Federal Court  Cour fédérale

Date: 20160907

Dockets: T-1379-13
T-1468-13
T-1368-14

Citation: 2016 FC 1013

Ottawa, Ontario, September 7, 2016

PRESENT: The Honourable Mr. Justice Fothergill

Docket: T-1379-13

BETWEEN:

BAYER INC. and BAYER PHARMA AKTIENGESELLSCHAFT

Plaintiffs
Defendants by Counterclaim

and

COBALT PHARMACEUTICALS COMPANY

Defendant
Plaintiff by Counterclaim

Dockets: T-1468-13
T-1368-14

AND BETWEEN:

BAYER INC. and BAYER PHARMA AKTIENGESELLSCHAFT

Plaintiffs
Defendants by Counterclaim

and

APOTEX INC.

Defendant
Plaintiff by Counterclaim

PUBLIC JUDGMENT AND REASONS
(Confidential version issued on September 7, 2016)

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I. Overview

[1] The plaintiffs are related companies. Bayer Pharma Aktiengesellschaft [Bayer Pharma] is a German corporation that discovers and develops pharmaceuticals for commercial purposes. Bayer Inc. is a Canadian corporation with its head office in Toronto.

[2] The defendant and counter-claimant Apotex Inc. [Apotex] is a generic pharmaceutical corporation with its head office in Toronto.

[3] The defendant and counter-claimant Cobalt Pharmaceuticals Company [Cobalt], now Actavis Pharma Company, is a generic pharmaceutical corporation with its head office in Mississauga.

[4] Schering Aktiengesellschaft [Schering], predecessor in title to Bayer Pharma, was a pharmaceutical company in Germany. On August 31, 2000, Schering filed an application for Canadian Letters Patent No. 2,382,426 [the '426 patent]. The title of the '426 patent is "Pharmaceutical Combination of Ethinylestradiol and Drospirenone for Use as a Contraceptive". The application claimed priority from both a United States and a European patent application filed on August 31, 1999. Bayer Pharma is now the registered owner of the '426 patent.

[5] Ethinylestradiol functions as an estrogen, while drospirenone functions as a progestogen. Together, they inhibit ovulation in the human female. When Schering applied for the '426 patent, it was known that ethinylestradiol and drospirenone could be used in the formulation of an effective oral contraceptive. However, no drug manufacturer had offered the precise formulation disclosed and claimed in the '426 patent for sale to the public.

[6] Based on laboratory tests conducted *in vitro*, drospirenone was known to be acid-labile at a pH of 1.0, meaning it would isomerize into an inactive compound when exposed to an acidic solution of pH 1. The normal pH range of the stomach is 1.0 to 3.0.

[7] Drospirenone is a steroid and is therefore poorly soluble in water. Poorly soluble compounds can be micronized (*i.e.*, ground into very small pieces) to increase their rate of dissolution. However, improving the dissolution rate of an acid-labile drug may cause it to degrade even more quickly in the gastric environment.

[8] A drug's rate of dissolution in the stomach depends in part on its formulation. An enteric coat may be used to protect the active pharmaceutical ingredients in a tablet from the gastric environment, ensuring that the drug is released in the less acidic environment of the small intestine. An immediate release formulation, which has no enteric coat, will rapidly disintegrate in the stomach.

[9] Schering initially developed an oral contraceptive comprising ethinylestradiol and drospirenone as an enterically-coated tablet. One difficulty with an enteric coat, however, is that it may cause variability in the drug's effectiveness in different people. Based on further experiments, including tests conducted *in vivo*, Schering discovered that it was possible to administer a low dose of ethinylestradiol and drospirenone in a micronized or other rapidly dissolving form without using an enteric coat, while still achieving good bioavailability as a contraceptive. Schering considered this to be a novel invention, and therefore sought to protect it by applying for a patent.

[10] Apotex and Cobalt also sell oral contraceptive pills with ethinylestradiol and drospirenone as the active pharmaceutical ingredients. The dosages are similar to those used in the plaintiffs' products. The tablets are also rapidly dissolving and do not have an enteric coat.

[11] The plaintiffs say that Apotex's and Cobalt's products infringe claims 31, 48 and 49 of the '426 patent. Apotex and Cobalt reply that their products are formulated in a manner that brings them outside the scope of the asserted claims. They also maintain that the claims are invalid.

[12] As is common in patent trials, the parties presented voluminous evidence and extensive arguments in support of their respective positions. In the reasons that follow, I have endeavoured to address all those that, in my view, have a potential bearing on the outcome of this dispute. Some aspects of the evidence and argument may not be fully canvassed below, but I have considered it all.

[13] I find that claims 31, 48 and 49 of the '426 patent are not invalid based on any of the asserted grounds of: (i) obviousness; (ii) anticipation; (iii) overbreadth; (iv) insufficiency or ambiguity of the specification; or (v) inutility. I also find that Apotex's and Cobalt's products are formulated in a manner that falls within the scope of claims 31, 48 and 49 of the '426 patent. Apotex's and Cobalt's products therefore infringe claims 31, 48 and 49 of the '426 patent.

II. Background

A. *The Products in Issue*

[14] Bayer Pharma is the registered owner of the '426 patent and is also the patentee. Bayer Inc. is a licensee of the '426 patent and sells oral contraceptive tablets under the names "Yaz" and "Yasmin" with the consent of Bayer Pharma. Both entities are persons claiming under the

patentee Bayer Pharma pursuant to s 55(1) of the *Patent Act*, RSC 1985 c P-4 [the Act]. I will refer to the plaintiffs collectively as Bayer.

[15] Apotex obtained from the Minister of Health a Notice of Compliance to sell generic versions of Bayer's Yasmin tablets under the names "Zamine 21" and "Zamine 28" [Zamine] on August 15, 2013, and a generic version of Bayer's Yaz tablets under the name "Mya" [Mya] on May 8, 2014. The Zamine tablets contain 3 mg of drospirenone and 0.03 mg of ethinylestradiol. The Mya tablets contain 3 mg of drospirenone and 0.02 mg of ethinylestradiol.

[16] Cobalt manufactures and sells generic versions of Bayer's Yasmin tablets under the names "Zarah 21" and "Zarah 28" [Zarah]. The Zarah tablets contain 3 mg of drospirenone and 0.03 mg of ethinylestradiol. Cobalt received regulatory approval to begin marketing the Zarah tablets in Canada on May 31, 2013.

B. *The '426 Patent Generally*

[17] The title of the '426 patent is "Pharmaceutical Combination of Ethinylestradiol and Drospirenone for Use as a Contraceptive". The patent names Wolfgang Heil, Jurgen Hilman, Ralph Lipp and Renate Heithecker as the inventors.

[18] The application for the patent was filed under the provisions of the *Patent Cooperation Treaty*, 19 June 1970, Can TS 1990 No 22 (entered into force 24 January 1978), with an effective filing date in Canada of August 31, 2000. It claimed priority from both a United States and a

European patent application, the international precursors to the ‘426 patent. Both patents were filed on August 31, 1999. The date of publication is March 8, 2001.

[19] The ‘426 patent was issued to Schering on February 28, 2006. Bayer Pharma became the registered owner of the patent on October 6, 2011. Bayer Inc. is a licensee.

[20] The application for the ‘426 patent was filed with the Canadian Patent Office after October 1, 1989. The provisions of the “new” *Patent Act*, which applies to all patent applications filed after that date, are therefore relevant to this action. Unless found to be invalid, the term of the ‘426 patent will expire on August 31, 2020.

C. *Previous Proceedings Involving the Parties*

(1) The Cobalt Proceedings

[21] In December 2011, Cobalt sought regulatory approval to sell a generic version of Bayer’s Yaz tablets. The proposed composition was similar to Cobalt’s Zarah tablets, but contained 3 mg of drospirenone and 0.02 mg of ethinylestradiol. Cobalt applied to the Minister of Health [the Minister] for a Notice of Compliance, alleging that the process by which its drug would be manufactured would not infringe claim 31, and dependent claims 48 and 49, of the ‘426 patent, and that all claims of the patent asserted by Bayer were invalid.

[22] In response, Bayer commenced an application under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [NOC Regulations] to prohibit the Minister from issuing

a Notice of Compliance to Cobalt until the expiry of the ‘426 patent. On October 22, 2013, in *Bayer Inc v Cobalt Pharmaceuticals Company*, 2013 FC 1061 [*Bayer v Cobalt*], Justice Hughes granted Bayer’s application for prohibition.

[23] One argument advanced by Cobalt before Justice Hughes was that claim 31 of the ‘426 patent was limited to micronized drospirenone particles. Justice Hughes found that claim 31 was not so limited, as it encompassed all drospirenone particles that dissolve rapidly in the manner specified in the claim. Justice Hughes held that none of Cobalt’s allegations of non-infringement and invalidity were justified. Specifically, Justice Hughes found that claim 31 was not obvious, and was not invalid on the grounds of inutility, lack of sound prediction, overbreadth, insufficiency or ambiguity. It does not appear that Cobalt challenged the ‘426 patent on the ground of anticipation.

[24] Cobalt’s appeal of Justice Hughes’ decision was dismissed by the Federal Court of Appeal on May 4, 2015 (*Cobalt Pharmaceuticals Company v Bayer Inc*, 2015 FCA 116 [*Cobalt v Bayer FCA*]). The Court of Appeal upheld Justice Hughes’ construction of the patent and confirmed that Cobalt’s allegations of non-infringement and invalidity were not justified. As a result, Cobalt is currently unable to offer its generic version of Bayer’s Yaz product for sale until the ‘426 patent expires.

(2) The Apotex Proceedings

[25] Similar proceedings under the NOC Regulations were commenced by Apotex against Bayer in July 2012. Apotex sought regulatory approval for its generic version of Bayer’s Yaz

tablets on the basis of non-infringement of claim 1 and dependent claims 2 and 8; claim 30; and claim 31 and dependent claims 36, 37, 39 to 42 and 47 to 50. In response, Bayer brought an application to prohibit the Minister from issuing a Notice of Compliance to Apotex.

[26] In a decision dated May 7, 2014, Justice Hughes dismissed Bayer's application (*Bayer Inc v Apotex Inc*, 2014 FC 436 [*Bayer v Apotex*]). He found that none of the allegations made by Apotex regarding the invalidity of the '426 patent on the grounds of anticipation, ambiguity and insufficiency were justified. However, he also concluded that Bayer had not met its burden of proving, on a balance of probabilities, that Apotex's allegations of non-infringement were unjustified. He ruled that Apotex's product did not fall within the claims in issue, and Apotex was therefore able to bring its generic version of Bayer's Yaz tablets to market.

D. *The Pleadings*

[27] Bayer commenced an action against Cobalt on August 14, 2013 (T-1379-13), after Cobalt began marketing its Zarah tablets in Canada. In its statement of claim, Bayer alleges that Cobalt has infringed claims 1, 2, 4-7, 30, 31, 48, 49 and 52 of the '426 patent. Cobalt denies the allegation of infringement and, by counterclaim, alleges that the claims are invalid.

[28] Bayer commenced an action against Apotex on August 30, 2013 (T-1468-13), alleging that Apotex has infringed claims 1, 2, 4-7, 30, 31, 48, 49 and 52 of the '426 patent by manufacturing and selling its Zamine tablets in Canada. Apotex denies the allegation of infringement and, by counterclaim, alleges that the claims are invalid.

[29] Bayer commenced a second action against Apotex on June 4, 2014 (T-1368-14), with respect to its Mya tablets. Bayer alleges that Apotex has infringed claims 1, 2, 4-7, 30, 31, 48 and 49 of the ‘426 patent by manufacturing and selling its Mya tablets in Canada. Apotex denies the allegation of infringement and, by counterclaim, alleges that the claims are invalid.

[30] The three actions were consolidated by order of this Court dated October 2, 2014. In these proceedings, Cobalt has agreed to be bound by this Court’s determination respecting the validity of the ‘426 patent in the Apotex case and any appeals that may follow. Cobalt therefore relies on Apotex’s evidence and submissions regarding validity.

[31] On January 11, 2016, the first day of trial, Bayer informed the Court that it is seeking a declaration of infringement against Apotex and Cobalt only in respect of claim 31 of the ‘426 patent and its dependent claims, claims 48 and 49. The proceedings have been bifurcated, and this decision concerns only the questions of validity and infringement.

III. The ‘426 Patent in Detail

[32] The field of the invention is described at page 1 of the ‘426 patent:

> FIELD OF THE INVENTION
>
> The present invention relates to a pharmaceutical composition comprising drospirenone and ethinylestradiol, a method of providing dissolution of drospirenone, methods of inhibiting ovulation by administration of drospirenone and the use of drospirenone and ethinylestradiol for inhibiting ovulation.

[33] This is followed by the "Background of the Invention", which acknowledges that oral contraceptives containing a combination of a gestagen and an estrogen have been common since the 1960s. The gestagen component provides contraceptive reliability. The patent recognizes that one such gestagen, drospirenone, is known to be useful in treating several disorders. It is acknowledged that a combination of drospirenone and ethinylestradiol has been suggested as a possible, but not a preferred, combination for an oral contraceptive.

[34] The next section is titled "Summary of the Invention", and states that a minimum and a maximum dosage level of drospirenone have been determined.

> SUMMARY OF THE INVENTION
>
> In the course of research leading to the present invention, it has surprisingly been found that a hitherto undisclosed minimum dosage level of drospirenone is required for reliable contraceptive activity. Similarly, a preferred maximum dosage has been identified at which unpleasant side effects, in particular excessive diuresis, may substantially be avoided.

[35] Page 4 sets out a "Detailed Disclosure of the Invention". The patent states that to ensure good bioavailability of drospirenone, it should be provided in a form that promotes rapid dissolution. It then discusses micronization and provides the parameters of particle size and particle distribution, as well as dissolution parameters. The patent states that it is possible to provide the product in micronized form or by spraying it from a solution on to an inert carrier.

> DETAILED DISCLOSURE OF THE INVENTION
>
> Drospirenone, which may be prepared substantially as described in, *e.g.*, US 4,129,564 or WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore

advantageously provided in a form that promotes rapid dissolution thereof.

It has surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm2/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 μm, and preferably ≤ 20 particles with a diameter of ≥ 10 μm and ≤ 30 μm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs *in vitro* ("rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes, in particular at least 80% over about 20 minutes, of drospirenone from a tablet preparation containing 3 mg of drospirenone in 900 ml of water at 37°C determined by the USP XXIII Paddle Method using a USP dissolution test apparatus 2 at 50 rpm). Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a suitable solvent, *e.g.* methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition.

Without wishing to be limited to any particular theory, it appears that the *in vitro* dissolution rate of drospirenone is connected to the dissolution rate *in vivo* resulting in rapid absorption of drospirenone *in vivo* on oral administration of the compound. This is an advantage because isomerization of the compound in the gastric environment and/or hydrolysis in the intestine is substantially reduced, leading to a high bioavailability of the compound.

With respect to ethinylestradiol which is also a sparingly soluble substance, though less sensitive to degradation than drospirenone under conditions prevailing in the gastrointestinal tract, it is also an advantage to provide it in micronized form or sprayed from a solution, *e.g.* in ethanol, onto the surface of inert carrier particles. This has the added advantage of facilitating a more homogenous distribution of the ethinylestradiol throughout the composition which might otherwise be difficult to obtain because ethinylestradiol is incorporated in extremely small amounts. When ethinylestradiol is provided in micronized form, it preferably has the following particle size distribution as determined under the microscope: 100% of the particles have a diameter of ≤ 15.0 μm, 99% of the particles have a diameter of ≤ 12.5μm, 95% of the particles have a diameter of ≤ 10.0 μm, and 50% of the particles have a diameter of ≤ 3.0 μm. Furthermore, no particle is larger

> than 20 μm, and ≤ 10 particles have a diameter of ≥ 15 μm and ≤ 20 μm.
>
> To obtain a more rapid rate of dissolution, it is preferred to include carriers or excipients which act to promote dissolution of both active substances. Examples of such carriers and excipients include substances that are readily soluble in water such as cellulose derivatives, carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, gelled starch, gelatin or polyvinylpyrrolidone. In particular, it appears as though polyvinylpyrrolidone might be particularly helpful to promote dissolution.
>
> The composition of the invention preferably comprises drospirenone in an amount corresponding to a daily dosage of from about 2.5 mg to about 3.5 mg, in particular about 3 mg. The amount of ethinylestradiol preferably corresponds to a daily dosage of from about 0.015 mg to about 0.04 mg, in particular from about 0.015 mg to about 0.03 mg. More particularly, the present composition comprises an amount of drospirenone corresponding to a daily dosage of from about 3.0 to about 3.5 mg and ethinylestradiol in an amount corresponding to from about 0.015 to about 0.03 mg.
>
> Apart from its ability to inhibit ovulation, the composition of the invention has been found to possess pronounced anti-androgenic properties and may therefore be used in the prevention or treatment of androgen-induced disorders, in particular acne. Such use may be independent from or concomitant with the use as a contraceptive disclosed above. Furthermore, since drospirenone is an aldosterone antagonist, it has diuretic properties and is therefore suitable for counteracting the water-retentive properties of ethinylestradiol.
>
> In a particular embodiment, the invention relates to a pharmaceutical preparation consisting of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days, wherein each of said daily dosage units comprises a combination of drospirenone in an amount of from about 2 mg to about 4 mg and ethinylestradiol in an amount from about 0.01 to about 0.05 mg.

[36] The detailed disclosure describes carriers and excipients, particular dosages, other uses, dosage packaging, daily dosages, and rest periods.

[37] The patent states at page 9 that the composition of the invention may be formulated in any manner known in the pharmaceutical art:

> The composition of the invention may be formulated in any manner known in the pharmaceutical art. In particular, as indicated above, the composition may be formulated by a method comprising providing drospirenone and, if desired, ethinylestradiol in micronized form in said unit dosage form, or sprayed from a solution onto particles of an inert carrier in admixture with one or more pharmaceutically acceptable excipients that promote dissolution of the drospirenone and ethinylestradiol so as to promote rapid dissolution of drospirenone and preferably ethinylestradiol on oral administration.

[38] There follows a list of examples of suitable excipients, together with the observation that the tablets may be film-coated and that the composition may be in liquid form. Packaging units, parenteral formulation and transdermal formulations are also discussed.

