent patent. That testing was replicated, in part, in 2011 in connection with this proceeding.

[19] Dr. Davies designed and oversaw the 2004 and 2011 experiments that were carried out in his laboratory. He gave evidence that he observed the vast majority of the experiments and the recording of data. He was responsible for reviewing the data and formulating the opinions he provided in the United States and in Canada.

[20] Dr. Davies was provided with samples of the Apotex uncoated omeprazole cores, capsules containing fully formulated enterically coated omeprazole pellets and the Apotex excipients.

[21] Dr. Davies removed the enteric coating from some of the Apotex pellets by dissolving the MACP coating in acetone/isopropanol [IPA] solvent. IPA is known to dissolve MACP. The solvent wash procedure was conducted for 2 minutes in 2004 and for 4 minutes in 2011. This

was followed by a solvent rinse and drying on paper. A number of washed pellets were then randomly sectioned near their equators and fixed to metal discs using adhesive UV curable resin for microscopic examination.

[22] In 2004, Dr. Davies combined MACP and PVP in solution and observed that a precipitate readily formed. That precipitate was washed three times in water and kept for further analysis. This procedure was not repeated in 2011.

[23] The imaging techniques that Dr. Davies used involved Confocal Laser Scanning Microscopy [CLSM] and wide-field-UV fluorescence microscopy (2004 only) at 10X and 50X magnification.

[24] Dr. Davies also exposed his samples to Attenuated Total Reflectance Fournier Transfer Infrared Spectroscopy [ATIR] as a means of detecting their molecular “fingerprints”.

[25] In 2004 and in 2011 Dr. Davies exposed washed pellets to a water bath and video-imaged the reaction that took place.

[26] Finally, in 2004 Dr. Davies carried out pH and water content measurements on the Apotex samples.

[27] In 2004 Dr. Davies examined over 20 bisected enteric coated Apotex pellets and over 20 washed pellets with UV fluorescence and CLSM fluorescence and reflectance microscopy.

Many individual and "representative" CLSM optical slices were examined for each pellet. The same process was followed in 2011 with CLSM imaging. According to Dr. Davies, all of the images he obtained showed the presence of a distinct and continuous brightly fluorescing ring or corona at the interface of the pellet cores and the enteric coating. No gaps in the fluorescent ring could be seen. The ring was detected both within the enterically coated pellets and at the surface of the washed pellets. When Dr. Davies examined some 20 bisected Apotex pellet cores using CLSM and UV fluorescence microscopy, he found the cores to be weakly fluorescent but there was no bright fluorescent ring at the surface of the samples [see Schedule 27 to Exhibit 6]. According to Dr. Davies, the fact the fluorescent ring remained intact after the enteric coating was washed off in solvent indicates the chemical solubility of each structure was different.

[28] When Dr. Davies measured the thickness of the fluorescent layer in 2004 from individual CLSM images, he obtained a range of between 2 and 6 microns. His thickness measurements from 2011 fell between 1 micron and 6.8 microns. On a recorded sample size of 50, the average thickness measurement came to 3 microns.

[29] In 2004 and in 2011, Dr. Davies performed ATIR analysis on the surface of the Apotex enteric coated pellets, on the fluorescing layer of the washed pellets and on the uncoated cores. He then compared the spectra obtained to the known spectra for the components used by Apotex (omeprazole, povidone [PVP], mannitol, MACP and the known omeprazole degradation products) and to the MACP-PVP complex he had prepared.

[30] When Dr. Davies scanned the Apotex cores, he observed spectral peaks he attributed to omeprazole, mannitol and PVP. In particular, he found PVP to be present on the surface of the cores. The spectra he took from the enteric coating of the Apotex pellets matched the spectrum for a sample of MACP supplied by Apotex.

[31] Dr. Davies then examined the fluorescing layer. In 2004 he assessed ten washed pellets and recorded spectra from five. The ATIR spectra he obtained disclosed differences from the spectra for MACP. In particular, the spectra for the fluorescing layer disclosed an additional absorption peak that he attributed to a complex that had formed in a reaction between the MACP enteric coating and PVP in the pellet cores. Dr. Davies noted that those two polymers are known to complex with each other due to hydrogen bonding. He described the complex as a methacrylic acid copolymer-PVP complex chemically distinct from the enteric coating. To confirm this finding, Dr. Davies compared a spectrum taken from the fluorescing layer to a spectrum taken from the MACP-PVP complex precipitate he prepared. The two spectra were comparable.

[32] In addition to finding the complex in the Apotex sublayer, Dr. Davies found evidence of the presence of MACP magnesium salt. This compound, he said, formed from a reaction with magnesium hydroxide during the enteric coating process. Mannitol peaks that appeared in the washed pellet spectra were said by Dr. Davies to arise from the detection of mannitol immediately below the sublayer. No evidence of omeprazole or its degradation products was observed.

[33] The ATIR data led Dr. Davies to conclude that both the complex and MACP magnesium salt in the fluorescing sublayer formed from a reaction between MACP and PVP and magnesium hydroxide during the Apotex enteric coating process.

[34] Dr. Davies' visual inspection of the Apotex pellets revealed no discolouration as an indication of degradation.

[35] After submerging 20 washed pellets in a water bath, Dr. Davies observed a film-like layer peeling away from the cores. The loss of the sublayer was complete at about 7 minutes and the pellets fully disintegrated within 10 minutes. Time-lapse videos of this reaction were recorded.

[36] Dr. Davies' 2004 pH measurements disclosed values of between 8.81 and 9.39. Similar results were obtained in 2011. When Dr. Davies compared the pH values for MACP and PVP to the values for the complex, he observed that the complex was 2 pH units higher. This indicated to Dr. Davies that the complex was chemically distinct from either of its constituent compounds. His measurement of water content in the Apotex pellets resulted in a range from between 1.52% to 1.97%.

[37] From the above test results, Dr. Davies drew the following conclusions:

a. The cores of the Apotex pellets contain omeprazole.

b. The presence of a subcoating outside of the Apotex pellet cores had been demonstrated by CLSM fluorescence and reflectance microscopy. The fluorescing ring that he observed conformed to the contours of the cores.

c. The subcoating layer has different chemical properties from the enteric coating. This was demonstrated by its continued presence after the enteric coating was removed with acetone/IPA solvent, by the different ATIR spectra that were obtained from both regions and by differences in their acidity levels.

d. Neither the MACP-PVP complex nor the MACP salt present in the sublayer appeared to degrade omeprazole. The pellets showed no evidence of discolouration and the ATIR data did not disclose omeprazole degradation products in the sublayer.

e. Although Dr. Davies did not rule out the presence of acidic functional groups from the enteric coating in the sublayer, he concluded that most would have been taken up in the MACP-PVP reaction. To the extent that unreacted acidic functional groups did remain in the sublayer, they were likely to be segregated away from the cores and not available to degrade the omeprazole at the surface of the cores.

f. In water, the subcoating does not dissolve but it rapidly disintegrates. This was evident from the water disintegration tests.

g. The ATIR data showed that the sublayer does not contain omeprazole or an alkaline salt of omeprazole.

h. The complex and MACP salt are polymeric film forming compounds. The film-like character of the complex is evident in the disintegration videos.

i. The enteric coating layer of the Apotex pellets is composed of MACP and is distinct from the sublayer containing the complex.

j. The Apotex cores exhibit pH values of between 8.81 and 9.39.

[38] In reply to the responding expert reports from Dr. Griffiths and Dr. Bright, Dr. Davies offered additional justification for his testing conclusions. Dr. Davies disagreed that he had attempted to use fluorescence data to identify the complex in the sublayer region. He acknowledged that fluorescence is not a suitable technique to identify a chemical composition but could be used to study the structure of pharmaceutical compositions. Fluorescence was only one technique he used to assess the presence and structure of the sublayer. Dr. Davies stated that he had not conflated the observed fluorescent ring with the complex nor had he concluded the complex was the only constituent compound in the sublayer.

[39] Dr. Davies confirmed that his ATIR interrogations consistently disclosed the presence of the complex in the sublayer and his multiple UV and CLSM examinations all exhibited a continuous bright fluorescent layer.

[40] Dr. Davies asserted again that the detection of mannitol bands in some of the ATIR spectra resulted from the detection of mannitol sitting below the sublayer in the omeprazole cores. According to Dr. Davies the suggestion that the presence of mannitol bands indicated gaps in the sublayer was based on a flawed assumption about the depth of penetration of his ATIR signal. He also observed that Dr. Griffiths' analysis of sublayer thickness was very indirect and that no attempt was made to replicate his direct measurements using a standard technique.

[41] Dr. Davies did not agree that omeprazole degradants were more likely to be the sources of the observed fluorescence. There was no reliable empirical evidence produced to show

degradants in the sublayer and, even if they were present below levels of ATIR detection, they would be insignificant.

[42] In responding to ATIR spectra obtained by Dr. Hawker, Dr. Davies noted an anomalous and significant signal from the starting control (the blank). According to Dr. Davies this rendered all of the Hawker data unreliable. Dr. Davies also criticized the method employed at Temple University to obtain CLSM images. He said the pellets were crudely cracked and not, as he had done, carefully sliced and, unlike his Z series of CLSM images, only one image was taken for each pellet examined.

[43] Dr. Davies' response to Dr. Griffiths' comment that he had not directly ascertained the chemical composition of the fluorescent layer is set out at paragraph 35 of his reply report and further discussed at pages 433-434 of his testimony:

> Q. So to begin with, Dr. Davies, I would like to ask you about part of your reply report which starts at page 12, under the heading "Experiments Conducted to Directly Analyze Composition of Fluorescent Subcoating Layer".
>
> In paragraph 35 of your reply report you note that Dr. Griffiths states that you carried out no experiments to elucidate directly the composition of the intense fluorescing layer observed in Apotex's enteric coated pellets. You say that that is untrue. Could you please explain your basis for saying so?
>
> A. My basis is that I employed ATR FTIR analysis on that subcoating layer on the surface of the solvent washed pellets to elucidate the composition of that layer to demonstrate that it contained the MACP PVP complex and the MACP salt.
>
> I also undertook the UV CLSM fluorescence and reflectance data on the bisected pellets which were enteric coated pellets, the washed pellets, the uncoated cores, to identify the presence of that layer and confirmed that it remained after

> washing. So it had different properties to that of the enteric coating.
>
> I then went on to make the complex to show that the complex had the same chemical signals, diagnostic signals for the complex in the ATR FTIR analysis.
>
> I then compared that spectra to the spectra I saw for the washed pellets. And, again, I showed that what I saw in the complex that I had made in the test tube was the same signal that I saw for the complex that I saw on Apotex's washed pellet.
>
> So I took a number of steps to show that, in fact, that I had done a number of experiments to show that I was directly analyzing the composition of that layer.

[44] Dr. Davies addressed Dr. Griffiths' identification of carboxylic acid groups (MACP that had not reacted with PVP) in the sublayer by pointing out that any unreacted MACP was unlikely to be in contact with the cores and that Dr. Griffiths had not tested his hypothesis. If these acid groups were available to react with omeprazole at the surface of the cores measurable degradation products ought to have been present. Apotex's own sensitive HPLC tests of its finished products showed only insignificant or undetectable levels of degradation products.

[45] The Apotex criticisms about the representativeness of Dr. Davies' testing were addressed. It was acknowledged that the area of ATIR interrogation carried out by Dr. Davies was 44 microns in diameter from a total pellet diameter of about 1000 microns. Dr. Davies examined at least 15 washed pellets and recorded 10 spectra for each. All of the spectra disclosed the presence of the complex. This was said to be consistent with Dr. Davies' UV and CLSM fluorescence microscopy where over 25 bisected coated pellets and 25 bisected washed pellets were imaged. In every case a bright fluorescent ring was observed. Dr. Davies noted that

Dr. Bright had not attempted to conduct his own testing to challenge the representativeness of Dr. Davies' data.

[46] In a further response to the suggestion that he had assumed the fluorescent band to be the complex, Dr. Davies answered in the following way:

> 56. However, merely because fluorescence is not a suitable technique for identifying the MACP-PVP complex does not mean that it cannot be used in combination with other tests to show where the complex is located. As set out in my 2011 Report, I used wide-field UV and CLSM fluorescence in combination with reflectance microscopy to show that a continuous brightly fluorescent layer is present in Apotex' s pellets on the outside of the pellet core where the enteric coating is first applied. I then used ATR-FTIR spectroscopy to show that the fluorescent subcoating layer contains an MACP-PVP complex, which is not present in either the core or enteric coating. In combination, these tests show that the MACP-PVP complex and the subcoating layer are located together.

[47] To Dr. Griffiths' postulation that omeprazole degradants were more likely than the complex to be the source of the fluorescent ring, Dr. Davies pointed out that the complex was actually detected in the sublayer and omeprazole degradants were not. In the absence of data to show the presence of omeprazole degradants in the sublayer and in the face of an acknowledgement that fluorescence alone cannot identify a particular molecule, Dr. Griffiths' opinion was described as speculation.

[48] The representativeness of Dr. Davies' sublayer thickness measurements was defended in the following way in his reply report:

> 72. First, the thickness data for the fluorescent subcoating layer was obtained using a standard analytical technique. Second, the thickness data was consistent across multiple pellets in both 2004

> and 2011. In particular, all the pellets examined in 2011 had a fluorescent subcoating layer with an average thickness of at least 2 microns, which was consistent with the range of thickness measured in 2004. Third, this thickness data is consistent with both CLSM reflectance microscopy and ATR-FTIR spectra of bisected washed pellets.

[49] Dr. Davies confirmed his thickness measurements were not conducted from maximum intensity images but, rather, from individual CLSM Z-slice images. This point was advanced to displace the suggestion that Dr. Davies' thickness measurements had been taken from maximum intensity images.

[50] Dr. Davies dealt with Dr. Griffiths' opinion concerning the presence of mannitol bands in some of the ATIR washed pellet spectra. Much of the debate focussed on the assessment of the depth of the penetration of the beam generated by Dr. Davies' ATIR spectrometer. According to Dr. Davies, Dr. Griffiths had significantly understated the depth of signal penetration and thus underestimated the thickness of the subcoating layer. A key point of disagreement between Dr. Davies and Dr. Griffiths concerned the angle of the spectrometer beam inherent to Dr. Davies' instrument. Dr. Griffiths assumed a median angle of incidence of 45º and Dr. Davies said it fell in a range of between 27º and 45º. I will say more about this later in these reasons.

[51] In response to Dr. Griffiths' doubt that the film-like layer falling away from the Apotex washed pellets when immersed in water was the complex and, instead, could be residual MACP, Dr. Davies said the MACP readily dissolved in a solvent wash and was unlikely to have remained except in minute amounts. Since the ATIR spectra of the washed pellets consistently

showed the complex to be present, it was the only film-like compound that could plausibly remain.

[52] The Apotex criticisms of Dr. Davies' testing methods were addressed in Dr. Davies' reply report. Dr. Bright's concern about possible contamination by Dr. Davies' use of drying paper and adhesive resin was countered in the following ways:

a. The fluorescent ring was present in both the washed and unwashed pellet and therefore could not have resulted from paper residue.

b. Paper contamination would have been localized. The fluorescent ring formed a corona around the pellet cores.

c. The pellets were never embedded in resin but instead were affixed at the base well away from the area under inspection.

[53] To Dr. Bright's concerns that Dr. Davies bisected the Apotex pellets only near their equators and otherwise failed to obtain representative data, Dr. Davies said that he wanted to avoid a plane that intersected the sublayer at an angle and that, unlike Dr. Rez Fassihi, he took numerous CLSM images through each pellet sample. Having regard to the uniformity of Apotex's manufacturing methods, the location of pellet analysis would not be expected to allow for significant coating anomalies.

[54] Dr. Davies challenged Dr. Bright's opinion that the CLSM images showed discontinuities in sublayer fluorescence. He noted that the bisected pellets had irregular surfaces such that portions of the image will typically be out of focus. According to Dr. Davies, in order to

properly analyze the entire surface of a non-planar pellet, a series of CLSM sections is required to discern which portions of each image are in focus. With a non-transparent sample, the intensity of fluorescence diminishes as the focal plane moves into the interior. This attenuation effect means that the fluorescent image obtained from the in-focus surface of a partially opaque sample imparts the most reliable information. Multiple Z-scan images of each sample are thus required to accurately determine the continuity of any observed fluorescence. According to Dr. Davies, Dr. Bright failed to appreciate these points and took his discontinuity observations from single and unrepresentative CLSM Z-scan images from well above and below the pellet surface. For those CLSM images where the focal plane intersected the pellet surface, no discontinuities in sublayer fluorescence could be observed.

[55] Dr. Davies expressed the same concern about Dr. Bright's use of 3D images reconstructed from individual CLSM images. His reply report at paragraphs 167-169 addressed the problem as follows:

> 167. Based on my CLSM three dimensional ("3D") images for Apotex's enteric coated pellets, capsule Lot FD9104B and the 3D montages Dr. Bright created using my 2011 CLSM data, Dr. Bright concludes that discontinuities in the subcoating layer are "many and obvious". I disagree for the following reasons.
>
> 168. It is improper to assess continuity of the subcoating layer by visual inspection of the 3D images reconstructed from the CLSM sections of the bisected pellet. The image formed using CLSM reflects the intensity of the fluoresced light detected in the focal plane. However, as previously explained, the intensity depends on the depth and orientation of the focal plane in relation to the bisected pellet surface. CLSM images with focal planes taken above or below the bisected pellet surface will not accurately reflect the level of fluorescence at the surface. Even when a focal plane intersects a bisected pellet surface, some portions of the surface may be out of focus if the focal plane is not exactly parallel with the pellet surface. A 3D stack of such CLSM images suffers from the same limitations. Dr. Bright did not account for this effect

> when analyzing the 3D CLSM images. As a result, he misinterpreted the dark areas in the images as discontinuities.
>
> 169. Moreover, had there been actual discontinuities in the subcoating layer, they would have presented themselves as gaps in portions of the 2D CLSM images where the bisected pellet surface is in focus. However, no such gaps were evident. [Footnotes omitted]

[56] To Dr. Bright's opinion that the overall intensity of fluorescence emanating from the sublayer was not appreciably different from the surrounding areas, Dr. Davies observed that when intensity was assessed from in-focus areas at the sample surface it was appreciably brighter than its surroundings. In those areas a distinct bright fluorescing layer could be seen resting on the weakly fluorescing cores. In contrast, fluorescence arising from background noise would be random and would not be represented in the images as a bright continuous corona.

[57] Dr. Davies took umbrage at Dr. Bright's allegation that many of his CLSM images had been artificially altered to highlight specific regions. He pointed out that the images were automatically generated by his CLSM instrument and not altered by any operator manipulation.

[58] In commenting on the Temple University CLSM 10X fluorescence images, Dr. Davies pointed out that the pellets were crudely bisected and therefore difficult to clearly image. Because each sample was only imaged once, the images were insufficient to support any meaningful conclusions. Multiple images are required to determine which areas are in focus.

[59] In response to Dr. Amos' opinion that Dr. Davies' CLSM images were saturated, Dr. Davies stated that he took the steps necessary to avoid this problem.

B. Dr. Roland Bodmeier

[60] Dr. Bodmeier was qualified as an expert in pharmaceutical formulation, particularly the formulation of coated oral doseage forms, including enteric coatings. He has extensive experience as an academic and in working with different coating technologies including the application of coatings in drug formations (often to obtain specific release profiles). He is a prolific scientific author and researcher. He also frequently acts as a consultant to the pharmaceutical industry.

[61] Dr. Bodmeier was initially retained by AstraZeneca to construe the relevant claims of the 693 Patent as read by the notional person of skill and to assess whether, in view of Dr. Davies' test results, the Apotex omeprazole capsules infringe Claims 1, 5 and 6 of the 693 Patent. In a subsequent responding report [Exhibit 67] Dr. Bodmeier addressed Apotex's invalidity evidence bearing on anticipation, obviousness, overbreadth, utility, sufficiency, claims broader and ambiguity. In a final report [Exhibit 68], he addressed a few specific evidentiary points raised by the Apotex experts mainly concerning the degradation of omeprazole.

[62] Dr. Bodmeier described the object of the 693 Patent as the provision of a storage stable and gastric acid resistant omeprazole formulation. Because omeprazole was known to be unstable in acidic aqueous environments, it required a protective enteric coating to pass through the stomach for release in the intestine. However, in that formulation, long term storage stability was compromised as evidenced by discolouration.

[63] Dr. Bodmeier noted that when the inventors addressed the storage instability problem by adding either an alkaline reacting compound [ARC] to the omeprazole cores or by using an alkaline omeprazole salt, a new problem arose in the form of a decrease in gastric acid resistance. This was caused by the premature degradation of the enteric coat. What was found to be happening was that some gastric juice would diffuse through the enteric coat into the cores, forming an alkaline solution. The alkaline solution caused the enteric coat to dissolve from the inside leading to premature failure after administration.

[64] According to Dr. Bodmeier, the inventors' solution to the formulation problem lay in the inventive combination of an alkaline core separated from the enteric coat with a water soluble or rapidly disintegrating subcoating layer. With the use of a subcoating layer the alkalinity of the cores could be reduced without compromising the long term storage stability of the formulation.

[65] Dr. Bodmeier was asked to construe Claims 1, 5 and 6. In particular, he was asked to determine whether Claim 1 included within its ambit a subcoating that formed *in situ* as the product of a chemical reaction between the enteric coat and an alkaline omeprazole core. He was also asked to interpret the term "inert" as it related to the subcoating.

[66] Dr. Bodmeier interpreted Claims 1, 5 and 6 as formulations *per se* without any limitation to the process of manufacture. He construed the words "disposed on" as describing only the location of the subcoating. His conclusion is set out in the following passage from his initial report:

> 48. In response, as noted above, claims 1, 5 and 6 of the '693 patent are not limited to a particular method of formation of

> the composition, provided that the subcoating achieves the goals of the patent, namely a storage stable and gastric resistant dosage form. In particular, the advantages of the invention arise from the finished dosage form structure and not from any particular process by which the structure is made. Contrary to what Apotex suggests, the patent is not directed to avoiding all possible reaction products. In certain circumstances, a reaction product may provide the necessary subcoating layer which will assist in achieving gastric resistance and storage stability. For example, the application of an enteric coating material to a core can, depending upon process conditions and ingredients, lead to a subcoating layer which is formed *in situ*. This subcoating can comprise material distinct from the core and the enteric coating. There is nothing in the disclosure teaching that such a reaction product must be avoided. The skilled person would not read such a limitation into the claims.

[67] Dr. Bodmeier's interpretation of the term "inert" was relative. The person of skill would not expect the subcoating to be perfectly inert or entirely non-acidic, but only to the extent necessary to avoid functional interference. As to whether the subcoating was required to be entirely continuous, Dr. Bodmeier again expressed a relative view. If the subcoating was sufficiently robust to achieve good gastric acid resistance and long term storage stability, the avoidance of all structural anomalies would not be thought by the person of skill to be a requirement.

[68] Concerning the degree of acceptable water content, Dr. Bodmeier said that the person of skill knew that moisture had to be minimized or otherwise managed. According to this view Claims 1, 5 and 6 were not limited by any specific level of water content.

[69] Based on his construction of the relevant claims language and, in the face of the consistency of Apotex's batch records and its manufacturing practices, Dr. Bodmeier concluded that all of Apotex's omeprazole batches would have infringed Claims 1, 5 and 6 of the

693 Patent. Having regard to Apotex's quality control practices, Dr. Bodmeier was of the view that all of its shipped omeprazole product would have met minimum storage stability and gastric acid resistance criteria and would necessarily have incorporated a functioning and inert subcoating.

[70] In his responding report, Dr. Bodmeier went on to address Dr. Kibbe's validity opinions. Dr. Bodmeier was of the view that Dr. Kibbe's assessment of the prior art was simplistic and was based on hindsight. This general criticism is set out below:

> 279. Drs. Hopfenberg and Kibbe's analysis demonstrates a certain amount of prevision. They are able to find their way through the formulation maze because they know the route in advance. Interestingly, they make no mention of alternative pathways or problems that would have inevitably been encountered during the formulation exercise. In my view, even if a skilled person ultimately came to the invention (which I do not think they would have been able to do), the path would have been much, more torturous than that described by Drs. Hopfenberg and Kibbe and would have inevitably involved extensive experimentation, including dead ends. Moreover, the research would be exploratory and not simply confirmatory. A skilled person would not have conceived of all the elements of the 693 patent prior to the start of experimentation. [Also see para 108]

[71] Given the research limitations that prevailed in the 1980s, Dr. Bodmeier also doubted that several of the prior art references relied upon by Apotex would have been available to the person of skill, particularly with reference to some foreign trade publications.

[72] Dr. Bodmeier considered the 1985 Pilbrant reference to be the principal piece of prior art because it dealt specifically with omeprazole. Pilbrant taught that omeprazole was unstable in aqueous solution and required a protective enteric coat. Omeprazole was also sensitive to

moisture and required a desiccant in its packaging. Dr. Bodmeier disagreed with Dr. Kibbe that Pilbrant warned the person of skill about acid sensitivity of omeprazole in solid state formulations. In 1986 the person of skill could not predict the stability of an active pharmaceutical ingredient [API] in a solid state doseage form from its behaviour in solution. Similarly, Pilbrant did not teach that an ARC would be necessary to achieve good storage stability for enterically coated omeprazole. Although Pilbrant administered omeprazole in solution along with sodium bicarbonate, that combination was required to neutralize gastric acid and not to achieve long term storage stability.

[73] Dr. Bodmeier considered the significance of EP 495 to Dr. Kibbe's anticipation opinion. He acknowledged that this reference disclosed that the alkaline salts of omeprazole were more stable than its neutral form and that such a formulation could be protected by an enteric coat. Nevertheless, because different salts have different solubility properties, it would not have been obvious to the person of skill to apply this information to the stability problem encountered by the 693 Patent inventors. According to Dr. Bodmeier, EP 495 and the other prior art references relied upon by Dr. Kibbe would not have led the person of skill away from Pilbrant which taught that neutral omeprazole could be successfully formulated with an enteric coat and that there was no apparent need to introduce a stabilizing ARC.

[74] As for the need for a subcoating, Dr. Bodmeier accepted that this was a generally known formulation strategy for separating pharmaceutical components. However, contrary to Dr. Kibbe's view, this step would not have been the first and only solution available to the person of skill. Faced with evidence only of discolouration, the person of skill would not know

the source of the problem. A subcoating would only be of value if the discolouration was caused by a reaction between the enteric coat and the omeprazole core. It was also known that some acid sensitive or alkaline drugs are sufficiently protected by conventional enteric coats.

[75] Dr. Bodmeier expressed the view that the first method the person of skill would attempt to overcome a known incompatibility was to find alternative ingredients and not to add a processing step. Dr. Bodmeier's testimony described the problem facing the person of skill in the following way:

> So, first, you maybe see something, discolouration, but you don't know the problem, you don't know what discolours. You don't know what is responsible for gastric resistance. I think this is all with hindsight, you know, these references are, in my opinion, are collected because one knows the solution to the problem and then you look for a subcoating, maybe for the alkaline reacting compounds.
>
> But a formulator in those days, that's not his starting point. He starts, let's say, with a discolouration or he starts, even Pilbrant which says it's stable, he starts at point zero. And, in my opinion, these references are of no help to him to identify the problem, what's the cause of the problem or what's the cause of the observation and then to find a solution.
>
> I think this is really very important to think back as a formulator where we stand, and I think it's obviously difficult with hindsight, you know, once you have a solution to look and to make it look obvious, but I think omeprazole, if I can just give my opinion, is such a complex molecule that when somebody starts to formulate this, I think these references would not be found by a skilled person.

[76] According to Dr. Bodmeier, faced with evidence of discolouration, the person of skill would not assume an incompatibility between omeprazole and the enteric coat. Other possibilities were present that required examination. Adding an ARC was also not an inevitable

choice because the addition of excipients can create other undesirable reactions, as turned out to be the case with omeprazole. Another stabilizing option identified by Dr. Bodmeier was the use of anti-oxidants.

[77] Once the gastric acid resistance problem arose it, too, required a solution, Dr. Bodmeier's report describes the options then facing the person of skill:

> 239. Even if the skilled person became aware of the reduced gastric resistance problem, he or she would need to conduct experiments to solve the problem.
>
> 240. The skilled person would likely first search in the enteric film coating itself for the reasons for the insufficient gastric resistance, systematically investigating formulation and process parameters. Insufficient gastric resistance can be caused by insufficient thickness of the coating or uneven coating. The skilled person might also consider the following:
>
> - amount and/or choice of plasticizer;
> - process parameters, including temperature, spray pressure, spray rate, air throughput, drying;
> - remaining solvent;
> - porosity of the coating;
> - choice of solvent.
>
> 241. Contrary to Dr. Kibbe's view at para, 224 of his report, a logical response to insufficient gastric resistance would have been to increase the thickness of the coating and thus try to improve gastric resistance. Another logical response would have been to consider the removal of the alkaline reacting compound.

[78] Dr. Bodmeier was of the view that omeprazole was a very difficult drug to formulate and he summarized his obviousness evidence in the following way:

> 265. In my opinion, a tremendous amount of effort would be required to achieve the invention as described in claims 1, 5 and 6

> of the 693 patent. Omeprazole is an exceptionally difficult compound to formulate, as it is highly acid sensitive, sensitive to heat, moisture, and solvents, and is only effective when released in the intestinal tract. As noted above, the task of identifying each of the problems encountered by the inventors of the 693 patent would be challenging. Further, arriving at the synergistic solution of the addition of an alkaline reacting compound to the core and an inert subcoating layer of polymeric water-soluble film-forming compounds between core and enteric coat to solve the degradation and gastric resistance problems would not be considered routine. As noted, there would have been a multitude of possible paths that the skilled person would likely have taken, while the solutions described in the 693 patent would have remained non-obvious.

[79] Dr. Bodmeier addressed Dr. Kibbe's argument that Claims 1, 5 and 6 are broader than the invention disclosed because they claim formulations that are not limited by the essential parameters of water content and subcoating thickness. Dr. Bodmeier considered these features to be non-essential to the inventive concept because the person of skill inherently knows to control for water and for subcoat thickness and would expect and tolerate some variability.

[80] Dr. Bodmeier agreed with Dr. Kibbe that the 693 Patent promises good long term storage stability and gastric acid resistance. That objective was shown to be achieved with a doseage form having the essential structural elements of Claim 1. Nevertheless, Dr. Bodmeier acknowledged that not every omeprazole doseage form having the essential structural features of Claim 1 would achieve the promise of the 693 Patent. The formulator would still need to test the formulation to ensure that it provided the expected advantages of long term stability and good gastric acid resistance: [pp 1596-1601]. Dr. Bodmeier described the nature of this required testing as routine.

C. Dr. Frank Bright

[81] Dr. Bright was accepted as an expert in analytical chemistry, spectrochemical analysis, chemical instrumentation, fluorescence and luminescence spectroscopy and microscopy-based imaging. He has unquestionable experience and expertise in these general areas. He acknowledged, however, that he has no prior experience in using his expertise to analyze pharmacological products [p 4060] and he carried out no testing of his own [p 4072].

[82] Dr. Bright was retained to comment on Dr. Davies' methods and his findings. In particular, he was asked to assess the evidence to determine if the observed "intense fluorescing layer" in the Apotex omeprazole pellets is an inert, continuous layer of MACP-PVP complex, with a minimum thickness of 2 microns, which is soluble or rapidly disintegrating in water and which acts as a separating layer between the pellet cores and the enteric coating. Dr. Bright was also asked to assess the significance of the emission spectra obtained by Dr. Hawker and the CLSM images produced Dr. Fassihi on behalf of Apotex.

[83] Dr. Bright was directed to assume that the term "continuous" meant without gaps, breaks or holes and that "inert" meant non-reactive with the components of the pellet cores and the enteric coating or, alternatively, chemically unreactive with omeprazole such that the sublayer does not contain omeprazole degradation products. He was also told to assume that the complex was shown by Dr. Davies to be present "at a single point of interrogation on each pellet".

[84] Dr. Bright's principal conclusion was that Dr. Davies had failed to prove that the source of the CLSM fluorescence in the sublayer region was the MACP-PVP complex. According to Dr. Bright the observed fluorescence was more likely coming from other compounds in the sublayer and, in any event, the presence of fluorescence is insufficient to prove the "location, distribution or thickness" of the complex or any other substance that may be present. Even if one were to assume that the fluorescent ring in the sublayer coincided with the complex, no conclusions about the continuity, thickness or the separating value of the complex could be drawn. Since Dr. Davies had not ruled out the presence of other compounds within the fluorescent ring, the layer had not been demonstrated to be inert.

[85] Dr. Bright had several concerns about Dr. Davies' testing methods. In particular, he stated that the detection of fluorescence on the surface of the washed pellets "could have been due in whole or in part to, or at least affected by, contamination" from impurities transferred from drying paper to the pellet surfaces. Dr. Bright thought that this should have ruled out experimentally. Dr. Bright had similar concerns about contamination from the use of an "incorrect mounting medium" (ie. adhesive resin) or by Dr. Davies fully embedding the pellets in resin.

[86] Dr. Bright was critical of Dr. Davies' failure to bisect the pellets along their major axis or near their ends. Dr. Davies had consistently bisected close to the pellet equators (the minor axis). Dr. Bright's concern was that a sublayer anomaly that commonly existed outside of the equatorial region would be missed.

[87] Dr. Bright was troubled by what he took to be discontinuities in the fluorescent ring. Some of Dr. Davies' Z-scan images did not show a fluorescent ring and Dr. Bright believed this to be evidence of fluorescent discontinuity. At paragraph 70 of his report he explained the problem as he saw it:

> 70. Inspection of Dr. Davies experimental CLSM data presented in Exhibit "O" shows the following: (i) a discontinuous ring in the *x*- and *y*-planes that is also discontinuous in the *z*-plane (e.g., compare *z*=0 and *z*=35 and *z*=49 images in Exhibit "O" noting how the ring appears broken in *z*=0 and totally absent in *z*=49); (ii) an enteric coating layer that is also clearly fluorescent (cf., *z*=39 and *z*=42 in Exhibit "O"); and (iii) a core region that is also clearly fluorescent (cf., *z*=39 and *z*=42 in Exhibit "O"). These results are inconsistent with Dr. Davies' description of the "intense fluorescing ring" as a continuous structure between a non-fluorescing core (see para. 139 of Dr. Davies' report) and a non-fluorescing enteric-coating region (see para. 148 of Dr. Davies' report). Similar observations apply to images from Dr. Davies' 2011 testing, set out in Exhibit "P". [Footnotes omitted]

[88] Further analysis of the pellet fluorescence led Dr. Bright to conclude that the sublayer fluorescence "is not appreciably different from the intensity of the surrounding area" and that the "purported bright fluorescing ring is often not reliably detectable (ie. greater than 99% confidence) above the strong background emission" from surrounding areas. According to Dr. Bright, notwithstanding the visual presence of a bright ring in the sublayer, Dr. Davies had not established that a bright ring exists. In Dr. Bright's report this deficiency was described as a discontinuity. In his testimony he conceded that this <u>may</u> be evidence of sublayer discontinuity.

[89] Dr. Bright maintained that many obvious discontinuities were apparent in Dr. Davies' CLSM images. The discontinuities identified by Dr. Bright in his chosen CLSM images were almost all detected below the surface of the sample [see Figures 16 and 17 of his report].

[90] Dr. Bright criticized Dr. Davies' apparent failure to follow appropriate image integrity policies based on perceived unspecified alterations to his images. According to Dr. Bright "many" of Dr. Davies' images had been "somehow colourized or somehow artificially highlighted specific regions within the image".

[91] Dr. Bright considered the presence of undetected omeprazole degradants within the fluorescent sublayer that were possibly causing or contributing to the fluorescence. Dr. Davies could not rule this out because the limits of detection of his ATIR instrument were markedly inferior to his CLSM instrument. In reviewing the Hawker spectra, Dr. Bright concluded that several known omeprazole degradation products were substantially more fluorescent than MACP, PVP or the prepared complex. Dr. Bright did note that Dr. Hawker's control (the blank) was "anomalously high" but "this happens from time to time, especially in analysis of solid samples". According to Dr. Bright's report this problem did not "cast doubt on the remaining data". Nevertheless, in his testimony he appeared to question the validity of the MACP/PVP complex readings obtained by Dr. Hawker because they all fell below the false signal generated by the blank [p 3978].

[92] Notwithstanding Dr. Bright's acknowledgement that fluorescence cannot distinguish between different molecules that fluoresce under the same conditions and there "is simply no way to know based on the testing conducted by Dr. Davies", Dr. Bright concluded that the "fluorescence in Dr. Davies' 'bright ring' is more likely to be attributed to [omeprazole] degradants than to his MACP-PVP and MACP-Mg complex".

[93] Dr. Bright summarized his views about the scientific significance of Dr. Davies' fluorescence data in the following way:

> 116. Therefore, assuming that some amount of Dr. Davies' complex is present on the surface of the bisected, washed *pellets*, there is no way to ascertain, based on Dr. Davies' fluorescence work, how much complex is present, where it is located, its minimum or average thickness, its extent of spatial and/or chemical continuity around the core including the presence of small or large breaks, gaps or holes, or whether MACP, PVP, omeprazole or its degradants (*i.e.*, other species capable of fluorescing in Dr. Davies' system) may be present. In other words, Dr. Davies cannot distinguish between the following scenarios, all of which are consistent with the data;
>
> (a) A layer composed of complex that contains a quantity of a fluorescent species below his ATR-IR detection limits (*e.g.*, omeprazole degradants) and continuous as a shell or corona around the core that has an average thickness of 2 μm (*i.e.*, his own interpretation);
>
> (b) Discrete patches of complex that are 500 nm thick within a minimum 2 μm-thick region that contains omeprazole degradants and other species; or
>
> (c) Any number of other possible geometries and/or species distributions,
>
> 117. For the same reasons, there are no data in Dr. Davies report to support a conclusion that the "intense fluorescing layer" detected within the bisected, *enteric-coated pellets* must also contain a continuous layer of the complex.

[94] Dr. Bright also considered Dr. Davies' and Dr. Hawker's CLSM data. He regarded Dr. Hawker's sample preparation to be preferable because it avoided exposing the pellets to resin. Dr. Bright plotted radial intensity profiles across three vectors for two of the Hawker CLSM 10X resolution images. In each case for two of the three measured profiles the fluorescent intensity of the sublayer was said to be no higher than that of the core region.

Dr. Bright attributed this to a discontinuity in the sublayer. Dr. Bright concluded that the Hawker images "show significant discontinuity" at the core-enteric coating interface "that is inconsistent with a continuous layer". Dr. Bright summed up the Hawker data in the following way:

> 136. In short, the NEW CLSM image data demonstrate behaviour that is clearly inconsistent with the features of Dr. Davies' proposed subcoat. One or more fluorescing species (*e.g.*, omeprazole degradation products) are amongst the more likely causes of the observed fluorescence in all the CLSM images. The MACP-PVP complex is an unlikely contributor to the fluorescence.

[95] Dr. Bright questioned the value of Dr. Davies' visual inspection of the Apotex pellets. Not all of known omeprazole degradants were likely to appear in the form of discolouration. Accordingly, neither ATIR nor a visual inspection could rule out their presence and Dr. Davies, therefore, failed to establish that his proposed sublayer "is inert by reason of not degrading omeprazole".

[96] Based on the assumption that, in 2004, Dr. Davies had measured sublayer thickness at a single location on a single pellet, Dr. Bright stated that the data were insufficient to allow for any representative determination of thickness. Also, because Dr. Davies had failed to establish what was fluorescing in the sublayer, it was an inappropriate proxy for measuring the thickness of the complex. Dr. Davies' thickness measurements from 2011 were not sufficiently documented for Dr. Bright to assess their representativeness. Dr. Bright also noted that some of the 2011 thickness measurements were less than 2 microns.

[97] Dr. Bright's assessment of Dr. Davies' disintegration video was limited to the observation that since it had not been established that a continuous layer of the complex existed in the sublayer region, he could not agree that the video images showed the rapid disintegration of the complex. Dr. Bright offered no other explanation for what it was that was peeling away from the pellet core.

[98] In response to Dr. Davies' reply report, Dr. Bright continued to assert that paper contamination may have "contributed" to the fluorescence that was observed in his washed pellet samples. In response to Dr. Davies' point that the observed fluorescence was the same for the washed and unwashed pellets, Dr. Bright raised the "possibility" that the sources of the fluorescence for each could be different. Dr. Bright did not indicate how this would occur but he, nevertheless, challenged Dr. Davies' assumption that the fluorescent species were the same.

[99] Dr. Bright also continued to express a concern that Dr. Davies' use of adhesive resin may have had an effect on the observed fluorescence and he pointed to traces of fluorescence in some of Dr. Davies' images at locations well away from the sample under investigation.

[100] Dr. Bright asserted in his Sur-reply report that Dr. Davies made a critical error by assuming that the Apotex pellets were completely opaque. The pellets could not be completely opaque because Dr. Davies' raw CLSM data were detected from well below the surface of the samples. Dr. Bright went on to give several examples from the data to show that Dr. Davies was wrong about the opacity of the samples and to illustrate "major breaks and defects" in the fluorescence from below the pellet surface [Figure 3]. This, in turn, led Dr. Bright to consider

the possibility that Dr. Davies had used maximum intensity projections that had an obscuring effect and prevented a proper assessment of fluorescent continuity and thickness. After reviewing the raw CLSM data, it became clear to Dr. Bright that Dr. Davies had used maximum intensity projections for some of his CLSM images. Dr. Bright then went on to explain in detail how maximum intensity imaging can create a false visual impression of homogeneity. He described Dr. Davies' approach as "highly inappropriate" and a "manipulation of data". Nevertheless, he was able to use these images at 10X magnification to illustrate the presence of discontinuities in the fluorescence sublayer [Figure 9] along with the gaps he observed in Dr. Davies' individual Z-scan images.

[101] In response to Dr. Davies' point that he had not identified sublayer discontinuities at the surface of the Z-scan images, Dr. Bright referred to one such image where the intensity of the fluorescence did not vary to a material degree as the scan progressed over the pellet surface. Dr. Bright continued to assert that Dr. Davies had failed to establish a correlation between the observed fluorescent ring and the presence of the complex. Thus, Dr. Davies' CLSM images showed only that some unknown amount of an unidentified chemical species was fluorescing. According to Dr. Bright, this disclosed nothing relevant about the continuity of the complex. Dr. Bright agreed with Dr. Davies that any omeprazole degradants in the sublayer would be in very small amounts but would still be capable of producing significant fluorescence. He clarified that he was not suggesting that the sublayer fluorescence was attributable to omeprazole degradants and nothing else. He was merely saying that Dr. Davies could not reliably use that fluorescence to establish the location of the complex.

[102] In examining the Temple University CLSM images, Dr. Bright acknowledged that the fractured surfaces of the pellets created a less planar surface than Dr. Davies' microtomed pellets. In testimony he agreed that the failure by Temple University to obtain multiple Z-scan images of each sample weakened the available data [p 3949-3950, p 4155]. Dr. Bright did not accept, however, that a surface irregularity could result in an inability to detect a gap below the pellet surface. The gaps in fluorescence identified by Dr. Bright below the pellet surface were more likely caused by a gap in the subcoating layer.

[103] Dr. Bright addressed Dr. Davies' point that because the pellet cores do not fluoresce as brightly as the sublayer, the core constituents (eg. omeprazole, omeprazole degradants and PVP) could not be responsible for the sublayer fluorescent ring. Although Dr. Bright seemingly accepted that in some of the CLSM images the sublayer fluorescence was brighter than its surroundings, it was not always the case to a relevant degree of confidence. It was, therefore, difficult for Dr. Bright to conclude that increased intensity at the enteric coating core interface was due to the complex or to magnesium salt rather than some other unknown chemical species.

[104] In responding to Dr. Davies' point that he had failed to offer an explanation for the likely migration of core constituents into the sublayer, Dr. Bright postulated that the sublayer fluorescence may result from a chemical change to the core during enteric coating or afterwards. In response to a question by the Court, he was unable to suggest other possibilities beyond paper or resin contamination [p 3989].

[105] Dr. Bright addressed Dr. Davies' clarification of his thickness measurements. Dr. Bright seemingly accepted that Dr. Davies had used a standard method but he continued to question whether the data obtained were representative. He complained that Dr. Davies had failed to provide enough information to allow for a meaningful assessment of his work and he again criticized what he believed was Dr. Davies' use in 2004 of a maximum intensity projection to measure sublayer thickness. Dr. Bright appeared to accept, however, that Dr. Davies' thickness measurements in 2011 came from individual Z-scan images and not from maximum intensity projections. Dr. Bright explained his failure to take his own thickness measurements on the basis that he had insufficient 50X images to obtain representative data and because Dr. Davies had failed to clearly explain what he had done to take his measurements.

D. Dr. Peter Griffiths

[106] Dr. Griffiths was qualified as an expert in analytical chemistry, photon spectroscopy, infrared spectroscopy and instrumentation, particularly, including Fourier transform infrared spectroscopy, Ramon spectroscopy and chromatography.

[107] Dr. Griffiths is very experienced in the field of spectroscopy and, in particular, in the use and interpretation of infrared and fluorescence microscopy. He had little experience in applying those techniques to pharmaceutical products.

[108] Dr. Griffiths was asked to assess Dr. Davies' data to determine if they supported his conclusion that the Apotex pellets contain a continuous and inert separating sublayer made up of the complex and the magnesium salt of MACP, having a minimum thickness of 2 microns (or,

alternatively, with an average thickness of 2 microns) and that is soluble or rapidly disintegrating in water. Dr. Griffiths was also asked to comment on Dr. Davies' analytical techniques including the levels of detection for omeprazole degradants that were available from his testing equipment.

[109] Like Dr. Bright, Dr. Griffiths concluded that Dr. Davies' data were insufficient to support his opinions concerning the continuity, thickness and distribution of any complex that may be present at the enteric coating-core interface of the Apotex pellets. Dr. Griffiths' analysis of the data indicated to him that "if there is a layer of complex on the surface of the washed pellets", it was either not continuous or it was less than 2 microns thick and would not act as a separating layer. He also stated that the presence of fluorescence could not, as Dr. Davies seemingly suggested, be spacially equated with the complex. Unidentified chemical species, possibly including omeprazole degradants, could be the source of the observed fluorescence. These uncertainties led Dr. Griffiths to challenge Dr. Bodmeier's opinion that all of the Apotex omeprazole pellets would contain Dr. Davies' asserted subcoat layer.

[110] As with all of the other expert witnesses, Dr. Griffiths acknowledged that fluorescence microscopy cannot be used to identify a particular compound in a mixed sample. In contrast, subject to the limits of detection, infrared spectroscopy can be used to identify specific compounds in a sample of unknown composition.

[111] Dr. Griffiths asserted that Dr. Davies did not directly elucidate the composition of the fluorescent layer depicted in his CLSM images. Instead, Dr. Davies is said to have inferred from

his limited ATIR testing that the CLSM sublayer fluorescence is a continuous layer of the complex and MACP salt.

[112] Dr. Griffiths pointed to the variation in Dr. Davies' ATIR spectra for the complex in both 2004 and 2011. This lack of uniformity suggested that the "proposed" layer of complex was either not uniform in thickness or that poor experimental conditions existed. Dr. Griffiths also noted the presence of clear signs of carboxylic acid in the washed pellet samples which indicated the presence of MACP that had not reacted with PVP. This free MACP was said to be "presumably in contact with the core region", meaning the "proposed subcoat is not inert because acidic groups would be in contact with the core and, omeprazole found in the core, reacts with acidic groups".

[113] Dr. Griffiths also identified a "large amount of mannitol detected on the surface of the washed pellets" in several of Dr. Davies' ATIR spectra. This suggested to him that the sublayer was either not continuous or was, in some locations, very thin.

[114] In Dr. Griffiths' initial report, he characterized Dr. Davies' identification of MACP-magnesium salt in the sublayer as having "no basis whatsoever". According to Dr. Griffiths, the ATIR "shoulder" that Dr. Davies relied upon could not be magnesium salt because the same feature was present in the spectrum obtained for the pure complex. The firmness of this view was abandoned in Dr. Griffith's testimony where he acknowledged that the presence of magnesium salt was a possibility [pp 3373-3376].

[115] In Dr. Griffiths' reports, he expressed reservations about the actual presence of the complex at the enteric coating-core interface of the Apotex pellets. Despite Dr. Davies' ATIR data showing the presence of the complex, Dr. Griffiths said that the complex "may be present in some amount" [see paras 25 and 140], "if there is a layer of complex on the surface of the washed pellets" [see paras 25 and 140] or "assuming that MACP-PVP / MACP-Mg is present" [see para 25]. Nowhere in his reports does Dr. Griffiths clearly acknowledge that the ATIR data proved the presence of the complex in the Apotex sublayer. As with Dr. Bright, Dr. Griffiths thought that Dr. Davies' correlation of the CLSM fluorescence data with the ATIR data, ostensibly to show continuity of the complex, was speculative.

[116] Dr. Griffiths stated that the presence of omeprazole degradants in the pellet sublayer could not be ruled out by the ATIR data. Degradation products in the amounts reported by Apotex for its pellets would be below the ATIR limits of detection but still be capable of fluorescing. The presence of undetectable amounts of omeprazole degradants would establish that the sublayer is not inert according to the definition of that term that Dr. Griffiths was asked to assume.

[117] Dr. Griffiths challenged Dr. Davies' sublayer thickness measurements in several ways. He questioned the sufficiency of Dr. Davies' measurements and the paucity of reported testing details. He also pointed out that, in a few of the 2011 measurements, the reported thicknesses were less than 2 microns.

[118] Several of Dr. Davies' ATIR spectra for the washed pellets disclosed the presence of mannitol. Dr. Griffiths proposed four possible explanations for this result:

a. the ATIR beam was detecting mannitol from below the sublayer of 2 to 6 microns thick;

b. mannitol was detected below a sublayer less than 1 micron thick;

c. mannitol was present in the sublayer; or

d. there are gaps in the sublayer that allowed the ATIR beam to probe directly into the pellet core.

[119] Dr. Griffiths challenged Dr. Davies' opinion that his ATIR beam was capable of detecting mannitol below a 2 micron or greater sublayer thickness. Dr. Griffiths concluded that Dr. Davies was relying on improper calculations. His own calculations for the ATIR depth of penetration indicated that "there is no way for the IR beam to see through a thickness of 2 microns" given the presence of mannitol bands at 3400 cm^{-1} in the 2011 spectra. At that point in the spectra the depth of penetration was said to be only 0.25 microns.

[120] Dr. Griffiths' preferred explanation for the presence of mannitol bands in some of Dr. Davies' ATIR spectra was that gaps were likely present in the sublayer such that the ATIR beam was able to probe the pellet cores without sublayer interference. This explanation was said to be consistent with the relative intensity of the mannitol and complex bands in the 2011 spectra. According to Dr. Griffiths, a gap in the sublayer was the best explanation for the relatively high intensity of some of the observed mannitol bands.

[121] Dr. Griffiths considered Dr. Davies' video of the Apotex washed pellets undergoing water immersion. Based on his view that Dr. Davies had failed to establish a continuous layer of the complex was present on the surface of the pellet cores, Dr. Griffiths was unprepared to attribute any significance to the video beyond suggesting that what Dr. Davies said was flaking off "could well be MACP".

[122] Dr. Griffiths' Reply report addressed matters addressed in Dr. Davies' and Dr. Bodmeier's Reply reports.

[123] Based on the larger area of ATIR interrogation reported by Dr. Davies, Dr. Griffiths concluded the sublayer gaps he had previously identified were either more numerous or larger than he had initially assumed. He also dismissed Dr. Davies' contention that the mannitol bands in the washed pellet ATIR spectra were detected beneath a 2-micron-thick sublayer. These bands, he said, could only be explained by the presence of gaps in the sublayer.

[124] Dr. Griffiths then set out in detail his calculation for the depth of penetration for Dr. Davies' ATIR instrument. He concluded, once again, that mannitol bands in the area of 3300 to 3400 reciprocal centimetres should not be seen if the core was covered by a layer that was more than 1 micron thick. This would be true for either his or Dr. Davies' assumed depth of penetration. This confirmed to Dr. Griffiths that mannitol was being directly detected through gaps in the sublayer. In one spectrum, he estimated the gaps represented about 40% of the area under interrogation. For two other spectra, the gaps were said to be between 25% and 40% of the size of the ATIR beam.

[125] Dr. Griffiths drew additional support for his belief from the variation in intensity of the mannitol bands and from their relative strength. In the presence of a continuous and uniform sublayer of more than 2 microns, Dr. Griffiths would have expected to see more consistency and less intensity in the mannitol bands. Much of this technical evidence was canvassed in cross-examination about which more will be said later in these reasons.

E. Dr. Arthur Kibbe

[126] Dr. Kibbe holds a PhD in pharmaceutics. He is a Professor at the Wilkes University School of Pharmacy. Among other accomplishments, Dr. Kibbe acts in an advisory capacity to the Food and Drug Administration. He was qualified as expert in pharmaceutics, pharmaceutical doseage form design, development, and manufacture; including the evaluation of the physical and chemical stability of formulations and the regulation of pharmaceutical formulations, and pharmacokinetics.

[127] Dr. Kibbe's definition of the person of skill was essentially that of a pharmaceutical formulator or the equivalent professional with experience in treating patients with gastric acid-related diseases. That person would have at least two years of practical experience as a formulator in addition to a Bachelor's degree in pharmacy or a closely related discipline.

[128] Dr. Kibbe was retained by Apotex primarily to address validity and construction issues. His first report described in detail the state of the art concerning the use of enteric coatings to protect acid-sensitive compounds, with particular reference to omeprazole. He noted that polymeric or "film" coatings were frequently used as early as the 1940's to protect active

pharmaceutical ingredients from prematurely degrading in the stomach. Before 1986, such coatings were developed with various solubility profiles in order to target a specific site of release along the intestinal tract.

[129] The protective feature of polymeric coatings was said to lie in their molecular structure – specifically the presence of acidic carboxyl groups which makes them insoluble under acidic conditions but soluble in the higher pH of the intestine. In more neutral conditions, the acidic groups ionize and convert to a water soluble salt. Typically enteric coatings were and continue to be tested by simulating the conditions of human ingestion. The product will be exposed for 2 hours or more in acidic solution followed by a measurement of how much of the API was released. If too much was released (often set at 10%), the product would have failed the gastric acid resistance test. If the product passes the gastric acid resistance test, it is exposed to a buffer solution to determine whether the API is sufficiently released in conditions that mimic intestinal pH. Assuming the product passes this test, it is then exposed to accelerated storage conditions to ensure its long-term stability. This can include a visual inspection for discolouration which may indicate degradation.

[130] According to Dr. Kibbe, in the development of any pharmaceutical formulation routine testing is always carried out to select compatible ingredients and to avoid undesirable reactions. Where incompatibilities are observed, alternate ingredients can be selected or the offending ingredients can be separated in a variety of ways including the use of subcoatings.

[131] Dr. Kibbe reviewed the 693 Patent against the background of what would have been known by the person of skill on its date of issue, December 3, 1991. He drew from the Patent disclosure that it was directed at the discovery of an enteric coated doseage of omeprazole that is resistant to degradation in the stomach and dissolves rapidly in the intestine. The skilled person would also expect the formulation to be stable in storage conditions (less than 10% omeprazole degradation) over a period of years.

[132] According to Dr. Kibbe, the person of skill knew before December 1991 that omeprazole was acid sensitive and susceptible to rapid degradation in acid media. He cited the Pilbrant reference from 1985 as the source of this knowledge. With this knowledge the person of skill would know that omeprazole required an enteric coating.

[133] Dr. Kibbe noted the teaching of the 693 Patent that direct or indirect contact between the enteric coating and omeprazole in the core causes omeprazole to decompose as manifested by discolouration and the loss of omeprazole content over time. Discolouration was said to be a marker for assessing the stability of the formulation examples tested by the inventors.

[134] According to Dr. Kibbe the person of skill already knew that omeprazole could be stabilized for long-term storage by using an alkaline salt form of omeprazole. This knowledge came from EP 495 referenced as prior art in the 693 Patent.

[135] Dr. Kibbe addressed the inventors' use of an ARC as an alternative means of improving the storage stability of omeprazole. This approach was said by the inventors to cause the

unwanted degradation of the enteric coat from the diffusion of gastric juice through the enteric coat, resulting in an undesirable reaction with the ARC. This reaction created an alkaline environment that dissolved the enteric coat from the inside of the formulation. According to Dr. Kibbe there was nothing surprising about this problem. The person of skill would understand the observed difficulty and would also be aware that a successful omeprazole formulation would require the avoidance of absorbed moisture from any source. The means of minimizing water content were routinely employed by pharmaceutical formulators including the use of special packaging. The skilled person was also said to know from the 693 Patent that a separation between the enteric coat and the omeprazole containing cores was necessary. In the absence of sufficient ARC, omeprazole would degrade in storage and, in the presence of sufficient ARC, the enteric coat was at risk of dissolution after ingestion. According to Dr. Kibbe the Patent examples teach that it is not possible to achieve good gastric acid resistance and good long-term stability in an omeprazole formulation where the enteric coating is applied directly to the alkaline cores. The problem is overcome by the use of a separating subcoating that is vital to the success of the preparation.

[136] Dr. Kibbe contended that the person of skill would understand that the subcoating must be a continuous layer to prevent the enteric coating from contacting the core “at any stage during the manufacturing process or thereafter”. It would also be understood that the subcoat “is not to be a water insoluble material” and it must be “inert” in the sense “it should not react with either the core or enteric coating constituents”. To be inert, the subcoating “should not contain optional alkaline reacting compounds” or be made of any anionic material unless covered by a second

subcoating devoid of such materials. According to Dr. Kibbe a further essential feature of the subcoating is a minimum thickness of 2 microns.

[137] Dr. Kibbe noted that an essential teaching of the Patent was to maintain a low water content in the final doseage form and preferably not more than 1.5% by weight. He referred to the Patent examples showing considerable omeprazole degradation in the presence of water concentrations of 2% and 5% with successful storage stability achieved at a water level of 1%. He took this to be a teaching that any formulation with a concentration of 2% or more of water would lack stability.

[138] Dr. Kibbe went on to consider the 693 Patent claims. The person of skill would know that an "effective amount" of omeprazole or its alkaline salt form was an amount that achieved the desired therapeutic effect. The words "disposed on" meant applied to or placed on the core. "Inert" meant the subcoat "does not adversely affect omeprazole or the other ingredients in the core or in the outer enteric coating".