[39] Beginning at page 11, the patent provides five examples of tests conducted by the named inventors. Example 1 deals with the preparation of tablets containing drospirenone and ethinylestradiol, both micronized. Example 2 deals with the dissolution rate of the drospirenone in such tablets. Example 3 deals with the dissolution rate of ethinylestradiol. Example 4 addresses the bioavailability of drospirenone and ethinylestradiol. Example 5 deals with the contraceptive efficacy of formulations containing those components.

[40] The Claims of the patent, 53 in total, then follow.

IV. The Claims in Issue

[41] Claim 31 is the only independent claim in issue. It reads as follows:

> A pharmaceutical composition comprising:
>
> from about 2 mg to about 4 mg of drospirenone particles, wherein the drospirenone is in a form, which when provided in a tablet containing 3 mg of drospirenone, has a dissolution such that at least 70% of said drospirenone is dissolved in 900 ml of water at 37° C. (±0.5° C) within 30 minutes, as determined by USP XXIII Paddle Method using a USP dissolution test apparatus 2 at a stirring rate of 50 rpm, including 6 covered glass vessels and 6 paddles;
>
> about [*sic*] 0.01 mg to about 0.05 mg of 17α-ethinylestradiol; and one or more pharmaceutically acceptable carriers; the composition being in an oral dose form, and the composition being effective for oral contraception in a human female.

[42] Claims 48 and 49 are also in issue, but only as they depend from claim 31.

[43] Claim 48, as it depends from claim 31, reads as follows:

> A composition or kit according to claim 31, wherein the amount of drospirenone is from 2.5 mg to 3.5 mg, and the amount of 17α-ethinylestradiol is from 0.015 mg to 0.04 mg.

[44] Claim 49, as it depends from claim 31, reads as follows:

> A composition or kit according to claim 31, wherein the 17α-ethinylestradiol is provided in an amount of from about 0.01 to about 0.04 mg and the drospirenone is provided in a form whereby the drospirenone is exposed to the gastric environment upon dissolution.

V. Comity and *Stare Decisis*

[45] The parties disagree on the extent to which this Court is bound by the findings of fact and law made by the Federal Court of Appeal and by Justice Hughes in the related NOC proceedings.

The parties accept the general proposition that pronouncements of law made by higher courts are binding pursuant to the doctrine of *stare decisis*. However, they differ on whether this Court is bound to follow prior findings of law that are heavily dependent on expert evidence, such as claim construction. They also disagree over the extent to which I should abide by Justice Hughes' conclusions pursuant to the doctrine of comity.

[46] Bayer submits that this Court should adhere to the Federal Court of Appeal's construction of the '426 patent unless the evidence demonstrates the prior construction was wrong, or if different evidence compels a different result. Bayer relies on the Federal Court of Appeal's decisions in *Allergan Inc v Canada (Minister of Health)*, 2012 FCA 308 at paragraphs 50-51 [*Allergan*] and *Pfizer Canada Inc v Apotex Inc*, 2014 FCA 250 at paragraph 59 [*Pfizer Canada*]. Bayer also urges this Court to adopt additional conclusions reached by the Federal Court of Appeal and by Justice Hughes in the NOC context, including that the '426 patent is not invalid on the grounds of obviousness, insufficiency or overbreadth.

[47] Cobalt says that findings made in a NOC proceeding do not, as a matter of law, constitute a final determination of the validity or infringement of a patent, citing the Supreme Court of Canada's decision in *Eli Lilly & Co v Novopharm Ltd*, [1998] 2 SCR 129 at paragraphs 95-96, [1998] ACS No 59. Cobalt submits that the scope of the evidence adduced in an action for infringement is much broader than in a NOC proceeding, and this Court is therefore free to depart from the conclusions reached by the Federal Court of Appeal and by Justice Hughes.

[48] Cobalt also says that a court's construction of a claim in the NOC context is not binding in a subsequent action for infringement, but may carry persuasive weight where the claim was construed without the need for specialized knowledge (citing *AstraZeneca Canada Inc v Apotex Inc*, 2015 FC 322 at paras 175-79). Cobalt cautions that, given the different evidentiary record in an action for infringement, relying on the conclusions of the judge who heard the NOC proceeding may constitute a grave error (citing *AstraZeneca Canada Inc v Apotex Inc*, 2014 FC 638 at paras 34, 36, 42, aff'd on other grounds 2015 FCA 158, leave to appeal to SCC granted [*AstraZeneca*]).

[49] Apotex says that findings made in the NOC context should have no bearing on this action (citing *Eli Lilly Canada Inc v Novopharm Ltd*, 2007 FCA 359 at para 41). Apotex takes the position that the Federal Court of Appeal's findings, even on questions of law, are not strictly binding, but acknowledges they may be "very persuasive". With respect to comity, Apotex says that individual judges may determine how the doctrine is to be applied having regard to the particular jurisdiction that is being exercised (citing *Allergan* at para 48). Apotex, like Cobalt, cautions that it would be an error for this Court to defer to findings made in the NOC proceedings because different jurisdictions are being exercised and the evidence is not the same.

[50] It appears that the law on this point is not entirely settled. It is clear the principles of *stare decisis* and comity apply within the NOC context, where the courts are exercising the same jurisdiction (*Allergan* at paras 50-51). However, it is less clear whether these principles apply with the same force, or in the same manner, between NOC proceedings and a subsequent action

for infringement and impeachment. While the legal principles may be the same, the evidentiary context is markedly different.

[51] Claim construction is a question of law for the judge (*Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 61 [*Whirlpool*]). Through the operation of *stare decisis*, pronouncements of law made by higher courts are binding on lower courts. However, as noted by Cobalt and Apotex, this Court has also held that NOC proceedings cannot result in a final determination of the validity or infringement of a patent because they are summary in nature, they address different issues than those that arise in trials, and they are decided on the basis of affidavit evidence (*AstraZeneca* at para 27).

[52] In this case, the principle of *stare decisis* is relevant only to the question of claim construction. The Federal Court of Appeal construed claim 31 as embracing all rapidly dissolving drospirenone particles which, when formulated in a tablet, meet the required dissolution properties (*Cobalt v Bayer FCA* at paras 33, 76). This is a finding of law. However, in the Cobalt proceedings, Justice Stratas remarked in *obiter* that claim construction should not be viewed as a "pure question of law" because the court does not construe a patent in a factual vacuum. He remarked that it is difficult to "cleave off" those aspects of claim construction that flow from an appreciation of the expert evidence and the words of the patent (*Cobalt v Bayer FCA* at paras 17-20). Justice Stratas nevertheless acknowledged that binding jurisprudence treats claim construction as a pure question of law. I agree with this conclusion.

[53] To the extent that this Court may have discretion to follow or depart from the previous construction adopted in the NOC proceedings, I consider the Federal Court of Appeal's prior construction to be *prima facie* binding, but acknowledge that it may be revisited if warranted by the evidence. In other words, I will adhere to the construction given to the '426 patent by Justice Hughes and by the Federal Court of Appeal unless a party provides good reason not to. The same holds true when defining the "inventive concept" of the patent and determining the "promise" of the patent, both of which are aspects of claim construction and are therefore questions of law (*Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61 at para 67 [*Sanofi-Synthelabo*]; *Weatherford Canada Ltd v Corlac Inc*, 2011 FCA 228 at para 24, leave to appeal to SCC refused [*Weatherford*]; *Astrazeneca Canada Inc v Mylan Pharmaceuticals ULC*, 2011 FC 1023 at para 87, aff'd on other grounds 2012 FCA 109 [*Astrazeneca Canada*]).

[54] Previous findings of fact or mixed fact and law made in the NOC context are potentially persuasive, but they must be approached with caution. For example, Justice Hughes previously defined the "person of ordinary skill in the art" [POSITA, skilled person or person skilled in the art] in the NOC proceedings, but this is a question of mixed fact and law. It must therefore be determined anew based upon the evidence adduced in these proceedings. Obviousness is generally considered to be a question of fact or mixed fact and law, to which the principle of comity does not apply (*Wenzel Downhole Tools Ltd v National-Oilwell Canada Ltd*, 2012 FCA 333 at para 44 [*Wenzel*]; *Allergan* at para 44). The same holds true for the issues of ambiguity, overbreadth, utility, and insufficiency.

VI. Issues

[55] Bayer maintains that claims 31, 48 and 49 of the ‘426 patent are valid and have been infringed by Apotex and Cobalt. Apotex and Cobalt deny the allegations of infringement and, by counterclaim, allege that the claims in issue should be declared invalid.

[56] Apotex asserts invalidity on five grounds: (i) obviousness; (ii) anticipation; (iii) overbreadth; (iv) insufficiency or ambiguity of the specification; and (v) inutility.

VII. Preliminary Observations Regarding the Evidence

A. *Objections to the Expert Evidence*

[57] All parties submitted objections in writing to the expert reports filed by opposing parties. None of the parties devoted any significant time to addressing these objections in their oral submissions, although many were raised in the course of the trial and were ruled on accordingly.

[58] Bayer submitted three documents titled “Particulars of Objection to Expert Witnesses”, one dated November 16, 2015, and a further two dated January 4, 2016. Bayer indicated that it would object at trial to any reference to documents that were not included in the defendants’ pleadings, and to any expert opinions that were based on those documents. Bayer also stated that it would object to the admissibility of certain reply statements filed by Apotex’s experts on the ground that they were outside the scope of the pleadings. In addition, Bayer asserted that the evidence strayed beyond the mandate of the experts, the experts were not granted leave to file

replies, and the reports relied on inadmissible testing because they did not comply with the Notice to the Parties and Profession re: Experimental Testing dated February 27, 2014 [Notice].

[59] Bayer made similar objections with respect to the admissibility of expert reports filed on behalf of Cobalt, and also to testimony regarding these matters. Bayer alleged that Cobalt had failed to abide by the deadlines contained in the Notice, failed to abide by the Code of Conduct for Expert Witnesses [Code of Conduct] pursuant to Rule 52.2 of the *Federal Courts Rules*, SOR/98-106 [*Federal Courts Rules*], relied on undisclosed materials, attempted to present evidence contrary to an admission made in its pleadings, and offered information that strayed beyond the experts' mandates.

[60] Apotex submitted extensive written objections to the expert reports submitted on behalf of Bayer. Cobalt largely adopted the objections made by Apotex, and submitted a document that cross-referenced the expert reports prepared by Bayer's experts for the Apotex case with those they prepared for the Cobalt case.

[61] Apotex raised the fundamental objection that Bayer had not produced all relevant documents related to the testing that was carried out by their experts. Apotex also objected to specific paragraphs of Bayer's expert reports on a wide range of grounds, including non-compliance with the Code of Conduct. Apotex expressed concern about the adequacy of the experts' qualifications to offer certain opinions, inconsistency in testing methods, novelty of testing methods, and unwarranted speculation.

[62] I am satisfied that all parties disclosed sufficient information to ensure that opposing parties were not taken by surprise and were given an adequate opportunity to challenge the expert evidence that they considered to be unhelpful to their respective cases. Cross-examination did not reveal any shortcomings in disclosure or lack of notice that may have caused unfairness to any party. Bayer abandoned its reliance on K-means cluster analysis, which was one of the novel testing methods to which Apotex objected. Limitations in the qualifications of all expert witnesses to offer certain opinions were explored in cross-examination, as were any conclusions that might be considered speculative.

[63] The parties had ample opportunity in the course of cross-examination to challenge expert witnesses on their opinions, and they did so. I have based my conclusions on evidence that I found to be both admissible and probative. I have disregarded evidence that in my view exceeded an expert witness' qualifications, and I have placed no weight on viewpoints that were unsupported by the evidence or unduly speculative. My reasons for accepting some evidence and opinions, and rejecting others, may be found in the analysis that follows.

B. *"Blinding" of Expert Witnesses*

[64] Apotex argues that the evidence of its expert witnesses should be preferred to those who testified on behalf of Bayer, because they reached their conclusions without knowing the nature and content of the patent in issue or the legal positions of the parties. In contrast, Apotex notes that Bayer's expert witnesses have testified in support of this and similar patents on many occasions, and are intimately familiar with its subject-matter.

[65] Although the "blinding" of experts has recently found some favour in this Court, it is not a principle of law that applies in all cases (*Shire Canada Inc v Apotex Inc*, 2016 FC 382 at para 45 [*Shire*]; *Eli Lilly Canada Inc v Apotex Inc*, 2015 FC 875 at para 166 [*Eli Lilly*]; *AstraZeneca* at para 322). The fact that expert witnesses were blinded may be persuasive and helpful in weighing their evidence where credibility concerns arise (*Shire* at para 45; *Eli Lilly* at paras 163-66). However, the Court's principal concern remains the substance of the expert's opinion and the reasoning that led to that opinion.

[66] As Justice Locke has observed, if an expert's opinion is well supported, then there may be no reason to place less weight on the expert's evidence merely because he or she was not blinded to certain facts when forming that opinion (*Shire* at para 45). Moreover, the blinding of an expert witness is "no guarantee" that the expert's evidence is reliable. There is always a possibility that an unscrupulous party may seek opinions from a number of blinded experts, and retain only those whose opinions the party considers favourable to its legal position (*Shire* at para 46). I have not found the blinding of expert witnesses to be a significant factor in deciding the legal and factual issues raised by this case.

VIII. Claim Construction and Validity

A. *Fact and Expert Witnesses*

[67] Apotex, the plaintiff by counterclaim on the issue of validity, submitted the evidence of the following expert witnesses to address patent construction and validity:

a) **Dr. Kenneth Morris** of Brooklyn, New York. He is a professor and Director of the Lachman Institute for Pharmaceutical Analysis at Long Island University. He was qualified as an expert in pharmaceutics and pharmaceutical materials science. Dr. Morris provided his opinion on whether the ‘426 patent is invalid based on obviousness, ambiguity, insufficiency, overbreadth, and inutility.

b) **Dr. Alan F. Parr** of Cary, North Carolina. He is an independent consultant on biopharmaceutics and pharmaceuticals. He was qualified as an expert in the biopharmaceutics of pharmaceuticals and transport and fate of drugs and dosage forms through the gastrointestinal tract. Dr. Parr provided his opinion on whether the ‘426 patent is invalid based on obviousness, ambiguity, insufficiency, overbreadth, and inutility.

c) **Dr. James Simon** of Washington, D.C. He is a clinical professor in the Division of Reproductive Endocrinology and Infertility in the Department of Obstetrics and Gynecology at George Washington University School of Medicine. He was qualified as a medical doctor and clinician expert in gynecology, reproductive endocrinology and fertility, including specifically the study of the female reproductive system, sex hormones used in contraception, oral (including combined) contraceptives, and the practice of clinical trials that study and develop contraceptives. Dr. Simon provided his opinion on whether the ‘426 patent is invalid based on anticipation.

d) **Dr. Michael Cima** of Cambridge, Massachusetts. He is the David H. Koch Professor of Engineering and MIT Professor of Materials Science and Engineering at Massachusetts Institute of Technology. He was qualified as an expert in materials science and engineering, pharmaceutical technology development, and manufacture of drug delivery

systems and products, ascertaining the physical chemical properties of drug substances and pharmaceutical excipients, and the instrumentation and methods used in the analysis of drug substances and pharmaceutical products, including infrared and Raman spectroscopy and optical microscopy. Dr. Cima provided his opinion on whether the ‘426 patent is invalid based on anticipation.

[68] Bayer, the defendant on validity, called three fact witnesses:

a) **Dr. Johannes W. Tack** of Berlin, Germany. He was a formulation scientist during the 1980s and 1990s at Schering. He was responsible for developing a drospirenone formulation for use as an oral contraceptive and is a named inventor of a patent involving drospirenone in the United States.

b) **Dr. Renate Heithecker** of Berlin, Germany. She worked as a pharmacist and clinician at Schering during the 1980s and 1990s. She designed and conducted clinical studies to determine the contraceptive efficacy of a drospirenone and ethinylestradiol formulation. She is a named inventor of the ‘426 patent.

c) **Dr. Michael Karl Hümpel** of Lubeck, Germany. He worked as a pharmacokineticist at Schering during the 1980s and 1990s and was involved in developing a drospirenone formulation for use as an oral contraceptive.

[69] Bayer also submitted the evidence of the following expert witnesses:

a) **Dr. Kurt Barnhart** of Philadelphia, Pennsylvania. He is a professor of obstetrics and gynecology at the University of Pennsylvania. He was qualified as an expert in obstetrics and gynecology with a particular expertise in reproductive endocrinology and fertility;

the female reproductive system; the development of new contraceptives, including combined oral hormonal contraceptives, clinical trials for contraceptives, and the conduct of those involved in clinical trials for contraceptives. Dr. Barnhart provided his opinion on whether the ‘426 patent is invalid for anticipation based on clinical trials performed by Schering and Berlex, an affiliate of Schering.

b) **Dr. Martyn Davies** of Nottingham, United Kingdom. He is a professor in biomedical surface chemistry at the University of Nottingham and co-founder of Juniper Pharma Services [Juniper], a pharmaceutical development and advanced characterization company. He was qualified as an expert in pharmaceutical formulation, including the research, development, manufacture, characterization, testing and analysis of pharmaceutical formulations, including ascertaining the physical and chemical properties of drug substances and pharmaceutical excipients using, among other techniques, confocal Raman spectroscopy, Fourier Transform Raman spectroscopy [FT Raman spectroscopy], infrared spectroscopy, polarized light optical microscopy, dissolution testing, and high performance liquid chromatography [HPLC]. Dr. Davies provided his opinion on whether the ‘426 patent is invalid based on obviousness, overbreadth, ambiguity and insufficiency.

B. *General Observations Regarding the Evidence*

[70] The expert and fact witnesses called to testify regarding the issues of claim construction and validity were generally credible. They all presented impressive qualifications and testified in a manner that was forthright and responsive, if sometimes opinionated and overly defensive of their conclusions.

C. *Governing Principles and Relevant Date*

[71] Before determining whether a patent is valid and whether it has been infringed, it is first necessary to construe the claims in issue. The claims must be construed as of the date of publication, which is March 8, 2001 (*Whirlpool* at para 55). The Court examines the description contained in the patent to identify its "essential elements", and may be aided by expert evidence regarding the meaning of specific terms (*Whirlpool* at paras 43, 45, 57).