[139] Dr. Kibbe was asked to compare the subject matter of the 693 Patent claims to EP 495. EP 495 describes alkaline salts of omeprazole said to have improved storage stability over neutral omeprazole. It also describes various formulations including enterically coated doseage forms and gelatine capsules. According to Dr. Kibbe, the EP 495 claim to enterically coated gelatine capsules containing an omeprazole salt describes a subject matter covered by Claim 1 of the 693 Patent. EP 495 also provides the person of skill with sufficient information to prepare the claimed composition with no more than routine testing.

[140] Dr. Kibbe was asked to comment on how the person of skill would interpret the promise of utility of the 693 Patent and whether the claimed formulations have the promised utility. He stated that the Patent promises omeprazole formulations with good gastric acid resistance, rapid dissolution in neutral to alkaline media and good long-term storage stability against degradation and discolouration. As to whether the 693 Patent delivers on those promises, Dr. Kibbe said it did not. He asserted that Claim 2 of the Patent contemplates formulations which include the presence of an alkaline reacting compound in the subcoating. These formulations would, however, only have good long-term storage if a second subcoating was employed. Since the Patent did not appropriately limit the use of an ARC in the subcoating layer, Claims 1, 5, 6, 11 to 13, 18 and 19 necessarily include preparations lacking the promised characteristic of good long-term storage stability.

[141] A similar argument was advanced by Dr. Kibbe with respect to water content. Despite the advice in the Patent disclosure that it is critical to keep the water content low, the scope of Claim 1 was not limited in any way with respect to water content. Claim 13, however, covers a formulation which limits water content to 1.5% or less. Dr. Kibbe asserted Claim 13 is rendered redundant if Claim 1 is interpreted as being similarly limited. This led Dr. Kibbe to the view that Claim 1 would be interpreted by the person of skill to be unlimited with respect to water content. Since omeprazole preparations having a water content of more than 2% were shown to be unstable, Claims 1, 5, 6, 11, 12, 18 and 19 necessarily lack the promised utility of good long-term storage stability. Claim 13 also fails, according to Dr. Kibbe, in the absence of any evidence of a useful omeprazole formulation with a water content as high as 1.5%. On the basis

of the testing reported in the Patent, the inventors had no basis to soundly predict the utility of an omeprazole formulation with a water content any greater than 1%.

[142] Although none of the Patent claims specify a minimum subcoat thickness, the disclosure states that a thickness value not less than 2 microns is required for a pellet formulation. According to Dr. Kibbe the person of skill would nevertheless interpret the claims to include subcoatings less than 2 microns thick and, therefore, Claims 1, 5, 6, 11 to 13, 18 and 19 encompass more than what is disclosed for utility.

[143] Dr. Kibbe expressed the opinion that the 693 Patent claims would have been obvious to the person of skill as of April 30, 1986. His obviousness analysis includes the following assertions:

a. All of the information in the Background section [paras 33-62] of the 693 Patent would have been known to the person of skill;
b. Omeprazole and its salts were known to be useful to treat gastric acid-related diseases;
c. Omeprazole was known to be sensitive to acid and to degradation from high temperatures and high humidity;
d. Water content was a known concern and was something the skilled formulator routinely seeks to control;
e. The person of skill would know storage stability for an omeprazole formulation could be improved with the creation of an alkaline environment around the omeprazole molecules and by reducing water content;

f. Omeprazole salts were known to be more stable than neutral omeprazole;

g. The use of alkaline compounds with benzimidazole formulations was known in the prior art. The person of skill knew that omeprazole was very closely related to other benzimidazole formulations where alkaline reacting compounds had been used. Although this prior art did not expressly identify the purpose of using an ARC, the person of skill knew that it was used to improve the stability of the API;

h. The use of enteric coatings in conjunction with plasticizers was widely known and routinely done;

i. The use of subcoatings to avoid adverse pharmaceutical reactions was known; and

j. The potential for an adverse reaction between enteric coating polymers and alkaline materials was well-known along with the avoidance of their incompatibility with non-reactive undercoats.

Based on the foregoing understandings, Dr. Kibbe concluded that there was no inventive difference between the state of the art on April 30, 1986 and the inventive concept of Claim 1 of the 693 Patent or its dependant claims.

[144] Dr. Kibbe concluded his report by stating that the 693 Patent teaches away from the direct application of an enteric coating to the omeprazole containing cores. He was aware of nothing in the prior art describing an *in situ* subcoating layer and thus the person of skill would have no cause to consider that possibility or the information required to make it. Furthermore, there is nothing in the Patent to show that such a subcoating would actually work or be predicted to work. On the issue of prediction Dr. Kibbe stated:

> 265. It is impossible in my view to predict all of the potential reactions that might occur between potential excipients within the alkaline core or between any one or more of those excipients and an enteric coating polymer. It is thus impossible to predict whether any inert, water soluble reaction product formed by the interaction of excipients or film-forming polymers which might arise at the interface of the core and the outer coating - whether ionic or covalently bound material, or a complex of one or more substances bound by weak or strong forces - would confer on the resulting formulation good gastric acid resistance and good long-term storage stability to degradation/discoloration.

All of this Dr. Kibbe contrasted with the teaching of the subsequently issued 037 Patent. The 037 Patent specifically describes an omeprazole formulation with an *in situ* subcoating and the means to make it. According to Dr. Kibbe this supports his view that such formulations were not part of the 693 Patent invention.

[145] Dr. Kibbe's Reply Report addresses Dr. Bodmeier's evidence that the person of skill would not equate a gelatine capsule with the subcoating described in Claim 1. Dr. Kibbe took a contrary view. The person of skill would not identify a distinction between a separating layer describing a gelatine capsule and a subcoating layer. Both served the same purpose of effecting a separation.

[146] Dr. Kibbe's Further Expert Report discusses the potential presence of omeprazole degradants in the Apotex omeprazole product and the limitations inherent in their detection by visual inspection. Some degradation of omeprazole would be expected from the process of manufacture. In response to Dr. Bodmeier's opinions on subcoating continuity and inertness, Dr. Kibbe stated that the person of skill would contemplate some variation in thickness but not

breaks in continuity and would not accept the presence of any material that could lower pH, such as acidic functional groups.

F. Dr. William Amos

[147] Dr. Amos is an Emeritus Research Staff Member at the Medical Research Council, Laboratory of Molecular Biology at Cambridge University. He has a PhD in the field of cell biology but the major focus of his research for more than 30 years has been in the area of optical microscopy. He, along with others, was instrumental in the development of the confocal laser scanning microscope. He has lectured and published extensively on the theory and practice of confocal microscopy. However, before this case, he had never used the equipment to analyse the structure of a pharmaceutical doseage form.

[148] Dr. Amos was accepted as an expert in optical microscopy with particular expertise in the theory and practise of CLSM.

[149] Dr. Amos was asked by Apotex to consider Dr. Davies' various reports and his imaging results. For comparison purposes, he was also asked to review CLSM imaging conducted at Temple University. He did no testing of his own.

[150] A particular focus of Dr. Amos' assessment had to do with Dr. Davies' methods and his analysis of the imaging results concerning the presence and structure of a subcoating layer in the Apotex omeprazole pellets.

[151] Dr. Amos criticized Dr. Davies for a supposed error concerning the opacity of the imaged specimens. Dr. Amos said that Dr. Davies was wrong in saying the specimens were totally optically opaque. Much of his report was then dedicated to proving why Dr. Davies was wrong on this point [see paras 40 to 52].

[152] While Dr. Amos recognized the presence of a band of fluorescence in the region between the pellet cores and the enteric coating, he stated Dr. Davies' 10x images were not suitable for assessing the continuity of that band.

[153] After examining Dr. Davies' 50x images, Dr. Amos concluded the depicted subcoating "clearly shows microheterogeneity and possible holes or a flaky structure". Dr. Amos criticized Dr. Davies for not using a frame averaging technique to improve the quality of his images.

[154] While recognizing that the Temple University images were not obtained as a Z-scan series, Dr. Amos observed that, where those images were in focus, gaps similar to those seen in Dr. Davies' images could be seen.

[155] Dr. Amos also considered the quality of Dr. Davies' images for purposes of measuring the thickness of the observed fluorescent band. At paragraph 76 of his report, he said that he could see nothing in Dr. Davies' reports to suggest that measures were taken to avoid image saturation. Dr. Amos tested one of Dr. Davies' images and found it to be strongly suggestive of saturation. Dr. Amos also noted "it seems likely that many of the 'images' used by Dr. Davies to assess continuity and for thickness measurements may in fact be projections of all of the

confocal images from many levels". Such a use of projections was said to be "highly inappropriate", "unjustified", and "misleading". In testimony, Dr. Amos said these particular data were "manipulated". Dr. Amos also described Dr. Davies supposed use of projected images to measure the thickness of the fluorescent band as invalid.

[156] Under cross-examination, Dr. Amos acknowledged that he made no inquiries about Dr. Davies' methods.

[157] With respect to the analysis of the continuity of the observed fluorescent band, Dr. Amos acknowledged the following points:

a. The presence of large gaps can be produced by a gross loss of focus [p 3038];

b. The large gaps in the zone of fluorescence in the Temple University CLSM images are due to a loss of focus [p 3046, pp 3063-3064];

c. The CLSM signal will diminish at depth [p 3047];

d. The value of the Temple University images was diminished by the failure to make a full Z series [p 3048, p 3059];

e. Some of the images Dr. Bright had used to assess continuity of the fluorescent band were not suitable for that purpose [p 3051];

f. The opacity of the sample will give an appearance of low fluorescence due to signal absorption at depth [p 3071] – an effect that may not be uniform [p 3075];

g. CLSM 50x images are better for assessing small scale continuity and thickness [pp 3078-3079];

h. All other things being equal, 50x images are better than 10x images for assessing continuity and thickness [p 3082];

i. Dr. Amos had not included any 50x in-focus images taken at the surface of a sample in his report [p 3197];

[158] Dr. Amos was questioned about a montage of images he had put together during Dr. Davies' cross-examination. On a number of those images, he had placed question marks beside perceived anomalies. When asked about these images and his apparent equivocation, he gave the following answers:

> Q. The image beside AP5417 1, you agree that the confocal section of this image was not at the surface of the bisected pellet?
>
> A. I agree.
>
> Q. The image was taken below the surface of the bisected pellet?
>
> A. It, it, it may well have been below the surface because I don't see the telltale reflection artifact that one sees at the surface.
>
> Q. And you don't know how far down this image was taken?
>
> A. I don't.
>
> Q. Will you agree that where you have arrows with "hole" followed by a question mark, that there is pale fluorescence in those regions?
>
> A. Certainly.
>
> Q. And when you use the question mark, would you agree that it is possible that the features that you identify as holes are not, in fact, holes?
>
> A. Yes.

Q. And can I take it that that's the same for the other two montages?

A. Yes. Although as I said before, I think that the montage of Stub 12 is different from the others in that it is clearly very close to the surface.

Q. I will take you to that.

MR. HACKETT: This isn't an objection, but my friend said they are the same. I just don't know if it's perfectly clear now, especially in light of what Mr. Biernacki said about "we will come to the last one", what he means by "same". Maybe we should have just a bit of clarity on that.

MR. JUSTICE BARNES: It is up to Mr. Biernacki. I suppose if he doesn't want to go there, you can go to it in re examination.

MR. HACKETT: Fair enough, good.

BY MR. BIERNACKI:

Q. By "same", I was referring to your use of the labels and the meaning of the question mark. Is that what you understood me as asking, Dr. Amos?

A. Yes. And so my answer is, yes, the label and the question mark has the same significance in all of the images in these montages.

Q. Thank you.

And perhaps we can short circuit this. With the exception of Stub 12, which I will come to specifically, do you agree that none of the remaining three images in the other two montages are from the surface of a bisected pellet?

A. Yes.

Q. And would you agree that you do not indicate how far below the bisected pellet those images were taken?

A. I do not. In other words, I do not indicate.

[159] In describing the effect of signal attenuation, Dr. Amos provided the following useful analogy:

> A. Absorbant material quite widespread causing attenuation, and it is something that you see in hollow shells and spirals and objects of all kinds, also in totally homogeneous materials.
>
> Now, I think if you - - let me see. Let's suppose you have the misfortune to be involved in an avalanche and snow piles up on top of you. As the snow covers you, you will, at first, be able to see light. Then as the layer gets thicker and thicker, you will see less and less. We would not say that you are in a shadow there. We would say that there is absorption, in general, above you, and so you are receiving less light.
>
> I think it is a difference in the lateral extent of the effect that is crucial here.
>
> Q. You accept that absorbant material can reduce signal below it in CLSM; correct?
>
> A. Absolutely.

III. Claims Construction

A. Principles of Claims Construction

[160] The outcome of this case turns on several issues of claims construction. These are matters of law for the Court to determine, to a greater or lesser extent, with the aid of expert witnesses: see *Pfizer Canada Inc v Canada (MOH)*, 2007 FCA 209 at para 39, [2007] FCJ no 767 (QL). The first step in a patent suit is always to construe the claims without regard to issues of validity or infringement.

[161] The parties agree that the construction of patent claims must be carried out purposively and in accordance with the principles discussed in *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at paras 55-56, [2000] 2 SCR 1067 [Whirpool], and *Free World Trust v Électro Santé Inc*, 2000 SCC 66, [2000] 2 SCR 1024 [Free World].

[162] I have previously discussed the principles that apply to the construction of claims language in *Bristol-Myers Squibb Canada Co v Mylan Pharmaceuticals ULC*, 2012 FC 1142 at paras 67-72, 222 ACWS (3d) 230 and I apply those principles here:

> [67] Claims language is a critical component of the public notice requirement and subsection 27(4) the *Patent Act*, RSC 1985, c P-4, emphasizes its importance:
>
> | | |
> |---|---|
> | 27.(4) The specification must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed. | 27.(4) Le mémoire descriptif se termine par une ou plusieurs revendications définissant distinctement et en des termes explicites l'objet de l'invention dont le demandeur revendique la propriété ou le privilège exclusif. |
>
> [68] The Supreme Court of Canada emphasized the purpose and importance of requiring clear language in the drafting of patent claims in *Free World*, above, at paragraphs 14, 15 and 42:
>
> > 14 Patent claims are frequently analogized to "fences" and "boundaries", giving the "fields" of the monopoly a comfortable pretence of bright line demarcation. Thus, in Minerals Separation North American Corp. v. Noranda Mines, Ltd., [1947] Ex. C.R. 306, Thorson P. put the matter as follows, at p. 352:
> >
> > > By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and

> he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

15 In reality, the "fences" often consist of complex layers of definitions of different elements (or "components" or "features" or "integers") of differing complexity, substitutability and ingenuity. A matrix of descriptive words and phrases defines the monopoly, warns the public and ensnares the infringer. In some instances, the precise elements of the "fence" may be crucial or "essential" to the working of the invention as claimed; in others the inventor may contemplate, and the reader skilled in the art appreciate, that variants could easily be used or substituted without making any material difference to the working of the invention. The interpretative task of the court in claims construction is to separate the one from the other, to distinguish the essential from the inessential, and to give to the "field" framed by the former the legal protection to which the holder of a valid patent is entitled.

…

42 The patent system is designed to advance research and development and to encourage broader economic activity. Achievement of these objectives is undermined however if competitors fear to tread in the vicinity of the patent because its scope lacks a reasonable measure of precision and certainty. A patent of uncertain scope becomes "a public nuisance" (R.C.A. Photophone, Ld. v. Gaumont-British Picture Corp. (1936), 53 R.P.C. 167 (Eng. C.A.), at p. 195). Potential competitors are deterred from working in areas that are not in fact covered by the patent even though costly and protracted litigation (which in the case of patent disputes can be very costly and protracted indeed) might confirm that what the competitors propose to do is entirely lawful. Potential investment is lost or otherwise directed. Competition is "chilled". The patent owner

> is getting more of a monopoly than the public bargained for. There is a high economic cost attached to uncertainty and it is the proper policy of patent law to keep it to a minimum.

[69] Notwithstanding the above cautions, the law is clear that a purposive approach requires the Court to examine claim language in the sense that the patentee is presumed to have used it and not through the lens of strict literalism. Even a term that appears to be plain and unambiguous may, when read in the context, reasonably support a different meaning. *Whirlpool*, above, also counsels that the search for meaning is not carried out through the eyes of a grammarian, but rather in light of the common knowledge of the person of ordinary skill in the field to which the patent relates. Thus, it is permissible to look to the patent disclosure to ascertain the technical meaning of terms used in the claims.

[70] I have no difficulty with the point that purposive construction is capable of expanding or limiting a literal text: see *Whirlpool*, above, at para 49. It seems to me, though, that there is some judicial concern about importing essential features of an invention from the disclosure to the claims, particularly where the disclosure is somewhat unclear about the scope of the invention. In other words, even if one resorts to the disclosure to interpret the claims "the precise and exact extent of the exclusive property and privilege claimed" must always be identifiable: see *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504 at para 26, 122 DLR (3d) 203.

[71] In *BVD Co v Canadian Celanese Ltd*, [1937] SCR 441, [1937] 3 DLR 449 [BVD], the Court declined to read into a patent claim an "essential" feature of an invention and struck the patent down because the claims, as written, exceeded the scope of the invention. This decision predates the decisions in *Whirlpool* and *Free World*, above, and their elaboration of the principles of purposive construction. Nevertheless, *BVD* has not been overruled and it continues to underscore the importance of ensuring that a patent clearly delineates the subject matter of an invention and the importance of the claims language in achieving that end: see also *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 77, [2008] 3 SCR 265; *Amfac Foods Inc v Irving Pulp & Paper, Ltd*, [1986] FCJ no 659 (QL), 72 NR 290 (CA).

[72] What I take from the authorities is that resort to the disclosure is permissible, but only for the purpose of comprehending the meaning of words or expressions found in the claims. Essential information that is contained in the disclosure

> that is not relevant to the search for meaning of claims language cannot be imported by implication to qualify the claims: see *Janssen-Ortho Inc v Canada (MOH)*, 2010 FC 42 at para 119, 361 FTR 268 [Janssen-Ortho]. It is also not appropriate to ascribe meaning to words in the claims by reference to "stray phrases" found in the disclosure: see *Electric & Musical Industries, Ltd v Lissen Ltd*, [1938] 4 All ER 221 at p 227, 56 RPC 23 (HL (Eng)).

I would add to the above that the claims and the specification serve different purposes. The former describe the limits of the asserted monopoly and the latter describes the invention.

B. The Construction Issues

[163] There is no dispute that the Apotex product contains omeprazole and an ARC in the pellet cores. There is also no disagreement that Apo-Omeprazole is enterically coated. The parties disagree, however, about the meaning of several terms that are found in Claim 1 with reference to the disclosed subcoating. In particular, they disagree about the meaning of "inert", "subcoating" and "disposed on". Apotex's principal argument is that, on a purposive reading of Claim 1, a subcoating that forms *in situ* from a chemical reaction is not covered. According to Apotex, Claim 1 covers only a subcoating that is physically applied to the pellet core and which is wholly free of holes, gaps or structural anomalies. A sublayer that forms from a chemical reaction is not a "subcoating" nor is it "disposed on" the core.

[164] Apotex also asserts that the person of skill would interpret "inert" as it applies to the subcoating to be a compound that is wholly unreactive with any of the other constituents of the omeprazole pellet whether or not there are functional implications.

[165] AstraZeneca maintains that Claim 1 is a product claim. It covers a class of omeprazole formulations defined by three basic structural elements:

a. An omeprazole core region that can include an alkaline reacting compound;

b. An inert subcoating; and

c. An outer enteric coating.

AstraZeneca says that if these basic elements are present and if they constitute a viable formulation, it does not matter how the structure is formed. In particular, a subcoating that forms *in situ* from a reaction between the core and the enteric coating is a matter of process that does not circumscribe or limit the claim to the product.

[166] AstraZeneca also asserts the requisite subcoating need not be perfect. It can contain minor gaps, holes or defects provided its functional integrity is not compromised.

[167] AstraZeneca makes a similar argument about the meaning of "inert". The person of skill would interpret this word to mean a compound that will not cause a deleterious reaction with either the enteric coating or with the omeprazole core. According to this view, the word is not used in Claim 1 in its purest scientific sense but in a relative way, teaching the person of skill to avoid materials that will lead to undesirable reactions.

C. Does Claim 1 Cover Subcoatings That Form in Situ?

[168] Apotex raises a number of interesting grammatical points in support of its argument that Claim 1 does not include a subcoat which forms *in situ*. Most of these arguments are drawn

from the language of the disclosure and not directly from the language of the claims. This, it says, is consistent with current jurisprudence emphasizing the importance of using the disclosure as a guide to the purposive interpretation of claims language.

[169] Apotex advances the following points in support of its favoured construction:

a. In the pharmaceutical arts, a coating is a covering that is physically applied to a formulation (from the verb "to coat"); coatings formed *in situ* were not known in the art at the time.

b. The words "disposed on" and "selected from" connote a deliberate choice of materials to be applied to the product and not to *in situ* reaction products.

c. The Patent disclosure teaches away from the direct application of an enteric coat to the pellet core to avoid the very reaction problem that the patent formulation is said to solve.

d. The Patent discloses only processes of direct application of a subcoating layer and nowhere discloses or enables an *in situ* reaction product.

e. The properties and performance of an *in situ* reaction product would be difficult for a formulator to evaluate or control.

f. The decisions in *Rhoxalpharma Inc v Novartis*, 2005 FCA 11, 3 FCR 261, and *Miken Composites, LLC v Wilson Sporting Goods Co*, 515 F 3d 1337 (Fed Cir 2008), recognize that what may, at first blush, appear to be process limitations can be, in fact, structural limitations.

g. On reading the 693 Patent, the skilled formulator would never contemplate that it covered a subcoating formed *in situ* and neither did the inventors.

[170] None of the experts who were asked to interpret the disputed claims language provided much in the way of specialized insight. For example, Dr. Kibbe and Dr. Bodmeier agreed the phrase "disposed on" was not a term of art in the world of a formulator. The remainder of the arguments advanced by the parties concerning the scope of the word "subcoating" are largely matters of grammar and context where expert opinion adds little, in any, interpretive value. Although the experts gave their respective opinions, they were essentially conclusions.

[171] A significant impediment to Apotex's construction argument is the decision by the Federal Court of Appeal in *Apotex Inc v AB Hassle*, 2003 FCA 409, 126 ACWS (3d) 690. That decision arose from a proceeding brought by AstraZeneca under the Patented Medicines (Notice of Compliance) Regulations concerning the 693 Patent. AstraZeneca had prevailed on the application on the strength of an argument that Apotex's Notice of Allegation was legally deficient. Accordingly, the application Judge found it unnecessary to construe the language of Claim 1.

[172] When the matter came before the Federal Court of Appeal, Apotex argued that the application Judge erred by failing to construe the disputed claims language – the same language contested here. It also argued that the application Judge erred by finding its Notice of Allegation to be legally deficient.

[173] The same interpretation arguments advanced by Apotex to the Federal Court of Appeal were advanced to me. Each of those arguments was rejected. The decision by Justice Marshall Rothstein bears repeating in substantial measure:

[14] There is no issue about paragraphs (a) and (c) of claim 1. It is paragraph (b) that is in controversy. Apotex says that paragraph (b) does not cover inert material formed between the core and enteric outer layer *in situ* from reaction between certain components of the core and the enteric outer layer. Rather, Apotex submits that paragraph (b) only covers a subcoating which is applied to the core and which is then covered by the enteric outer layer.

[15] In support of this interpretation of paragraph (b), Apotex relies upon certain paragraphs of the patent disclosure. Apotex says that the patent disclosure excerpts upon which it relies indicate that the scope of the invention described in patent claim 1 only covers a product in respect of which the intermediate subcoating is applied to the core before the outer enteric coating is applied to the subcoating. Apotex says that the description of the product requires the core and the enteric coating to never come into contact with each other. Rather, it says the core and enteric coating must be separated during the coating process, as well as during storage. The excerpts relied upon by Apotex are:

Outline of the invention

Cores containing omeprazole mixed with alkaline compounds or an alkaline salt of omeprazole optionally mixed with an alkaline compound or coated with two or more layers, whereby the first layer/layers is/are soluble in water o [sic] rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating (page 4).

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise cause degradation/discolouration of omeprazole during the coating process or during storage (page 6).

Enteric coating layer

The enteric coating layer is applied onto the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers (page 7).

The cores are coated with an inert reacting water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating.... the subcoated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

...

Process

A process for the manufacturer [sic] of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above (pages 8 and 9). [Emphasis in original]

Apotex further argues that of all the examples shown in the patent, none disclose a subcoating formed *in situ* from the reaction of components in the core and enteric coating.

[16] I have some difficulty with Apotex's reliance on the patent disclosure. In this case, patent claim 1, as a product claim, appears to be clear and in such a case, it is not appropriate to look to the disclosure to construe the claim and, in particular, to vary the scope or ambit of the claim (*Dableh v. Ontario Hydro*, [1996] 3 F.C. 751 at paragraph 30 (C.A.)). I will, therefore, first construe claim 1 itself. However, since Apotex largely rested its case on the patent disclosure, I will then deal with Apotex's argument based on the disclosure.

[17] Claim 1 describes an "oral pharmaceutical preparation" or, in every day language, a tablet. The tablet is described as having a core region, an inert subcoating and an outer layer or enteric coating. Claim 1 does not purport to place any limitations on the inert subcoating. It does not say that the inert subcoating must be created in any particular manner.

[18] Claim 1 does provide that the inert subcoating is to be "disposed on said core region". Apotex says this must mean that the core is coated with the subcoating or that the subcoating is placed on or applied to the core. Apotex says this is not just a process limitation but a limitation on the product which would exclude a tablet whose inert separating layer was formed *in situ* by the reaction of certain materials in the core and enteric coating.

[19] The evidence of Dr. Rees, expert for Astra, was that the term "disposed on said core region" should be construed to describe the need to have a subcoating located between the core and the enteric coating in the finished preparation. The evidence of Apotex's experts, Dr. Niebergall and Dr. Schnaare, was that, since the purpose of the inert subcoating was to avoid any reaction between the enteric coating and the medicinal core, the product of a reaction between the enteric coating and the core could never be a subcoating within the meaning of the patent. Dr. Niebergall further stated that a reaction between the enteric coating and the core could never produce a continuous subcoating at least 10 µm thick, which he believed the patent required.

[20] In respect of the required thickness of the subcoating, it appears that Dr. Neibergall misread the disclosure. The disclosure indicates that the thickness of the separating layer cannot be less than 2 µm, although a greater thickness is preferable. His evidence does not say that a 2 µm thickness could not be formed *in situ*.

[21] I would give greater weight to Dr. Rees's evidence. Because claim 1 is clearly a product claim and not a process claim, I construe the term "disposed on said core region" as describing the structure of the finished pharmaceutical preparation. The term, in the context of a product claim, describes the location of the subcoating and not the process by which it was formed.

[22] If, as I construe it, claim 1 describes a finished product, nothing in the disclosure detracts from the interpretation that the inert subcoating need not be formed by any particular process or formation. In the finished product, a subcoating applied to the core or a subcoating formed *in situ* would separate the core from the enteric coating. That the disclosure provides that the core and enteric coating must be separated "during the coating process" might help to construe an ambiguous process claim. But I do not see those words as having any application to a claim that clearly describes a finished product. Similarly, the other references in the disclosure relied upon by Apotex describe one process for making the pharmaceutical preparation - sequentially applying the subcoating to the core and then the enteric coating to the subcoating. But nothing in claim 1 purports to place a process limitation on the finished pharmaceutical preparation.

[23] Apotex argues that such a construction is inconsistent with the disclosure because the very problem the invention was designed to solve is that direct contact between the omeprazole core and the enteric coating results in discolouration and the eventual degradation of the core. However, the patent goes on to

> teach that this storage stability problem can be solved by adding sufficient alkaline reacting constituents to the core. A subcoating is only needed to prevent the premature dissolution in the stomach of the enteric coating of tablets with an alkaline core. That problem only occurs when the tablet is ingested and thus claim 1 does not preclude the core and the enteric coating from coming into contact during the manufacturing process so long as a subcoating exists in the final product.
>
> [24] I conclude that patent claim 1 describes a pharmaceutical preparation which, in its finished product form, contains a subcoating or separating layer between the core and enteric coating, however the subcoating or separating layer is formed.

[174] This decision was subsequently applied by Justice Carolyn Layden-Stevenson in NOC proceedings in *AB Hassle v Genpharm*, 2003 FC 1443, [2003] FCJ no 1910, and, later, in *AB Hassle v Apotex,* 2005 FC 234, 2005] 4 FCR 229.

[175] I accept Apotex's point that a decision by the Federal Court of Appeal in a NOC proceeding is provisional only, and it does not bind me. On the other hand, in a case like this where the construction issues are not to be resolved on the strength of much, if any, specialized knowledge, the unanimous views of the Federal Court of Appeal carry some persuasive weight.

[176] Apotex argues that more recent Supreme Court of Canada jurisprudence recognizes the increased importance of the disclosure in the purposive construction of claims language. At the time of Justice Rothstein's decision, resort to the disclosure was, as he noted in paragraph 16, more limited. The difficulty with this point is that, notwithstanding Justice Rothstein's observation that resort to the disclosure was not justified, he went on to address Apotex's disclosure-based arguments and rejected them all.

[177] Additional support for this construction holding can be found in the decision of the United States District Court in *Astra Aktiebolag v Andrx Pharmaceuticals Inc*, 222 F Supp 2d 423 at pp 46-47 and upheld in the Court of Appeal for the Federal Circuit, 84 Fed Appx 76. In second wave litigation involving Apotex, the construction decisions were maintained: see *In re Omeprazole* Patent Litigation 490 F Supp 2d 381 upheld at 536 F 3d 1361.

[178] If I had any material reservation about the correctness of this prior jurisprudence, I would not hesitate to differ. In my view, however, the Apotex position is not persuasive.

[179] Although AstraZeneca undoubtedly did not contemplate the *in situ* method of creating a subcoat when it applied for patent protection, that is not a point which detracts from its claim to a novel product. The fact that, in places, the 693 Patent disclosure refers to the "coating process" or like terms in the discussion of the omeprazole formulation does not thereby incorporate a process limitation into Claim 1. Indeed, this speaks to the danger of relying too heavily on the disclosure as an interpretive guide to claims language. Having regard to the requirement of enablement, one could well expect some blending of product and process language in the disclosure narrative. Such general references may not be helpful as interpretive guides to claims language. It is in the claims where the use of precise and consistent language is important and expected. If Claim 1 of the Patent is limited to subcoats physically applied to the cores, the question arises as to why the words "disposed on" were used. Those words can refer to spacial arrangements or to the relative position of things and are not limited to the means of their placement. The objective reader would understand the purposive use of a general term to define the product would be insufficient to import a process limitation. Indeed, the person of skill

would be hard-pressed to understand what purpose is served by limiting the scope of a product claim to any particular process of manufacture.

[180] Dr. Kibbe testified that the term "disposed on" was not a term of scientific art[1]. Under cross-examination, he acknowledged the word "applied" would have been a more obvious way of expressing a process limitation of this sort [p 4776]. I would add, even though the Apotex sublayer presumably forms from a chemical reaction, it does so in the course of applying the enteric coat to the core. In this sense it is a product that immediately results, perhaps unexpectedly, from a process.

[181] The only references in the 693 Patent to "disposed on" are in Claim 1 and in the matching language found at page 5 of the disclosure. In all other passages in the disclosure different language is used. For instance at page 5 the process for making the formulation speaks to "coating a core region". At page 6 there are references to "the coating process" and to "[t]he separating layers(s) can be applied to the cores". At page 7 "another method to apply the coating" is described. If Claim 1 was limited to subcoatings formed by direct application, one would expect to find an appropriate distinguishing verb and not the more generic term "disposed on". Furthermore, assuming that the verb "to coat" originates from the noun "coat" there is no interpretive rule of which I am aware that would equate their meanings in common use.

[182] The fact that neither the notional person of skill nor the actual inventors would have had an *in situ* subcoat in mind or, indeed, any other means by which a subcoat could be formed does

[1] This was also Dr. Bodmeier's view. He took these words to refer to location and not to the means of application [p 1672-1673].

not help to define the scope of Claim 1. There may well be a number of methods available to produce the essential elements of a novel formulation that have not been identified or contemplated by the inventors. All that is required is the disclosure of one viable method of manufacture.

[183] In the case of the 693 Patent the inventors disclosed processes for making the claimed formulation. They did not disclose the process for making an *in situ* subcoating. I am not favourably disposed to the suggestion that a product claim ought to be interpreted to exclude a process that the Patent never mentions and, at the same time, to limit the claim to the processes that are disclosed. The patentee is entitled to protect the product regardless of the means of its creation.

[184] Dr. Kibbe was asked by Apotex to comment on the ability of the skilled person to understand how to avoid infringing Claim 1. The underlying premise of the question was that a patentee is required to communicate to the world what is being fenced-in and, conversely, what may be practised safely. Not surprisingly Dr. Kibbe obliged by concluding that the 693 Patent claims fail to teach the person of skill how to avoid a subcoating which forms *in situ* as a reaction product. Dr. Kibbe's proposition is effectively a variation on Apotex's construction argument that the 693 Patent does not include subcoats which form *in situ*.

[185] I reject the notion that AstraZeneca had an obligation to teach its competitors how to avoid an infringement. A patentee has no obligation to inform the world of all the processes

which may give rise to an infringing product. AstraZeneca described its formulation and explained how to make it. It was up to others to avoid an infringement.

[186] According to Apotex, the 693 Patent taught away from the very method that Apotex employed. If Apotex was relying on that teaching, it ought to have been surprised to see that its product actually worked. If, as Dr. Kibbe testified, the person of skill would expect a possible reaction between the Apotex cores and a conventional enteric coating, Apotex could have looked to see what, if anything, had formed between those layers – just as Dr. Davies did.

[187] I accept Apotex's point that a skilled reader of the 693 Patent would understand that there was found to be a problem associated with a formulation where a conventional enteric coat rested on an omeprazole core. I do not agree, however, that such a reader would thereby exclude the possibility that a separating subcoat formed *in situ* could never be a viable solution to the recognized gastric acid resistance and storage stability problems associated with omeprazole formulations. The Patent speaks generally to "a demand for the development of new enteric preparations of omeprazole with better stability" [p 3, line 5] and to effecting a separation of the core from the enteric coating [p 4, lines 34-36]. How the separating layer is obtained is not a subject addressed by Claim 1. In my view, the general admonition in the Patent disclosure to separate the enteric coating and the cores would not be seen as an impediment to a subcoat formed by a transitory *in situ* reaction during pellet manufacture. Once the subcoat is formed it represents the barrier that is said to be part of the invention and the problem of ongoing incompatibility is avoided. On this point, I accept Dr. Bodmeier's evidence at paragraph 48 of

his initial report that the advantage of the invention lies in its finished doseage form structure and not by how one gets there.

[188] The authorities relied upon by Apotex on this issue have no application. *Rhoxalpharm Inc v Novartis*, above, concerned an *in situ* reaction which occurred after the completed formulation was ingested by the patient. This is a far different situation than this one where the *in situ* reaction is said to occur during the manufacture of the product.

[189] *Miken Composites, LLC v Wilson Sporting Goods Co*, above, concerned the claim term "insert". The patent claim described the structural improvement to a baseball bat as an "insert". The alleged infringing product achieved the same advantage by composite layering. In upholding the trial decision the Court held that the layering approach did not involve the use of an insert. The Court was influenced by the consistent use of the term in the disclosure and in the claims and found it meant "something inserted or intended for insertion". This unambiguous language did not "impermissibly import a process limitation into [the] product claim". In this case the words "disposed on" do not carry a clear and particular meaning. If Claim 1 had used a limited verb such as "applied", "coated" or "sprayed", Apotex's argument would likely have prevailed.

D. What is the Meaning of the Term Inert?

[190] Claim 1 stipulates that the subcoating must be "inert". The question, of course, is what the skilled formulator would make of that word in attempting to follow the teaching of the Patent.

[191] According to Dr. Kibbe: “Inert is inert. Inert by definition, means it doesn’t react with the components. Even if the reaction is limited in nature, it is still a reaction, and that means it is no longer inert. And that is – the simplest way of looking at it is, we are trying to put something there that will do nothing to affect either side [the enteric coat or the core] except to keep them separate from each other” [p 4779].

[192] Although it is apparent that Dr. Kibbe understood “inert” to be limited to the potential for the subcoating to react with other formulation constituents, he was adamant that there was no permissible reaction margin whatever the functional consequences might be [pp 4784-4787].

[193] Dr. Bodmeier adopted a more flexible view. He stated that “inert” meant only that the subcoating will not interfere with the function of the enteric coating or the stability of omeprazole in the core [p 1773]. Dr. Bodmeier further stated that the skilled formulator knows that “some minor level of reaction is expected in any formulation”. According to this view “inert” is a relative and not an absolute term. Dr. Bodmeier found support for this view in the disclosure where potentially acidic subcoating materials are identified as acceptable. The person of skill would also know that the presence of an ARC in the core would neutralize acidic reactions particularly within the subcoating layer which, according to the Patent, acts as a pH buffering zone. According to Dr. Bodmeier, the Patent reference to “non-acidic, otherwise inert” would be read by the person of skill to permit some level of acidity provided that the efficacy of the formulation was not compromised.

[194] The evidence shows that all compounds will react and degrade in their particular environments in their own time. That is precisely why pharmaceutical products have a stipulated storage life. In the context of a pharmaceutical compound the term “inert” cannot be purposively construed in an absolute sense. No person of skill would consider an inert subcoat to be completely unreactive within its environment. The word “inert” in Claim 1 would be read to be limited to reactions that adversely affect the functionality of the formulation. The Patent teaches the person of skill to avoid a subcoat material that will compromise the enteric coat or the omeprazole core. A purposive construction does not preclude any and all reactive potential between the subcoat and the other formulation constituents however trivial or functionally inconsequential it may be. Indeed, the person of skill knows without being told to avoid ingredients that could cause unwanted reactions. In reading the Patent the skilled formulator is thinking about what will work and would not dismiss a promising coating material simply because it is not perfectly or absolutely inert in a strict scientific sense.

[195] I therefore reject Dr. Kibbe’s view of this word and instead adopt Dr. Bodmeier’s more nuanced interpretation.

E. *What are the Essential Structural Features of the Claimed Subcoat?*

[196] Apart from stating that the desired subcoating should be a polymeric film former and achieve a minimum thickness of two microns, the Patent offers no other guidance about its structural characteristics or integrity.

[197] Apotex asserts that the claimed subcoating must be continuous and free of pinholes or gaps that would permit any direct contact between the enteric coating and the omeprazole cores. AstraZeneca says that minor breaks or defects in the subcoating would be expected and that substantial continuity of the subcoating is all that is required, provided that the formulation works.

[198] Dr. Kibbe did acknowledge that the continuity of the subcoating was related to its protective function [p 4474]. According to Dr. Kibbe, in the presence of through holes or gaps, the subcoating would simply not work. This evidence was somewhat tempered in Dr. Kibbe's testimony under cross-examination. There he conceded that "everything we do in formulation has a certain amount of variability" [p 4633] and some discontinuities "are not necessarily functional discontinuities" [p 4670]. He also observed that most polymorphic films are hydrophilic and attract water [p 4704].; as they absorb water they thicken into a gel [p 4705]. This process slows the passage of more water and allows for an "acid based neutralization to occur long before it gets to the bottom of the enteric coat" [p 4713]. This would also probably close any small gaps or holes that were present in the dry state [p 4744].

[199] It seems to me that the person of skill would view the presence of small gaps or holes in a polymorphic subcoating with these considerations in mind. If they did not compromise the formulation, they would not present a practical concern.

[200] I do not agree with Apotex that the person of skill would expect the subcoating to be structurally perfect. Even the best processes of manufacture will give rise to some anomalies and

imperfections. The person of skill is looking for a formulation that sufficiently separates the enteric coating and the cores so as to achieve acceptable storage stability and gastric acid resistance. Defects that do not compromise the efficacy of the product would be tolerated. If perfection was the standard to be achieved, a party could easily avoid an infringement by creating a poor but still effective copy.

[201] The person of skill knows that the sublayer must have sufficient physical integrity to constitute an effective barrier between the enteric coating and the pellet cores. The disclosure informs the person of skill that a minimum subcoat thickness of 2 microns is required to fully obtain the promised advantage. The fact that Claim 1 does not include this information does not mean that the person of skill is oblivious to the disclosure advice. The same is true of the stated need to minimize water content and of the implicit need to employ a subcoat that provides substantially continuous coverage of the cores. A skilled formulator would understand that a subcoating that manifestly fails to meet these requirements simply would not work.

[202] All of this is not to say that minor lapses or deviations from these disclosure teachings would be sufficient to take a formulation outside of the scope of Claim 1. The person of skill understands that processes of manufacture allow for some variation in the finished product. As to the requirement for a minimum subcoat thickness, the person of skill would interpret Claim 1 with some allowance for variability and not as an absolute threshold that would render the product useless for its intended purpose. Claim 1 encompasses a subcoating that is substantially continuous in coverage with a thickness that is sufficient to achieve its intended purpose.

[203] For what it is worth, I do not accept Dr. Bodmeier's evidence that the thickness advice provided by the disclosure means an "average" thickness of 2 microns. Dr. Bodmeier expresses the opinion that the person of skill would essentially read out of the Patent the words "not less than" in reference to the expected thickness of the subcoating and substitute for it an "average" thickness of 2 microns [p 1457].

[204] I do not understand Dr. Bodmeier's interpretation. If the intention was to state an average thickness, one would expect to see that language. "[N]ot less than" is an absolute and invariable expression. Furthermore, in terms of achieving efficacy, an average thickness is meaningless to the formulator. The fact that the person of skill would expect to see some variation in the uniformity or continuity of the subcoating does not exclude the advice that a minimum thickness is desired. Indeed, in the context of an applied subcoating where the process can be well-controlled, the idea of a minimum effective thickness is hardly surprising.

[205] I do agree with Dr. Bodmeier that the numerical convention of rounding does apply to a value that is expressed without a decimal point. That evidence was not challenged by the Apotex witnesses. In the result, I accept that the person of skill would interpret the reference to 2 microns to include the value of 1.5 microns but, in any event, I do not agree that the Patent claims incorporate a thickness limitation beyond the expectation that the sublayer needs to be sufficiently robust that it constitutes an effective barrier.

[206] Apotex also contends that Claim 1 would be construed as though it includes no limitation for water content. It draws this interpretation from the explicit limitation in Claim 13 to a

formulation with a water content of less than 1.5%. According to Apotex, the person of skill would take from Claim 13 that Claim 1 was unlimited as to water content. If it were otherwise, Claim 13 is rendered redundant.

[207] I do not agree with this suggested approach to the construction of Claim 1 and its dependant claims. The claims are to be read in conformity with what the person of skill knows or is otherwise taught by the Patent. The person of skill knows that water content can be a problem for maintaining the stability of omeprazole (and many other compounds) and would employ techniques to deal with it. The person of skill is also aware that, while some variations in water content can be tolerated or managed, there is a point of saturation where the formulation will fail: see Bodmeier Infringement Report at para 83. According to Dr. Bodmeier, the level of acceptable water content will vary according to the constituents of the formulation, and in the context of the teaching of the 693 Patent, the person of skill would not assume an "absolute number" [p 1747]. The subject claims should not be read as though the person of skill would ignore the clear teaching of Patent favouring, instead, a highly technical rule of interpretation.

[208] On this issue, I accept Dr. Bodmeier's evidence at pp 1550-1551:

> A. Yes. So the water content and the minimum thickness, they are important, and I think I mentioned this already yesterday. Like the 693 Patent that allow water content is important and also talks about a certain minimum thickness, but it's my opinion that this is not part of the inventive concept which is this oral pharmaceutical formulation.
>
> And I think if we first talk about the water content, I think that a skilled person knows that water content has to be low, I think that's mentioned in the patent at several occasions. There are also numbers given, but a skilled person would not see these numbers as a limit of the claim, he would know that a low water content is important, but that will depend on the formulations. There are

> some formulations, they can take a little bit more water and others less. That depends on the excipients, also depend on the packaging, on a variety of factors.
>
> And the same with regard to minimum thickness. I think the patent clearly states that there is a minimum thickness, we had the argument yesterday -- or I had the argument with the experts of Apotex that I see there is an average minimum thickness, that there is a clear statement in the patent that the minimum thickness, what I see as an average minimum thickness, is not less than 2 micrometre.
>
> Q. And so --
>
> A. But I don't see these two parameters as an essential concept of the invention.

In my view, Claim 1 and its dependant claims do not incorporate a water content limitation.

[209] Apotex asserts that the terms “subcoating” and “separating layer” mean the same thing. It draws this interpretation from a passage at page 6 of the description stating that “[t]he subcoating layer, in the following defined as the separating layer, also serves as a PH buffering zone…” This position is helpful to Apotex because the Patent also discusses the use of gelatine capsules as a means of separating the enteric coating from the pellet cores.

[210] AstraZeneca maintains that a gelatine capsule can perform a separating function but it does not, by definition, constitute a subcoating as that term is used in Claim 1.

[211] The Patent language on this issue is certainly not free from difficulty. I agree with Dr. Bodmeier that in normal parlance a gelatine capsule is a type of container and not a sublayer

disposed on a pellet core and that, while a subcoating is included within the more general term "separating layer", the reverse was not intended.

[212] At page 7, gelatine capsules are said to "serve as [a] separating layer". This latter phrase suggests to me that, by "serving as" a separating layer, gelatine capsules are not to be construed as separating layers *per se*. At page 5b gelatine capsules "are used as cores for further processing". This language suggests that the inventors did not consider gelatine capsules to be subcoatings as that term is used in Claim 1. In a number of the succeeding claims, the subcoating is described but not with reference to a gelatine capsule. Accordingly, I do not accept that the reference to a subcoating in Claim 1 includes the use of gelatine capsules. In my view, the Patent contemplates the use of gelatine capsules as part of the core region providing a separating function but not acting as an inert subcoating within the meaning of Claim 1.

IV. Validity

A. Anticipation

[213] In *Free Word Trust v Electro Santé Inc*, 2000 SCC 66, [2000] 2 SCR 1024 at para 26, the Court applied Hugessen's J.A.'s classic statement of the disclosure element for anticipation by prior publication from *Beloit Canada Ltd. v Valmet OY*:

> The test for anticipation is difficult to meet:
>
> > One must, in effect, be able to look at a prior, single publication and find in it all the information which, for practical purposes, is needed to produce the claimed invention without the exercise of any inventive skill. The prior publication must contain so clear a direction that a skilled person reading and

> following it would in every case and without possibility of error be led to the claimed invention.
>
> (*Beloit Canada Ltd. v. Valmet OY* (1986), 8 CPR (3d) 289 (FCA), per Hugessen JA, at p. 297)

[214] The above statement continues to be the legal standard on this issue (see *Bell Helicopter v Eurocopter*, 2013 FCA 219 at paras 109-110, [2013] FCJ no 1043).

[215] A useful summary of the requirements for proving anticipation can be found in *Abbott Laboratories v Canada*, 2008 FC 1359, [2009] 4 FCR 401 aff'd 2009 FCA 94, [2009] FCJ no 345 where Justice Roger Hughes said:

> [75] To summarise the legal requirements for anticipation as they apply to the circumstances of this case:
>
> 1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.
>
> 2. The disclosure does not have to be an "exact description" of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.
>
> 3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.
>
> 4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.
>
> 5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the

> claimed use is the same as the previously disclosed and enabled use, then there is anticipation.
>
> 6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.
>
> 7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.

[216] The burden of proof on this issue rests with Apotex on a balance of probabilities.

[217] Apotex asserts that Claim 1 of the 693 Patent is anticipated by Hässle's European Patent Application 124,495 [EP 495] published on November 7, 1984. The anticipatory passage in EP 495 is said to be the following:

> Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules are preferably enteric coated as described above. Hard gelatine capsules may contain enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier e.g. lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine; the hard gelatine capsules are preferably enteric coated as described above. [Footnote omitted]

[218] Dr. Kibbe maintained that the above example includes all of the structural features of Claim 1. His evidence at p 4788 was as follows:

> Q. Okay. And whether it's Example 12 or the general discussion of the 495, or any discussion about an enteric coated gelatin capsule in the 495, none of those discussions would disclose to the skilled reader whether such a formulation would, in fact, have the three functional properties that we have been talking about? That's pretty clear; isn't it?

A. I am sorry, the 495 says that the alkaline salt of omeprazole is more stable. And the alkaline salt of omeprazole is one of the components of the core that is described in the 693 as a way of improving the stability. Okay. So that is in the game, as it were.

And then the composition

Q. Let's look at the 495, your D 8.

MR. RADOMSKI: Sorry, sorry, Dr. Kibbe was in mid sentence.

BY MR. GAIKIS:

Q. Go ahead.

A. That's okay.

And the composition that is described in the patent as an example composition, and it contains the magnesium salt of omeprazole and an enteric coat, and it doesn't include a separating layer, but the if I could check my own little notes to myself okay, so, therefore, the 495 has both a compound which is considered to be a more stable form of omeprazole according to the 693 Patent, and it has an enteric coat.

And according to the 493 (sic), enteric coatings may be applied to granules, tablets or gelatin capsules, hard or soft, okay, which means that the 495 is telling you, you could take the alkaline salt of omeprazole, put it in a capsule and enterically coat it.

And if that's the case, then we could look at the 693 which says that that would be one of the uses or one of the ways of making the product in that patent, and that's in the detailed description of the patent where it says specifically on page 7, line 11:

"In case of gelatin capsules, the gelatin capsule itself serves as a separating layer, and then it has a core and an enteric coat."[as read]

So it seems like the 495 has each of the three elements of the 693.

Q. Structural elements?

A. Yes.

[219] The simple and complete answer to this evidence is that, as discussed above, the term "subcoating" found in Claim 1 does not include a gelatine capsule and, therefore, EP 495 does not anticipate that essential feature of the 693 Patent. On this point I much prefer the evidence of Dr. Bodmeier to that of Dr. Kibbe.

[220] It is true that EP 495 discloses, among other approaches, an enterically coated alkaline salt formulation of omeprazole and the means of making of it. It does not, however, disclose the use of a subcoating to overcome the stability/gastric acid resistance problem addressed by the 693 Patent. Indeed, Example 12 discloses an enteric coated tablet containing an alkaline omeprazole salt and it fails to identify a problem.

[221] There is no evidence that the application of an enteric coating to an omeprazole core containing an ARC will inevitably lead to the formation of an *in situ* subcoating layer. There may well be effective combinations of such compounds where an infringing subcoating layer does not form. In the absence of evidence that, by practising the teaching of EP 495, a subcoating layer will be the inevitable result, I do not accept Apotex's argument that the 693 Patent teaches only an inherent characteristic of what was already disclosed in the EP 495. EP 495 does not anticipate.

B. Obviousness

[222] The principles that apply to obviousness are well-known. The party asserting the defence - in this case, Apotex - has the burden of proof on a balance of probabilities.

[223] In *Novartis Pharmaceuticals Canada Inc v Cobalt Pharmaceuticals Co*, 2013 FC 985, 440 FTR 1 (Eng.), Justice Hughes described the concept in the following way:

> [60] One of the most difficult issues faced by a Court in patent litigation is that of obviousness. The Court must address the alleged invention through the eyes of a person skilled in the art and ask whether it is deserving of patent protection; that is, whether it is either inventive or obvious.
>
> [61] The rationale has been put well by Professor Carl Moy of William Mitchell College of Law, author of *Moy's Walker on Patents*, Thomson/West, in addressing a Master of Law Class at Osgood Hall Law School. He said that a patent is a bargain between the public and the patentee which provides a monopoly to a person (patentee) in respect of certain scientific subject matter, provided that it is purchased from the public by disclosing something that is new, useful and inventive. If it is not new, then the monopoly has been purchased for nothing and cannot be valid. If it is something that that the public would get anyway from a person of ordinary skill practicing their craft, then nothing has been paid for the monopoly and the monopoly cannot be valid.
>
> [62] The concepts of inventiveness or obviousness are elusive, which has caused the Courts to endeavour to articulate tests and criteria to be examined and assessed against the evidence. The current state of such tests in Canada is that set out by the Supreme Court of Canada in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61, [2008] 3 SCR 265 ("Plavix"), per Rothstein J, for the Court, at paragraphs 67 and 69 to 70:
>
> > *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, [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.

…

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.*

[224] It is clear from the authorities that the mere possibility of finding an invention is not enough to establish obviousness. The invention must be self-evident from the prior art and the common general knowledge of the person of skill. The fact that known methods were used by an inventor to obtain the desired result is not a determinative consideration. What always remains is the question of how likely was it that the discovery would emerge from the application of those methods. This involves an assessment of whether the distance between the common general knowledge and the inventive concept could be bridged by routine experimentation. This, in turn, can be informed by the inventors' course of conduct in getting to the discovery – the so-called invention story: see *Sanofi Aventis v Apotex Inc*, 2013 FCA 186 at paras 73-74, 81, 137.

[225] The parties agree that the person of skill is someone with a university degree in natural sciences and practical experience in the development of pharmaceutical doseage forms – in other words, a skilled pharmaceutical formulator.

[226] It is in its post-trial Brief Apotex succinctly and fairly set out its position on obviousness in the following paragraphs:

> 18. At bar, the parties agree that the inventive concept of the claims is a formulation of omeprazole containing an alkaline core, an inert subcoating and an enteric coating which provides good long-term storage stability and gastric acid resistance.

> 19. It follows that the central issue to be decided in the obviousness inquiry is whether inventiveness was required to obtain such a formulation.
>
> 20. Apotex submits that no inventive ingenuity was required: the solution provided by the 693 Patent is little more than a straightforward solution to an easily recognizable formulation problem.
>
> - No more than routine work would be required to achieve the claimed invention.
>
> 21. A significant amount of evidence was devoted to the issue of obviousness at trial. Nevertheless, the issue turns on two, straightforward, matters.
>
> - What was known about omeprazole and its formulations as of April 30, 1986 — the priority date of the 693 Patent?;
>
> - Would a person skilled in the art have arrived at the solution taught by the 693 Patent without the exercise of inventive ingenuity? [Footnotes omitted]

[227] The above arguments rest primarily on the evidence of Dr. Kibbe.

[228] Dr. Kibbe recognized the tension that existed between the competing properties of acceptable gastric acid resistance and long-term storage stability. His evidence on this point can be found on pages 4351-4353 of the trial transcript where he discussed the problem described by the inventors in the 693 Patent:

> A. I am going to do two things simultaneously.
>
> Q. Okay, I am going to let you do what you need to do.
>
> A. Okay. We are talking about the two comparative examples, okay. And basically what they have done is they have made tablets without an intermediate layer, and they have looked at what goes on with those tablets, and they have noticed that when the levels of alkaline material is sufficient to prevent colour

change, which would be what is Roman numeral 3, then the coating, the enteric coating, begins to fail and it allows a large amount of material to escape during the two hour test in the acid media. If they add sufficient amount of - - or insufficient amount of alkaline material, the core changes colour to brown, but the enteric coat is relatively stable.

And the amount of material, I think, is in a, if I remember correctly, is in a wonderful table, and it goes from - - there we are.

Q. What page?

A. If you go to page 22 of the patent itself, these three examples are laid out. Okay.

And the key here is that the only difference between these three examples is that 1 and 2, have two grams of alkaline material and 8 grams of alkaline material respectively, and Number 3 has 24.

Q. You are talking about the disodium hydrogen phosphate?

A. Yes, I am. I apologize. Disodium hydrogen phosphate is an alkalizing material.

And so what they show here is that 24 grams is sufficient to prevent discolouration, but it causes a deleterious effect to the enteric coat, causing the enteric coat to release 42 per cent of the drug during the two hour stress test.

However, if you give lower amounts of alkaline material, 2 grams and 8 grams, then the core is not stable but the coat is stable. And so the issue is in front of them, how do I do both things? And the answer is, in all of their examples and in their patent, is the intermediate subcoat or separating layer.

Q. Okay. And I think that's what you say in your paragraph 81?

A. In fact, I even quote them from page 4.

Q. Right.

So then in paragraph, if we can skip to paragraph, I guess, 86, you talk about Examples, I guess, 2 to 10?

> A. Right.
>
> Q. And Comparative Examples 1 to 5, Roman numeral 1 to 5, and you draw from that as to what the skilled person would understand, and I am going to ask you to explain what you say at the end of paragraph 86.
>
> A. Okay. It's really quite clear from all the examples that whenever they wanted to make a stable product, they applied an intermediate coat of an inert polymeric material to separate the core with an alkaline material from the coat, which is the enteric coat. And whenever they omitted that, then they made the comparative examples, okay. And that means they are making examples to compare to what they are suggesting is the examples within the patent.
>
> And in every one of those cases, they failed one way or the other, they either discoloured or they released prematurely.

[229] Dr. Kibbe's opinion is that the incompatibility problem faced by AstraZeneca was to be expected and its solution was routine and non-inventive. His initial report described the problem facing the person of skill in the following way:

> 217. In my opinion, there is no inventive difference between the state of the art at April 30, 1986 and the inventive concept of claim 1 of the '693 Patent, as described above. Further, since there is nothing inventive in the additional elements of claims 5, 6, 11 to 13, 18 and 19 of the '693 Patent, it follows that there is no inventive difference between the state of the art and the inventive concept of those claims.
>
> 218. Given the known sensitivity of omeprazole to acid, as for example set out in Pilbrant (Exhibit "D-13") and the '495 Application (Exhibit "D-8"), the skilled person would have appreciated that omeprazole could not be administered as such, because it would not survive the low pH environment of the stomach. For an oral solid dosage form — a dosage form which would be strongly preferred — the use of an enteric coating was required.
>
> 219. From the '495 Application, it was known that alkaline salts are more storage stable. The skilled person would have realized that the same stabilizing effect in the presence of moisture could be

> achieved by admixing omeprazole and an alkaline reacting compound, *e.g.*, a base. The skilled person would have known that stability of the API is one of the most important parameters in pharmaceutical formulation development and would have been motivated to prepare oral solid dosage forms containing an alkaline salt of omeprazole or omeprazole and an alkaline material.
>
> 220. From standard texts, the skilled person would have known that enteric coatings are intended to dissolve in an alkaline environment, and that these coatings have exposed acidic functional groups which ionize above a certain pH. The skilled person would have anticipated a potential incompatibility between such polymers and an acid sensitive API like omeprazole in the presence of water (there would be no concern if the oral dosage form could be kept perfectly dry, a condition which cannot practically be achieved). The potential for such a problem would have been confirmed by the technical bulletins (Exhibits "D-25", "D-26", "D-27"), Dechesne (Exhibit "D-21") and the '764 Application (Exhibit "D-22").
>
> 221. The skilled person would thus have tested for incompatibilities between omeprazole or a salt thereof and candidate excipients, including enteric coating materials, as part of routine preformulation work. The incompatibility between omeprazole or a salt thereof and enteric coating compounds would have been identified.
>
> 222. While a number of different approaches to solving API-excipient incompatibilities were known at April 30, 1986, for the reasons that follow, the skilled person would not have pursued solutions other than the use of a barrier coat or layer between the alkaline API-containing core and the acidic enteric coat.