[72] The canons of claim construction are found in the Supreme Court of Canada's decisions in *Whirlpool* at paragraphs 49-55; *Free World Trust v Électro Santé Inc,* 2000 SCC 66 at paragraphs 44-54 [*Free World Trust*]; and *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504 at paragraph 27, 122 DLR (3d) 203. They are as follows:

- Claims are to be read in an informed and purposive way with a mind willing to understand, viewed through the eyes of the person skilled in the art as of the date of publication having regard to the common general knowledge;
- Adherence to the language of the claims allows them to be read in the manner the inventor is presumed to have intended and in a way that is sympathetic to accomplishing the inventor's purpose, which promotes both fairness and predictability; and
- The whole of the specification should be considered to ascertain the nature of the invention, and the construction of claims must be neither benevolent nor harsh, but should instead be reasonable and fair to both the patentee and the public.

D. *Person of Ordinary Skill in the Art*

[73] In order to construe the claims in issue, the Court must define the person skilled in the art. This is "the person to whom the patent is said to be addressed, through whose eyes the Court is to read the patent, and who stands as the criterion for the determination of obviousness" (*Amgen Canada Inc v Apotex Inc*, 2015 FC 1261 at para 42).

[74] Bayer says that the '426 patent is directed to a pharmaceutical formulator with a degree in pharmacy or chemistry, along with several years of industrial experience in the field of pharmaceutical formulation. This closely follows the definition Justice Hughes provided in *Bayer v Cobalt* (at para 38).

[75] Apotex does not take serious issue with Bayer's definition. According to Apotex, the only point of contention between the parties is the POSITA's degree of speciality in the area of pharmacokinetics. Apotex argues that "where a patent is of a highly technical nature, the person skilled in the art will be someone possessing a high degree of expert scientific knowledge in the particular field of art to which the patent relates" (citing *Apotex Inc v Merck & Co*, 2010 FC 1265 at para 58). Apotex says that the '426 patent specifically relates to pharmacokinetics and therefore cannot be understood without adequate experience and knowledge in that field.

[76] Apotex's experts, Drs. Morris and Parr, defined the skilled person as a team of individuals whose members include pharmaceutical materials scientists, pharmaceutical formulators, pharmacokineticists, pharmacologists and clinician researchers, all of whom would

be persons working in their relevant fields. Dr. Davies was not averse to characterizing the skilled person as a team, but insisted that the skilled person would be primarily focused on drug formulation, not pharmacokinetics. He acknowledged that the skilled person would have at least some knowledge of pharmacokinetics.

[77] Based on the evidence and submissions of the parties, I would define the POSITA as a pharmaceutical formulator with a degree in pharmacy or chemistry along with several years of industrial experience in the field of pharmaceutical formulation. This pharmaceutical formulator would have at least a working knowledge of pharmacokinetics.

E. *Common General Knowledge of the POSITA*

[78] The patent must be construed taking into account the "common general knowledge" shared by persons skilled in the art (*Free World Trust* at para 44; *Whirlpool* at para 53). This is the knowledge possessed by the POSITA at the relevant time, and includes what the POSITA would reasonably be expected to know (*Sanofi-Synthelabo* at para 70; *Whirlpool* at para 74). The common general knowledge of a POSITA must be established on a balance of probabilities and cannot be assumed (*Uponor AB v Heatlink Group Inc*, 2016 FC 320 at para 47 [*Uponor*]).

[79] The assessment of the common general knowledge is governed by the principles that are found in *Eli Lilly & Co v Apotex Inc*, 2009 FC 991 at paragraph 97 and *General Tire & Rubber Co v Firestone Tyre & Rubber Co*, [1972] RPC 457 at 482-483, [1971] FSR 417 (UKHL):

- The common general knowledge imputed to the POSITA must be carefully distinguished from what in patent law is regarded as public knowledge;

- Common general knowledge is a different concept derived from a common sense approach to the practical question of what would in fact be known to an appropriately skilled addressee – the sort of man, good at his job, who could be found in real life;
- Individual patent specifications and their contents do not normally form part of the relevant common general knowledge, although there may be specifications which are so well known that they do form part of the common general knowledge, particularly in certain industries;
- Regarding scientific papers generally:
    - It is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, or in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates;
    - A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated;
    - Such a piece of knowledge only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art; and
    - It is difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art.

[80] Based on the evidence adduced in this case, I am satisfied that a POSITA would have understood the following as the common general knowledge as of the relevant date for claim construction, *i.e.*, March 8, 2001:

- Drospirenone could be used in the formulation of an effective oral contraceptive, and also in treatments for diuresis, hypersensitivity, hormonal imbalance, drug dependence and symptoms of androgenisation;
- Ethinylestradiol could be used in the formulation of an effective oral contraceptive;
- Drospirenone could be used in the formulation of an effective oral contraceptive in amounts ranging from 1 mg to 10 mg (preferably 3 mg) when combined with 0.01 mg to 0.05 mg (preferably 0.03 mg) of ethinylestradiol;
- Drospirenone was a steroid and therefore poorly soluble in water;
- Poorly soluble compounds could be micronized to increase their rates of dissolution;
- Drospirenone was acid-labile *in vitro* at a pH of 1, leading to isomerization *in vitro*;
- The normal pH range of the stomach is 1.0 to 3.0;
- In Michael E Aulton, ed, *Pharmaceutics, The Science of Dosage Form Design* (London, UK: Churchill Livingstone, 1998) [Aulton], a leading pharmaceutical formulation textbook, it is stated that the gastric emptying time (*i.e.*, the time it takes for a drug in solution to leave the stomach and enter the small intestine) is between 0.5 and 4.5 hours for a non-disintegrating tablet. Other dosage forms which disintegrate into small subunits are emptied gradually with a mean emptying time of 1.5 hours; and
- Formulators would commonly rely on *in vitro* test results to streamline formulations for further drug development; however, the correlation between *in vitro* results and *in vivo* results could not be assumed, and needed to be confirmed by further testing.

[81] In addition, the POSITA would have been aware that spirorenone, a compound that closely resembles drospirenone, also isomerizes *in vitro* at a pH of 1, albeit more slowly than drospirenone. Spirorenone had been successfully formulated as an immediate release tablet that provided good bioavailability *in vivo* when administered in a non-micronized form at relatively high doses for use as an aldosterone antagonist, diuretic or anti-hypersensitivity drug.

F. *Claim Terms Needing Construction*

[82] Patent construction is a matter of law for the judge. The parties, through their expert witnesses, offered the Court divergent opinions on the meaning of certain terms that appear in the claims in issue. Expert evidence is necessary only where the meaning of a term is not evident based on a reading of the patent specification. I found expert evidence to be helpful in construing the following disputed terms: (a) "drospirenone particles"; and (b) "upon dissolution in the gastric environment".

(1) "Drospirenone Particles"

[83] Each of the claims in issue describes the compositions or kits as containing specified amounts of "drospirenone particles". In the NOC proceedings involving Bayer and Cobalt, Justice Hughes construed claim 31 as including all rapidly dissolving drospirenone particles that meet the dissolution rate specified in the claim (*Bayer v Cobalt* at para 59, aff'd 2015 FCA 116). In other words, claim 31 includes drospirenone in any form, whether micronized or sprayed. In addition, in *Bayer v Apotex* at paragraph 60, Justice Hughes construed the term "drospirenone

particles" as it appears in claim 31 so as "not to include a drospirenone solution nor particles of a matrix into which drospirenone has previously been dissolved".

[84] Dr. Parr defined "drospirenone particle" as "a small solid state form of drospirenone". Dr. Webster said the term refers to "solid state units of an active pharmaceutical ingredient". Dr. Davies defined a particle as "a solid state, non-dissolved form of matter".

[85] In these proceedings, Apotex raises a new issue that does not appear to have been argued before Justice Hughes: whether the term "drospirenone particles" in claims 31, 48 and 49 limits those claims to compositions wherein the drospirenone is exclusively in particulate form, or whether the claims include compositions that contain a mixture of drospirenone in particulate and non-particulate form.

[86] According to Dr. Cima, the word "particles" refers to "discrete solid masses" and the term "drospirenone particles" refers to solid masses composed exclusively of drospirenone. He expressed the view that the POSITA would therefore understand pharmaceutical compositions containing non-particulate forms of drospirenone to fall outside the scope of the claims in issue. I disagree. The words "exclusively" or "solely" do not appear in the claims in issue. It would be inconsistent with a purposive reading of the patent to add them. Moreover, Dr. Cima acknowledged in cross-examination that a formulation that includes at least 2 mg of drospirenone and 0.03 mg of ethinylestradiol in particulate form falls within the scope of the patent.

[87] Cobalt called Dr. Graham Buckton as an expert witness. His qualifications are described at paragraph 297, below. According to Dr. Buckton's proposed construction of the patent, the term "drospirenone particles" excludes drospirenone that has been sprayed on to inert carrier particles, as well as drospirenone that is incorporated into a tablet. Dr. Buckton's testimony was that drospirenone that is sprayed on to inert carriers forms a "composite" or "construct" with the carrier particle. He maintained that the drospirenone in a construct shares a boundary with the carrier particle and therefore no longer exists in the form of individual particles. According to Cobalt, if the inventors had intended the patent to encompass drospirenone that results from the sprayed-on method in claim 31, the word "particles" would not have been used.

[88] I discuss Dr. Buckton's evidence in the context of Bayer's allegation of infringement against Cobalt (see Further Observations Regarding Construction of the Claims, *infra*). Suffice it to say that I am not persuaded by Dr. Buckton's characterization of particles that are sprayed on to inert carriers and then incorporated into a tablet as forming a "composite" or "construct". In my view, particles of drospirenone that undergo this process, which is specifically contemplated by the '426 patent, remain particles as described by Dr. Davies.

(2) "Upon Dissolution in the Gastric Environment"

[89] Claim 49 provides that the drospirenone in the composition or kit is exposed "to the gastric environment upon dissolution". The term "gastric environment" would be understood by the POSITA to mean the stomach. According to Dr. Parr, "dissolution" means the process whereby solid drospirenone particles become a dissolved component of a solution.

[90] Apotex argues, and Drs. Parr and Morris testified, that the POSITA would understand this term to impose a limitation, in that "the claimed amount of drospirenone particles in the composition must be exposed to the stomach (or its contents) after these particles dissolve". In other words, all of the drospirenone particles must fully dissolve in the stomach, and not the intestine; otherwise the particles would not be "exposed to the gastric environment". According to Drs. Parr and Morris, since claims 31 and 48 do not include such a limitation, the POSITA would construe these claims as allowing some or all of the drospirenone particles to dissolve in the stomach or small intestine, or elsewhere. Dr. Parr's evidence was that an enteric coat would dissolve at the pH of water, and would therefore meet the dissolution profile described in claim 31. According to Dr. Cima, if claim 31 were limited in the same way as claim 49, in that the drospirenone particles must also be exposed to the gastric environment upon dissolution, then the term found in claim 49 would be redundant.

[91] Dr. Davies testified that the term "exposure to the gastric environment upon dissolution" simply means that the formulation has no enteric coat. In Dr. Davies' opinion, none of the claims in issue encompass enterically-coated compositions, because they are all directed to rapidly dissolving formulations. Dr. Davies said that the skilled person would not construe claims 31 and 48 otherwise merely because claim 49 specifies that the "drospirenone is exposed to the gastric environment upon dissolution". He testified that an enterically-coated tablet would not meet the dissolution profile described in claim 31.

[92] I prefer the evidence of Dr. Davies in this respect. In my view, Apotex is offering an unduly technical interpretation of "dissolution in the gastric environment". It is true that not all

of the pharmaceutically active ingredients in Bayer's tablets dissolve completely in the stomach. However, Dr. Cima acknowledged that the term would be understood to mean that the primary site of dissolution is the stomach, and even if a *de minimis* amount of drospirenone particles were to dissolve in the intestine, the composition would still fall within the scope of the claim. Furthermore, I agree with Dr. Davies that none of the claims in issue include enterically-coated tablets, since they would not meet the dissolution profile specified in claim 31. I am satisfied that, when read as a whole, it is clear that the claimed invention is a rapidly dissolving formulation that exhibits surprisingly good bioavailability as a contraceptive despite being exposed directly to the gastric environment.

IX. Validity

A. *Burden*

[93] Subsection 43(2) of the Act provides that a patent is presumed to be valid in the absence of evidence to the contrary. As the parties alleging invalidity, Apotex and Cobalt bear the burden of adducing evidence to support their assertions. This Court must decide the matter on the civil burden of proof, namely the balance of probabilities.

B. *Developments Leading to the '426 Patent*

[94] Schering initially developed an uncoated micronized drospirenone formulation in the late 1970s and early 1980s in order to assess its utility as a cardiovascular drug. In one of Schering's studies, Report 4417, an uncoated micronized drospirenone formulation was found to provide good bioavailability *in vivo*.

[95] Schering subsequently applied for a German patent in June 1980, for the use of drospirenone as an oral contraceptive, in which it disclosed that drospirenone is orally bioavailable when formulated "in the known manner". It is unclear whether this referred to an immediate release formulation, a rapidly dissolving formulation, or something else. The testing that supported these conclusions was limited to male subjects, and involved comparatively high dosages (10, 40 and 160 mg) administered for a different therapeutic purpose (an aldosterone antagonist).

[96] On April 21, 1983, several managing directors and departmental heads at Schering met to discuss the development of two molecules as potential commercial products: spirorenone and drospirenone. These are two different but closely related compounds. As Schering had previously investigated drospirenone as a potential cardiovascular drug, it knew drospirenone was acid-labile and isomerized in the presence of acidic solution.

[97] At the meeting, Dr. Krause, a chemist at Schering, presented his research findings on the rate of isomerization of spirorenone under acidic conditions, as described in Schering Report 4627 dated March 11, 1981. Dr. Krause also authored Schering Report 4928 dated August 25, 1981, in which he described the results of his experiments on plasma levels of spirorenone in male volunteers. Dr. Krause was the author of three published articles describing his findings (Krause W & Jakobs U, "Determination of Plasma Levels of Spirorenone, a New Aldosterone Antagonist, and One of its Metabolites by High-Performance Liquid Chromatography" (1982) 230:1 Journal of Chromatography at 37-45); Krause W & Kühne G, "Isolation and Identification of Spirorenone Metabolites from the Monkey (Macaca Fascicularis)" (1982) 40:1 Steroids at 81-

90; Krause W, Sack C & Seifert W, "Pharmacokinetics of the New Aldosterone Antagonist, Spirorenone, in Healthy Volunteers after Single and Repeated Daily Doses" (1983) 25:2 Eur J Clin Pharmacol at 231-36). The parties refer to Dr. Krause's reports and publications collectively as the "Krause Papers".

[98] The minutes of the meeting at Schering confirm that "Dr. Krause reported the results of kinetic studies in humans. These were performed almost exclusively with spirorenone and little information could therefore be presented in practice on [drospirenone]". There appears to have been a consensus at Schering that Dr. Krause's spirorenone studies were not particularly relevant to the development of a low dose drospirenone contraceptive.

[99] Dr. Tack testified that he was aware of the Krause Papers when he began developing drospirenone as a potential oral contraceptive. However, he believed that the conclusions reached by Dr. Krause regarding the isomerization of spirorenone could not be used to inform the development of drospirenone because Dr. Krause's studies concerned a different drug that was not in micronized form, and were conducted in a particular experimental setting.

[100] As one of his first tasks, Dr. Tack conducted an experiment to assess the dissolution of drospirenone *in vitro* using enteric and non-enteric-coated 1 mg drospirenone tablets. The studies suggested drospirenone would rapidly degrade when exposed to the gastric environment of the stomach. Dr. Tack reported these results in Schering Report 5728 dated November 29, 1983.

[101] Based on these results, Dr. Tack concluded that drospirenone would have to be administered using an enteric coat to provide resistance against gastric fluid, as recorded in Schering Report 5728. His recommendation was approved by Schering's senior staff, including Dr. Hümpel, the head of pharmacokinetics at Schering.

[102] Schering conducted further pharmacokinetic studies in 1984, which demonstrated that the enterically-coated formulation displayed large variability in the bioavailability of drospirenone in dogs and humans. Concern over this variability led Schering to conduct a "three-arm study" in 1988, which measured the absolute bioavailability of enteric and non-enteric coated drospirenone tablets in comparison with an intravenous formulation.

[103] In November 1990, Dr. Tack was asked to look into whether an immediate release tablet should be used. From 1993 to 1995, Schering continued to investigate the isomerization of drospirenone. On August 31, 2000, Schering filed the '426 patent for a rapidly dissolving drospirenone formulation.

C. *Obviousness*

[104] Pursuant to ss 28.1 and 28.3 of the Act, a patent may not issue for an invention that was obvious on the date of the patent claim to a person skilled in the art or science to which the patent pertains. The parties agree that obviousness must be assessed as of August 31, 1999.

[105] Obviousness is generally considered to be a factual determination, or a question of mixed fact and law (*Wenzel* at para 44). When considering obviousness, hindsight is prohibited. Simply

because another person could have discovered the invention does not make it obvious (*Sanofi-Synthelabo* at para 66). To determine whether a claim is obvious, courts generally follow a four-part test outlined in *Sanofi-Synthelabo* at paragraph 67:

- Identify the notional "person skilled in the art" and the relevant common general knowledge of that person;
- Identify the inventive concept of the claim in question or, if that cannot readily be done, construe it;
- 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;
- 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?

[106] The fourth step of the inquiry may require consideration of whether the claimed invention was "obvious to try". This aspect of the test tends to arise in areas of endeavour where advances are often made through experimentation, and where numerous interrelated variables may affect the desired result (*Sanofi-Synthelabo* at paras 68-71). The development of pharmaceutical products is such an endeavour, and I must therefore consider whether the claimed invention in this case was "obvious to try". This involves a consideration of the following non-exhaustive factors:

- Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?

- What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
- Is there a motive provided in the prior art to find the solution the patent addresses?

[107] The term “obvious to try” has been interpreted strictly by the Federal Court of Appeal and the Supreme Court of Canada. A patent will be found to be invalid on this ground only if it was “very plain” or “self-evident” that the invention as claimed would work (*Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8 at para 29). The mere possibility that something might turn up is not enough (*Sanofi-Synthelabo* at para 66; *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FCA 286 at para 4). The actual course of conduct that culminated in the making of the invention is an important factor to be considered (*Sanofi-Synthelabo* at paras 70-71).