[230] In my view neither the problem faced by AstraZeneca nor its solution were as simple as Dr. Kibbe suggests. His approach to the prior art was also highly selective and, in the result, his obviousness opinions were effectively rendered in hindsight with the 693 Patent solution in mind.

[231] I have particular concerns about the approach Dr. Kibbe took to his assessment of the prior art. He did no independent prior art search and, instead, relied upon a set of documents produced by Apotex [p 4505]. An expert who carries out an obviousness analysis largely or solely on the strength of prior art references selected by retaining counsel runs a real risk of offering a hindsight opinion. A thorough prior art review necessarily includes a search for all of the available relevant literature whether it supports inventiveness or not. It requires consideration of relevant art in the larger context of other possible pathways to the patent solution or to ideas that point away from that solution.

[232] Dr. Kibbe's selective review is confirmed in the following exchange in cross-examination:

> Q. So let me put it to you this way: You looked at the 693 Patent; you made an assessment of what is the invention that's claimed --
>
> A. Right.
>
> Q. -- and then you went to the references that Apotex gave to you, and you looked for those elements of the invention claimed?
>
> A. Well, obviously, I did a background piece, and then I laid out what the claims meant and what have you, and then I said, "Would this have been obvious a person of ordinary skill in the art"? And I believed that it would, and then we looked to see if there was corroborating evidence in the literature. [Emphasis added]

[233] Dr. Kibbe also read too much into the prior art. In particular, he initially read the Pilbrant reference to teach the person of skill that the acid lability of omeprazole would be similar in aqueous and solid-state formulations. Under cross-examination, he conceded that Pilbrant

provided no solid state stability data [p 4547] and that the instability of an API in solution does not necessarily apply to solid state formulations [p 4513]. The limited value of Pilbrant to the person of skill looking for a solid state formulation for omeprazole was effectively acknowledged by Dr. Kibbe in the following exchange:

> Q. But insofar as Pilbrant applied an enteric coating to omeprazole, then the enteric coating would not be considered the acidic substances or amongst the acidic substances referred to on page 113, right-hand column, of the language that you were referring to; is that correct?
>
> A. I think that's a little bit of a stretch. He was talking about mostly acidic, the studies he did, the acidic materials that he exposed it to. I don't think he spoke directly to the acidic nature of enteric coats.
>
> Q. No, no, but I didn't say that.
>
> Wouldn't it be fair that a person reading this, realizing that Pilbrant applied an enteric coating to a core containing omeprazole, no reference to an ARC, and he said the stability for his purposes was fine, wouldn't that person conclude that there shouldn't be a problem applying an enteric coating to a core containing omeprazole? Isn't that fair?
>
> A. I think that a formulator with Pilbrant in their hand, that might be their first experiment, but then if they found a problem, they would go back and try to correct it. And the correction would clearly be to make the core more alkaline. And if that, then, create a second problem, they would go back and correct it, and the correction for that would be to put intermediate layer.
>
> And so if we start with Pilbrant and ignore everything else we know, then we would go through a set of experiments and arrive at the same place I think the 693 arrived at.
>
> Q. Last question on Pilbrant, at least for now. You agree that Pilbrant does not teach a problem applying an enteric coating to a core containing omeprazole?
>
> A. It does not teach that the enteric coat they used created a problem. [Emphasis added]

This particular passage generally corroborates Dr. Bodmeier's evidence that once the stability problem is identified a cascade of choices and experimentation is required to find a solution.

[234] In other testimony Dr. Kibbe accepted that there were numerous acid sensitive API formulations on the market that successfully employed the direct application of enteric coatings [p 4518]. This, too, would suggest to the person of skill that a conventional enteric coated formulation would be the place to begin in attempting to formulate omeprazole.

[235] The uncertainty faced by the person of skill is further reflected in Dr. Kibbe's evidence at p 4527:

> Q. In fact, it is the role of enteric coatings to protect acid sensitive drugs from the stomach; isn't that the case?
>
> A. Yes. Or protect the stomach from irritating drugs.
>
> My point is that, even if you could, in the past, coat an acid sensitive material with an enteric coat without a subcoat, then it's the degree of acid sensitivity that <u>might lead you to question</u> whether that would be successful and if I would have to do something else to stabilize that compound, because it was extremely sensitive to acid.
>
> Q. So you say it might lead you to do something else?
>
> A. <u>It might</u>. Everything you do is a function of how to get a commercially viable formulation prepared that would be stable and deliver the drug appropriately, <u>and you test as you go</u>. [Emphasis added]

[236] What the above evidence acknowledges is that the person of skill would not have anticipated the formulation problem that AstraZeneca ultimately faced and overcame. Indeed, the person of skill would have thought that an enteric coating of a simple omeprazole core might

be sufficient for a successful formulation. What Dr. Kibbe is left with is the assertion that the subsequently encountered problems of poor gastric acid resistance and storage stability could be overcome by the person of skill through the routine and singular steps of adding an ARC, introducing an intermediate layer and testing for efficacy.

[237] Dr. Kibbe's selective approach is further borne out by what he failed to address in his obviousness opinions but ultimately acknowledged in cross-examination.

[238] Dr. Kibbe acknowledged that the presence of discolouration in an omeprazole formulation would be interpreted by the person of skill only as "something happened, and it could be an excipient changing colour" [p 4535]. In other words, no assumption about the degradation of omeprazole would be justified without a further assay of the formulation. The person of skill "would want to figure out what was discolouring and how to prevent it" [p 4535]. At page 4530, he also said:

> Q. And do you agree that a formulator, in April 1986, seeking to formulate omeprazole would have been aware of numerous possible causes of discolouration if they, in fact, saw discolouration as part of such a formulation exercise?
>
> A. Okay. Formulations can discolour either due to changes in the active ingredient or the excipients. And so you would be cognizant that colour meant change, but you wouldn't know exactly what had changed.

This is relevant to the obviousness issue because the inventors' recognition that a problem exists can be considered to be relevant to inventiveness just as well as its solution: see *Bayer AG v Novopharm Ltd*, 2006 FC 379 at para 44, 289 FTR 263.

[239] Similarly, as Dr. Kibbe acknowledged, in the presence of a gastric acid resistance problem, the person of skill would look at "a limited number of things" [p 4536] including the choices for an enteric coating and plasticizer [pp 4536-4537], the prevailing process conditions [p 4537] and possible alterations to the core [p 4539]. Dr. Kibbe conceded he had failed to identify all of these issues in his reports [p 4539].

[240] Although adding an ARC to the core was a potential answer to the storage stability problem faced by AstraZeneca, I accept Dr. Bodmeier's evidence that the usual instinct of a formulator is to minimize the use of excipients. According to this view, adding excipients creates more room for unexpected and undesired reactions within the formulation [see p 1527]. This, in fact, is precisely what happened when an ARC was added to AstraZeneca's omeprazole formulation. That combination presented an unexpected gastric acid resistance problem when the ARC in combination with gastric juice diffusing through the enteric coating created sufficient alkalinity to degrade the enteric coating from the inside. Dr. Bodmeier then fairly described the choices facing the person of skill in the following testimony:

> A. Yes. So, again, let's say the scientist observes this gastric resistance problem and then he has to think about how to solve it, he doesn't have the solution of the 693 Patent in front of him just waiting for it to be used. There is a multitude of solutions which he can think about, and they are described in 240.
>
> So the skilled person would likely first search in the enteric film coating itself for the reasons for the insufficient gastric resistance, because you have insufficient gastric resistance, you can say, okay, must be something wrong with my enteric polymer, so systematically investigating formulation and processing parameters.
>
> So insufficient gastric resistance can be caused by insufficient thickness of the coating or uneven coating. So one could just, for example, make a -- try to solve it with a thicker coating.

Then you could, for example, try other enteric polymers, you know. We have worked with different enteric polymers and sometimes you use this one, sometimes you use the other ones. So there is a choice in polymer.

You could choose, for example, plasticizers, different amounts, different choices, they add a little bit of flexibility to the polymer, may change the properties of the polymer.

Then process parameters, including temperature spray, pressure spray rate, air thru put drying. So sometimes when you have, for example, poor processing conditions, it could happen that you get a very porous film and then the acid goes through and you fail your gastric resistance test.

So the structure of the film is important, we have seen that many times, that the processing conditions, even if you coat with the same polymer, can result in films with completely different properties.

And then the remaining solvent is also a point, residual solvent in the coating can affect the performance and that is why you also have certain minimum levels required for the residual solvent. Primarily not actually because of toxicity reasons, because the solvents which are often used, like ethanol, they are not that toxic, but because the solvent can affect the performance of the coating negatively.

Porosity of the coating, I mentioned already. That depends how you spray. You can make a porous film, so you have some holes in it, the medium can go through. Or you can make a more denser film, that's also a question of processing conditions. For example, if you spray faster, you have wetter, it's overall wetter, you get a denser film compared to when you spray drier, you get a more porous film. And also the choice of solvent.

So it's not just like I say, 'okay, let's put the subcoating there, I have the solution'. This is with hindsight, I can only mention this and repeat myself, a formulator, when he sees a problem, first he needs to know the cause and they already went through it, he may not know that it's an interaction between the omeprazole and the enteric polymer, or between the alkaline reacting agent and the enteric polymer. So he has a multitude of possibilities to find a solution.

[241] I also accept Dr. Bodmeier's testimony at pages 1523-1530 where he described the cascade of issues and potential solutions that the person of skill would face in attempting to overcome the gastric acid resistance/storage stability incompatibility problem (i.e. enhancing alkalinity in the core to improve stability degraded the viability of the enteric coat and led to unacceptable gastric acid resistance). There, too, the usual first option for the person of skill would be to attempt to eliminate the conflict by substitution and not by adding things. This evidence seems to me to be a far more objective assessment of the prior art than the simplified and categorical views expressed by Dr. Kibbe.

[242] Dr. Bodmeier was taken in cross-examination to numerous prior art references that discuss the use of subcoats and alkaline compounds to resolve a variety of pharmaceutical formulation problems. While acknowledging that adding subcoatings and ARCs were known techniques to resolve, among other problems, incompatibility and stability issues, he effectively distinguished these references as being largely unhelpful to the person of skill looking for an effective formulation specific to omeprazole.

[243] I accept Dr. Bodmeier's evidence that the person of skill starts the process of formulating omeprazole with reference to Pilbrant and believes that a conventional enteric coating may suffice. There is no beginning expectation that storage stability will be a problem because not all acid sensitive molecules will degrade in the presence of an acidic enteric coat. When discolouration became evident, the person of skill must first determine its cause. When the person of skill identifies the cause of the stability problem, he would not turn immediately to the addition of an ARC. I agree with Dr. Bodmeier that the skilled formulator would not

immediately add another excipient but would be more inclined to look for a compatible substitute for the offending enteric coating material. Adding more excipients can create another set of issues just as it did when AstraZeneca added an ARC to its omeprazole cores to improve the storage stability of its formulation. The ARC then became the source of gastric acid resistance problem that required its own solution. Adding an appropriate subcoat was one potential solution to the gastric acid resistance problem but it was not the only option available to the person of skill[2]. The general idea of separating reactive materials in pharmaceutical formulations was known to skilled formulators but there was no expectation that any particular subcoat material in combination with any particular amount of an ARC would achieve the desired balance of storage stability and good gastric acid resistance. I also accept Dr. Bodmeier's evidence that the selection of a water soluble subcoat was a non- obvious choice as protective barrier for the reasons he gave.

[244] Omeprazole turned out to be a particularly difficult API to formulate. Not all of its idiosyncrasies were known in the prior art and AstraZeneca did not know from the outset the difficulties it was facing or the means by which they could be overcome. The person of skill is certainly aware of enteric coats, ARCs and subcoats in various formulation applications but would not be drawn immediately and without difficulty to combine those elements into the particularized arrangement described in the 693 Patent as a means to solve the several formulation issues presented by omeprazole. If the solution was as simple as applying a conventional enteric coating, nothing inventive would have taken place. But the solution obtained here was multifaceted. It required AstraZeneca to finely balance the incompatibility

[2] Dr. Bodmeier did not rule out the possible use of a subcoat and candidly testified "I don't exclude subcoats as an option". In contrast, Dr. Kibbe testified that a subcoat was the only viable option.

between alkalinity necessary for acceptable storage stability and the preservation of the enteric coating necessary for good gastric acid resistance. In my view the process required to obtain the solution was neither routine nor obvious.

[245] Dr. Bodmeier's evidence also conforms very closely with the history of the invention.

[246] Dr. Kurt Lovgren testified on behalf of AstraZeneca. He was one of the six inventors named in the 693 Patent. The others were Mitsuru Yasumura, Satoshi Morigaki, Minoru Oda and Naohiro Ohishi, all of Japan and Dr. Ake Pilbrant from AstraZeneca in Sweden.

[247] Dr. Lovgren holds a PhD in pharmaceutical sciences. He began employment with Hässle in 1974 as an organic chemist in the chemistry department. At that point, he was involved in making new compounds. He described Hässle at that time as "a minor pharmaceutical company" focussing on cardiovascular and gastrointestinal research.

[248] Dr. Lovgren and Dr. Pilbrant were leaders of the research teams that were principally involved in the search for an effective omeprazole formulation at AstraZeneca. The role of the Japanese inventors was limited to the work described in Example 1 of the 693 Patent.

[249] Dr. Lovgren identified the assignment of the inventors' interest in the 693 Patent to Hässle executed by all of the inventors in the early part of 1987 [see Exhibit 85, Tab 2] and confirmed the financial consideration that he received in return.

[250] When Dr. Lovgren joined Hässle, it was already looking at synthesizing benzimidazoles as promising compounds in the treatment of peptic ulcers. One of its early candidates was timoprazole. Ultimately timoprazole was dropped because of toxicity concerns. In 1976 picoprazole was identified and studied. This was followed in 1979 by the synthesization of omeprazole. Because omeprazole was found to be more potent than picoprazole, it became Hässle's lead compound. At that point Dr. Lovgren was working in Hässle's pharmacy department as a research scientist focussing on the development of solid doseage forms. In that capacity, he was directly involved in the research and development of solid doseage forms for picoprazole and omeprazole. That work included the making of cores and coatings suitable for further research including bioavailability and clinical studies.

[251] In 1982, Dr. Lovgren became an Assistant Manager in Hässle's pharmacy department with responsibilities for hands-on experimentation and the supervision of others engaged in formulation research.

[252] Dr. Lovgren testified that over the course of his work with omeprazole formulations, he conducted or supervised hundreds of experiments. The goal of this work was to develop a doseage form which could be conveniently administered to human patients in all phases of Hässle's clinical trials.

[253] Dr. Lovgren described omeprazole as a particularly difficult molecule to formulate. It has very low solubility and is very acid and moisture sensitive. For Phase I clinical trials, it was necessary to administer omeprazole in a suspension. For Phase II clinical trials, the goal was to

develop a solid doseage form. The formulation used in Phase II trials included an ARC in the cores and an enteric coating. It did not incorporate a subcoating layer. Dr. Lovgren testified that the formulation used in Phase II trials proved to be inconsistent in terms of gastric acid resistance.

[254] Hässle's first attempts to overcome the gastric acid resistance problem were directed at the enteric coating. It was thickened and different polymers, plasticizers and hydrophobic materials were tried. Dr. Lovgren described these efforts in the following way:

> We also decided to mix different enteric coating polymers to see if that -- they -- the mixture behaved better. We used -- in an enteric coating, normally you can have, or normally you have a plasticizer, and we did different attempts with that plasticizer, different types and concentrations. ,
>
> We used hydrophobic material. The idea there is that hydrophobic material is normally water repellant, so, by including hydrophobic material, we thought that that could resist permeation of water or gastric juice in the stomach and, therefore, maybe leading to better results. So we included hydrophobic material into the enteric coating.
>
> We made a layer of hydrophobic material on top of the enteric coat, and we used laminate, thinking that we should have more than one layer. As I said earlier, one could be a hydrophobic layer, but it could also be two different layers of enteric coating.
>
> And we also did experiments around the core, surface of the core, tried to have smoother surface. We tried to have thinking about what sort of ingredients you should use in the core.
>
> [p 2138]

[255] The initial adjustments to the enteric coating described by Dr. Lovgren were mainly directed at making it less permeable. Adjustments to the core involved substitutions and

quantitative variations to the ARC. It was only after these attempts failed that a water soluble subcoating layer was introduced. This approach led to the formulation used in Phase III clinical trials and described in Claim 1 of the 693 Patent.

[256] Dr. Lovgren was taken through Hässle's research records detailing the work that went into the development of a stable and gastric acid resistant omeprazole formulation between 1980 and 1986. Those records are primarily contained in Exhibit 85 and they corroborate Dr. Lovgren's evidence about the amount of effort that went into the development of the patented formulation. A representative example confirming the work undertaken can be found at Exhibit 85, Tab 13 where testing was carried out with varying amounts of enteric coating and with additives. Dr. Lovgren described the work as follows:

> What is going on there?
>
> A. Yes, it's attempt now to also coat granules, and the note saying that the best film from 2 should be added to the omeprazole granules with varying buffer. So it's, stepwise, that we are evaluating a different amounts of enteric-coating polymers on the same granules under 2, and then we are spraying one selected coating onto the granules that I should prepare for different amounts of alkaline material.
>
> [p 2200]
>
> …
>
> Q. Okay, page 3 at the top, there is a reference to "Christina" and some tests. And I see there is a reference to L 100; would that be the Eudragit that you mentioned earlier?
>
> A. That is an enteric-coating polymer, Eudragit, with a brand number 100, yes.
>
> Q. Okay, so it looks like she is mixing it with different, like 10 per cent ethyl cellulose, et cetera, she is mixing the enteric coating with other ingredients?

A. Correct.

Q. And what is ethyl cellulose?

A. Ethyl cellulose is an insoluble polymer. So the idea here was to see could we obtain a tighter enteric coat by adding 10 per cent of an insoluble material like ethyl cellulose.

As well as we used different plasticizers, you'll see next line, Citroflex, DB phthalate, two different plasticizers, and we even made a mixture of ethyl cellulose and racemic oil as hydrophobic material into the film to see how that impacted the film properties.

[p 2201]

[257] A problem with enhancing the impermiability of the enteric coating is noted at Exhibit 85, Tab 14. In discussing this reference, Dr. Lovgren noted that a drawback with a tighter enteric coating is that it may inhibit dissolution at the desired point of release.

[258] Dr. Lovgren summed up the situation as of the end of November 1980 in the following way:

Q. Okay. So this memo we just looked at was the end of November 1980. Can I ask you, by the end of 1980, where did things stand in terms of the development work on an oral solid dosage form of omeprazole?

A. I think as is reflected in these minutes, in these results we have seen for these experiments, that we were far away from being close to a proper functioning dosage form that behaved, had properties that was acceptable for any sort of further clinical testing of efficacy and effect and even stability concerns. So we had a lot of work to do still from this point, from this time point, end of 1980.

[p 2230]

[259] In early 1981, Hässle began to look at subcoats. Exhibit 85, Tab 22 is a work protocol comparing a subcoated formulation with an un-subcoated formulation. Dr. Lovgren testified that this was the first record of a subcoating experiment [p 2246].

[260] A summary of Hässle's work as of May 27, 1981 can be found in Exhibit 85, Tab 30. According to Dr. Lovgren, this confirmed Hässle was then still looking at a variety of formulation approaches including a laminated enteric coating.

[261] A meeting Minute from June 25, 2981 [Exhibit 85, Tab 32] notes the project was then 6 months behind schedule due to the previous lack of substance and difficulties with doseage forms.

[262] Minutes of a meeting on September 14, 1981 indicate that a Phase II formulation had been selected subject to bioavailability studies. Dr. Lovgren also noted that long term storage stability was still an unresolved issue with respect to finding a commercially viable formulation [p 2282].

[263] According to Dr. Lovgren, the Phase II formulation lacked the necessary stability for Phase III studies and for commercial use [p 2295]. When he was asked what was then understood about the source of the gastric acid resistance problem, he gave the following evidence:

> Q. Did you have an understanding at that time as to what caused inadequate gastric acid resistance in the Phase II formulations, at least by Hassle's standard, at that point in time?

A. I think we had an understanding after all these investigations, so for up to this, say, end of 1981, where we are right now in the development, that we had permeation of gastric juice, and being acidic water, and we had some ideas that that penetration could eventually coming through the enteric coating and starting to dissolve alkaline material being present in the core, and maybe, during that way, started to dissolve the enteric coating from the inside, and maybe then have some impact on the total quality. If it was started to be eating up from the inside, then even more could, during the test, penetrate. And so that was discussed, and we had some idea about that.

Q. Were you ever able to confirm that idea in terms of that mechanism that you described?

A. I think I will say yes to that.

[p 2296]

[264] The Minutes of a meting held on December 10, 1981 described the status of Hässle's search for a formulation in the follow way:

4. The development of granules continues according to the following guidelines:

- Buffer quantity adjusted for maximum stability and minimum degradation during passage through the stomach.

- Formulation of spherical granules will be studied with regard to excipients and technical properties. The influence of granule size on technical properties, such as the coating process will be studied.

- The possibility to obtain a more diffusion tight (i.e. less permeable) film is to be further examined.

- The possibility of using a subcoat will be studied.

5. Process parameters, among others regarding milling is to be studied.

6. Questions of stability to be further studied. The importance of buffering for stability in solid phase to be clarified.

When Dr. Lovgren was asked about the status of Hässle's testing at this point with particular reference to the use of a subcoating, he gave the following answer:

> Q. Okay. Just back, I guess, to point 4 and the reference to the possibility of using a subcoat there with reference to the granules. So did you ultimately try a subcoating there?
>
> A. Yes, we did. I think we addressed all of these points that are mentioned in paragraph 4, and I think we should consider this to be efforts to obtain better gastric acid resistance when we are talking about more diffusion tight films, and we are talking about use of a subcoat.
>
> Q. What kind of a subcoating did you try after this point in time?
>
> A. Yes. We tried a water soluble subcoat.
>
> Q. Did you have, before trying the water soluble subcoat, did you have any expectation as to whether it would work or not?
>
> A. No. I think the expectation was not that optimistic that a water soluble substance or a water soluble coat should do anything dramatic in relation to gastric acid resistance.
>
> Q. Why did you that view?
>
> A. We, I think if we had a problem which we thought we had and which we understood we had, that it was diffusion of acidic water through the enteric coating, then how could water a soluble substance lead to any dramatic differences when we already had experience to making that enteric coating, for instance, thicker in itself? And that wasn't the solution to the problem. Then we were not optimistic that a water soluble substance should have any effect in leading to a better acid resistance, for instance.
>
> Q. Why not try a water insoluble subcoat?
>
> A. Yes. I agree that that should have been much more logical. However, we had already done experiments in these lines by using hydrophobic or water insoluble material in relation to the enteric coating experiments.
>
> Q. And is that -- do you have any examples of that in terms of what we have looked at so far?

> A. Yes. We have already seen how we are discussing using hydrophobic material, being the water repellent. We have seen examples of including stearyl alcohol. We have seen examples of including ethyl cellulose, being a water insoluble polymer, so we had experience of that. The experience there we had was that, yes, we saw positive effects; we saw increased gastric acid resistance. However, we entered into a new problem, and that was the dissolution rate.
>
> Q. And what was the problem with dissolution rate?
>
> A. The problem was that, by making the enteric coating tighter, less permeable by water repellant or hydrophobic or water insoluble material, that led to consequences that, when we then exposed these cores, coated cores, to buffer solutions in which we wanted a fast dissolution rate of omeprazole, we got very low figures.
>
> [pp 2299-2301]

[265] Comparative testing of subcoated and non-subcoated formulations is reported in February and March 1982. Those tests showed that subcoating improved the gastric acid resistance of the formulation. Some of the test results are exemplified in the 693 Patent and are found at Tabs 44, 46 and 49 of Exhibit 85.

[266] A meeting Minute dated September 17, 1982 indicates that the search for a Phase III formulation had been narrowed to two choices, one of which was preferred. A small pilot study was proposed before a choice would be made. By the end of 1982, the essential structural elements of the patented formulation appear to have been identified subject to some additional testing carried out over a period of years [see Dr. Lovgren evidence at pp 2339-2340 and Tabs 55, 59 and 60 of Exhibit 85].

[267] Dr. Lovgren concluded his evidence in chief by confirming that Example 2 of the 693 Patent is the formulation that is marketed by AstraZeneca.

[268] In cross-examination Dr. Lovgren was extensively questioned about the importance of minimizing water content in the patented formulation. Dr. Lovgren acknowledged that this was an important process parameter but an absolute maximum value for water was not required for a viable formulation.

[269] A report authored by Dr. Lovgren and dated January 14, 1986 outlined the work done to develop an omeprazole formulation for all phases of Hässle's clinical studies. That report discussed the modifications to the Phase II formulation leading to the formulation used in Phase III studies in the following passage:

> During the enteric-coating process the phase II formulation is discoloured due to the direct contact between the alkaline reacting pellet core and the free carboxyl groups of hydroxyl-propyl methylcellulose phthalate. The discolouration is avoided in the formulation used in phase III clinical studies.
>
> 4.3 Omeprazole enteric-coated pellets used in phase III clinical studies
>
> In order to achieve better technical properties a modified pellet core formulation was developed and used in phase III studies. A better product stability was also obtained by using mannitol as filler agent. The introduction of a separating layer of hydroxypropyl methylcellulose between the core and the enteric-coating improves the discolouration and stability during storage. [Exhibit 94]

[270] Although Dr. Lovgren acknowledged that he had not found any earlier explicit record reflecting a discolouration/gastric acid resistance concern, he did reference earlier Phase II test

data where the gastric acid resistance data was inconsistent and, in some instances, fell below Hässle's required standard [p 2709, p 2710, pp 2712-2714]. He also relied on the Minutes of research meetings where the problem and approaches to overcoming it were discussed.

[271] Dr. Lovgren was not effectively impeached under cross-examination. I accept his evidence describing the efforts that went into the development of the formulation described in Claim 1 of the 693 Patent. What this evidence discloses is that, while the incorporation of an ARC was an early feature of Hässle's work with omeprazole, the idea of using a subcoating came much later in the development process and not before a number of other options were explored and rejected. The subcoat idea first appears in the research record in February 1981 but it did not become a focal point for study until late that year. I accept as accurate Dr. Lovgren's evidence that the intervening references to a subcoat had to do with attempts to smooth out the surface of the cores and not as a means of effecting a separation between the enteric coat and the pellet cores.

[272] I am satisfied the work that went into the development of the patented formulation was complex and time-consuming. It was decidedly not routine bench-work. The research team at Hässle struggled to overcome the formulation problems it encountered and explored a number of options before it found an omeprazole formulation that was viable for Phase III clinical studies and, ultimately, for commercial exploitation.

[273] Based on the foregoing, I find that the discovery claimed by the 693 Patent was inventive and, therefore, non-obvious.

V. Overbreadth, Inutility and Ambiguity

[274] Apotex argues that there are a number of ways a stable and gastric acid resistant omeprazole formulation can be made that do not involve a subcoating. Because AstraZeneca concedes the person of skill would not know without further testing whether a formulation with the structural features of Claim 1 would actually work, Apotex says that Claim 1 is overbroad and ambiguous. This argument is put in the following way:

> 8. Apotex submits that AstraZeneca's suggestion that the claims embrace any formulation with the generalized structure provided they ate gastric resistant and storage stable is a classic example of overbroad claiming.
>
> - In effect, AstraZeneca defines *any* subcoating which generates a storage stable and gastric resistant product to be a subcoating within the meaning of the claims.
>
> - A subcoating made up of highly reactive products is nevertheless deemed inert, because the resulting formulation is storage stable and gastric resistance.
>
> - A subcoating made up of acidic products is nevertheless deemed non-acidic, because the resulting formulation is storage stable and gastric resistance.
>
> - A subcoating that is 0 μm thick in certain places (i.e. has gaps) is deemed to have a minimum thickness of 2 μm, for the same reason.
>
> - The approach, as explained by Dr. Kibbe, is scientifically unintelligible:
>
> Whether a product has a subcoating cannot be determined by considering the stability of the formulation - there are many other ways apart from subcoatings that these types of formulations can be made stable. In my

> view, whether a product has a subcoating is determined by the presence of a subcoating as described in the claims... (e.g., inert, soluble or rapidly disintegrating in water). I see no basis to change that definition to encompass a different set of attributes - *i.e.* the stability and acid resistance of the final product.
>
> - The approach, as explained by Justice Snider, is also legally flawed.
>
> - In *Schering-Plough Canada v. Pharmascience*, the Court considered a claim to an "anhydrous pharmaceutical composition". The applicant, Schering-Plough, contended that any compound that was stable was properly defined as anhydrous. In rejecting the viability of this construction, the Court held:
>
> This, in my view, is a blatant example of overbroad claiming. The requirement of stability is analogous to growing hair on bald men. . . one cannot stretch Claim 16 to cover everything that is stable.
>
> - There is no basis for this Court to take a different approach in the case at bar. [Footnotes omitted]

Essentially the same argument is advanced in support of the plea of ambiguity. Apotex complains no one could, with any measure of accuracy, determine the boundaries of Claim 1.