(1) The POSITA and Common General Knowledge

[108] I have already discussed the person of ordinary skill in the art to whom the patent is addressed and the relevant common general knowledge of that person. While obviousness is to be assessed as of August 31, 1999, and construction occurs as of March 8, 2001, neither party identified any relevant considerations arising from this minor difference in dates.

(2) The Inventive Concept

[109] The inventive concept must be discerned from the claim itself. However, where this is not possible, it is permissible to look to the specification of the patent, provided the Court does not

construe the claim more broadly or narrowly than the text of the claim will allow (*Sanofi-Synthelabo* at para 77).

[110] In *Bayer v Cobalt*, Justice Hughes found the inventive concept of the ‘426 patent to be that the drospirenone in an oral contraceptive comprised of drospirenone and ethinylestradiol may be provided in micronized, or other rapidly dissolving form, without an enteric coat (at para 81). This finding was affirmed by the Federal Court of Appeal (*Cobalt v Bayer FCA* at para 69).

[111] Construing a patent in order to identify the inventive concept when it is not readily discernable from the claim itself is a question of law (*Allergan* at para 50, citing *Weatherford* at para 24). Therefore, as discussed above, Justice Hughes’ characterization, cited with approval by the Federal Court of Appeal, may be regarded as *prima facie* binding unless there is good reason to depart from it.

[112] Apotex says that Justice Hughes did not provide sufficient reasons to support his view of the inventive concept, and his definition did not accord with the evidence. Apotex submits that I should make my own determination based on the evidence before me.

[113] Apotex’s position, advanced through the evidence of Drs. Morris and Parr, is that the skilled person would understand the inventive concept of claim 31 to be that an oral contraceptive containing a combination of drospirenone and ethinylestradiol is effective for oral contraception in women, wherein the drospirenone particles are in a form that allows for their

rapid dissolution. According to Dr. Morris, the POSITA would be able to determine the inventive concept from the language of claim 31 alone.

[114] Dr. Davies was critical of the definition offered by Drs. Morris and Parr because it does not specify that drospirenone may be provided in an immediate release form while still achieving high bioavailability. Dr. Davies' evidence was as follows:

> I read the inventive concept of the '426 patent to be that a 2 mg to 4 mg drospirenone formulation for use as an oral contraceptive could be formulated as a rapidly-dissolving dosage form that surprisingly exhibits high bioavailability.

[115] In my view, the definition proposed by Dr. Davies, which accords with the inventive concept as construed by Justice Hughes and the Federal Court of Appeal, is preferable. It captures the critical dimensions of the inventive concept, *i.e.*, the unexpectedly good bioavailability of the pharmaceutically active ingredients in an immediate release, rapidly dissolving tablet that has no enteric coat.

(3) The Differences Between the Prior Art and the Invention

[116] The crux of the dispute between the parties regarding this issue is whether the prior art would lead the POSITA to anticipate an isomerization problem for drospirenone *in vivo*; and whether the prior art disclosed that drospirenone could be developed as an immediate release formulation for use as an oral contraceptive.

[117] Bayer acknowledges that the prior art taught that techniques such as micronization or deposition could be used to increase the dissolution rate of poorly soluble drugs to improve their

bioavailability. However, the prior art cautioned against improving the dissolution rate of an acid-labile drug because this would inevitably lead to degradation of the drug in the gastric environment. Bayer therefore submits that the prior art "taught away" from the inventive concept, because the skilled person, based on the common general knowledge, would not have administered an acid-labile drug such as drospirenone without protecting the formulation from gastric acid, including through the use of an enteric coat.

[118] Dr. Parr disagreed. He testified that in the late 1990s, it was common to incorporate micronized drug particles in a formulation of low dose, poorly water-soluble drugs, including hormonal steroids. According to Dr. Parr, the literature taught that drospirenone was to be formulated in a manner that was conventional for a combination oral contraceptive, and that a "conventional formulation" would have been understood by the POSITA to include an immediate release tablet. Dr. Morris testified that the skilled person would have been aware, based on the literature and previous clinical studies, that the claimed dosage ranges for drospirenone and ethinylestradiol would provide contraceptive effect in women. Apotex therefore argues that there were no differences between the inventive concept of claim 31 (as defined by Apotex) and the information comprising the state of the art and common general knowledge as of August 31, 1999.

[119] Again, I prefer the evidence of Dr. Davies. The parties agree that as of August 31, 1999, no pharmaceutical company had formulated a contraceptive pill in the manner disclosed in the patent. As stated by Dr. Davies, the generic statement found in the prior art that drospirenone could be formulated by "conventional methods" does not provide sufficient teaching to

overcome the fact that the prior art taught that drospirenone was acid labile and should not be provided in rapidly dissolving form.

[120] Furthermore, even if the skilled person would have understood the term "conventional methods" to include immediate release formulations, this would not entail that the formulation would also be rapidly dissolving, or that drospirenone would not isomerize. In many of the prior art publications relied upon by Apotex, the form of the drospirenone, the particle size, and/or its dissolution rate were not disclosed; nor did they link the use of a rapidly dissolving formulation to bioavailability.

[121] The difference between the prior art and the claimed invention may be simply described as the realization that drospirenone, which was known to be acid-labile *in vitro*, could be administered in a rapidly dissolving formulation that exhibited surprisingly good bioavailability *in vivo*. The discovery that a low dose, rapidly dissolving formulation did not isomerize in the gastric environment to any significant extent was new.

(4) Whether the Differences were Obvious or Required Invention

[122] In *Bayer v Cobalt*, Justice Hughes found that the difference between the prior art and the inventive concept was not more or less self-evident (at para 83). He stated that "[t]he prior art pointed away from providing an acid-labile drug such as drospirenone in a rapidly dissolving form. Previous attempts were tested *in vitro*; the breakthrough was to ignore the *in vitro* results and test *in vivo* with the unexpected result". While this conclusion is not binding upon me, it may be considered persuasive.

[123] Bayer says that Schering's course of conduct is indicative of what the skilled person would have done, and in fact did, at the time. Schering first pursued the use of an enteric coat to protect the drospirenone against isomerization in the gastric environment before discovering, apparently to its surprise, that this was unnecessary.

[124] Apotex maintains that the difference between the prior art and the inventive concept would not have required ingenuity to overcome. To the extent that the skilled person might have been concerned that drospirenone would be susceptible to *in vivo* isomerization, the skilled person would have been able to, and would have, carried out a routine experiment to confirm that drospirenone does not isomerize *in vivo*. The skilled person would have expected that, as with spirorenone, there would be no *in vivo* isomerization.

[125] Apotex says that Schering's course of conduct is not indicative of the path the skilled person would have taken in 1999. Between the commencement of Schering's internal development work and the relevant date for the obviousness assessment (*i.e.*, between the early 1980s and 1999), substantial information describing the use of drospirenone as an oral contraceptive had been published. This included articles authored by Dr. Oelkers, another Schering scientist, in 1991 and 1995, where he concluded that drospirenone showed promise as a partner for ethinylestradiol in the formulation of an oral contraceptive. The drug had been shown to be effective in human clinical trials without mention of the need to protect it against isomerization in the gastric environment. Ultimately, Apotex asserts that Bayer's course of conduct defies explanation.

[126] Apotex also submits that Dr. Tack had little experience in drug formulation at the time he made his recommendation, and was wrong to assume that the isomerization of drospirenone *in vitro* would also occur *in vivo*. Apotex says that Dr. Tack ignored the results from previous studies conducted by Schering, including the Krause Papers and another study which concluded that an uncoated micronized drospirenone formulation could provide good bioavailability in humans. Apotex says, and Dr. Parr testified, that even if there was a reasonable concern about isomerization at the time, the skilled person would not have proceeded with the use of an enteric coat without first conducting *in vivo* studies.

[127] However, Dr. Davies testified that Dr. Tack did not need to confirm an *in vitro*/*in vivo* correlation before recommending the use of an enteric coat. The Aulton text, which all parties accepted as an authoritative source, does not discuss the need for an *in vitro*/*in vivo* correlation at the pre-formulation stage of drug development. Dr. Parr admitted in cross-examination that in a piece of prior art cited in his report, United States Patent 5,356,896, the named inventors recommended protecting the drug fluvastin from isomerization based on *in vitro* data alone. Ultimately, although an *in vitro*/*in vivo* correlation may be relevant at a later stage of drug development, it is not required at the pre-formulation stage. Given that Schering's *in vitro* data clearly showed that drospirenone was unstable in gastric acid, there was no motivation for Schering to establish an *in vitro*/*in vivo* correlation before proceeding with an enteric coat.

[128] I am therefore satisfied that Dr. Tack's reliance on *in vitro* data to recommend the use of an enteric coat was in keeping with industry standards. Schering's course of conduct demonstrates that the discovery that led to the rapidly dissolving drospirenone formulation was

not routine. Rather, it occurred over a five year period, after initially developing an enterically coated tablet.

[129] Bayer disagrees with Apotex that the skilled person would have placed any reliance on the Krause Papers when developing drospirenone as an oral contraceptive. Bayer contrasts Dr. Krause's studies of spirorenone with Schering's development of drospirenone as follows: Dr. Krause dealt with a (i) high dose, (ii) macro-crystalline (iii) spirorenone tablet (iv) intended for use as an anti-hypertensive, while Dr. Tack's team of researchers was concerned with developing a (i) low dose, (ii) rapidly dissolving (iii) drospirenone tablet (iv) intended for use as a contraceptive. As a result of these differences, Bayer submits that Dr. Tack's decision to place little reliance on the information contained in the Krause Papers does not defy explanation, but rather, reflects what the skilled person would have done with such information.

[130] Bayer notes that, in order for an oral contraceptive to be effective, it must be stable across the entire pH range of the stomach that women may experience. The skilled person seeking to formulate an acid-labile compound would need to ensure that it would not degrade in the normal pH range of the stomach – especially in the case of a contraceptive, where a compromised dose could lead to an unwanted pregnancy. According to the literature cited by Dr. Davies, the gastric emptying rate is highly variable across individuals. In particular, the gastric emptying rate for solutions is from 30 minutes to about two hours, and multiple hours for small pellets (which are formed from particles of a rapidly disintegrating formulation).

[131] Bayer also argues that the therapeutic purpose of a drug must be considered during its formulation. This principle is critical when formulating contraceptives, which must be effective in all women and under all expected conditions (including at a gastric pH of 1). In contrast to other medications where there are acceptable degrees of effectiveness (*e.g.*, pain relief), a contraceptive pill must always be effective. Dr. Hümpel explained that Schering was particularly apprehensive about the risk of isomerization in its development of a contraceptive, a concern that is not as important when developing a higher dose cardiovascular drug.

[132] The Aulton text cautioned against improving the dissolution rate of acid-labile drugs, because this would lead to greater drug degradation in gastric acid. While an *in vivo* test may have been "obvious to try" in the case of a drug such as spirorenone with a generous margin of error, I am not persuaded that the skilled person would have administered drospirenone as a contraceptive in a rapidly dissolving form without first protecting the formulation from gastric acid (*e.g.*, with an enteric coat). The formulation of drospirenone as a rapidly dissolving tablet offered a low likelihood of success. The skilled person would not have tried a formulation that was not expected to succeed. Furthermore, although there was no enterically-coated oral contraceptive product available on the market as of 1999, the use of enteric coats for acid-labile drugs was generally well-established in the literature at the time.

[133] I accept that, based on the available literature, a POSITA may have been curious about whether a low dose formulation of drospirenone intended for use as a contraceptive would offer good bioavailability *in vivo* when administered without an enteric coat. However, the result of

such a test would not have been obvious. In this sense, *in vivo* testing would not have been "obvious to try", but rather "worth a try". This is insufficient to satisfy the "obvious to try" test.

[134] As an alternative argument, Apotex raises the possibility that a skilled person who was concerned about the isomerization of drospirenone could have simply added an alkaline excipient as a "buffer" in an immediate release formulation.

[135] Dr. Davies agreed during cross-examination that an immediate release formulation with an alkaline buffer could possibly fall within claim 31 so long as the formulation allowed for rapid dissolution and protected the composition from isomerization. Apotex points to United States Patent 5,356,896 as a piece of prior art that demonstrates the skilled person would have known that an alkaline buffer could be used to protect against isomerization. Relying on Richard Miller et al, eds, *Terrell on the Law of Patents*, 7th ed (London, UK: Sweet & Maxwell, 2011) at 298, Apotex says that if any embodiment falls within the scope of the claim, and that embodiment is obvious, then the claim is invalid. In Apotex's view, there is no limitation in claim 31 that would exclude an alkaline stabilizing agent such as a buffer being incorporated into the formulation.

[136] In my view, this alternative theory finds only weak support in the prior art. The bulk of the literature and existing patents taught that pharmaceutically active ingredients that are prone to isomerization in acidic solutions should be protected through the use of an enteric coat. There was no example in the prior art of drospirenone being administered in an immediate release

formulation coupled with an alkaline buffer. Nor was this formulation ever used in the manufacture of a contraceptive tablet. I am not persuaded that the skilled person would have known that an alkaline buffer could be used to protect against isomerization of drospirenone in this context.

[137] Apotex's alternative theory was not extensively developed in the evidence. Although Dr. Davies agreed that an alkaline buffer could be used to protect against isomerization of drospirenone, he insisted that such a formulation, though not excluded by the language of claim 31, would have to meet the other essential elements of the claim. This was never established.

[138] In sum, I agree with Bayer that Schering's course of conduct is indicative of what the skilled person would have done as of August 31, 1999. Schering's decision to formulate its contraceptive product as an enterically-coated tablet was in accordance with the teachings of the prior art and standard pharmaceutical practices at the relevant time. The claims in issue are therefore not invalid on the ground of obviousness.

D. *Anticipation*

[139] Pursuant to s 28.2 of the Act, a patent claim will be invalid for anticipation if the subject matter defined by the claim was disclosed in such a manner that it became available to the public more than one year before the filing date of the application, and was enabled to a skilled person (*Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FC 125 at para 145).

[140] More than one year before the filing date of the patent application, Bayer conducted clinical studies in Europe and the United States, and provided participants with tablets containing drospirenone and ethinylestradiol. Apotex argues that the claims in issue were anticipated because their essential elements were disclosed in the course of these trials.

[141] Apotex's allegation of anticipation raises two issues. The Court must first determine whether the subject matter of the claims was disclosed in a manner that constitutes an anticipation pursuant to s 28.2(1)(a) of the Act. If so, the Court must then consider whether the disclosure is exempted from the provisions of the Act because it was experimental.

[142] The law of anticipation may be found in the Supreme Court of Canada's decision in *Sanofi-Synthelabo*. Disclosure need not reveal an exact description of the subject matter of a claim, but must be sufficient so that, when read by a person skilled in the art and willing to understand the invention, it can be understood without undue burden, taking into account the nature of the invention (*Sanofi-Synthelabo* at para 33).

[143] In *Baker Petrolite Corp v Canwell Enviro-Industries Ltd*, 2002 FCA 158 at paragraph 42 [*Baker Petrolite*], the Federal Court of Appeal provided a non-exhaustive list of eight principles that should be considered when assessing anticipation by prior use. These were summarized by Justice Hughes in *Bayer v Apotex* at paragraph 117 as follows:

> 1. Sale to the public or use by the public alone is insufficient to prove anticipation. Disclosure of the invention is required to constitute anticipation under paragraph 28.2(1)(a).
>
> 2. For a prior sale or use to anticipate an invention, it must amount to "enabling disclosure".

> 3. The prior sale or use of a chemical product will constitute enabling disclosure to the public if its composition can be discovered through analysis of the product.
>
> 4. The analysis must be able to be performed by a person skilled in the art in accordance with known analytical techniques available at the relevant time.
>
> 5. In the context of patent anticipation under paragraph 28.2(1)(a), when reverse engineering is necessary and capable of discovering the invention, an invention becomes available to the public if a product containing the invention is sold to any member of the public who is free to use it as she or he pleases.
>
> 6. It is not necessary to demonstrate that a member of the public actually analyzed the product that was sold.
>
> 7. The amount of time and work involved in conducting the analysis is not determinative of whether a skilled person could discover the invention. The relevant consideration, in this respect, is only whether inventive skill was required. There must be some evidence from which the use of inventive skill may be inferred. Complexity or time and work involved alone are insufficient.
>
> 8. It is not necessary that the product that is the subject of the analysis be capable of exact reproduction. It is the subject matter of the patent claims (the invention) that must be disclosed through the analysis. Novelty of the claimed invention is destroyed if there is disclosure of an embodiment which falls within the claim.

[144] Disclosure must be to a member of the public. The "public" has been defined as "a person who [is] free in law and equity to use the information" (*Baker Petrolite* at para 42, citing *Lux Traffic Controls Ltd v Pike Signals Ltd*, [1993] RPC 107 (Eng Patents Ct)).

(1) Disclosure and Enablement

[145] Between December 1992 and July 1998, more than one year before the filing date of the '426 patent, Schering conducted at least three advanced (Phase III) clinical trials in Europe and

the United States involving 3 mg drospirenone / 0.03 mg ethinylestradiol tablets (referred to in the evidence as Clinical Trial Nos. 2, 3 and 4). Participants were given a large number of the tablets, which were to be self-administered over several months outside of a clinical setting. In all three trials, participants were told what the tablets contained, and knew that the tablets were intended to be used as oral contraceptives.

[146] No restriction was imposed on participants regarding the disclosure of information concerning the tablets. The participants did not sign confidentiality agreements. Indeed, Dr. Barnhart acknowledged that Schering could not, and would not, attempt to prevent participants from discussing their involvement in the trial with their sexual partners, family members, physicians or anyone else. Participants were asked to ingest all of the tablets distributed to them or to return any unused tablets. However, in the course of Clinical Trial Nos. 2, 3 and 4, hundreds of Schering's drospirenone/ethinylestradiol tablets were recorded as "lost" or "not returned". Dr. Barnhart described this loss as "inevitable".