[275] I have no doubt there are ways to make a useful omeprazole formulation that would not involve a subcoat and, in the United States litigation, this proved to be the case for some defendants. Indeed, Dr. Sherman looked for ways to work around the 693 Patent and thought he had succeeded.

[276] One fundamental problem with Apotex's overbreadth argument is that the 693 Patent does not claim formulations with "highly reactive products" or with no limitations concerning the physical characteristics of the required subcoating. The person of skill brings to the workbench considerable background knowledge and experience. The requirement that the subcoating be "inert" directs the person of skill away from highly reactive constituents. The person of skill also knows water and heat are undesirable and seeks to minimize or control them. The person of skill knows a subcoating replete with fissures, gaps or other continuity deficiencies is unlikely to work and, therefore, avoids them.

[277] A patent claim is not overbroad because it leaves it to the person of skill to avoid known unsuitable choices: *Burton Parsons v Hewlitt Packard Ltd*, [1976] 1 SCR 555 at pp 565-566, 1 NR 553. It is also not invalid because it is not a model of concision and lucidity. It is to be read by the notional person of skill who brings practical knowledge and experience to the exercise: see *Letourneau v Clearbrook Iron Works Ltd*, (2005), 44 CPR (4^{th}) 345 at para 37, [2005] ACF no 1589.

[278] In my view, the 693 Patent imparts useful and sufficient information to the person of skill to craft an omeprazole formulation that would be expected to solve the incompatibility problem the inventors encountered. That some routine stability and gastric acid resistance testing would still be required to know whether a formulation with the structural features of Claim 1 actually worked as expected does not mean the claim is overbroad or unclear.

[279] Furthermore, the 693 Patent does not contain a promise that every omeprazole formulation with the structural features of Claim 1 will fulfill the dual objective of good storage stability and gastric acid resistance. Instead, it teaches the person of skill that by following its instructions and by applying common general knowledge a useful formulation will be the expected - not the inevitable – result. With routine testing and some adjustments, if necessary, the person of skill is able to obtain a useful formulation.

[280] Even Dr. Kibbe seems to have conceded this point at least for the purpose of comparing the teaching of EP 495 to that of the 693 Patent:

> A. In order for a formulation to fall within Claim 1, it has to have the elements within Claim 1.
>
> Q. Just the structural elements, not the functional elements?
>
> A. Well, Claim 1 doesn't describe any functional elements. That all comes from the background and the intent of the benefit of the invention. But we can assume that a product made using the information from the 495 would be as successful as a product made using the three elements in Claim 1, but we would, of course, test it.
>
> Q. Okay. Obviously Claim 1 says what it says, but I had assumed, reading your report, that you had come to the opinion that the disclosure portion of the 693 would tell the skilled reader that the whole purpose of this exercise was to come up with a gastric resistant and storage stable product that would dissolve in the small intestine, that that was, that that was the invention here, and that those elements, then, are understood to be part of the dosage form that is claimed to be the invention.
>
> A. The elements of the Claim 1 are clearly present in the description of the 495. The intent of Claim 1 is to have a viable product. But there is no guarantee that just having those essential elements will make every product you make a viable product. And so the product described in the 495 would be expected to work but would have to be tested. And the examples in the 693 which had the three elements that the patent eventually

> patented were expected to work, but they were tested. And in some cases, the products without one element or another didn't work as well. [Emphasis added]

[281] The difficulty facing a patentee in a case like this is to draft the claims in a way that will afford a reasonable level of protection. If the claims are drafted too narrowly, they are easily avoided and if they are drafted too broadly, they are vulnerable to validity attack. If AstraZeneca had claimed a very specific structural formulation, a competitor could easily design a work-around. At the same time, AstraZeneca had to provide sufficient information for others to work the invention at the close of the patent monopoly. The formulation claimed in the 693 Patent achieves the appropriate balance in the sense that it affords protection for a useful discovery without sacrificing the enablement requirement. The fact that the person of skill needs to apply some basic knowledge or routine testing to work the invention is not fatal to the claims as drafted because the essential framework of the invention is provided. I made the same point in *Delp v Fresh Headies Internet Sales Ltd*, 2011 FC 1228 at paras 13 to 19:

> [13] The Defendants' contention that the patent contains a promise of utility at all temperature points within the stated range of 0°C to 15°C is, therefore, incorrect. The promise of the patent is that it will work for different plants at different temperatures and that the person skilled in the art will be quite capable of optimally working the invention through some routine trial and error.
>
> [14] The fact that some adjustments may be required by a person skilled in the art to work an invention does not render a patent void for inutility. I am reinforced in this view by the Supreme Court of Canada decision in *Burton Parsons Chemicals Inc v Hewlett-Packard (Canada) Ltd*, [1976] 1 SCR 555, 54 DLR (3d) 711 and by the House of Lords decision in *Henriksen v Tallon Limited*, (1965) RPC 434 HL (Eng).
>
> [15] *Burton Parsons* concerned a patent for the invention of a conductive cream useful in facilitating electrocardiograms. The argument advanced there for inutility was similar to the one advanced in this case: that the patent claims were broader than the

effective scope of the invention. The Court did acknowledge the basic point that where the scope of a claim includes some method which is useless, the claim cannot be saved by showing that no skilled person would ever try that method. Nevertheless, the Court found that a patent does not fail simply because it leaves some room to the person skilled in the art to employ suitable methods or materials.

[16] I do not read *Burton Parsons*, above, as narrowly as counsel for the Defendants urged. It did not turn solely on the language of the impugned claim which included a reference to the product being compatible with normal skin. The Court went further than that as can be seen from the following passages:

> This is the distinguishing feature from the other cases in which the properties of xanthates in froth flotation and those of some substituted diamines as antihistamines were the object of the invention. The inutility of cellulose xanthate in Minerals separation as well as that of some isomers of tripelennamine in Rhône-Poulenc was not known to the prior art. This is totally unlike the undesirable properties of some highly ionizable salts which Hewlett-Packard listed as objectionable. Their noxious character was well known and no man skilled in the art would have thought of using them in making a cream for use with skin contact electrodes any more than any such worker would have needed to be told that in making such a cream, he had to use such proportions of liquid and of emulsified material as to obtain a suitable consistency.
>
> Such applications of the art of a skilled person is to be put on the same footing as the addition of a pharmaceutically acceptable carrier to a drug when this is required for its proper administration. In Commissioner of Patents v. Farbwerke Hoechst A.G. [[1964] S.C.R. 49], this Court held that this last step in the production of a drug in dosage form was not patentable because there is no invention involved in it. In my view, the avoidance of unsuitable salts due to their known noxious properties is similarly nothing but the application of the proper knowledge to be expected from a man skilled in the art. In Sandoz Patents Ltd. v. Gilcross Ltd. [(1973), 8 C.P.R. (2d) 210], we had

> no hesitation in upholding claims for "therapeutically tolerable salts" of thioridazine to be obtained by reacting "with a therapeutically acceptable acid". I cannot think that the omission of the qualification "therapeutically acceptable" would have voided the patent and I will note that in the Rhône-Poulenc case this question was left open.

[17] To similar effect is the House of Lords decision in *Henriksen*, above. There the Court emphasized the point that a patent need only describe the invention in a way that will permit the skilled reader to work it. Beyond that, the patentee "is entitled within fairly wide limits to leave it to the addressee to choose appropriate material from a class which he specifies if he makes it plain that the choice is left to the addressee." [see p 441]. This point is made again in the following passages from the decision:

> I can now return to what I have called the crucial question. Claim 1 applies to jumbo as well as to capillary tubes. One must approach its construction with the knowledge of the skilled man that a liquid can form a satisfactory plug in a capillary tube but that no liquid can do so in a jumbo tube. There a paste-like mass is required. If the patentee has asserted or represented that even for a jumbo tube a liquid can be used (if the right one is chosen) then, the claim is invalid and it is not saved by the fact that the skilled man knows that that is untrue. But if he has merely asserted that the addressee must choose a suitable liquid or viscous or paste-like mass as the case may be according to the kind of tube he wants to make then the objections of inutility and false representation disappear. Applying the ordinary methods of construction I have no doubt that the latter is the true meaning.
>
> It is a general principle of construction that, where there is a choice between two meanings, one should if possible reject that meaning which leads to an absurd result. One must construe this claim with the knowledge that the skilled addressee would know that it would be absurd to claim that any kind of liquid plug could be effective in a jumbo tube. That factor, added to those to which I have already referred, tips the scale conclusively in favour of the latter meaning. I have therefore no doubt that claim 1 is valid.

[per Lord Reid at p 443]

…

The claim must be fairly and reasonably construed and words must be given a natural and not a strained meaning. As a matter of construction it may well be that the words in claim 1 give rise when they are read to a moment of hesitation. In the words "a liquid or a viscous or paste-like mass" does the word "or" denote that each one of several kinds of plugs may in each and every one of several kinds of pens be used, or does it denote that a process of rational selection is involved? When construing the specification it is reasonable to pay regard to the fact that the claim is addressed to persons skilled in the art. How, then, would the skilled pen-maker understand claim 1? He would, I consider, understand it as giving him an answer to the problem of preventing that deterioration of ink which contact with the air will cause. He and he alone would know what variety of ball tip fountain pen he proposed to produce: he and he alone would know what size and type of reservoir he intended to use: he and he alone would know what kind of ink he proposed to use (which might be in a fluid or pasty condition). If he were following the direction contained in claim 1 and wished to have a plug for the purpose of keeping the air from the ink he would choose that form of plug (within the range of a liquid or viscous or paste-like mass) which would be appropriate for his pen. He would know that (within the range of a liquid or viscous or paste-like mass) he must choose so that (a) his plug will not mix with his ink and (b) so that his plug must move with the surface of the ink column and (c) so that his plug will prevent air from contacting the surface of the ink. He would not consider that any and every kind of viscous or paste-like mass would do for any and every kind of pen or for any and every kind of ink. He would not consider that a liquid plug would do for any and every pen and for any and every size of reservoir. He would not consider that the inventor was so claiming. He would understand that in following claim 1 he would be directed to choose such form of plug (within the range of a liquid or viscous or paste-like mass) as

> would be appropriate for the pen he was producing having the kind and size of tubular ink reservoir that he was adopting and with the kind of ink that he was using. A pen maker skilled in the art could by trial and error and without the exercise of any inventive faculty readily discover for himself the particular type of plug that suited his particular type of pen (compare *No-Fume Ltd. v. Pitchford* (1935) 52 R.P.C. 231).
>
> [per Lord Morris at pp 446-447]

> [18] In this case, the 815 Patent claims an invention over a new method for extracting resin from different plant species by using an ice-water bath. I have no doubt that the skilled person would be capable of working the invention by the described method without adding any inventive ingenuity to the exercise and, indeed, the patent expressly contemplates the application of some practical skill depending on the nature of the plant material being utilized.
>
> [19] Counsel for the Defendants submitted that the 815 Patent could have been saved by omitting any temperature range from the claims and by substituting a reference to "water at a suitable temperature". However, that is what the drafter did by the device of leaving it to the skilled person to find a suitable operational temperature. Such a person would not assume from the patent language that the claimed method would work optimally, or necessarily at all, with any beginning temperature in the stipulated range. [Emphasis in original]

[282] If, as I have found, the promise of the patent is a formulation meeting the essential structural elements of Claim 1 that would be expected to provide good gastric acid resistance and long-term storage stability, the utility of the invention has been demonstrated. This point was effectively acknowledged by Dr. Kibbe in the following exchange:

> A. Right. If they made something that was identical to one of the examples, then they would be very confident that when they tested it, it would work in their hands. Then if they wanted to use different excipients, let's just say they wanted to use mannitol instead of lactose, that probably would work. It fits the general requirement of the active ingredient plus an ARC or an enteric coat and an intermediate coat. But they certainly would test it.

Q. Right, so in a sense, the patent, it shows the reader the way; that, you know, these are the elements, this is my concern, I got to have an ARC, the reader knows about solubilities, et cetera, and so the reader can assimilate that information and apply it to make other formulations that the reader would have a reasonable expectation would work?

A. Right.

Q. But they'd have to test to make sure?

A. Well, we always test.

Q. Okay.

A. I mean, you -- well, you just can't go on faith.

Q. And then, I guess there is some more of the same in paragraph 89, looking at this about six lines down, you are talking about Examples 2 to 8, and six lines down, you say:

"I note that there is no indication in the patent disclosure as to whether any of Examples 2 to 8 were tested for all three characteristics."[as read]

And then you set those out in parenthesis, and then you say:

"But given the similarities between the preparations, the skilled person would understand that each preparation would have the properties that the patent promises for them."[as read]

So that's the same notion, that there is a teaching, and the skilled person would understand that it should work, but they would always have to test.

A. Right. And the point would be, like, for instance, Example 5, it has 93 per cent acid resistance but there is no appearance. Well, I would have to check, you know, you go back and look; right? And that's the same with this missing data, you would go back and test that study that wasn't done.

Q. Right, but you are saying that based on the information in the patent, the skilled reader would have an understanding that even though test results for all three things were not included for every example, as you put it, given the similarities between the preparations, the skilled person would understand that each preparation would have the properties promised.

A. They would -- the skilled person --

Q. They would expect?

A. -- they would expect it. [Emphasis added]

[283] I am accordingly satisfied that the promised utility of the 693 Patent has been demonstrated.

VI. Infringement

[284] What remains for determination is whether Apo-Omeprazole infringes Claim 1 of the 693 Patent and its dependant claims and, in particular, whether that product incorporates an inert subcoating that is soluble or rapidly disintegrating in water disposed on the core comprising one or more layers of polymeric film forming compounds.

A. Criticisms of Dr. Davies' Testing Methods

[285] The Apotex experts went to considerable length to attack Dr. Davies' methods and his scientific integrity with the intent of casting doubt on his findings. Virtually all of their methodological criticisms fell well short of the mark.

[286] Dr. Amos was specifically retained by Apotex to review Dr. Davies' CLSM methods and to comment on the reliability of Dr. Davies' opinions concerning those images. Dr. Amos was also asked to consider the CLSM images obtained at Temple University. Dr. Amos carried out no independent imaging of the Apotex omeprazole pellets.

[287] Dr. Amos is an exacting scientist with very high methodological standards. He is particularly knowledgeable about the use of CLSM technology having been intimately involved in its development between 1983 and 1986 and he is a recognized expert in the field. Nevertheless, he has had virtually no experience using CLSM technology to analyze pharmaceutical doseage forms. This substantially weakened his evidence insofar as he was attempting to interpret the relevant images.

[288] Although I accept that Dr. Amos is extremely bright and intimately aware of the intricacies of CLSM theory and practices, he was a less reliable witness when he was making assumptions – particularly with reference to Dr. Davies' opinions and motivations. The overall impression left by Dr. Amos was that his concerns about Dr. Davies' methods unduly coloured his assessment of the data that Dr. Davies obtained. In my view those data had considerably more scientific value than Dr. Amos was prepared to credit to them.

[289] Many of Dr. Amos' criticisms of Dr. Davies' opinions relate to deviations from his own preferred methods. He expressed concern about the quality of Dr. Davies' images and was of the view that better evidence could have been obtained had better practices been followed. In some cases Dr. Amos made unwarranted assumptions about what Dr. Davies had actually done and he assumed the worst.

[290] For example, Dr. Amos was sharply critical of Dr. Davies for failing to explicitly state in his initial report that some of the CLSM images he had used were maximum intensity images

that could visually misrepresent the underlying data. Similar concerns were expressed by Dr. Bright.

[291] The problem with the use of maximum intensity images is one of potential bias. These images are effectively composites because they draw three dimensional data from below the surface of the sample and project all of the data onto a two-dimensional image. To the uninformed viewer this can magnify or intensify the resulting fluorescence and may suggest it is all emanating from the surface of the sample. Dr. Amos testified that by not appropriately advising the reader, Dr. Davies was attempting to pass off his projections as raw data:

> Q. The absence of any depth information, wouldn't that have been an indication to a skilled microscopist, such as yourself, that it was some sort of projection?
>
> A. No. Because other images were individual Z scans, and the mere omission of information from a title in a report was not clear enough an indication that this was manipulated data rather than raw data. And the difference between the maximum brightness projection and raw data is so significant in a scientific report that it should be explicitly stated in the legend to the figure. It's not something that should be left for somebody to infer from the absence of figures. It's really I am trying to keep this to the facts, but let's just say that somebody looking at the report of Dr. Davies could be deceived by this, because there is not a clear enough indication that what is being shown is manipulated data using a dangerous and inappropriate method of projection and that that is not raw data. That is the uncharitable view would be that he was passing it off as raw data.
>
> Q. You weren't deceived?
>
> A. Well, I was, I was at first a little confused, but I worked it out in the end. I certainly was not able to work out that it was a maximum brightness projection until I saw Dr. Davies doing the same manipulation and showing that it generated this remarkably, apparently continuous fluorescent layer.
>
> MR. HACKETT: This is not an objection. I just think Dr. Amos misspoke when he said he saw Dr. Davies doing it.

THE WITNESS: Sorry, Dr. Bright. [pp 3090-3091]

[292] The above evidence was, in fact, an excessively pejorative view of Dr. Davies' approach and it was not untoward for Dr. Davies to characterize the criticism as "scurrilous". Dr. Davies gave extensive evidence in the proceeding in the United States involving Apotex and clearly acknowledged his use of maximum intensity imaging. Those acknowledgements were well-known to Apotex and they were also contained in the evidentiary record that Dr. Davies included with his reports in this proceeding. With a careful examination of Dr. Davies' data, Dr. Bright was able to discern that some of the images were maximum intensity projections. The problem identified by Dr. Amos, such as it was, was more the making of Apotex than of Dr. Davies. The information was known to Apotex and therefore available to its experts. It was, accordingly, unwarranted for Dr. Amos and Dr. Bright to suggest Dr. Davies was attempting to pass off maximum intensity images as something else.

[293] Dr. Amos, Dr. Griffiths and Dr. Bright all went out of their way to identify issues with Dr. Davies' testing methods or to challenge his results whether or not there was evidence to support their purported concerns.

[294] No reasonable reading of Dr. Davies' report would attribute to him a belief that the Apotex omeprazole pellets and, in particular, the sublayer, were totally opaque. Nevertheless, Dr. Amos and Dr. Bright made that assumption and then went to considerable effort to prove Dr. Davies was mistaken. Dr. Amos' attribution of a mistake to Dr. Davies is even more surprising in the face of his concession under cross-examination that "opaque" is not a precise scientific term [p 3092] and that it can be used in a relative sense [p 3093, p 3096]. He also

accepted that a substance shown to emit fluorescence at depth (as Dr. Davies had shown) cannot be considered totally opaque [p 3101]. Notwithstanding that evidence, Dr. Amos also testified that "opaque is opaque" and we do not normally speak of degrees of opacity [p 3092]. This is an example of both Dr. Amos and Dr. Bright going well out of their way to unjustifiably find fault with Dr. Davies and it detracts from their credibility.

[295] Other examples of unwarranted criticism by the Apotex expert witnesses include the suggestion by Dr. Bright that Dr. Davies' washed pellets may have been contaminated by drying paper or by the resin he had used to fix the samples for imaging. Those assertions were clearly intended to discredit Dr. Davies and to characterize him as a sloppy scientist. In the end, there was no reliable evidence produced to back up these points and, indeed, the evidence that did emerge was to the contrary. Dr. Bright was unable to satisfactorily explain why the fluorescent ring that was present in the images of the unwashed pellets that had not been exposed to drying paper looked the same as the imputed contaminated washed pellets. No fair-minded observer would speculate that Dr. Davies had buried every one of his pellet samples in resin before they were imaged, particularly after Dr. Davies had explained what he had done. And yet, even in his trial testimony, Dr. Bright refused to completely abandon these concerns.

[296] The Apotex witnesses were also critical of Dr. Davies' efforts to remove the enteric coating from the Apotex pellets by washing the pellets in acetone. In my view those criticisms were unjustified.

[297] There is no basis for questioning the acetone washing technique employed by Dr. Davies. He used a solvent known to solubilize the enteric coating in a simple washing experiment. As he expected, the wash readily removed the enteric coating and he was able to examine what was left behind. The CLSM images he obtained showed the presence of a distinct layer both before and after the wash. In other words, the sublayer remained intact. In comparison, the fluorescent ring was not detected when the naked Apotex cores were similarly analyzed. The reflectance images taken from the washed pellets depict the same layer with a distinct composition from the inner core material. The same layer is seen in Dr. Davies' water disintegration videos. Dr. Davies and Dr. Bodmeier established that the sublayer has distinct chemical properties. If the sublayer had a similar solubility profile to the enteric coat, one would expect it to be completely removed by the relatively large volume of acetone used, particularly after 4 minutes. These results cannot be explained away by hypothetical criticisms and possibilities.

[298] An implicit criticism of Dr. Davies' results is that he may have been selective in the choice or use of test data. I reject any suggestion that Dr. Davies manipulated his data. In particular, there is absolutely no evidence that Dr. Davies or his research team selected their data to fit a hypothesis or ignored or discarded contradictory or ambiguous results. The experiments Dr. Davies designed and carried out or supervised were readily reproducible. Apotex was well aware of those methods having been a party to the United States litigation where Dr. Davies testified at length. With only a few variations, the tests he carried out in this case were identical to those performed in the United States. The Apotex expert witnesses were, therefore, well informed and quite capable of replicating Dr. Davies' work or of modifying that work to attempt to improve upon it. In large measure, they failed to do so and, instead, focused their criticisms

on methodological matters. It is easy to take pot-shots from the sidelines; it is riskier to challenge experimental data head-on. The limitations inherent to Apotex's approach were noted by Justice Hughes in *AbbVie Corporation et al v Janssen Inc*, 2014 FC 55 at para 62, [2014] FCJ no 59, 116 CPR (4th) 399, 237 ACWS (3d) 473, where he said:

> [62] Only AbbVie conducted tests on the Janssen STELARA product. Notwithstanding that STELARA is Janssen's product, and that Janssen undoubtedly has the means to perform the necessary tests on its product, it did not provide in evidence the results of any such tests. Janssen chose only to offer criticisms of the tests performed at the request of AbbVie. Accordingly, I must weigh the AbbVie tests only against criticisms, and not against other tests. If Janssen clearly believed that its product did not fall within certain parameters, I would have expected it to provide evidence as to testing that demonstrated that fact.

[299] Apotex also objects to Dr. Davies' evidence, in part, because his testing was carried out *ex parte*. The Court now has a testing protocol dealing with this issue but at the time of Dr. Davies' work there was no strict requirement that expert testing be opened up to opposing parties. The legal considerations that apply to this situation were described by Justice Hughes in *AbbVie Corporation et al v Janssen Inc*, above, at para 64:

> [64] Unlike the practice in the United Kingdom as described in the "White Book", Civil Procedure, Volume 2, 2013, Sweet & Maxwell, London at page 730, there is, as of yet, no Federal Courts of Canada Rule specifically directed to testing conducted for the purposes of trial. In *Omark Industries (1960) Ltd v Gouger Saw Chain Co*, (1965) 1 Ex C R 457 at page 516, Justice Noel discussed a "salutary" rule to the effect that an opposite party should be given notice of and an opportunity to attend at such experiments. He did, however, also say that an *ex parte* test may be admissible, subject to weight, particularly where, in his case the opposite party could readily have conducted the same test. Most recently Justice O'Reilly of this Court in *Apotex Inc. v. Pfizer Canada Inc.*, 2013 FC 493 at paragraph 40, held that where a party had ample notice as to the testing and ample knowledge as to what would be done, a party cannot be held to say that the testing results are inadmissible because the party did not attend.

[300] Dr. Davies' work was appropriately recorded and the results were subject to review and criticism. Indeed, the Apotex experts did not appear to be disadvantaged in criticizing Dr. Davies' work. Although Dr. Davies did not record every test he performed, he did produce reviewable, representative data. He also testified that no results were obtained that were inconsistent with the data he produced. In this context, there is no basis for Apotex to complain that the work was performed without prior notice.

[301] I had a good opportunity to assess Dr. Davies. He is a cautious and careful person not prone to excess or exaggeration. He has developed a solid academic and professional reputation that would be jeopardized by taking an unprofessional approach to research. In a situation like this where Dr. Davies' work could be easily reproduced, I reject any suggestion the results he obtained were anything other than he has reported.

[302] I take Apotex's point that Dr. Davies' memory of the 2004 testing methods was shown to be somewhat inconsistent and there is no doubt, had all of the methods used been recorded contemporaneously, those gaps in memory would have been overcome. But in the end, the points of uncertainty do not materially impact the results he had obtained. There is no basis for the Court to refuse to consider Dr. Davies' test results or to treat them with suspicion. What remains to be determined is how those results should be interpreted.

B. What Are the Constituent Elements and Structural Makeup of the Apotex Subcoating and to What Extent is it Compromised by Holes, Gaps or Other Anomalies?

[303] There is no question on the evidence that a distinct structural layer is present at the interface of the Apotex pellet cores and the enteric coating. It is also not a matter of serious controversy that MACP-PVP complex is present within that sublayer. The complex is indisputably the end product of an *in situ* chemical reaction that occurs when the enteric coat is applied by Apotex to the pellet cores. Although Dr. Griffiths was unjustifiably coy in his reports about the presence of the complex [paras 25, 126, 131, 140, 158, 162, 165, 194 and para 7 of his Reply report] he did admit in his testimony that the complex was present in the sublayer [pp 3533-3534; also see Dr. Bright's testimony at p 4079]. Even Dr. Sherman seems to have anticipated a reaction between the enteric coating and the pellet cores although he disputed the possibility of an *in situ* subcoating [see p 183 of Volume 23B].

[304] One example of Dr. Griffiths' initial lack of objectivity on this issue can be seen at paragraph 165 of his report. Instead of acknowledging that some of the spectra from the surface of the washed pellets were, in fact, identical to those seen in the spectra of Dr. Davies' pure complex, all Dr. Griffiths would say was that "some of the major bands in these two spectra <u>may</u> be identical [emphasis added]". Dr. Griffiths was not otherwise hesitant to ascribe unreserved meaning to spectral peaks when it supported a point he was making.

[305] Dr. Griffiths' initial unwillingness to concede the obvious reflects a lack of objectivity and detracts from his credibility. It bears repeating that expert witnesses are not advocates. The role of an expert witness is to fairly acknowledge points of agreement and to take issue only

where an honest scientific disagreement arises. Dr. Griffiths should have conceded from the outset the factual matters that were not in dispute.

[306] What fairly remains in dispute in this case is whether the complex is a polymeric film forming compound (or is comprised of such compounds) and whether the complex constitutes a substantially continuous and inert subcoating that is an effective barrier between the pellet cores and the enteric coating. According to the Apotex witnesses, AstraZeneca failed to establish the complex is sufficiently present to constitute an effective separating layer. They also maintain, whatever the precise composition of the sublayer may be, it is replete with holes and gaps. Given the likely presence of omeprazole degradants and unreacted acidic functional groups in the sublayer, it also cannot be considered to be inert.

[307] Apotex argues that AstraZeneca failed to prove the "alleged" subcoating that forms in its pellets from a reaction between MACP and PVP is a polymeric film forming compound. Apotex challenges the weight of the evidence offered by Dr. Davies and Dr. Bodmeier on this point but it put forward no evidence of its own.

[308] Dr. Davies' initial report characterized the MACP-PVP complex in the following way:

> 147. The MACP-PVP complex and MACP salt are polymeric film forming compounds. Further, the film forming characteristic of the subcoat is demonstrated by the fact that the complex forms and adheres to the core in the Apotex product as shown by CLSM. The polymeric film is also visible as a sheeting or coating in the disintegration images and videos.

This evidence was corroborated by Dr. Bodmeier at para 136 of his initial report.

[309] Dr. Davies testified that MACP and PVP are each well known polymeric film formers and he provided references to that effect [p 795-797]. He also testified that he observed the MACP-PVP complex coming away from the Apotex pellets in his water disintegration tests in the form of a film [p 799]. This testimony is fully consistent with the associated videos tendered in evidence.

[310] In the absence of a direct challenge to this evidence, I am satisfied AstraZeneca has met its burden of proof on this point.

[311] The evidence concerning the structural continuity of the Apotex subcoating layer was troubling. Dr. Davies stridently resisted the suggestion the subcoating layer presented any holes or gaps. Dr. Amos and Dr. Bright were equally dogmatic in their views that the Apotex sublayer was replete with major discontinuities in the form of gaps and holes and presumably the sublayer served no useful purpose by being there.

[312] In my view the truth lies between these extremes but much closer to the views expressed by Dr. Davies than by Drs. Amos, Griffiths and Bright whose evidence was successfully challenged on many points under cross-examination. I am satisfied the Apotex sublayer does contain minor defects of no functional significance – perhaps, in part, because of Dr. Kibbe's explanation that, in the presence of water, the complex could absorb water and close down any imperfections present in the dry state.

[313] On this issue there was some common ground developed between Dr. Amos and Dr. Davies. For instance, Dr. Amos agreed with Dr. Davies that the presence of large undefined areas or gaps in Dr. Davies' and the Temple University CLSM images was likely caused by a loss of focus [see p 3038, p 3046, p 3048 and para 68 of the Amos report] or from a loss of signal at depth [p 3047]. Dr. Amos agreed that these areas of the images were not appropriate to assess the continuity of the sublayer [p 3050] or its thickness [p 3051]. Dr. Amos attributed the loss of focus to the sample surface not being planar [p 2955].

[314] Dr. Amos also partially accepted Dr. Davies' interpretation of five CLSM images that Dr. Bright had used to attempt to show discontinuity in the fluorescing sublayer. Dr. Amos agreed that one of those images (z=49) was not suitable to assess the continuity or thickness of the sublayer [pp 3051-3052]. He also said that the absence of sublayer fluorescence in a CLSM image taken at depth (z=0) could be caused by a weak or absent signal or it could be from a large gap in the sublayer [p 3053]. Nevertheless, in the end, he adopted the view that most of the gaps evident in the sublayer fluorescent ring were caused by breaks or holes in the sublayer and not by a loss of signal.

[315] Dr. Amos did acknowledge the general absence of fluorescence in those areas of the images taken below the pellet surface could be explained by signal attenuation in the partially opaque sample [pp 3071-3072]. This would not, however, explain the apparent discontinuities he said he could see in those areas where the signal was very strong [p 3056]. According to Dr. Amos those were actual holes [p 3056]. To Dr. Amos this explanation was a "unifying theory" that best reconciled all of the available CLSM data.

[316] Dr. Amos' testimony about the presence of gaps and holes was substantially less equivocal than the language used in his reports. In his report, he described the sublayer anomalies as "apparent gaps", "possible holes", "seems to have holes or lacunae" and "perhaps consist of isolated flakes". He also labelled the images he chose with similar expressions of uncertainty and question marks. Dr. Amos justified his initial use of equivocal language as a cautious scientific approach taken to each piece of evidence. He characterized his ultimate written conclusion about the existence of holes in the sublayer as being firm. This is not completely borne out by his report where, after a lengthy critique of Dr. Davies' methods and the quality of his images, he offered his conclusion without much conviction [see paras 61 and 69 of the Amos report].

[317] In contrast, under cross-examination about his description of a "possible hole" in Figure 8, his opinion had reached the point of "overwhelming probability", it was "really a hole" [p 3187] and beyond a reasonable doubt [p 3188].

[318] Although Dr. Amos testified that he observed holes in the CLSM images depicting the surfaces of samples, it is noteworthy that the one image he relied upon in his report to depict a "possible hole" [ie Figure 8] was taken at depth. The other images he produced at trial [Exhibit 110] were also taken at depth and Dr. Amos conceded that he could not be certain that the loss of fluorescence in places represented actual holes [pp3204-3205]. The failure to directly challenge Dr. Davies' opinion that the most reliable evidence of fluorescent continuity came from the surface of the samples is striking. One would have expected Dr. Amos to produce

multiple surface CLSM images at 50X magnification showing holes instead of the less reliable images taken at depth where signal attenuation was a confounding variable[3].

[319] At one point Dr. Amos appeared to revert to his initial qualified view of Figure 8 ("the things could be holes and that frame averaging should have been done") only to conclude Dr. Davies' response to his guarded approach contained "a certain degree of mockery" [p 3199]. This answer suggests Dr. Amos' views about sublayer continuity hardened somewhat in the face of what he took to be unjustified and unscientific criticism by Dr. Davies.

[320] What is also difficult to comprehend about Dr. Amos' views about sublayer continuity is how he could express so much confidence about what he claimed to see in Dr. Davies' images in the face of his strong criticisms about the quality of those images. If Dr. Davies' images were insufficient to support his opinions, they were equally insufficient to support Dr. Amos' contrary view. My impression of Dr. Amos' evidence is that what was written under the supervision of legal counsel was a more accurate representation of his views than his sometimes firmer trial testimony.

[321] When Dr. Amos was taken to Dr. Davies' 50X magnification CLSM images from stub 6 [Exhibit 11], he agreed the sublayer fluorescence at the sample surface was in focus and depicted no obvious holes. This evidence was qualified by his belief the image (along with many others) was saturated and unreliable [pp 3227-3233]. Dr. Amos accepted that CLSM data from the pellet surface could be important but he apparently felt Dr. Davies had destroyed their value by saturating his images.

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[3] The phenomenon of signal attenuation was accepted by Dr. Amos [p 3212].

[322] What these images show is, at the sample surface, there is a substantially continuous fluorescent band. As the Z-scan images depart from the surface, the continuity of the band begins to break up. Dr. Davies attributed this to the attenuation effect. To some extent even the Apotex witnesses eventually acknowledged that signal attenuation in a substantially opaque and heterogeneous sample could interfere with the quality of the received signal. For example, Dr. Bright was asked about the concept of signal attenuation. He answered in direct examination that, although the CLSM signal will lose strength as it probes deeper into a partially opaque sample, the loss would be expected to be uniform. Accordingly, if a feature of a sample was continuous, defects ought not to appear in the image at depth. The signal would simply deplete in a uniform way [p 3888]. This expected pattern was not what Dr. Bright observed in Dr. Davies' CLSM images where, at depth, numerous defects, holes and breaks appeared throughout the sublayer fluorescence [p 3894].

[323] This evidence was not fully consistent with Dr. Bright's evidence under cross-examination. In a lengthy exchange [pp 4097-4104] Dr. Bright agreed the Apotex pellets are not homogenous in terms of their opacity and, even within the various pellet structures, the CLSM signal was unlikely to be homogenously absorbed [p 4099]. Dr. Bright simply could not say with certainty whether sublayer absorbance would be homogeneous or heterogeneous [p 4101] or that the loss of signal at depth would be uniform in all places [p 4104].

[324] Dr. Bright also held to his view that it was wrong for Dr. Davies to draw a correlation between the presence of a fluorescent ring at the enteric coating-core interface and the infrared

data showing the presence of the complex in that area. His testimony at pp 4160-4161 explained the problem as he saw it:

> A. So the fluorescence doesn't -- does not tell one anything about the MACP-PVP per se because it doesn't detect it. It's telling me that there is some fluorescence there. And that's the disconnect, is there is no connection between the fluorescence and the infrared in terms of connecting what is fluorescent to the infrared characteristics. One has to make an assumption to do that.

[325] What is interesting about the way Dr. Bright approached this issue is how selective he was in the choice of relevant data. He acknowledged that his primary focus was on "the fluorescence aspect and the microscopy aspect of things" [p 4072]. He paid scant attention to the reflectance images that, by his own somewhat guarded acknowledgement, depicted a different "average topology" to the core. Dr. Bright's reluctance to attribute significance to the distinct topology depicted in the sublayer reflectance images and their substantial physical conformity to the fluorescent sublayer band detracts from his overall opinion. His testimony on these points [p 4165] was unconvincing as was his very non-committal evidence dealing with Dr. Davies' water disintegration videos. An objective assessment would have required Dr. Bright to consider all of the data obtained by Dr. Davies and from the Apotex testing and not to essentially ignore evidence that did not fit with his views.

[326] I agree with Dr. Davies: the best available evidence of fluorescent continuity comes from data obtained at or very near the sample surface where the image is in focus. The fact that continuity anomalies commonly appear at depth and hardly ever at the surface of the bisected pellets indicates the anomalies are related to a loss of signal or the loss of focus and they do not represent actual gaps or holes.

[327] I reject Dr. Amos' singular view that many of Dr. Davies' CLSM images were "grossly" saturated. Dr. Amos claimed he was able to visually detect saturation. His concern about saturation appeared to grow as his evidence unfolded. By the time he was cross-examined, he offered the opinion that the "majority" of Dr. Davies' Z-scan images were saturated and, when projected, gave a false impression of continuity.

[328] None of the other witnesses professed to have the ability to visually detect saturation nor did they express any concern about this issue. Dr. Bright assessed some of Dr. Davies' images and found no evidence of saturation [p 4219, pp 4222-4223]. He was apparently not comfortable with the idea that saturation could be visually observed and testified "I would measure it".

[329] Dr. Amos empirically assessed one of Dr. Davies' images for saturation using image analysis software. The data he obtained are set out at Figure 12 of his report in the form of a curve that flattens at a gray level value just about 150. Those data are equivocal and Dr. Amos' attempt to explain their significance was not compelling [p 2993].

[330] Dr. Davies testified that he used the appropriate method to avoid the problem of saturation. I do not accept that Dr. Davies was unmindful of the need to avoid saturation and failed to employ the available and routine safeguards. Dr. Amos' evidence on this point was not believable and it detracts significantly from his overall credibility.

[331] Dr. Bright's evidence about the presence of numerous gaps and holes in the fluorescent ring depicted in Dr. Davies' CLSM images was similarly not convincing. His initial report

contains a significant error based on a false assumption. In his initial report he stated that as individual Z-scan images were recorded through the Apotex pellets the expectation would be that the fluorescent ring would be largely the same [para 69 of Dr. Bright's report]. He contrasted this with Dr. Davies Z-scan images where he noted discontinuities in the fluorescent sublayer. In making this observation, he included images taken from deep in the sample and also from above the pellet surface. On cross-examination, he conceded that his reliance on these images was wrong and that he also did not appreciate the pellets were being imaged on a slant. He went on to acknowledge that, as the CLSM probes more deeply into a partially opaque sample, the signal is attenuated and provides less reliable information because of the interference of background noise:

> MR. JUSTICE BARNES: I think you said a minute ago that, and correct me here if I am wrong, that the further down you go, the less reliable the image for assessing continuity? The deeper you go, you are losing some signal, and does it make those scans less reliable as evidence of continuity?
>
> THE WITNESS: So I apologize for interrupting.
>
> I think as one gets as the total signal drops in an experiment, at a given Z position, you become completely noise dominated, and, therefore, you can't discriminate. It becomes difficult to tell if there is anything there. So I think that's the answer you are looking for.

[332] This evidence is generally consistent with Dr. Davies' view that the best evidence of sublayer continuity is obtained at or very near the pellet surface.

[333] Dr. Griffiths' testimony concerning the existence and extent of gaps in the Apotex sublayer was also not convincing. The opinion he gave in his report manifestly overstated the significance of the mannitol signal obtained from some of the ATIR spectra. His initial opinion

given in direct-examination was that up to 50% of the recorded signal was contributed by mannitol in the pellet cores thus showing gaps in the MACP-PVP complex of about 50% of the area of interrogation [p 3400]. Under cross-examination he acknowledged the spectra in question exhibited enormous variability [p 3558] and were not internally consistent. He attempted to explain the variability in band intensities by a possible contact problem between the internal reflection element of the instrument and the sample [p 3465, pp 3471-3473]. Notwithstanding the unexpected intensity in the spectra for the complex, he maintained his position that the intensity of the mannitol bands was evidence of large gaps in the complex [p 3467].

[334] When Dr. Griffiths was asked about the range of error that applied, he said that "[t]here is quite a lot of estimation around here" and he reduced his estimate of gaps in the complex to a range of between 25% to 50%. He said that 25% would represent the bottom end of the range and 50% "was probably at the top end" [p 3474].

[335] Under further cross-examination Dr. Griffiths conceded that, in order to accurately quantify the extent of gaps in the complex, "you probably would have to control a lot of these variables more carefully" [p 3556].

[336] In a particularly effective cross-examination by Mr. Biernacki, Dr. Griffiths acknowledged a significant error in one of his assumptions about the relative absorbances of mannitol and the complex. Dr. Griffiths had assumed equivalent absorbancies. When this error

was pointed out to him, he further reduced his estimate of the extent of gaps in the complex to about 10%. His testimony at pp 3563-3566 was as follows:

> Q. Okay. And so based on what we looked at with reference spectrum for mannitol versus the reference spectrum for the complex, it appears that the mannitol spectrum produces intensity five times as high at the 1030 to 1090 band as the complex does at 1700?
>
> A. Okay.
>
> Q. Correct?
>
> So in order to make a comparison regarding the relative contribution or concentration of these ingredients in this spectrum, you should be multiplying the mannitol peak by 5; is that fair? Either that or dividing the complex by 5?
>
> A. Remember that I didn't look at -- in my report, I didn't give concentrations, I gave absorbances. And so when I was looking at the effect, for example, of layer thickness, 6 in the table in my report, I was looking at absorbances, not at concentrations.
>
> Q. We will get to your chart and analysis that you did there, but when you were looking at washed-pellet Spectrum 2, you were doing an internal analysis between relative peak heights assuming that those compounds absorbed equally at their particular wavenumbers. And I think we have shown, albeit very roughly, that that's not correct. And what I would like to do is to see how the adjusted relative absorbances would affect that analysis.
>
> So am I correct that if the mannitol generates a signal at the lower band, so the 1030 to 1090, it is five times as high as the 1700 band?
>
> A. The signal is not five times as high.
>
> Q. The intensity.
>
> A. Okay, but the intensity isn't five times as high either.
>
> Q. Oh, no, it's not in this spectrum, but if you wanted to take a look at those relative peak heights and make an assessment about the relative contribution, you would have to divide the complex by 5, at least the intensity, to be comparing --

A. Divide or multiply?

Q. Well, you are either going to have to multiply the mannitol by 5 or divide the complex by 5.

A. If you multiply the mannitol by 5, you are talking about enormous mannitol bands. So I think I see where you are going, I think you got it exactly wrong, around the wrong way, but, nonetheless, I think --

Q. My friend is pointing out to me, you are correct, I think everyone is correct other than me on this point, we should be dividing the mannitol peaks by 5?

A. Yes.

Q. So, then, when you made a comparison between the mannitol peaks with the complex peaks, you would not have a 50 to 50 ratio but a ratio of closer to 20 per cent or even less?

A. Okay. That's if you, that's -- it doesn't negate the table that I made which was based on absorbencies and not concentrations.

It may affect the gap size and may even bring it down to 10 per cent, but 10 per cent is still a whole lot more than zero. It's still not -- this spectrum here shows the existence of gaps in the layer. Otherwise, you would not see those mannitol bands as you don't in the, certainly the one spectrum where you see only complex. And the complex is there to about the same height. So it doesn't, it doesn't affect the potential, the probable -- excuse me, that is the word I meant to say, the probable existence of gaps which, when you bring your argument in, rightly or wrongly, and I think there is some, there are some changes that have to be made based on lambda and I think there are some changes that have to be made based on the fact that you are using the most -- you are not using a representative number for the mannitol bands in the uncoated core, but, nonetheless, I mean, it is still showing, this does not negate the existence of gaps in the sample.

Q. Well, wait a second. I am not using the most extreme signal of mannitol from the core. We avoided that by going to the reference spectrum for mannitol and comparing that to the reference spectrum for the MACP complex; correct?

A. Okay, yeah.

Q. So whatever other issues there may be, that is not one of them. And so if there is --

A. There is still a contact issue.

Q. There is not a contact issue with respect to the reference spectra for mannitol and complex --

A. Not a contact of the bottom of the sample with the internal reflection element but the probe -- I will withdraw that.

Q. If you divide the mannitol peaks by 5, taking the analysis that you had done earlier, would that leave you to estimate the relative proportions of the signal between mannitol and the complex to be around -- actually, let me rephrase that.

If you did that analysis, would that lead you to conclude that the signal from mannitol was around 20 per cent or less?

A. If you made that assumption, yes.

Q. Yes. And so that would be the kind of spectrum that you might see if 20 per cent of the signal was coming from mannitol?

A. Yes.

The clear impression left by this evidence is that Dr. Griffiths' indirect method of assessing the continuity of the complex through the interpretation of Dr. Davies' ATIR spectra was subject to so many uncontrolled variables and subjectivity that it was unreliable. As used by Dr. Griffiths, the technique is, at best, only a very approximate means of assessing the relative concentration of two or more substances and it was not useful as a measure of sublayer continuity in this case. There is no other plausible explanation for the profound change in Dr. Griffiths' evidence that began with continuity breaks of up to 50% and ended with gaps approaching 10%. I agree with Dr. Davies that his ATIR data are not useful to assess the continuity of the complex and they cannot be used as a reliable proxy for that purpose.

[337] Apotex adopted an unusual approach to its own CLSM and FTIR analysis. Instead of asking its expert witnesses to conduct or supervise that work, it was independently assigned to Dr. Reza Fassihi at Temple University and to Dr. Craig Hawker at the University of California. Both were given considerable latitude in the conduct of their work and, in some instances, they adopted practices inconsistent with those the Apotex experts would have preferred. The Apotex experts were then asked to analyse the Fassihi and Hawker data.

[338] In the end the Apotex testing did not undermine Dr. Davies' results. The Temple University CLSM images depict a fluorescent ring at the interface of the pellet cores and the enteric coating. This is particular evident in Tabs 41 through 48 of Exhibit 158. Where the images are in focus, the fluorescent corona is quite distinct. Dr. Bright acknowledged as much under cross-examination [p 4128 and pp 4156-4159]. Dr. Bright also expressed reservations about the comparative value of the Temple images in the following exchange:

> Q. Will you agree that Dr. Davies' 50x images had better lateral pixel resolution than any of the new CLSM images?
>
> A. As I recall the Temple University CLSM, the best resolution was 20x, two times digital on ten. So I would agree with what you said.
>
> Q. The Temple CLSM images were all single optical plane images?
>
> A. Yes.
>
> Q. You were not provided with a Z series for any pellets from Temple - - from Temple University?
>
> A. I was not.
>
> Q. And so the single plane images that you obtained from Temple don't tell you where within the pellet that plane is from?

A. That's true. Obviously when the analyst took the images they were focused and so on. I mean, obviously the image didn't come out of the blue straight out of the gate, so I suspect there was some optimization to get a position. But I don't know, the answer to your question.

Q. Parts of the image may have been below the surface of the pellet?

A. That's possible.

Q. Similarly, parts of the image - - let me be more precise. In parts of the image, the optical plane could have been above the surface of the pellet?

A. In certain regions?

Q. Yes.

A. Perhaps, yes.

Q. And without a Z series, it's impossible to make that assessment?

A. What is "that" that you are saying to me?

Q. Whether part of the optical plane is above or below the surface and to what degree?

A. I believe that's true.

[pp 4154-4155]

Also see Dr. Bright's evidence at p 3950 and p 3998.

[339] Under cross-examination, Dr. Amos agreed the large gaps in the zone of fluorescence in the Temple University CLSM images were due to the sample being out of focus [p 3046]. Like Dr. Bright, he agreed the value of the Temple University images was reduced by the failure to obtain a full Z series and by other imaging deficiencies [p 3048 and pp 3181-3181]. Dr. Amos

also acknowledged that Dr. Davies' 50x images provided better resolution than those obtained by Dr. Fassihi [p 3082].

[340] Dr. Bright was sufficiently troubled by the anomalous signal in Dr. Hawker's blank that he expressed reservations about the validity of some of the data [p 3978]. In a case as important as this one, it is surprising that a problem of this sort would be left unresolved. I do not accept Dr. Hawker's attempt to explain away this problem as insignificant. The taking of a blank is an important experimental control and the anomalous reading should have been addressed. I, therefore, agree with Dr. Davies that the Hawker data were insufficient to counter Dr. Davies' contrary findings.

[341] It was apparent to me that Dr. Bright and Dr. Amos were not particular impressed by the quality of the Temple CLSM images and, had they been asked to carry out that work, they would have adopted different methods. This placed the Apotex witnesses at a disadvantage relative to Dr. Davies who ran his own tests and interpreted his own data. In some instances, the Apotex experts were left to guess about how Dr. Fassihi and Dr. Hawker obtained their data.

[342] This segregation of experimentation from data analysis was consistent with Apotex's overall approach. None of the Apotex experts was asked to consider all of the evidence with a view of expressing an over-arching opinion. Each was asked to consider pockets of data relevant to their area of expertise. This, in turn, unfairly discounted the value of the whole of the evidence. I am satisfied Dr. Davies' approach was the more reliable one and his opinion about the structure of the Apotex product is in all probability, correct.

C. Thickness

[343] At paragraph 170 of Dr. Griffiths' initial report, he estimated the thickness of the "layer of complex" in 4 of 5 of Dr. Davies' 2004 spectra at "about 0.5 microns". This was based on his estimate of a depth of signal penetration of 1 micron. Dr. Griffiths testified that a depth of penetration of 2.0 was more appropriate leading him to a revised sublayer thickness in a range of 0.5 microns to 1.7 microns. For one 2004 spectrum he acknowledged a thickness of up to 1.7 microns [pp 3584-3585]. When Dr. Griffiths was then asked to adjust his thickness values using an angle of incidence of 36º instead of the angle he had used of 45º, he provided a hypothetical thickness range from 1 micron to 2.92 microns for four of the 2004 spectra and higher than that for another [p 3588]. Using a depth of penetration of 2.0 and an angle of incidence of 36º, Dr. Griffiths agreed that a sublayer thickness of at least 2 microns was plausible. Nevertheless, he refused to accept that the angle of incidence employed by Dr. Davies' instrument was less than 45º [p 3590, p 3592].

[344] The first observation to be made about Dr. Griffiths' method for calculating the thickness of the Apotex sublayer concerns its inherent imprecision. The ranges of values it produced were extraordinary and fell markedly short of what would be necessary to rebut Dr. Davies' direct thickness measurements.

[345] A second observation to be made about Dr. Griffiths' thickness analysis concerns the vagaries of the assumptions he employed. The thickness values he obtained were based on generalizations about the depth of penetration of Dr. Davies' ATIR tests including the angle of

incidence employed. As Dr. Griffiths acknowledged, the median angle of incidence can affect the depth of penetration by a factor of two or more [p 3619].

[346] Dr. Griffiths was prepared to adjust his depth of penetration assumption up to a point but, despite Dr. Davies' evidence about the angle of incidence employed by his instrument, Dr. Griffiths refused to depart from an assumed angle of incidence of 45º. This, he conceded, was an after-the-fact justification [p 3610].

[347] The implication Dr. Griffiths was, in effect, advancing was that Dr. Davies was lying about the angle of incidence[4].

[348] It is surprising to me that after subjecting Dr. Davies' analysis to years of scrutiny in the United States and Canadian litigation there would remain any lingering doubt as to either his methods or his testing equipment. In the absence of any plausible evidence to establish Dr. Davies' ATIR tests were performed with a median angle of incidence of 45º, I accept his evidence to the contrary. It was open to Apotex to conduct its own equivalent testing and it chose not to do so. It should not be the beneficiary of any uncertainty that could easily have been dispelled.

---

[4] It is true that in Dr. Davies' initial report he reported a conventional angle of incidence of 45º but there the point he was advancing was not a matter of controversy. It was only later when Dr. Davies was challenged on the issue of depth of penetration that the actual angle of incidence became relevant. I accept Dr. Davies' explanation of this evidence. I draw no negative inference from his initial use of a conventional value or from his subsequent clarification and I reject the suggestion that he was being untruthful.

[349] The third observation to be made about Dr. Griffiths' approach concerns his avoidance of any direct thickness measurements. I understand the concern that the fluorescent band seen on top of the Apotex cores in Dr. Davies' CLSM images is, at least arguably, not coincident with the MACP-PVP complex. However, measuring the thickness of the band is not an acknowledgement of its chemical make-up. Furthermore, the reflectance images taken from the washed pellets are strong evidence of a well-defined structure distinct from the underlying pellet core. The chemistry of this structure was also shown to be different from that of the enteric coating. Direct measurement of the reflectance images was a simple exercise and yet it was avoided by the Apotex witnesses with reliance, instead, placed on Dr. Griffiths' less accurate indirect thickness assessment.

[350] Dr. Griffiths' approach to measuring sublayer thickness by reference to the relative intensity of the mannitol peaks seen in some of Dr. Davies' spectra was also subject to some professional judgment. As with his continuity analysis, Dr. Griffiths acknowledged that the various spectra showed variation in the intensity of mannitol peaks [p 3656]. He then selected a representative value by simply looking at the spectra [p 3661]. He did no measurements to confirm the ratio he employed across the available spectra nor did he calculate the median angle [p 3659, p 3661]. He also failed to account for the contribution of the background signal to the complex when he measured peak heights [p 3662-3663]. His response to this omission was not a compelling endorsement of the validity of his thickness assessment:

> A. Right.
>
> Q. And one way of doing so could have been to take a spectrum for a washed pellet, which has what appears to be a thick

> layer and no signal for mannitol, and use that as a background; couldn't you have done that?
>
> A. Umm... Yes -- I'm sorry to equivocate on this one, but the answer is yes and no, because the spectra where you are predominantly measuring the spectrum of the complex have varying amounts of carboxylic acid on there. And the carboxylic acid is going -- the amount of carboxylic acid in the spectrum, as shown by the 1700 wavenumber band, is going to affect the lower frequency region of the spectrum. I know that as a spectroscopist. So there are going to be other bands which are associated with carboxylic acid's relatively broad bands in the spectrum, which contributes to that baseline.
>
> So either way, you are making approximations. Even if you did the procedure that you just outlined, which is not unreasonable, you would still get probably an incorrect value, so taking the baseline at zero, I felt, was as good a way of doing it as any.
>
> Q. There is a difference between not being perfect and being better. And I suggest to you that had you taken into account the background, to the best of your abilities, that that would have provided a more accurate measure of the mannitol peaks in the washed pellets, which would have provided a more accurate analysis?
>
> A. I will agree with you, yes.

[351] On this issue I also accept Dr. Davies' evidence that assessing the thickness of the Apotex sublayer with ATIR data was unreliable.

[352] Dr. Bright criticized Dr. Davies' thickness measurements principally on the basis that Dr. Davies inappropriately used maximum intensity images and because he did not adequately explain or document his work. Dr. Davies answered this criticism by providing additional detail. He confirmed that his thickness measurements were performed on representative individual Z-scan fluorescence and reflectance CLSM images at evenly spaced intervals along the subcoating

layer – not from maximum intensity images. In response to Dr. Bright's criticism that Dr. Davies had not identified precisely where the thickness measurements were taken from, Dr. Davies pointed out that Dr. Bright had all of the data required to perform independent measurements. Dr. Bright answered in the following way at paragraph 159 of his Sur-Reply Report:

> 159. In paragraph 229, Dr. Davies comments that I could have analysed the thickness of the asserted subcoating layer of the washed pellet myself to calculate an average thickness. I disagree. The thickness measurements were obtained by Dr. Davies using images at 50x magnification from a very small portion of bisected, washed pellets. By failing to provide an adequate selection of 50x images (the number would be huge), it would be impossible for me to obtain measurements representative of the pellet. Using Dr. Davies' images, I could only take measurements in that tiny region. Furthermore, I cannot use the raw CLSM images to determine thickness in the manner that Dr. Davies did in 2011, because he has not explained in sufficiently clear terms what he did to take those measurements.

[353] I do not accept this evidence as a sufficient response to Dr. Davies' point. It is easy to raise theoretical methodological issues in the work of others. The weight of this type of criticism is significantly diminished where the critic has the ability to carry out an independent assessment of the available data and decides or is directed not to do so. Dr. Bright did not need to know precisely where or how Dr. Davies took his thickness measurements. He could easily have taken his own measurements with any of the available images using his own method to determine if the range of thicknesses of the sublayer matched Dr. Davies' results [p 3999]. In the absence of any reliable evidence to challenge Dr. Davies' thickness measurements or to show that those measurements were not representative, I accept those data unreservedly. I also accept that Dr. Davies' measurements are sufficient to support a finding that they are representative of all of Apotex's omeprazole pellet production.

[354] I do not accept Dr. Griffiths' indirect method of assessing the continuity or thickness of the Apotex sublayer. This approach is subject to too many uncontrolled variables. The totality of the evidence presented by Dr. Davies is much more persuasive. I accept that any one of Dr. Davies' tests would, on its own, be insufficient to establish a continuous MACP-PVP subcoating of at least 2 microns thickness. However, when all of Dr. Davies' tests are considered together, his conclusion is the most probable.

[355] I do accept the point that Dr. Davies' fluorescence images are, on their own, insufficient to establish the presence or the topology of the Apotex subcoating. Dr. Davies did not contend otherwise. However, in the presence of the other testing carried out by Dr. Davies, I have concluded that the fluorescent corona that can be seen at the core/enteric coating interface of the washed and enterically coated pellets is substantially the product of the MACP-PVP complex that is present at that location.

[356] The Apotex expert witnesses were given selective mandates. This allowed them to avoid the integration of all of the available data into their respective opinions. Two particularly strong examples of this involved the approach they took to the reflectance images and to the water disintegration videos. Very little attention was paid to this evidence and how it could be reconciled with the other evidence. To the extent that it was addressed by the Apotex witnesses, it was treated very thinly or with speculation. Their treatment of the water disintegration videos was particularly troubling.

[357] In my view, compelling evidence of the presence of a substantially continuous subcoat layer in the Apotex pellets comes from Dr. Davies' videos of the Apotex washed pellets submerged in a water bath. The videos depict a fairly rapid disintegration of a film-like layer. It does not float off in isolated or discontinuous pieces but as cloak. The layer floats away from the core in sheets. Dr. Griffiths ultimately conceded the complex is present on the surface of the washed pellets and he agreed the observed film coating is the complex, possibly with some "free" MACP. This point came out in cross-examination and was not apparent from any of Dr. Griffiths' reports. At paragraph 187 of his first report, Dr. Griffiths said only that "the material that Dr. Davies observes 'flaking off' the solvent washed pellets…could well be MACP". Left unchallenged, this statement and the following paragraph strongly suggest the film was not the complex at all. The weakness of Dr. Griffiths' evidence is exemplified by the convoluted explanation he offered under cross-examination between pages 3668 and 3672 of the trial transcript. My interpretation of the evidence is that Dr. Griffiths could not scientifically reconcile the disintegration videos with his other opinions. In writing his reports, he, therefore, chose to ignore what he saw.