[147] This led Justice Hughes to conclude in *Bayer v Apotex* at paragraphs 118-121, with respect to Clinical Trial No. 4, that there was a "theoretical" possibility that a tablet could have been kept and analyzed, and that this met the requirements of s 28.2(1)(a) of the Act. However, Justice Hughes found that the experimental use exception applied.

[148] Bayer says numerous restrictions were placed on participants regarding the permitted use of the tablets. They were to be either self-administered or returned. The tablets were therefore not made available to the public "without inhibiting fetter" (citing *Baker Petrolite* at para 42).

[149] Furthermore, Bayer argues that study participants would have understood that they had "a duty not to use that information for any purpose other than that for which it was conveyed", because any reasonable woman or man, standing in the participant's shoes, would have understood the information to have been given in confidence (citing *Lac Minerals Ltd v International Corona Resources Ltd*, [1989] 2 SCR 574, [1989] SCJ No 83 and *Weatherford*). Bayer submits that information received in circumstances of confidentiality should not constitute public disclosure for the purposes of anticipation.

[150] Apotex responds that, absent any confidentiality agreement, participants were under no legal obligation to ingest or return the tablets as directed. Apotex therefore says that the participants were free to use the tablets "without inhibiting fetter", which might include sharing information about the tablets with members of the public.

[151] Mere disclosure to the public is not sufficient. The disclosure must be of a kind that enables discovery of the subject matter defined in the claim, through reverse engineering if necessary. Bayer argues that the essential elements of claim 31 and its dependent claims were not in fact disclosed. Crucially, participants did not know the dissolution profile of the drospirenone in the tablets, or that it was exposed to the gastric environment upon dissolution. Bayer says that a member of the public could not have discerned these essential elements using known analytical techniques and without the use of inventive skill.

[152] Dr. Davies testified that at the time the clinical trials were conducted there was no commercially available source of drospirenone and no publicly available information regarding

its solubility. According to Dr. Davies, inventive skill would have been required to discover that drospirenone was present in particulate form and met the dissolution parameters specified.

[153] Apotex responds that participants in the studies were told that the tablets contained 3 mg drospirenone and 0.03 mg ethinylestradiol, and knew they were administered for use as oral contraceptives. Although the dissolution profile was not disclosed, Apotex says this would have been easily discernible by the skilled person using the dissolution method disclosed in the Krause Papers, or by obtaining a reference standard through the synthesis of drospirenone. Dr. Cima's evidence was that the United States Pharmacopeia [USP] XXIII Paddle Method was known in 1999, and that the skilled person could have used it to determine the dissolution rate of the drug. This would in turn allow the POSITA to discern that the tablets were designed to allow for drospirenone's rapid release.

[154] While I accept, as did Justice Hughes, the theoretical possibility that one or more tablets may have found their way into the hands of persons skilled in the art, I am not persuaded this would have been sufficient to enable the skilled person to discover the invention through reverse-engineering and without inventive insight.

[155] The central components of the claims in issue include its rapid dissolution and the exposure of the pharmaceutically active ingredients to the gastric environment upon dissolution. This could not have been discovered without access to a minimum of six to twelve tablets, the ability to obtain a reference standard through the synthesis of drospirenone, the establishment of

a dissolution profile and, most importantly, the insight that the location and speed of dissolution were central to the inventive concept of the claims. Apotex has not provided sufficient evidence to show that the skilled person would have been able to gather such information without inventive insight, and I am therefore not persuaded that the subject matter of the claims was disclosed in a manner that constitutes an anticipation pursuant to s 28.2(1)(a) of the Act.

(2) The "Experimental Use" Exception

[156] In the alternative, I agree with Justice Hughes that Bayer benefits from the experimental use exception.

[157] Section 28.2 of the Act does not provide for an exception for experimental use. However, as recently noted by Justice Hughes in *Bayer v Apotex* at paragraph 119, the law in Canada has long held that there is no public disclosure for the purposes of anticipation where a prior use is experimental (citing *Gibney v Ford Motor Co of Canada* (1967), 2 ExCR 279 at para 49, 52 CPR 140 (Can Ex CT) [*Gibney*] and *Elias v Grovesend Tinplate Co* (1890), 7 RPC 455 at 466). In *Gibney*, Justice Noel held that an inventor may use any means of testing available to him or her, so long as any experimentation is reasonable and necessary, and done in good faith for the purpose of perfecting the invention or testing its merits (*Gibney* at paras 48, 56).

[158] The experimental use exception was also recently canvassed in *Wenzel Downhole Tools Ltd v National-Oilwell Canada Ltd*, 2011 FC 1323, affirmed in part 2012 FCA 333, in which Justice Snider held that the rental of a tool for use in an oilfield was not experimental, and there

was anticipation because the tool had been made available for inspection. She stated at paragraph 90 of her decision that a "use will only be experimental if it is so in the mind of the user". On appeal, the Federal Court of Appeal affirmed Justice Snider's finding on anticipation, but clarified that the test for anticipation by prior disclosure is objective (*Wenzel* at para 118).

[159] In *Bayer v Apotex* at paragraph 119, Justice Hughes noted that the experimental use exception "applies in particular, where, of necessity, the experiment must be conducted in public". He continued at paragraph 121:

> In the present case clinical studies were necessary to prove that the drug was safe and effective and, thereby, gain government approval for sale. Until this had been demonstrated, no commercial sale of the drug could have been made. Bayer took reasonable steps to ensure the confidentiality of the relevant documents and to ensure that unused tablets were returned. The theoretical possibility that some tablets were retained and analyzed is just that, theoretical. This theoretical possibility does not preclude the fact that the studies were experimental, and of necessity, conducted by the provision of tablets to members of the public. Thus these clinical studies are exempted from public use.

[160] Apotex argues that the Phase III trials (including Clinical Trial Nos. 2, 3 and 4) were not experiments conducted to prove that Schering's drug was safe and effective, but were undertaken solely for the purpose of obtaining government approval for commercial sale. According to Apotex, the trials were not necessary for Schering to establish that drospirenone/ethinylestradiol tablets were useful as an effective oral contraceptive, as this had already been established during the Phase II trials. Apotex submits that experiments conducted after an invention has been achieved are anticipatory, and no exception should apply to clinical trials conducted to confirm that the invention works as intended (citing *Gibney* at paras 44, 50).

[161] Bayer responds that its Phase III clinical trials were reasonable and necessary to perfect and test the merits of its invention. Unlike prior studies, the Phase III trials were necessary to evaluate pregnancy prevention in real situations where women were not told to use alternative methods of birth control.

[162] While I agree with Apotex that the Phase III clinical trials, which are relied upon as the basis for public disclosure, were conducted for the purpose of gaining regulatory approval, this does not, in my view, bring them outside the experimental use exception. The purpose of regulatory trials is, in part, to confirm the safety and efficacy of a proposed drug before it is offered for sale to the public. The risks at this advanced stage have been assessed as minimal, but this does not detract from the inherently experimental nature of a regulatory trial. I agree with Justice Hughes' conclusions in this respect.

E. *Overbreadth*

[163] In order to be valid, the claims of a patent must not exceed the invention made or the invention disclosed. A claim cannot be stretched to grant the patentee a monopoly on anything that achieves a desired result (*Free World Trust* at para 32).

[164] The '426 patent discloses that drospirenone may be provided in micronized form, but that it is also possible to dissolve the drospirenone in a suitable solvent and spray it on to the surface of inert carrier particles. Unlike other claims found in the patent, claims 31, 48 and 49 are not limited to micronized drospirenone, but include any oral dosage form that meets the dissolution profile specified in claim 31.

[165] Apotex submits that the research conducted by the inventors of the ‘426 patent was limited to determining whether micronized drospirenone achieved rapid dissolution, which is only one of the methods over which a monopoly is claimed and the only method that is actually disclosed. Therefore, Apotex argues that the invention is limited to compositions that attain the stated dissolution profile through the micronization of drospirenone. Otherwise, the patent appears to claim a monopoly over all manner of achieving the required rapid dissolution, which Apotex likens to a patent for anything that “grows hair on bald men” (Justice Binnie’s well-known example in *Free World Trust* at para 32):

> [T]he ingenuity of the patent lies not in the identification of a desirable result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desirable result. It is not legitimate, for example, to obtain a patent for a particular method that grows hair on bald men and thereafter claim that anything that grows hair on bald men infringes.

[166] In addition, Apotex asserts that if the invention of the ‘426 patent is directed to compositions that are exposed to the gastric environment upon dissolution, then claims 31 and 48, which have no such limitation, are overbroad. As noted above, Drs. Morris and Parr suggested that without such a limitation, claims 31 and 48 must encompass dosage forms that include enterically-coated tablets.

[167] Bayer responds that the claims are not broader than what was invented or disclosed. Bayer says that Example 2 of the patent demonstrates that the dissolution profile specified in claim 31 was in fact achieved by the inventors. Bayer adds that the teachings and the claims were not directed simply to achieving the desired result of good bioavailability, but to a particular

means of achieving that result, namely a rapidly dissolving formulation. Bayer argues that the Federal Court of Appeal rejected an identical overbreadth argument in the Cobalt proceedings.

[168] In response to Apotex's submission that claims 31 and 48 are overbroad because they do not include the limitation found in claim 49 (exposure to the gastric environment upon dissolution), Bayer says that the person skilled in the art would not construe those claims to encompass enterically-coated formulations, but only rapid release formulations. As previously noted, Dr. Davies testified that an enterically-coated tablet would be unable to meet the dissolution profile described in claim 31 of the patent. Bayer therefore says that Apotex's position rests on a non-purposive interpretation of the patent.

[169] In my view, Apotex's argument once again depends upon a mischaracterization of the inventive concept disclosed by the claims in issue. The invention claimed is the surprising discovery that the drospirenone in an oral contraceptive comprised of drospirenone and ethinylestradiol may be provided in micronized or other rapidly dissolving form without an enteric coat. As the Federal Court of Appeal held in *Cobalt v Bayer FCA* at paragraph 76:

> Claim 31 embraces all drospirenone particles which, when formulated into a tablet, have the required dissolution properties. And as also described above, the disclosure of the '426 Patent extends to drospirenone in forms other than micronized particles. Therefore Claim 31 is not broader than the invention disclosed. Rather, Claim 31 claims exactly what was invented – the particular solution to a particular problem.

[170] I adopt the conclusion of the Federal Court of Appeal in this regard.

F. *Insufficiency of the Specification*

[171] Pursuant to s 27(3)(a) of the Act, the specification of a patent must correctly and fully describe the invention and its operation or use as contemplated by the inventor. Subsection 27(4) of the Act further provides that the specification must end with claims that define the subject matter of the invention in distinct and explicit terms. Adequate disclosure in the specification is a "precondition for the granting of a patent" (*Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 at para 34 [*Teva*]). In *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at paragraph 29, [1989] SCJ No 72, the Supreme Court of Canada described the adequacy of disclosure as follows:

> The applicant must disclose everything that is essential for the invention to function properly. To be complete, it must meet two conditions: it must describe the invention and define the way it is produced or built [citation omitted]. The applicant must define the nature of the invention and describe how it is put into operation. A failure to meet the first condition would invalidate the application for ambiguity, while a failure to meet the second invalidates it for insufficiency. The description must be such as to enable a person skilled in the art or the field of the invention to produce it using only instructions contained in the disclosure [citations omitted] …

[172] The analysis on insufficiency requires answers to three questions: (i) what is the invention? (ii) how does it work? and (iii) having only the specification, can a POSITA successfully produce the invention using only the instructions contained in the disclosure? (*Uponor* at para 172, citing *Teva* at paras 50-51). The Court must look at the specification as a whole to determine whether the patent meets the disclosure requirements.

[173] A claim is ambiguous when the patent fails to define the nature of the invention. According to Justice Hughes, "ambiguity is truly a last resort, rarely, if ever, to be used" (*Pfizer Canada Inc v Canada (Minister of Health)*, 2005 FC 1725 at para 53).

[174] Apotex's position is that claim 31 is ambiguous and insufficient because it encompasses any amount of drospirenone from about 2 to about 4 mg in any oral dosage form, yet the dissolution profile specified in the claim is determined only with reference to a 3 mg tablet of drospirenone. Apotex says that the '426 patent does not sufficiently describe how a dosage that is not in the form of a 3 mg tablet will achieve the required dissolution rate, such as capsules, suspensions or emulsions. According to Apotex, the person skilled in the art would have to guess whether and how oral dosage forms other than tablets at 3 mg will achieve the dissolution rate specified in the claims.

[175] Dr. Davies' evidence was that a person skilled in the art would have known how to scale a dose up or down to determine if the composition meets the dissolution requirement. According to Dr. Davies, the patent's disclosure is clear that the specified dissolution profile is determined by dissolving 3 mg of drospirenone, regardless of whether the skilled person uses an amount other than 3 mg in the formulation and regardless of the nature of the formulation.

[176] I find Dr. Davies' analysis to be coherent and persuasive. The dissolution profile is based on a 3 mg tablet, but this may be scaled or otherwise adapted by a POSITA without resorting to inventive means. The patent is sufficiently precise to enable a person skilled in the art to produce the invention using only the instructions contained in the disclosure.

G. *Utility*

[177] Pursuant to s 2 of the Act, an invention must be useful in order to receive protection.

[178] If the specification of the patent does not promise a specific result, a "mere scintilla" of utility will suffice. An inventor is not required to describe the utility of his or her invention. However, if the specification sets out an explicit "promise", utility will be measured against that promise (*Apotex Inc v Sanofi-Aventis Canada Inc*, 2013 FCA 186 at paras 48-50).

[179] Like the construction of a patent, the promise of a patent is a question of law (*Astrazeneca Canada* at para 87). It is for the Court to ascertain in a purposive manner whether there is a promise of the patent within the context of the patent as a whole, seen through the eyes of the person skilled in the art, keeping in mind the science and information available at the time of filing (*Pfizer Canada Inc v Canada (Minister of Health)*, 2011 FCA 236 at para 17, citing *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 at para 80, leave to appeal to SCC refused [*Eli Lilly Canada*]).

[180] If there is a promised utility, the patentee must have demonstrated or soundly predicted the promised utility by the filing date (*Eli Lilly Canada* at para 80). However, a patentee will be held to this elevated standard only where a "clear and unambiguous" promise has been made. Where the validity of a patent is challenged on the basis of an alleged unfulfilled promise, the patent will be construed in favour of the patentee where it can reasonably be read by the skilled person as excluding this promise (*Pfizer Canada* at para 66). The Court must keep in mind that

not all statements of advantage in a patent rise to the level of a promise. A goal is not necessarily a promise, but rather a "hoped-for advantage of the invention" (*AstraZeneca Canada* at para 139).

[181] Apotex says that the '426 patent contains three explicit promises: (i) to inhibit ovulation and be an effective oral contraceptive; (ii) to permit drospirenone to be administered at a lower dosage than was previously required to achieve a reliable contraceptive effect; and (iii) to permit drospirenone to be administered at a maximum dosage at which unpleasant side effects, in particular excessive diuresis, may be substantially avoided.

[182] Bayer says that the '426 patent does not contain any explicit promise of utility. However, in response to Apotex's first allegation, Bayer admits that the patent does state that the composition is effective to inhibit ovulation. Bayer asserts that this effectiveness is demonstrated in Example 5 of the patent. Bayer maintains, based on the evidence of Drs. Simon and Barnhart, that Example 5 demonstrates that a combination of 2 or 3 mg of drospirenone and 0.03 mg of ethinylestradiol is effective to inhibit ovulation, and that the rapidly dissolving formulation is well-tolerated. Furthermore, Bayer says Example 4 demonstrates that a rapidly dissolving drospirenone formulation exhibits good and relative bioavailability. Bayer therefore says that the patentee, although not required to as a matter of law, has met and demonstrated the claimed utility of effective inhibition of ovulation as of the filing date (citing *GlaxoSmithKline Inc v Pharmascience Inc*, 2011 FC 239 at para 96).

[183] With respect to Apotex's second allegation, Bayer argues that the '426 patent does not promise that drospirenone may be administered at a lower dosage than previously required. Bayer's position is that any reference to minimum dosing in the patent is an observation, rather than a promise, and that in any event the claimed minimum dosage level of about 2 mg for use in contraception is fully supported by Example 5.

[184] Bayer also denies Apotex's third allegation that the patent promises the avoidance of side effects at a preferred maximum dosage, and says that even if construed as a promise, Example 5 shows good tolerance and a lack of side effects for both the 2 and 3 mg dosages of drospirenone. Furthermore, Bayer says that Example 4 shows that the administration of up to 6 mg of drospirenone does not result in any reported issues or concerns with side effects.

[185] Justice Hughes found in *Bayer v Cobalt* at paragraph 95 that the "promise" of the patent could be said to be contained at page 4 of the patent:

> To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof.

[186] The Federal Court of Appeal, in upholding Justice Hughes' decision, did not specifically address this issue.

[187] Whether a patent contains a promised utility, and if so the nature of that promise, is a question of law [*Astrazeneca Canada* at para 87]. As previously discussed, the doctrine of comity creates a presumption that prior rulings of this Court will be adhered to unless there is good reason to depart from them. I see no reason to depart from Justice Hughes' characterization

of the promised utility of the patent. Furthermore, I am satisfied that the promise is demonstrated or soundly predicted by Examples 4 and 5. The asserted claims are not invalid for lack of utility.

H. *Conclusion on Validity*

[188] Based on the preceding analysis, I find claims 31, 48 and 49 of the ‘426 patent are not invalid based on the asserted grounds of: (i) obviousness; (ii) anticipation; (iii) overbreadth; (iv) insufficiency or ambiguity of the specification; or (v) inutility.

X. Infringement – Apotex

A. *Burden and Legal Principles*

[189] Section 42 of the Act grants the patent holder the exclusive right, privilege and liberty of making, constructing and using the invention and selling it to others to be used. A patent is infringed by any act that interferes with the patentee’s full enjoyment of the monopoly granted (*Monsanto Canada Inc v Schmeiser*, 2004 SCC 34 at para 34 [*Monsanto*]).

[190] Pursuant to s 55(1) of the Act, any person who infringes a patent is liable for all damages sustained by the patentee, after the grant of the patent, by reason of infringement. Infringement is determined by comparing the products that are said to infringe the patent with the patent’s claims as construed by the Court. If Apotex’s tablets comprise each of the essential elements of claims 31, 48 or 49, then Bayer’s patent has been infringed.