[358] The reflectance images also demanded meaningful consideration. Those images depict a substantially continuous and visually distinct structural band on the surface of the pellet cores. The CLSM fluorescence images of the sublayer band are also substantially coincidental with the matching reflectance images. There are a few variations in places but, for the most part, the contours of each band mirror one another [see for example the images at Tab 28 of Volume 6 of Dr. Davies' Statement]. It cannot be coincidental that the CLSM fluorescent coronas substantially overlap the sublayer structure depicted in the reflectance images. Nevertheless, the

Apotex witnesses failed to address this evidence in a meaningful way. That failure undermines their theoretical concerns about the inherent limitations associated with CLSM as a method for identifying sample structures and chemistry.

[359] Dr. Davies built his opinion on all of the evidence considered collectively. He was willing to accept that any one of his tests was insufficient to support his final opinion but, when viewed together, he found the evidence to be compelling. His opinion was based on the following points of evidence:

a. The presence of the complex – a chemically distinct compound – was detected each time the Apotex pellet sublayer was probed by ATIR.

b. MACP and PVP are both present in the Apotex pellets and were proven, as expected, to react with each other to form the complex.

c. A fluorescent ring is present in all of the CLSM images taken of the coated and washed pellets at the interface of the enteric coating and the cores.

d. The Apotex sublayer is chemically different from the enteric coating in that it did not dissolve with the enteric coating when washed in a solvent.

e. The reflectance images of the washed pellets show a structurally distinct sublayer sitting above the pellet cores. The boundaries of the sublayer from those images closely conform to the fluorescent ring boundaries when the images are compared.

f. Subject to the prevailing limits of detection, no compounds were proven to be present in the sublayer except for the complex, magnesium salt and some

unresolved acidic functional groups. Each of those compounds could reasonably be expected to be present in the sublayer.

g. The disintegration videos depict a substantially continuous film-like layer rapidly coming away from the washed pellet cores in a water bath. The Apotex experts offered no meaningful challenge to Dr. Davies' evidence that this film-like coating was the MACP-PVP complex.

[360] On balance, I much prefer the evidence of Dr. Davies to that offered by the Apotex experts. Dr. Davies' approach to testing may not have matched the approach of others but in several instances the data he obtained were not directly challenged. I reject any suggestion that Dr. Davies' data were compromised by his methods.

[361] The fact that a party may not agree with a chosen experimental design is not an excuse for failing to replicate the work to test the reliability of the reported data. The same applies to criticisms about the testing techniques employed by an opposing expert witness. An argument that other tests or controls could have been used loses much of its strength where a party chooses not to employ those same suggested methods in its own responding analysis to see if the results differ.

[362] The complaint by Apotex that not every test performed by Dr. Davies was recorded is a theoretical concern. Dr. Davies testified that his recorded tests were representative of the tests not recorded. If Apotex believed the recorded data was not representative, it was fully capable of doing its own testing and recording the data to determine if different results emerged.

[363] Dr. Davies proved the complex was present at every point he subjected to ATIR interrogation and he proved it is a chemically distinct compound. When matched, the contours of the sublayer seen in Dr. Davies' CLSM fluorescence images are substantially coincidental with the physical contours seen in his reflectance images [see Tab 28, Volume 6 of the Davies' report]. These reflectance images of the washed pellets depict a continuous structure resting above and distinct from the cores. Given the design, length and vigour of Dr. Davies' washing technique, I reject any suggestion that this observed layer could be a remainder of the enteric coating. When everything is considered in combination with Dr. Davies' water disintegration videos, the inescapable conclusion is that the film-like material peeling away from the pellet cores must be substantially comprised of MACP-PVP complex.

[364] For the reasons given above, I am satisfied that the Apotex omeprazole product contains a substantially continuous polymeric film subcoating that forms *in situ* from a reaction between the enteric coating MACP and the core excipient PVP during pellet manufacture. Notwithstanding the presence of some acidic functional groups and magnesium salt in the subcoating, it is primarily made up of the complex and it remains functionally inert. If it were otherwise one could reasonably expect to find meaningful levels of omeprazole degradants under ATIR analysis. None were found. It is also this structure that is depicted in Dr. Davies' water disintegration videos.

[365] I am also satisfied that the Apotex subcoating is sufficiently robust that it provides an effective protective barrier as described in the 693 Patent. It has the thickness characteristics described by Dr. Davies and in almost every instance exceeds a thickness of 2 microns.

[366] Apotex developed a formation that worked and could have looked to see if the subcoating was present before it took it to market – just as Dr. Davies was able to show. It could also have presented expert evidence that it had obtained a useful omeprazole formulation by different means than those claimed by the 693 Patent. It chose, instead, to challenge the quality and cogency of the evidence presented by AstraZeneca and there it came up short. The inference I draw from the evidence before me is that the Apotex omeprazole product works because its formulation matches the formulation described in Claim 1.

VII. Standing

[367] Apotex argues that neither AstraZeneca Canada Inc. nor AstraZeneca AB have standing to prosecute their respective claims to damages for infringement in these proceedings. No challenge to Hässle's standing has been advanced and it is clear that Hässle has standing as the patentee. As with many challenges to standing, this one has no merit.

[368] Section 55(1) of the *Patent Act* affords standing in patent infringement actions to the patentee and to "all persons claiming under him for all damages sustained". The question here is whether AstraZeneca AB and AstraZeneca Canada Inc. are parties with sufficient interests in the 693 Patent to claim under Hässle.

[369] The test for standing is not particularly onerous. The issue was thoroughly briefed by Justice Judith Snider in *Laboratoires Servier, et al v Apotex Inc*, 2008 FC 825, 332 FTR 193 (Eng). There, after reviewing much of the relevant jurisprudence, Justice Snider summarized the principles in the following way:

> [77] In sum, the Canadian jurisprudence has provided a broad interpretation of "persons claiming under" the patentee. The ability of a party to claim under a patentee does not necessarily require the existence of an express licence. Where no express licence exists, each case will be determined on its facts to determine whether an implied licence or other right exists that gives rise to a claim "under the patentee".

[370] In *Signalisation de Montreal Inc v Services de Béton Universels Ltée* (1992), 46 CPR (3d) 199 at pp 210-211 (FCA), [1993] 1 FC 341, the Court held that a claim under a patentee arise from a right of use of the invention that can be traced directly back to the patentee. The technical means of giving effect to the right of use could be by licence (express or implied), by assignment or by the terms of sale of an article.

[371] The evidence supporting the Plaintiffs' claims to standing was provided by AstraZeneca's former Chief Legal Officer, Göran Lerenius. In that capacity, he was familiar with the corporate arrangements that existed among the Plaintiffs in these proceedings. The substance of that evidence was not effectively challenged.

[372] Mr. Lerenius testified that Hässle was acquired by AB Astra in the 1960s. After a corporate merger, AB Astra became AstraZeneca AB and Hässle remained its wholly owned subsidiary. In about 1991, Hässle was reorganized and relinquished its research business. It then became a patent owning company. In that capacity it continued to own the 693 Patent.

[373] Mr. Lerenius identified a Company Commissioner Agreement between Hässle and AB Astra signed in 1985. That agreement provided for AB Astra to effectively control all of the business of Hässle. Mr. Lerenius said that there were no other agreements between those parties

concerning Hässle's patent interests. The Company Commissioner Agreement continued to govern the business relationship between Hässle and AstraZeneca AB (as the successor to AB Astra) without interruption. According to Mr. Lerenius, this was the simplest means of giving ongoing effect to AstraZeneca AB's control over Hässle and it fully accorded with Swedish law.

[374] Mr. Lerenius also testified that AstraZeneca AB and AstraZeneca Canada Inc. are affiliate companies in the sense that both are wholly owned subsidiaries of AstraZeneca PLC. He identified a Distribution Agreement entered into between AstraZeneca AB and AstraZeneca Canada Inc. that provided for AstraZeneca AB to supply products to AstraZeneca Canada Inc. intended for resale on a non-exclusive basis. Those products were agreed to be held after delivery at AstraZeneca Canada Inc.'s risk. The agreement makes the following provision for intellectual property rights:

> 24.1 All intellectual property rights relating to the Products shall remain the property of ASTRAZENECA at all times. The Distributor shall not acquire any intellectual property rights relating to the Products and shall only have permission to use rights in so far as is necessary to exercise the rights granted to the Distributor under this Agreement.
>
> 24.2 The Distributor will inform ASTRAZENECA of any intellectual or suspected infringement of any of ASTRAZENECA's intellectual property rights in the Market which comes to the notice of the Distributor. ASTRAZENECA will take all reasonable steps, at its own expense, to prosecute infringers. The Distributor will give ASTRAZENECA all reasonable assistance in such prosecution.

[375] I am satisfied by the evidence of Mr. Lerenius that, by virtue of AstraZeneca AB's control of the business of Hässle under the Company Commissioner Agreement, AstraZeneca

AB effectively controls the 693 Patent and the rights flowing from it. This is a sufficient interest in the Patent to establish AstraZeneca AB's standing as a Plaintiff in these proceedings.

[376] According to other unchallenged evidence, AstraZeneca AB has supplied LOSEC to AstraZeneca Canada Inc. for resale in Canada under the terms of their Distribution Agreement. AstraZeneca AB maintained title to that product up to the point of Canadian delivery. That agreement also grants permission to AstraZeneca Canada Inc. to use AstraZeneca AB's intellectual property rights to the extent necessary to give effect to AstraZeneca Canada Inc.'s contractual rights. Both parties are before the Court and it is implicit that AstraZeneca Canada Inc.'s prosecution of a claim to damages is conducted with the permission of AstraZeneca AB. AstraZeneca Canada Inc.'s rights to exploit the 693 Patent are limited but they are nevertheless contractually supported. I am, therefore, satisfied that the evidence provides a sufficient foundation to support AstraZeneca Canada Inc.'s standing as a Plaintiff in T-1409-04.

VIII. Foreign Issue Estoppel

[377] AstraZeneca argues the Court ought to apply the principles of issue estoppel and abuse of process by relitigation to a number of findings of "fact" made by the United States District Court for the Southern District of New York in earlier litigation between the parties: see *In re Omeprazole Patent Litigation*, 490 F Supp 2d 381 aff'd by the United States Court of Appeals Federal Circuit, *In re Omeprazole Patent Litigation* 536 F 3d 1361.

[378] The issues that Astra seeks to foreclose from an independent review are pleaded at paragraph 45 of its Fourth Amended Statement of Claim:

(a) Apotex's Omeprazole capsules all use identical pellets;

(b) Apotex's Omeprazole capsule pellet cores contain omeprazole, povidone ("PVP"), magnesium hydroxide, and mannitol;

(c) Apotex applies an enteric coating to its Omeprazole capsule pellet cores;

(d) Apotex's Omeprazole capsule pellets are dried until the moisture content is not more than 1.5% by weight;

(e) Apotex's Omeprazole capsule pellets contain an enteric coating layer that includes copolymerized methacrylic acid ("MACP") and triethyl citrate;

(l) Apotex's Omeprazole capsules are oral pharmaceutical preparations;

(g) Apotex's Omeprazole capsule pellets contain a therapeutically effective amount of omeprazole;

(h) Apotex's Omeprazole capsule pellets have cores with a microenvironmental pH between 7 and 12;

(i) Apotex's Omeprazole capsule pellets have a core region containing omeprazole, a sublayer around the core region, and an enteric coating;

(j) The sublayer in Apotex's Omeprazole capsule pellets 'is 2 to 6 microns thick;

(k) Apotex's Omeprazole capsule pellets have a continuous, inert sublayer that hugs the surface of the core and separates the core from the enteric coating; and

(l) Apotex's Omeprazole capsule pellets contain an in situ formed sublayer that is inert, continuous, and rapidly disintegrating in water.

[379] The application of estoppel, at least to the factual findings made by a foreign court, has some theoretical appeal. Permitting the same parties to relitigate identical evidentiary points and to ignore the findings of a competent foreign court may be seen to be a wasteful exercise,

particularly in an age where judicial resources are increasingly stretched and where the costs of litigation are steadily rising. Nevertheless, the practical problems of applying estoppel in a way that will actually protect judicial resources cannot be ignored. Those problems were quite apparent in this case.

[380] Given the discretionary nature of the application of foreign issue estoppel, AstraZeneca could not prudently assume the doctrine would be applied. It, therefore, independently led evidence on all of the above evidentiary points required to make its case. The practical effect of this was that no time was saved. In fact, by pleading estoppel, the trial was substantially lengthened. In response to AstraZeneca's plea of estoppel, Apotex led fact evidence from two attorneys involved in the United States omeprazole proceedings, Martin Endres and Robert Silver. It also led opinion evidence from two legal experts, Judge Benson Legg (retired) and Mr. John Whealan. That evidence described the approach that the United States District Court took to the management of its multi-party infringement actions including the separation of the proceeding into waves. The purpose of this evidence was to attempt to explain the differences between United States and Canadian procedures and substantive patent law and to show that the two systems are sufficiently distinct that the application of estoppel would work an injustice on Apotex.

[381] Considering the somewhat unusual process that was followed in the United States second wave proceedings involving Apotex, the practical disadvantages of applying issue estoppel to only a handful of findings made in that proceeding, and the fact that it is not necessary to rely upon the doctrine to fill a gap in the evidentiary record, I decline to apply the principle here.

IX. Remedies

A. Deception

[382] AstraZeneca argues that Apotex was deceptive in the context of the settlement obtained in earlier NOC proceedings involving the 693 Patent [T-1446-93] and claims, in the result, punitive damages or solicitor/client costs or both. This assertion is based on a misrepresentation that Apotex made in the NOC proceeding concerning its then proposed omeprazole formulation. There Apotex relied on an affidavit sworn by Dr. Paul Niebergall stating that the Apotex omeprazole formulation would contain dibasic sodium phosphate as an ARC. This is a compound exemplified by the 693 Patent. However, unbeknownst to AstraZeneca, when Apotex submitted its application for a New Drug Submission to the Minister, it substituted magnesium hydroxide as the proposed ARC, apparently motivated by the need to avoid another AstraZeneca patent [the 377 Patent] which claimed dibasic sodium phosphate. When Dr. Sherman was examined under oath in the earlier NOC proceeding, he was questioned about the Apotex formulation and the correctness of Dr. Niebergall's affidavit. There he gave the following evidence:

> Q. Now, Apotex then has pending a New Drug Submission which specifies this particular composition, the one that is set out in the Niebergall affidavit; is that correct?
>
> A. Yes, it is.
>
> Q. In that submission this is the only composition that is specified?
>
> A. That's correct. In fact, it's superior to your client's product, which may be irrelevant, but it's substantially superior.
>
> …

> Q. So you only have and you have only ever had only one New Drug Submission in respect of omeprazole; is that correct?
>
> A. Yes.
>
> Q. And the information that is Exhibit 2 to Niebergall's affidavit, that information discloses or those pages, rather, disclose the details of that composition.
>
> A. Yes.
>
> Q. I think you are saying that although in theory Apotex could make changes to that composition as part of the approval process there is no intention on the part of Apotex to do so in this case.
>
> A. That is correct. It has been optimized. That is an excellent formulation. It meets every regulatory requirement and it is superior to your client's product in that it is more stable.
>
> Q. Indeed are you prepared to undertake on the record that Apotex will not make any change to this formulation in respect of its seeking an NOC for omeprazole?
>
> A. No. I can only go so far as to tell you there is no intention to do so, nor can I envision any reason that I would want to do so, but I can't see any reason to bind myself should it ever be necessary to make a change. If the Health Protection Branch comes back and says we want some minor change for some reason we would have to have the right to do that, but I can tell you this categorically, that we will not change it in any way that will bring it within the scope of your client's patent. Your client's patent - - is this a confidential record? [Emphasis added] [See Exhibit 133, Tab 8 at pp 12-14]

[383] Dr. Sherman has acknowledged in this proceeding that Dr. Niebergall's affidavit was wrong insofar as it identified dibasic sodium phosphate and that his own evidence on the point in the NOC proceeding was also not accurate. These mistakes, he now says, were innocent and immaterial. According to Dr. Sherman, the Apotex product required an ARC and that, for the purpose of avoiding the 693 Patent, it did not matter what that substance was. The NOC

settlement was instead based on Apotex's assertion that its product would not incorporate a subcoating layer.

[384] AstraZeneca argues that it does not matter whether the Apotex misrepresentation in the NOC proceeding was innocent or deliberate. It relies on jurisprudence that indicates that "grave consequences" may flow from the failure of a second person to accurately represent the particulars of its proposed product in a NOC proceeding: see *Hoffman-LaRoche Ltd v Nu-Pharm Inc* (1996) 70 CPR (3d) 206 at 213, [1996] FCJ no 1333.

[385] In *AstraZeneca Canada Inc v Apotex Inc*, 2004 FC 1278 at paras 27-33 aff'd 2005 FCA 58, Justice Michael Kelen considered the significance of the Apotex misrepresentation in the context of an application by AstraZeneca to set aside the NOC issued to Apotex. Justice Kelen declined to set aside the Minister's NOC but not before he recognized that the issue of misrepresentation could be relevant in any later infringement proceeding:

> [27] Apotex represented to the Minister that its revised formulation is not materially different than the formulation already the subject of an Order of this Court in a prohibition proceeding under the Regulations between the same parties, with respect to the same patents, and with respect to the same drug.
>
> [28] In *Syntex (U.S.A.) L.L.C. et al. v. Minister of Health et al.* (2001), 15 C.P.R. (4th) 312 I held that if a generic drug company makes inaccurate, misleading, or untrue submissions to the Minister for the purpose of the Regulations, the proper recourse for the patentee is a common law action for infringement of the patent, not judicial review under the *Federal Courts Act*. At paragraph 17 I stated:
>
> > If the generic drug company's new drug submission contains inaccurate or misleading information, the Federal Court of Appeal has repeatedly held that a patentee will be in a position to test the accuracy of a generic drug manufacturer's statements with

> respect to the drug after the product reaches the market, and if the statements or omissions by the generic drug company are shown to be inaccurate, the consequences for the generic drug company "could well be very grave indeed". The patentee has a common law action for an infringement of patent, an injunction and punitive damages.

[386] If the evidence before me had established that Apotex's undisclosed substitution of one ARC for another was a material factor in the settlement of the earlier NOC proceeding, a good case for punitive damages would have been made out. That evidence is lacking here. I am also not satisfied that Apotex deliberately misrepresented its omeprazole formulation to deceive AstraZeneca. There does not appear to have been any particular advantage gained by Apotex misrepresenting its intended ARC to AstraZeneca. However, when the error was identified, Apotex failed in its duty to inform AstraZeneca. Both Dr. Niebergall and Dr. Sherman were careless about the accuracy of their sworn evidence and remiss in not correcting the record at the first available opportunity. The need for scrupulous accuracy and fair dealing under the NOC system is manifest. Parties must understand that carelessness and a lack of absolute candour cannot be condoned. These are matters which may bear on the issue of costs. The parties request that costs be held in reserve. I will, therefore, hear from them at a later point about the significance, if any, of this evidence to the award of costs.

B. Conclusions Re Infringement

[387] Beyond questioning the evidence of Dr. Davies and Dr. Bodmeier on the accuracy and representativeness of the testing data, Apotex did not assert that its Apo-Omeprazole product lacks uniformity. Given regulatory requirements, this is not surprising. The evidence also

discloses that all of the Apotex batches were made in accordance with the same specification using consistent process parameters and with the same concentrations. Apotex's quality control testing of representative batch samples as reported to Health Canada produced consistent and acceptable results. Dr. Davies' representative testing of the Apotex samples he was given consistently established infringement. Dr. Bodmeier testified that Dr. Davies' testing was sufficient to support an inference that every batch of Apo-Omeprazole would be expected to have the same characteristics as those reported by Dr. Davies. This evidence is sufficient to establish that Apo-Omeprazole consistently matches the characteristics found in Claim 1 of the 693 Patent.

[388] Fact evidence was given on behalf of Apotex by its vice-president of business operations, Gordon Fahner. Mr. Fahner has been employed by Apotex in various management positions since 1989, and is thus familiar with its manufacturing and distribution practises.

[389] Mr. Fahner testified that Apotex has made all of its Apo-Omeprazole in Ontario. In the period from 2004 to 2008, its customers included pharmacy wholesalers, large retain chains, banner stores, regional retail chains, independent pharmacies, and hospitals across Canada. Most customer orders have been processed from the Apotex order desk in Toronto and distributed from any of its Toronto, Calgary or Montreal distribution centres. Calgary typically supplied Saskatchewan and west and, until mid-2005 when it closed, Montreal supplied Quebec and New Brunswick. Toronto serviced the remainder of the country which, according to Mr. Fahner,

amounted to about 90% of shipped orders. Fifty-five to 60% of omeprazole sales were shipped to Ontario customers, in some cases for onward distribution[5].

[390] Under cross-examination, Mr. Fahner agreed that Apotex sold Apo-Omeprazole to customers across Canada. The product was then resold throughout Canada to patients. Apotex had sales representatives contacting customers throughout Canada and it promoted its Apo-Omeprazole product on its nationally accessible website and by other promotional means. Apotex also exported its Apo-Omeprazole capsules to its affiliates in the United States, and the Czech Republic, and into several other countries.

[391] I am satisfied on the evidence before me (including Dr. Sherman's evidence and AstraZeneca's read-ins) that, since 2004, Apotex directly and consistently infringed Claims 1, 5, 6 and 19 of the 693 Patent by promoting and selling its Apo-Omeprazole capsules across Canada, and by its international sales. I am also satisfied on the evidence before me that, with some exceptions, the Apo-Omeprazole capsules infringed Claim 13. Apotex also induced infringement by its customers and by end-users throughout Canada. I agree with AstraZeneca that Apotex actively promoted Apo-Omeprazole to customers and directly compared that product to LOSEC for the same medical indications. This is inducing activity as described by Justice Hughes in *Abbvie Corporation v Janssen Inc*, above, at para 106:

> [106] The law in Canada is clear. A person, such as Janssen, who sells a product for an infringing use by another, which product has no other significant commercial use, has induced that infringement,

[5] At a point during Mr. Fahner's direct examination, AstraZeneca objected to the above evidence on the basis that it had never been disclosed as a part of Apotex's document productions. It was conceded that because the evidence could not be corroborated or closely tested, it would not, at this stage of the litigation, be the basis of specific findings.

> and is itself an infringer (see eg. *Dableh v Ontario Hydro* (1996), 68 CPR (3d) 129, at pages 148-149 (FCA)).

C. Limitations

[392] Apotex has pleaded a partial defence to these proceedings based on what, it says, is a two year limitation period.

[393] Apotex contends that, with respect to its sales of Apo-Omeprazole in Ontario, AstraZeneca cannot pursue damages for more than two years before the commencement of these proceedings. This does not appear to present an impediment to the initial proceeding [T-1409-04] which was commenced in 2004. In the case of T-1890-11, Apotex says that, if the Ontario limitation period applies, the claim is statute barred after November 22, 2009. If the limitation period is six years, the claim to damages would be statute barred for any infringing activity that took place before November 22, 2005.

[394] The determination of the applicable limitation period turns on the interpretation of section 39 of the *Federal Courts Act*, RSC, 1985, c F-7, which provides:

39. (1) Except as expressly provided by any other Act, the laws relating to prescription and the limitation of actions in force in a province between subject and subject apply to any proceedings in the Federal Court of Appeal or the Federal Court in respect of any cause of action arising in that province.	39. (1) Sauf disposition contraire d'une autre loi, les règles de droit en matière de prescription qui, dans une province, régissent les rapports entre particuliers s'appliquent à toute instance devant la Cour d'appel fédérale ou la Cour fédérale dont le fait générateur est survenu dans cette province.
(2) A proceeding in the Federal	(2) Le délai de prescription est

Court of Appeal or the Federal Court in respect of a cause of action arising otherwise than in a province shall be taken within six years after the cause of action arose.	de six ans à compter du fait générateur lorsque celui-ci n'est pas survenu dans une province.

[395] Apotex argues that its sales into the Ontario market constitute a cause of action "in that province", such that a two-year limitation applies. Logic would, of course, dictate that sales into each provincial market would thereby be subject to the applicable provincial limitation period in each case.

[396] AstraZeneca contends that its cause of action in this Court cannot be parsed into pieces. Apotex's commercial activity was national and international in scope. While that activity could have been the subject of separate litigation in each province or, presumably, in each place of export, AstraZeneca framed its cause of action in recognition of the national and international character of Apotex's business. AstraZeneca says that it is, accordingly, entitled to the benefit of a six-year limitation period.

[397] It seem to me that one of the distinct purposes of section 39 of the *Federal Courts Act* is to facilitate a judicial forum providing for the one-time resolution of disputes that concern activity crossing provincial boundaries and international borders. If it were otherwise, the burden associated with the segregation and characterization of relevant evidence could be enormous. Problems with establishing when and where title to products passed or where effective delivery occurred would inevitably arise as the responsible party attempted to bring itself within the sphere of the most favourable provincial limitation period. In the case of patent

infringement proceedings the problem would be exacerbated because an infringing sale into one province could also constitute an infringement in another if the same product was resold or reshipped or where there was downstream inducement in other jurisdictions.

[398] The purpose of section 39(2) of the *Federal Courts Act*, was obviously to avoid these types of evidentiary difficulties and to provide a unitary limitation period in cases like this. Support for this view can be found in *Hislop v Canada*, 2008 Carswel Ont 1117, 165 ACWS (3d) 163 (Ont SCJ), which dealt with the same statutory language found in the *Crown Liability and Proceedings Act*, RSC, 1985, c C-50, at section 32.

[399] It follows that the limitation period that applies in this case is six years regardless of the place where the infringing activity took place.

D. Is AstraZeneca Entitled to an Elect an Accounting of Profits?

[400] Whether a successful plaintiff in an infringement action can elect to take an accounting of profits is at the complete discretion of the trial court and is based on equitable considerations. There is no presumption favouring a plaintiff in the granting of this remedy: see *Merck & Co v Apotex Inc*, 2006 FCA 323 at para 127, [2006] FCJ no 1490.

[401] The list of considerations that can apply is non-exhaustive but delay and market abandonment by the patentee were the basis of refusing an election in *Merck*, above.

[402] Apotex has not asserted any specific factors in its post-trial submissions and simply argues that it is up to AstraZeneca to prove its entitlement to this form of relief.

[403] There is not much evidence before me to explain the time this case took to come to trial but the causes for delay after the expiry of the patent in 2008 are of no apparent significance. The initial action was commenced not long after a NOC was issued to Apotex and, of course, the parties were actively involved in similar litigation in the United States. AstraZeneca also points to Apotex's continued infringement after its construction arguments were rejected by the Federal Court of Appeal in 2003 and after it was found to have infringed the equivalent patent in the United States in 2007. AstraZeneca also maintains that it did not abandon the market and made efforts to mitigate through a licensing arrangement with an authorized generic.

[404] I am satisfied that this is an appropriate situation to permit AstraZeneca to elect an accounting of profits. There is no evidence to suggest any of the Plaintiffs have engaged in inequitable conduct or that they have unduly delayed the advancement of this litigation. Apotex, on the other hand, did not alter course when its position did not find favour in earlier judicial proceedings. This is a factor that is relevant to the assessment of its good faith: see *Beloit Canada Ltd v Valmet-Dominion Inc*, [1997] 3 FC 497 (FCA) at para 119, 71 ACWS (3d) 138.

X. Conclusion Re Relief

[405] For the foregoing reasons, I have concluded that Claims 1, 5, 6, 13 and 19 of the 693 Patent are valid. A declaration to that effect is, therefore, granted.

[406] I also find that Apotex, by its manufacture, promotion, and sale of Apo-Omeprazole in Canada and elsewhere, has infringed the rights of the Plaintiffs as granted in the asserted claims.

[407] I will hear the parties concerning costs on a date to be arranged.

JUDGMENT

THIS COURT'S JUDGMENT is that:

[1] It is declared that Claims 1, 5, 6, 13 and 19 of Canadian Letters Patent 1,292,693 are valid and have been infringed by Apotex Inc. by its manufacture, promotion and sale in Canada and elsewhere of Apo-Omeprazole; and

[2] The issue of costs is reserved pending a further hearing to be arranged.

"R.L. Barnes"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1409-04
STYLE OF CAUSE:	ASTRAZENECA CANADA INC. AND AKTIEBOLAGET HÄSSLE v APOTEX INC.
AND DOCKET:	T-1890-11
STYLE OF CAUSE:	ASTRAZENECA AB AND AKTIBOLAGET HÄSSLE v APOTEX INC.
PLACE OF HEARING:	TORONTO, ONTARIO
DATE OF HEARING:	APRIL 7 TO 11, 2014 APRIL 14 TO 17, 2014 APRIL 22 TO 25, 2014 APRIL 28 TO MAY 1, 2014 MAY 5 TO 8, 2014 MAY 12 TO 15, 2014 MAY 20 TO 23 2014 MAY 26 TO 28, 2014 JUNE 2 TO 5, 2014 JUNE 23 TO 26, 2014
JUDGMENT AND REASONS:	BARNES J.
DATED:	MARCH 16, 2015

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