[191] The burden of proving infringement rests with the party that alleges it (*Monsanto* at para 29). The burden therefore lies on Bayer.

[192] Apotex's Zamine tablets, corresponding to Bayer's Yasmin tablets, are an oral contraceptive containing 3 mg of drospirenone and 0.03 mg of ethinylestradiol as the active pharmaceutical ingredients. Apotex's Mya tablets, corresponding to Bayer's Yaz tablets, contain 3 mg of drospirenone and 0.02 mg of ethinylestradiol.

[193] The sole point of contention between Bayer and Apotex is whether the Zamine and Mya tablets contain at least 2 mg of drospirenone particles. There is no issue that the Zamine and Mya tablets meet the dissolution criteria of claim 31.

[194] Apotex's defence to Bayer's allegation of infringement is that the Zamine and Mya tablets contain drospirenone in the form of a "molecular dispersion", *i.e.*, it is sufficiently dissolved in a medium so as to no longer be in the form of particles. If the drospirenone in the Apotex tablets is molecularly dispersed, then the tablets fall outside the scope of the patent, which refers only to "particles".

B. *The Evidence – Expert Witnesses*

[195] Bayer presented the evidence of the following expert witnesses:

a) **Dr. Shen Yung Luk** of Nottingham, United Kingdom. He is the Chief Scientific Officer of Juniper. He was qualified as an expert in the characterization and testing of pharmaceuticals, including ascertaining the physical and chemical properties of drug

substances and pharmaceutical excipients using a variety of analytical techniques, including confocal Raman microscopy, FT Raman spectroscopy, infrared spectroscopy, polarized light optical microscopy, dissolution testing, and HPLC. Dr. Luk helped design the Juniper experiments. His mandate was to describe the experimental testing performed on Apotex's tablets, and to present the test results.

b) **Dr. Martyn Christopher Davies**. His qualifications are discussed above. Dr. Davies designed the Juniper experiments and provided evidence regarding the interpretation of their results.

[196] Apotex presented the evidence of the following expert witnesses:

a) **Dr. André J. Sommer** of Oxford, Ohio. He is the Director of the Molecular Microspectroscopy Laboratory and a professor in the Department of Chemistry and Biochemistry at Miami University. He was qualified as an expert in molecular spectroscopy (infrared and Raman), microspectroscopy, confocal microscopy, optical instrument design and analytical chemistry, including the analytical techniques utilized in the identification and characterization of the physical and chemical properties of chemical substances including pharmaceuticals. Dr. Sommer gave evidence regarding the tests conducted on behalf of Bayer and Apotex, and concepts of materials and pharmaceutical chemistry.

b) **Dr. Michael J. Cima**. His qualifications are discussed above. Dr. Cima attended some of the experiments conducted by the parties and provided his opinion regarding infringement based on those experiments.

C. *The Evidence – Experimental Testing*

(1) Experiments Conducted by Bayer

[197] Bayer obtained samples of the Apotex tablets and asked Drs. Luk and Davies to determine whether they comprise at least 2 mg of drospirenone particles and meet the dissolution criteria specified in claim 31. To fulfill their mandates, Drs. Luk and Davies relied on a technique widely used in the pharmaceutical industry called Raman spectroscopy.

[198] Raman spectroscopy is used to analyze the properties of complex materials such as pharmaceutical tablets. This technique uses a Raman microscope (a modified version of a standard microscope) to observe the interaction of light, typically generated by a laser, with a chemical compound. A chemical compound contains atoms connected by chemical bonds to form molecules. Due to the inherent differences in the molecular structures of compounds, they can be identified and distinguished based on the characteristic manner in which they interact with light: the chemical bonds connecting the atoms in a molecule vibrate and gain energy, producing a "Raman effect". The light's interaction with the compound is displayed in a "Raman spectrum", which plots the light's wavelength against the light's relative intensity on a graph, measured in wavenumbers or cm^{-1}. A Raman spectrum may be described as a chemical's "fingerprint".

[199] A Raman spectrum displays peaks, and it is possible to identify a compound by comparing the spectrum it generates to known reference spectra. The relative intensity of the peaks can also be used to identify and quantify the constituent components of a compound.

Based on the width of a peak, it is possible to determine whether a compound is crystalline (*i.e.*, in the form of particles) or non-crystalline (*i.e.*, amorphous or in the form of a molecular dispersion).

[200] Drs. Luk and Davies analyzed the Apotex tablets using both confocal Raman spectroscopy and FT Raman spectroscopy, as described in further detail below.

[201] Drs. Luk and Davies also conducted dissolution tests to determine whether the Apotex tablets meet the dissolution profile specified in claim 31, namely whether 70% of the drospirenone in the tablets dissolves within 30 minutes when dissolved according to a well-accepted dissolution protocol described in the USP. There is no dispute that Apotex's tablets meet the required dissolution profile, and it is therefore unnecessary to comment further on this aspect of the experimental testing.

(a) *Confocal Raman Spectroscopy*

[202] Drs. Luk and Davies used confocal Raman spectroscopy to determine whether the Apotex tablets contain drospirenone in the form of particles, or alternatively in the form of a molecular dispersion. In this experiment, the Apotex tablets were cut to reveal cross-sections. Each cross-section was then subjected to confocal Raman spectroscopy, a Raman mapping technique. The location of drospirenone in the sample was identified and distinguished from other components (or "excipients") of the tablets based on the characteristic peak for drospirenone.

[203] The Raman maps were then analyzed by Drs. Luk and Davies to identify the form of drospirenone in the Apotex tablets. The laser used in Raman spectroscopy is sensitive to the orientation of chemical bonds in a crystal, which are fixed within the crystal. According to Dr. Luk, crystalline material produces differences in relative Raman peak intensities, which are dependent on the orientation of the crystal. In contrast, non-crystalline materials, including molecular dispersions, do not exhibit this "orientation effect" because the molecules are randomly distributed within the molecular dispersion. Since the orientation effect occurs only when crystalline materials are examined, confocal Raman spectroscopy can be used to confirm or discount the presence of crystals (*i.e.*, particles).

[204] Drs. Luk and Davies also performed confocal Raman spectroscopy on reference slides containing crystalline and molecularly dispersed drospirenone to act as controls. They compared these results to those obtained from the Raman spectroscopy performed on the Apotex tablets. The crystalline drospirenone reference slides contained pure USP crystalline drospirenone. The molecularly dispersed drospirenone reference slides contained drospirenone, [redacted], all of which are found in the Apotex tablets.

[205] Once the drospirenone within a particular region of the cross-section of a tablet was mapped, a statistical technique called K-means cluster analysis was used to quantify the size and surface area of the drospirenone particles present in the Apotex products. This technique was also used to differentiate between particles that exist as clusters composed of several smaller particles.

[206] In closing arguments, Bayer abandoned its reliance on the K-means clustering analysis performed by Drs. Luk and Davies. This aspect of the testing is therefore relevant only to the overall credibility of Juniper's methodology.

(b) *FT Raman Spectroscopy*

[207] Drs. Luk and Davies applied FT Raman spectroscopy to quantify how much of the drospirenone in the Apotex tablets was present in particulate form as opposed to a molecular dispersion. In this experiment, the tablets were crushed into a powder and then subjected to FT Raman spectroscopy, which generated a characteristic Raman spectrum.

[208] As with their confocal Raman spectroscopy experiment, Juniper created two drospirenone blends to generate an FT Raman reference standard. Both reference blends contained the same components as the Apotex tablets. The crystalline drospirenone reference blend contained all the excipients of the Apotex tablets and drospirenone in crystalline form. All of these components were commercially available. The same could not be said of the molecularly dispersed reference blend, and so Juniper created one consisting of a powder blend of all the excipients of the Apotex tablets and drospirenone in molecularly dispersed form. The reference blend was placed on a glass microscopic slide and left to dry overnight. It was then analyzed using FT Raman. Juniper conducted the FT Raman analysis twice for both the Zamine and Mya tablets.

[209] In order to confirm that the molecularly dispersed drospirenone reference blend comprised a true molecular dispersion, the reference slides were subjected to polarized light

optical microscopy. This technique is widely used in the pharmaceutical industry to investigate and visualize the structure of drugs and excipients through a microscope. It uses both polarized light (*i.e.*, light that travels in a vertical line) and non-polarized light (*i.e.*, light that oscillates in all directions). In combination with image analysis, the technique can be used to analyze particle size distribution and explore crystallinity.

[210] After confirming that the reference blend comprised a "true molecular dispersion", Drs. Luk and Davies compared the Raman spectra of the Apotex tablets to the spectra generated by the two reference blends, and sought to identify and quantify how much of the drospirenone in the Apotex tablets was present in particulate form as opposed to a molecular dispersion.

(2) Experiments conducted by Apotex

(a) *Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy*

[211] Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy [ATR] is a version of spectroscopy that uses infrared light. It can be used to create images or maps that provide chemical information about the different regions of an examined surface. These maps consist of many spectra, which can be interpreted to determine the composition of a pharmaceutical tablet.

[212] According to Dr. Cima, when drospirenone is present as a molecular dispersion, the individual molecules of drospirenone are surrounded by molecules of the substance in which it is dissolved, [redacted]. Therefore, if drospirenone is present in particulate

form in the Apotex tablets, one would expect to see discrete or separate regions containing drospirenone alone. Alternatively, if drospirenone exists as a molecular dispersion, the drospirenone will always be [redacted].

[213] Drs. Sommer and Cima used ATR to map two regions within two Mya and two Zamine tablets, the same number of tablets mapped by Drs. Luk and Davies. This was done to confirm whether or not drospirenone was co-located with other substances. Drs. Sommer and Cima created maps that provided chemical information about the different regions of the tablet surfaces they examined. Each spectrum that appeared on the generated map was representative of the material present at a specific location of the examined surface. By interpreting the spectra together, Drs. Sommer and Cima sought to determine the composition of different regions of the Apotex tablets. The spectra obtained from the ATR experiments were then subjected to a statistical analytical method called Principal Component Analysis [PCA] to better identify the compounds present in each region of the tablets examined.

(b) *Confocal Raman Spectroscopy*

[214] Drs. Sommer and Cima conducted their own experiments using confocal Raman spectroscopy, described above. However, as discussed below, they applied different parameters, including a longer integration time (*i.e.*, the time the laser is permitted to radiate in a single position). Drs. Sommer and Cima testified that this was necessary to ensure that the key excipients in the Apotex tablets could be detected.

(c) *FT Raman spectroscopy*

[215] Drs. Sommer and Cima also tried to replicate the preparation of the molecularly dispersed drospirenone reference slides created by Drs. Luk and Davies at Juniper. Drs. Sommer and Cima testified that Juniper's FT Raman results were flawed, principally because the reference standard for molecularly dispersed drospirenone prepared by Juniper contained residual solvent. To verify whether residual solvent was present in the reference films, they subjected the films to FT Raman, as described above.

D. *General Observations Regarding the Evidence*

[216] I found the expert witnesses who were called to testify for both parties regarding Bayer's allegation of infringement against Apotex to be generally credible.

[217] I was, however, troubled by the evidence of Drs. Luk and Davies regarding K-means clustering, a form of statistical analysis they used to interpret the results of their confocal Raman spectroscopy experiments. Numerous pages of the parties' expert reports and days of testimony were devoted to K-means clustering, but it proved difficult, if not impossible, for Apotex's experts and counsel to accurately reproduce Juniper's results either inside or outside the courtroom. Dr. Luk initially attributed this to the parties' use of different versions of the clustering software, but this turned out to be incorrect. Neither Drs. Luk nor Davies was fully conversant with the software in any event, and Bayer ultimately abandoned its reliance on this aspect of their evidence.

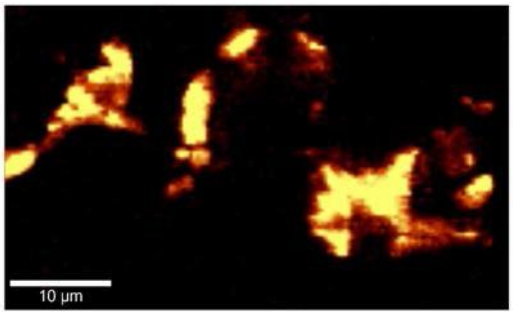
[218] In fairness to Bayer's experts, Drs. Sommer and Cima also struggled to explain the results of their PCA, the statistical sorting tool that is supplied by the ATR manufacturer.

[219] Despite my reservations regarding the testimony of Drs. Davies and Luk regarding K-means clustering, I find the results of Juniper's experiments to be compelling, including its use of confocal Raman spectroscopy, FT Raman spectroscopy and polarized light optical microscopy. In my view, the results of these experiments stand apart from the aborted K-means cluster analysis. I accept Dr. Davies' testimony that K-means cluster analysis was performed to provide further confirmation of what had been readily observed in the high resolution Raman data, namely that the Apotex tablets contain drospirenone in particulate form. I reject Apotex's submission that the problems associated with the K-means analysis cast doubt on the overall credibility of Drs. Luk and Davies. Moreover, I find that the results of Bayer's experimental tests are not refuted by the results of Apotex's ATR and confocal Raman spectroscopy experiments.

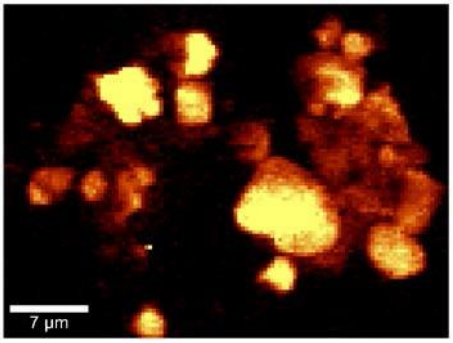
E. *Analysis*

(1) Bayer's Confocal Raman Spectroscopy Experiments

[220] As noted above, through confocal Raman spectroscopy, Juniper generated survey maps indicating the areas where the drospirenone was distributed on each cross-section of the Zamine and Mya tablets examined. Dr. Davies then conducted ten further, higher resolution scans of particular regions. According to Dr. Davies, the images that appear below, in addition to the spectral data and maps obtained by Juniper, clearly demonstrate that the Apotex tablets are comprised of drospirenone particles.

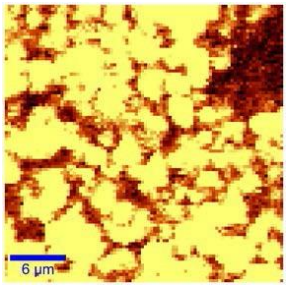


High resolution confocal Raman map of drospirenone in Zamine Tablet 2, Area 10

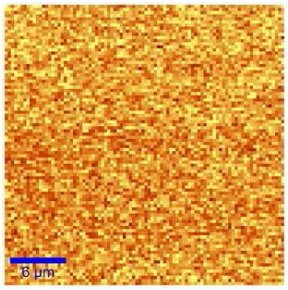


High resolution confocal Raman map of drospirenone in Mya Tablet 1, Area 2

[221] Dr. Davies compared these high resolution confocal Raman maps to the high resolution confocal Raman maps obtained for the crystalline (particulate) and molecularly-dispersed drospirenone references, and expressed the view that the Zamine and Mya tablets closely resemble the former and not the latter:



Crystalline Drospirenone Reference



Molecularly Dispersed Drospirenone Reference

[222] Dr. Davies testified that, even without resorting to K-means cluster analysis, the confocal Raman high resolution images allowed him to conclude that the drospirenone found in the Apotex tablets exists in particulate form.

[223] According to Apotex, the overriding and fundamental flaw in the confocal Raman experiments conducted by Juniper was their inability to detect the excipients that are known to be present in the Apotex tablets. The lactose and starch excipients account for approximately [redacted] of the ingredients in the Zamine and Mya tablets. Dr. Cima testified that the drospirenone present in the Apotex tablets cannot exist in isolation because the formulations are compressed to form the tablets, and one would therefore expect to see evidence of drospirenone-containing regions adjacent to excipient-containing regions. In the absence of such evidence, Dr. Cima concluded that Juniper's experiments did not allow for the detection of excipients, thereby undermining their reliability.

[224] Drs. Cima and Sommer suggested that Juniper's experiments were unable to detect the excipients because of the low "integration time" (*i.e.*, exposure time) of the microscope, coupled with the low power of the laser applied to the sample. According to Dr. Sommer, a poor "signal to noise ratio" can impair the ability of the microscope to detect components that scatter more

weakly than other components. “Noise” or static occurs when the microscope detects a signal that does not arise from the sample that is being examined. Compared to drospirenone, excipients such as [redacted], starch and lactose are all “weak Raman scatterers”, meaning they do not exhibit strong Raman spectral peaks in comparison to the strong peak generated by drospirenone. According to Drs. Sommer and Cima, the excipients are less likely to be detected over a noisy spectrum.

[225] In contrast to Juniper’s experiments, Dr. Sommer testified that the ATR mapping experiment performed on behalf of Apotex showed a good signal to noise ratio as a result of the enhanced acquisition time. According to Drs. Sommer and Cima, with the proper integration time, drospirenone is shown to be predominantly [redacted] and not, as asserted by Drs. Luk and Davies, isolated in the form of discrete particles. Apotex submits that its ATR Raman mapping experiments unambiguously showed that [redacted] in all but one instance, which confirmed the inability of Juniper’s confocal Raman spectroscopy experiments to detect excipients.

[226] Apotex maintains that the inability of Juniper’s confocal Raman spectroscopy experiments to identify the various excipients present in the Apotex tablets made it impossible for them to determine whether the drospirenone was [redacted], and might therefore be in the form of a molecular dispersion. Dr. Cima said that this undermined Drs. Luk’s and Davies’ conclusion that the Raman spectra from the high resolution maps exhibited orientation effects. According to Dr. Cima, before a signal can be attributed to orientation effects, the presence of confounding signals from other substances must be excluded. As this was

not done, Dr. Cima expressed the view that the conclusions reached by Drs. Luk and Davies regarding the orientation effect exhibited in the spectra could not be relied upon.

[227] Apotex notes that in prior South African litigation concerning tablets similar to Zamine and Mya, Drs. Davies and Luk designed experiments that evaluated the location of excipients as well as drospirenone (*Molecular Profiles Final Report: Determination of Drospirenone particle size in a Ruby (3 mg Drospirenone / 0,03 mg Ethinyl estradiol) solid dosage formulation*, October 26, 2011 [Ruby report]). At page 13 of the Ruby report, a colourful map shows the distribution of drospirenone, starch, lactose and [redacted] in the tablets examined. Apotex says that the mapping Dr. Luk performed in that case revealed substantial [redacted]. Apotex questions why Juniper adopted a different approach to its confocal Raman experiments in this case.

[228] During cross-examination, Dr. Davies admitted that he had not included a map that showed the distribution of excipients in the Apotex tablets, although he had provided such a map in the Ruby report. Dr. Davies noted that in the prior Ruby litigation, Juniper's testing was designed to determine the particle size and surface area of the tablets, not to determine whether drospirenone was in the form of a molecular dispersion or in particulate form.

[229] Apotex's second major criticism of Juniper's confocal Raman experiments concerns Juniper's use of reference slides that comprised pure drospirenone or [redacted], rather than reference slides that included the other excipients found in the Apotex tablets. According to Apotex, the reference standards were not subjected to the

milling, granulating, and blending process that the Apotex tablets undergo. Dr. Cima testified that a pure molecular dispersion does not look the same as a molecular dispersion that results from the formulation and manufacturing process that is applied to the Apotex tablets. However, he did not explain the nature or extent of the difference, nor was Dr. Davies pressed on this line of inquiry to any significant extent during cross examination.

[230] Dr. Luk testified that including the excipients found in the Apotex tablets in the reference slides would not have affected the images of the drospirenone particles, because they would simply "fill the space" around the particles. He acknowledged in cross-examination that there were regions in his intensity maps that contained drospirenone signal that may have been "in conjunction with the excipients" or "colocat[ed]". Although Dr. Davies' initial opinion was that all of the drospirenone identified in the intensity maps was crystalline, he ultimately agreed that some of the drospirenone in the tablets was not crystalline, and amorphous material in the tablets could potentially be a molecular dispersion. However, he maintained that the amount of non-particulate drospirenone was negligible.

[231] I am satisfied that the results of Bayer's confocal Raman spectroscopy experiments are strong evidence that the drospirenone found in Apotex's Zamine and Mya tablets is in the form of particles. The critical finding of Juniper's confocal Raman spectroscopy experiments is that the drospirenone in Apotex's Zamine and Mya tablets exhibits a characteristic crystalline appearance. As illustrated in the images reproduced above, the drospirenone resembles irregular clusters, not a homogenously dispersed substance. Although Bayer abandoned its reliance on K-means cluster analysis, upon which Drs. Luk and Davies relied to confirm orientation effects

within the Apotex tablets, Apotex does not dispute the general principle that crystalline material may exhibit orientation effects when interrogated with a polarized laser, as was done in Juniper's confocal Raman spectroscopy experiments. Therefore, despite the problems associated with the K-means analysis, Apotex's criticisms are not sufficient to undermine the strength of the conclusions reached by Drs. Luk and Davies. Furthermore, Apotex has not demonstrated that the decision of Drs. Luk and Davies to prepare reference spectra without excipients undermined the validity of their experiments. Nor did their failure to obtain images of the other excipients.

[232] The remaining criticisms levied against Juniper's confocal Raman spectroscopy experiments are predicated on the assumption that [redacted] necessarily indicates a molecular dispersion. For reasons that I explain in further detail below, I am not persuaded that co-location offers conclusive evidence of a molecular dispersion. Therefore, the fact that Juniper did not design its confocal Raman spectroscopy experiments to detect and locate the excipients in the Apotex tablets does not undermine their methodology.

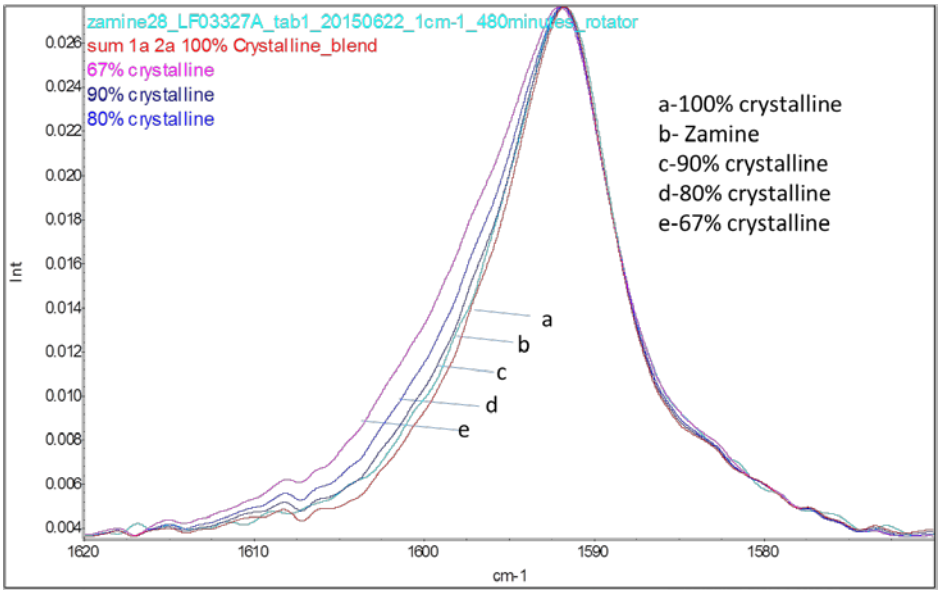
(2) Bayer's FT Raman Spectroscopy Experiments

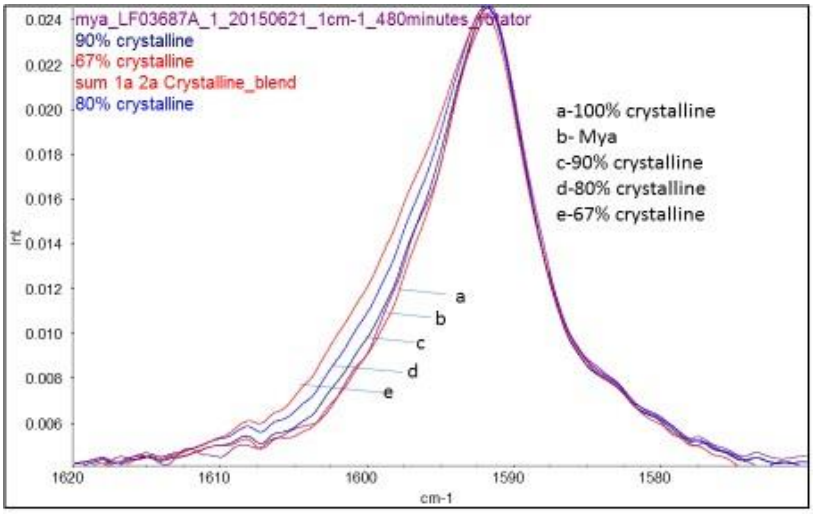
[233] Bayer's experts analyzed the Apotex tablets using FT Raman spectroscopy and concluded that there is at least 2 mg of drospirenone particles in each of the Zamine and Mya tablets. Dr. Davies relied on the phenomenon of spectral peak broadening and/or peak shifting to demonstrate that the drospirenone contained in the Apotex tablets is at least 90% (*i.e.*, greater than 2 mg) in particulate form.

[234] Drs. Luk and Davies created a reference standard containing 100% crystalline drospirenone and the Apotex tablet excipients, as well as a second standard containing molecularly dispersed drospirenone and the Apotex tablet excipients. They then generated composite spectra to calculate the drospirenone FT Raman peaks for tablets containing various ratios of crystalline to molecularly dispersed drospirenone.

[235] When Dr. Davies compared the characteristic drospirenone peak for the Zamine and Mya tablets (at approximately 1600 cm^{-1}), he found that those spectra corresponded more closely to the crystalline drospirenone spectrum than to the molecularly dispersed drospirenone spectrum. Specifically, the characteristic peak for drospirenone in the Zamine and Mya tablets had a shape and location which fell between the 100% crystalline standard and the 90% crystalline / 10% molecularly dispersed composite: the "full width/half height" of the Zamine and Mya peaks at 1600 cm^{-1}fell between the 100% crystalline standard and the 90% composite.

[236] The following two charts, generated by Juniper, illustrate the conclusions reached by Drs. Luk and Davies respecting the percentage of the drospirenone contained in Apotex's Zamine and Mya tablets that is in the form of particles as opposed to a molecular dispersion.





[237] Based on the FT Raman spectroscopy data, Dr. Davies concluded that at least 90% of the drospirenone in the Zamine and Mya tablets is in crystalline form, and therefore drospirenone particles. Dr. Cima agreed that such a tablet would infringe claim 31.

[238] Dr. Cima did not dispute that a molecular dispersion containing drospirenone would show Raman peak broadening when compared to the known Raman peak for crystalline drospirenone. Dr. Sommer also acknowledged the phenomenon of peak shifting/broadening

when drospirenone is in the form of a molecular dispersion as opposed to particles. However, Apotex argues that Bayer failed to establish that the reference standards used by Juniper were accurate, and that the comparisons with the Apotex tablets were therefore reliable.

[239] Apotex's first criticism of the experiment conducted by Drs. Luk and Davies is that the molecularly-dispersed reference slide created by Juniper was contaminated by the presence of solvent. According to Dr. Cima, the presence of solvent would cause the films to be rubbery, thereby enhancing the peak broadening that would be observed in the FT Raman experiment. This excessive broadening allegedly resulted in a reference standard for a molecular dispersion that was not representative of the molecular dispersion found in the Apotex product.

[240] Apotex says that the appearance of the films created by Juniper was consistent with the presence of solvent and inconsistent with the films being fully "dry". Apotex's experts explained that molecularly-dispersed films are in one of two states: above or below their "glass transition temperature" (Tg). When the Tg is below room temperature, the film is rubbery and soft. When the Tg is above room temperature, the film is a sheet of glass. Dr. Cima testified that the difference between these two states changes the properties of the dispersions and changes their Raman spectra.

[241] Dr. Cima initially testified that his opinion was based on his personal observation of the films created by Juniper, but he later admitted that he was not present for this portion of the experiments. His opinion was in fact based on his examination of photographs taken by Apotex's counsel during the *inter-partes* testing. Dr. Cima expressed the view that the films created by

Juniper were rubbery and soft, and did not exhibit the properties of a glass. In the photographs, the films appeared to curl when they were peeled off the slide on which they had been prepared. According to Dr. Cima, if the films were sheets of glass, then they would have crumbled and turned to dust. He said that the rubbery, curled appearance could only be explained by the presence of solvent in the films.

[242] Apotex takes the position, based on reported literature, that a dry film would have a Tg above room temperature, and that the Tg of the film could be lowered by the presence of solvent to below room temperature. Apotex suggests that there is no other scientific explanation for the reduction in Tg.

[243] Apotex says that the peak broadening observed by Juniper was inconsistent with properly prepared molecular dispersions as described in the literature. Dr. Cima provided two literature references related to peak broadening.

[244] One article reported peak broadening for another drug, nifedipine, which was prepared with a Tg above room temperature. The peak width increase was 2 cm^{-1}, not the 10 cm^{-1} observed by Dr. Davies. However, Dr. Cima said nothing about the nature of the drug nifedipine, or why one should infer anything about the peak broadening of drospirenone based upon the peak broadening of nifedipine. The peak broadening noted in the article was not said to be a general principle applicable to other compounds.

[245] The second article reported that drospirenone is “rather unusual” in that the Raman spectra of both crystalline and amorphous drospirenone are “very similar”. However, neither Dr. Cima nor the article he relied upon quantified the extent of this similarity, observing only that the difference is “small”.

[246] Apotex questions whether Juniper’s efforts to dry the reference slides were sufficient to remove the solvent from the films. As reported in the *inter-partes* testing protocol, the films were to be dried overnight under blown nitrogen. However, Juniper modified the drying protocol for the *inter-partes* experiments and did not always record the changes. Apotex suggests that this is indicative of a concern for the presence of solvent. Dr. Cima said that, according to the literature, drying could be achieved only at elevated temperatures and for a significantly longer period of time than was used in Juniper’s experiment.

[247] Dr. Sommer said that his attempts to reproduce the films created by Juniper resulted in the presence of solvent in the films. The FT Raman spectra generated by Dr. Sommer of a film dried overnight under blown nitrogen and a film dried for a further hour at an elevated temperature both showed the presence of solvent. Dr. Sommer did not prepare a fully dried reference slide and then subject it to FT Raman spectroscopy, although Bayer notes that he had the ability to do so.

[248] Apotex says that Drs. Luk and Davies did not perform the appropriate tests to determine whether solvent was present. According to Drs. Cima and Sommer, the most reliable test to determine the presence of solvent would be to acquire an FT Raman spectrum of the films prior

to mixing them with the other excipients; however, Juniper acquired FT Raman spectra of the films only once they had been blended with other excipients. Apotex is also critical of Dr. Davies' failure to employ "loss on drying" to ensure all solvent was removed.

[249] Apotex's second criticism of Juniper's FT Raman experiments is that the USP drospirenone reference relied upon by Drs. Luk and Davies may not have been 100% crystalline. According to Apotex, the USP does not certify the degree of crystallinity of its drospirenone sample, and the USP material was micronized which may have given rise to some amorphous material. Amorphous material may be in particulate form, or may be in the form of a molecular dispersion. The possibility that there may have been amorphous material present in Drs. Luk's and Davies' crystalline reference standards was not explored by Apotex to any great extent. Nor did Apotex show, to any convincing degree, the impact this may have had on Juniper's results.

[250] In my view, Juniper took reasonable steps to confirm the accuracy of their crystalline and molecularly dispersed drospirenone reference blends. They used polarized light microscopy for this purpose. This enabled them to confirm that the drospirenone used in the crystalline drospirenone reference blend was comprised of crystals (and therefore particles), while the molecularly dispersed drospirenone reference blend did not contain crystals or particles.

[251] I am not persuaded by Apotex's criticisms of Juniper's FT Raman spectroscopy experiments. The suggestion that Juniper's reference slides were contaminated by solvent rests on Dr. Cima's review of photographs taken by Apotex's counsel when Dr. Cima was not present. His assertion that the presence of solvent would enhance the peak broadening observed in the FT

Raman experiment is based on two references found in the literature, neither of which shed any light on the particular experiments conducted in this case. The complaint that the USP does not certify the degree of crystallinity of its drospirenone sample is rooted in speculation rather than evidence.

[252] Apotex points to other circumstantial evidence in support of its assertion that Juniper's molecularly dispersed film was contaminated by solvent. This evidence consists primarily of documentary references to *ex parte* testing done by Juniper, the results of which were not disclosed to Apotex. Counsel for Apotex insinuated that Juniper may have deliberately manipulated its reference films to achieve its desired results. This is not a plausible assertion, given that Bayer voluntarily disclosed ample evidence to enable Apotex to advance its argument concerning solvent contamination.

[253] More fundamentally, an allegation of fraud or perjury against a professional witness is a serious matter, and should not be made without clear and convincing evidence (*Blank v Canada (Minister of Justice)*, 2009 FC 1221 at paras 54-55). The circumstantial evidence relied on by Apotex falls far short of this standard, and I give it no weight.

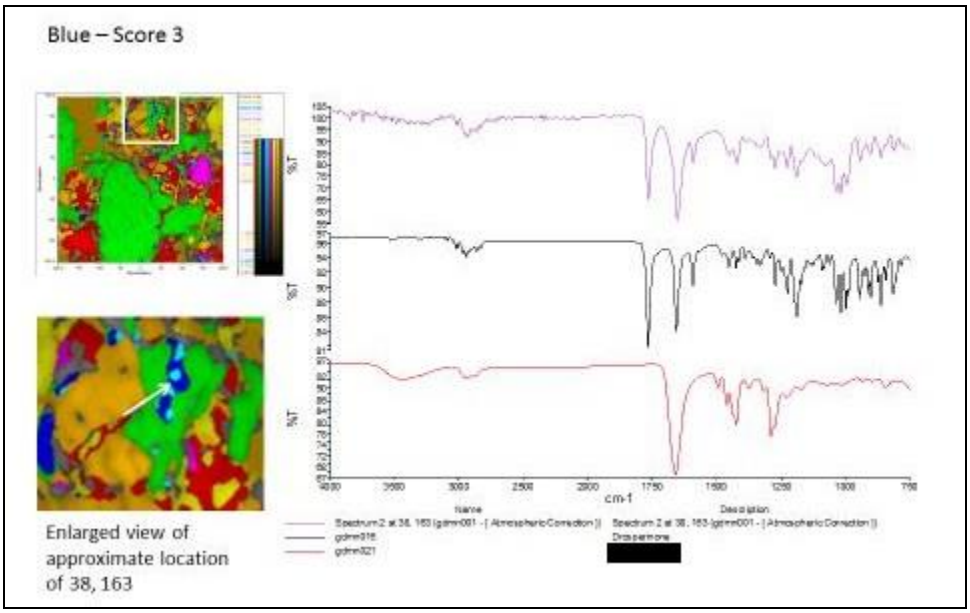
(3) Apotex's ATR Microscopy Experiments

[254] Apotex says that its tablets are made by a process whereby [redacted], causing drospirenone to dissolve or become dispersed within the [redacted]. Dr. Davies agreed that spectroscopic analysis of a molecular dispersion should generate signals for [redacted] in the same

location; however, when drospirenone is in the form of crystalline particles, then the molecules should generate signals for discrete, isolated regions containing only drospirenone.

[255] Using ATR microscopy, Dr. Sommer mapped two regions within two Mya and two Zamine tablets. The resulting maps were subjected to PCA, which, as noted above, is a statistical sorting tool that is supplied by the ATR manufacturer. PCA requires no user input, and always sorts the data into eight colour-coded components.

[256] Dr. Cima drew the Court's attention to a representative spectrum from the "blue" regions of a Mya tablet generated by the PCA. Reference spectra for [redacted] were shown for comparison:



Infrared spectrum from the blue regions of Mya 1, Area 1 (upper, purple line)
Infrared spectrum of drospirenone (middle, black line)
Infrared spectrum of [redacted] (lower, red line)

[257] Dr. Cima explained the PCA results as follows:

> The spectrum from the blue regions contains the 1765 cm^{-1} band that is characteristic of drospirenone. …

> The bands at 1655 cm^{-1} and 1765 cm^{-1} are also indicative of the presence of [redacted] in the blue regions. When one compares the relative strength of the 1655 cm^{-1} and 1765 cm^{-1} bands in the blue region spectrum (the upper line in the figure) against the relative strength of these same two bands in the drospirenone reference spectrum (the middle line in the 3400 cm^{-1} 1765 cm^{-1}1655 cm^{-1} figure), it is evident that the relative strength of these bands invert.
>
> This inversion is explained by the [redacted] in the blue regions. Essentially, both [redacted] are contributing to the intensity of the bands in the blue region spectrum. [redacted] will contribute to the peak intensity at 1655 cm^{-1}, but it will not contribute to the peak intensity at 1765 cm^{-1}. Thus, the inversion of the relative strength of the 1655 cm^{-1} and 1765 cm^{-1} bands is indicative of [redacted].
>
> Thus, all regions indicated as blue in the PCA map are a [redacted].

[258] He offered a similar conclusion regarding the cyan (turquoise or teal) regions: all regions indicated as cyan in the PCA map are a [redacted].

[259] According to Dr. Cima, the results of the PCA demonstrated that the overwhelming majority of the drospirenone contained in the Apotex tablets is [redacted]. Only one component of the four areas examined in the Mya tablets was found to be very rich in drospirenone. This area constituted “only a small fraction of the area occupied by the drospirenone-containing regions”, or 31 of the 29,580 pixels where drospirenone was detected. For the Zamine tablets, there was only one component within a single area that was very rich in drospirenone. It comprised approximately 6% of all of the drospirenone-containing regions in one of the Zamine tablets examined. Dr. Cima testified that the ATR maps showed that the

overwhelming majority of the drospirenone in the Apotex tablets was in the form of a molecular dispersion.

[260] Apotex notes that the ATR mapping conducted by Dr. Sommer encompassed more than twenty times the surface area examined in the same number of tablets by Juniper.

[261] Bayer responds that Apotex has erroneously conflated co-location and molecular dispersion. According to Bayer, co-location simply means that two or more particles are found next to one another within the field of view of the analytical instrument (in this case, the ATR instrument). A molecular dispersion, on the other hand, requires that drospirenone be dispersed in another substance at a molecular level. In a molecular dispersion, molecules of one substance (*e.g.*, drospirenone) are homogenously distributed [redacted].

[262] Bayer challenges Dr. Cima's PCA maps on the ground that they show numerous pairings of co-located substances that cannot possibly be found in molecular dispersions, including starch-magnesium stearate, [redacted], and lactose-starch. PCA results may indicate [redacted] near each other, but this does not mean the two exist as a molecular dispersion. Drospirenone particles may be surrounded by, or simply next to, [redacted].

[263] Dr. Cima acknowledged that one cannot conclude definitively from Dr. Sommer's mapping whether the drospirenone was molecularly dispersed or whether it was merely located near [redacted]. He accepted that the ability to infer a molecular dispersion from co-

location is dependent on detection limits. Dr. Sommer's ATR experiments were performed at a resolution of 3 µm. Bayer notes that Juniper's confocal Raman experiments were performed at a resolution of 1 µm, and detected particles of drospirenone in the Zamine and Mya tablets smaller than 3 µm.

[264] Dr. Sommer agreed that in a true molecular dispersion, one ingredient is distributed in the other ingredient homogenously. Bayer argues that Dr. Sommer's PCA results do not show that the drospirenone concentration is homogenous throughout the Zamine and Mya tablets he examined. Dr. Cima suggested the lack of homogeneity might be due to the intensive mixing process, similar to what occurs in a food blender, but admitted this was just a theory.

[265] Dr. Sommer's interpretation of the PCA results must be approached with caution. It became clear in cross-examination that he could not explain the results with confidence. He initially dismissed as typographical errors portions of his report where different colours were ascribed to the same region. He later acknowledged that the software had in fact selected multiple colours to be associated with the same score, conceding that he is not an expert in interpreting PCA.

[266] Dr. Cima also struggled to explain why the PCA would assign different colours to the same region, and suggested this might be due to the intensity of the image. He theorized that this may be caused by variations in the topology of the sample, or a lack of contact with the crystal through which the image was viewed, but concluded "I honestly can't tell you … it just does it".

[267] I am persuaded by Bayer's assertion that the co-location of two substances does not necessarily indicate that they are molecularly dispersed. This is convincingly illustrated by the pairings of co-located substances in the PCA maps that cannot possibly exist together as molecular dispersions. The PCA analysis also suggested the presence of drospirenone without [redacted]. At most, the PCA results indicate drospirenone and [redacted] are usually located near each other within the Apotex tablets. This does not establish that the two exist in a molecular dispersion. I note Dr. Cima's candid acknowledgment that, due to detection limits, Dr. Sommer's mapping does not permit one to conclude definitively whether the drospirenone was molecularly dispersed or whether it was merely located near [redacted].

(4) Apotex's Confocal Raman Experiments

[268] Drs. Sommer and Cima also analysed a subset of one area from each of the Apotex tablets using confocal Raman spectroscopy. They said they could not perform additional Raman mapping because the reliable detection of both drospirenone and the other excipients would take much longer than the time taken by Drs. Davies and Luk to detect only drospirenone.

[269] The maps generated were each approximately 100 microns by 100 microns, resulting in an overall surface area below 50% of the entire surface area examined by Juniper at high resolution (20,000 pixels compared to 53,800). Dr. Cima concluded that the confocal Raman maps were consistent with the results of the ATR microscopy. All regions containing drospirenone also [redacted], with the exception of a single region identified in the Zamine map. In Dr. Cima's opinion, this latter region was not of sufficient intensity to enable him to reach a definitive conclusion regarding the [redacted]. Dr. Cima

therefore expressed the view that his confocal Raman experiments were consistent with drospirenone being in the form of a molecular dispersion [redacted].

[270] Once again, Apotex's confocal Raman experiments demonstrate, at most, that the drospirenone in Zamine and Mya is commonly [redacted]. However, the results were not entirely consistent in this respect. Some regions exhibited a high concentration of drospirenone that may or may not have been [redacted]. Furthermore, for the reasons discussed above, the [redacted] does not necessarily mean the two exist together in the form of a molecular dispersion.

(5) Development of the Zamine and Mya Tablets

[271] The product monographs for the Apotex tablets describe them as oral dose contraceptive compositions for use in a human female comprising 3 mg of drospirenone and 0.03 mg of ethinylestradiol for Zamine, and 3 mg of drospirenone and 0.02 mg of ethinylestradiol for Mya. Zamine and Mya each contain one or more pharmaceutically acceptable carriers. The drospirenone in Zamine and Mya tablets is exposed to the gastric environment upon dissolution, *i.e.*, they are both immediate release formulations.

[272] Apotex's regulatory drug submissions for Zamine and Mya do not mention that the active pharmaceutical ingredients are provided in the form of a molecular dispersion. None of the documents produced by Apotex in this case suggest Apotex or its suppliers, [redacted], intended to manufacture a molecularly dispersed form of drospirenone. The Abbreviated New Drug Submission [ANDS] submitted to Health Canada for Zamine and Mya indicate that "a

formulation was developed on the bases of the reference product formulation". The reference products were Bayer's Yasmin and Yaz tablets.

[273] In the course of discovery, Bayer requested any communications between Apotex and [redacted] relating to Apotex's molecular dispersion defence. Apotex replied that "[a]part from the information regarding [redacted]'s process of manufacture of the Zamine and Mya tablets already produced, there have been no written communications exchanged between Apotex and [redacted] with respect to the form of the drospirenone found in the Zamine or Mya tablets".

[274] Apotex confirmed on discovery that: (i) Apotex did not have any involvement in the development of Zamine or Mya tablets; (ii) Apotex did not have any influence on the method of manufacture of Zamine or Mya tablets; and (iii) Apotex did not have any involvement in the choice of excipients used in the Zamine and Mya tablets. Apotex did not call any witnesses from [redacted] to confirm the presence of a molecular dispersion in the tablets.

[275] The Zamine and Mya tablets both [redacted]. Dr. Cima testified that [redacted] within a molecular dispersion: drospirenone molecules are dispersed [redacted] and therefore do not exist as particles. However, according to the ANDS for Zamine, [redacted]. This was confirmed by Apotex's representative on discovery, who also confirmed that the drospirenone in the Zamine and Mya tablets is manufactured in the same way.

[276] Bayer argues that if Apotex or its suppliers had manufactured a molecular dispersion of drospirenone in [redacted], then this would have been disclosed in its regulatory submissions. Instead, the ANDS submitted by Apotex indicates Zamine and Mya tablets are manufactured by a deposition method whereby drospirenone is dissolved in a solution and then applied to inert carrier particles. This method is contemplated by both claim 31 and the disclosure of the ‘426 patent.

[277] Dr. Cima testified that authorities such as the U.S. Food and Drug Administration and Health Canada may be concerned about the stability of molecular dispersions, and therefore require companies to prove the stability of those formulations. Dr. Cima also acknowledged that a person skilled in the art would have reservations about the physical stability of molecular dispersions. This is because a molecular dispersion is not in equilibrium and tends to crystallize, which leads to a decrease in its solubility and dissolution rate.

[278] Apotex argues that no adverse inference may be drawn from the absence of documents relating to the development of the Zamine and Mya tablets confirming that the active pharmaceutical ingredients were intended to be provided in the form of a molecular dispersion. Apotex notes that its refusal to produce documents or answer questions on discovery regarding these matters was upheld by Prothonotary Milczynski in her decision dated June 9, 2015. Apotex also points out that its list of proposed witnesses initially included a representative of [redacted], but an agreed statement of facts obviated the need for this witness to be called. Bayer did not insist that a representative of [redacted] testify in these proceedings.

[279] Apotex maintains that the evidence adduced before this Court regarding the manner in which its Zamine and Mya tablets are made supports its position that drospirenone is present in the form of a molecular dispersion and not as particles. Dr. Cima testified that the key processing feature in the formulation process is the creation of a solution wherein drospirenone, [redacted] are dissolved in methylene chloride and methanol. This solution is subsequently poured or sprayed onto the remaining tablet excipients (*e.g.*, lactose, starch, etc.) and then mixed together. Evaporation of the volatile methylene chloride and methanol solvents causes the drospirenone to be [redacted]. According to Dr. Cima, this is consistent with the manner in which molecular dispersions are generally made, *i.e.*, a drug dissolved in a polymer.

[280] Bayer says that it is not asking the Court to draw a formal adverse inference against Apotex. Nevertheless, Bayer asserts that the absence of corroborating evidence that one would expect to find regarding the development of Zamine and Mya detracts from the overall credibility of Apotex's defence.

[281] In my view, the absence of any documentary evidence to suggest Apotex's suppliers, [redacted], intended to manufacture a molecularly dispersed form of drospirenone is a factor I must consider in assessing the credibility of Apotex's defence. The ANDS for both the Zamine and Mya tablets do not refer to molecular dispersions, and describe [redacted] only as a binder. The formulations were developed on the bases of the reference product formulations, which were Bayer's tablets. The available evidence regarding the development of the Zamine

and Mya tablets reinforces my conclusion that they are formulated in the same manner as Bayer's tablets, with drospirenone in the form of particles.

F. *Conclusion*

[282] I am satisfied that Bayer has discharged its burden of demonstrating, on a balance of probabilities, that Apotex's Zamine and Mya tablets infringe claim 31 and dependent claims 48 and 49 of the '426 patent. Both tablets contain drospirenone that is at least 90% in the form of particles; the amounts of the pharmaceutically-active ingredients fall within the parameters specified in the claims in issue; and they meet the dissolution profile described in claim 31 of the patent. The Zamine and Mya tablets are also exposed to the gastric environment upon dissolution. The Zamine and Mya tablets therefore meet these and all other essential elements of claims 31, 48 and 49.

XI. Infringement – Cobalt

A. *Preliminary Issue – Cobalt's "Admission"*

[283] Bayer argues that Cobalt has made a formal admission in its Amended Amended Statement of Defence and Counterclaim that its Zarah tablets are comprised of drospirenone particles. Specifically, Bayer asserts that Cobalt has clearly admitted in paragraph 14 (now paragraph 11) of its pleading that the Zarah manufacturing process results in tablets that contain drospirenone particles:

> The Cobalt Product is made by dissolving drospirenone into solution and then spraying this solution onto inert carrier particles. The drospirenone particles that crystallize out once the solution is

> sprayed on in the Cobalt Product may or may not be in the micron range as per the standard sieve measurement …
>
> [Emphasis added]

[284] Cobalt tried and failed to amend its pleading to delete this paragraph in its entirety and replace it with a statement that its product does not contain drospirenone particles.

[285] In a decision dated August 12, 2014, Prothonotary Milczynski denied Cobalt leave to amend paragraph 14 of its pleading on the ground that this would constitute a "significant withdrawal of an admission", and a "radical departure" from Cobalt's original position that its product contains drospirenone particles. She noted that a party may be allowed to withdraw an admission, but must provide some explanation for seeking the withdrawal, *e.g.*, that the original pleading was in error, was inserted through inadvertence, hastiness, lack of knowledge, or that there has since been discovery of new facts (citing *Andersen Consulting v R* (1997), [1997] FCJ No 1433, [1998] 1 FC 605 (Fed CA)). She noted that Cobalt had not explained why, or on what basis, it was seeking to withdraw its admission, and denied leave for that reason.

[286] Cobalt commenced an appeal of Prothonotary Milczynski's decision and also brought a further motion to amend its pleading, supported by additional evidence. However, Cobalt subsequently abandoned both the appeal and the motion. Bayer says Cobalt should therefore be precluded from presenting any evidence in these proceedings that seeks to contradict the admission it tried unsuccessfully to withdraw. Cobalt denies that the statement contained in paragraph 11 of its pleading constitutes a binding admission of fact.

[287] *Black's Law Dictionary*, 10th ed, *sub verbo* "admission" provides that an admission is "a statement in which someone admits that something is true". The law draws a distinction between "formal" admissions and "informal" admissions.

[288] In Sopinka et al, *The Law of Evidence in Canada*, 3rd ed (Markham: LexisNexis, 2009) at 1263 [Sopinka], the authors note that a formal admission is made for the purpose of dispensing with proof at trial and is conclusive as to the matter admitted. A formal admission is further defined as a concession by a party that a certain fact or issue is not in dispute. The authors note at section 19.2 that a formal admission may be made by a statement in a pleading, which cannot be withdrawn except with leave of the court, or the consent of the party in whose favour it was made. The authors state that leave should not be granted unless: (i) the admission was made without authority; (ii) there exists a triable issue; and (iii) there will be no prejudice to the opposing party. An admission of law, in contrast to an admission of fact, may be withdrawn at any time. They further note that where a formal admission is made, all other evidence is precluded as being irrelevant.

[289] An informal admission, on the other hand, may be adduced in evidence as an exception to the hearsay rule and does not bind a party if it can be overcome by other evidence (Sopinka at s 19.1). In other words, informal admissions are items of evidence that can be explained away at the trial at which they are to be proven (*Vancouver Art Metal Works Ltd v Her Majesty the Queen*, 2001 FCT 265 at para 10, 2001 CFPI 265 (Fed TD); *Amfac Foods Inc v Irving Pulp & Paper Ltd*, [1984] FCJ No 105 at para 24, 25 ACWS (2d) 105, aff'd [1986] FCJ No 659, 12 CPR [*Amfac*]).

[290] Cobalt says that a statement made in a pleading must be an unambiguous deliberate concession to an opposing party, and disputes that its so-called "admission" can be characterized as such (citing *Apotex Inc v Wellcome Foundation Ltd*, 2009 FC 117 at para 34 (Proth); rev'd on other grounds 2009 FC 949).

[291] According to Cobalt, the statement found at paragraph 11 of its Amended Amended Statement of Defence and Counterclaim is made in the context of stating a negative: that the Cobalt product does not infringe the '426 patent because it does not contain micronized particles. Cobalt maintains that Bayer has neither accepted the admission nor treated the statement as a formal admission. Cobalt notes that Bayer has conducted extensive testing to prove that the Cobalt tablet is actually comprised of particles as Bayer defines them, and the statement therefore cannot be characterized as unambiguous. Cobalt says that, at its highest, the statement is an acknowledgement of one of the possible results of spraying a solution of drospirenone onto carrier particles and drying them.

[292] Cobalt also argues that the statement at issue is not an admission of fact because it involves a question of patent construction concerning the definition of the term "particle", which is a question of law for the Court (citing *Amfac* at para 24). Cobalt says that Bayer has always treated the Cobalt statement as a question of patent construction, and not as a "factual admission". Bayer admits that one of the issues in this case turns on the meaning of the phrase "drospirenone particles", over which the parties disagree. However, I note that Cobalt did not take the position before Prothonotary Milczynski that its statement could not be characterized as an admission because it concerned a question of patent construction.

[293] This Court may make a finding of fact that differs from what is asserted by the plaintiff and admitted by the defendant if the admission concerns a factual issue that ought to be tried in the interests of justice (*Morin v R*, 2002 FCT 1312 at para 109, [2002] FCJ No 1805 (Fed TD), aff'd 2005 FCA 52, citing *Andersen Consulting v Canada* (1997), [1998] 1 FC 605, [1997] FCJ No 1433 (Fed CA)). However, given Cobalt's decision to abandon its appeal of Prothonotary Milczynski's order, Cobalt's admission that its product contains at least some drospirenone particles must be taken as final. Any attempt by Cobalt to undermine that order by presenting evidence that contradicts this admission would amount to a collateral attack.

[294] In the alternative, Cobalt argues that the statement in its pleading is not an admission that all of the drospirenone in the Cobalt product is in the form of particles, but merely an acknowledgement that some of the drospirenone may be present in particulate form.

[295] As will be seen below, Cobalt does not dispute that its Zarah tablets contain at least some drospirenone in particulate form. The dispute concerns the amount of drospirenone in the form of particles, the nature of those particles, and whether Cobalt has infringed the claims in issue. Therefore, although Cobalt cannot present evidence that contradicts its admission, Cobalt is not precluded from presenting its defence to Bayer's allegation of infringement, namely that Bayer has not demonstrated that 2 of the 3 mgs of drospirenone found in the Cobalt product are particles.

B. *The Evidence – Expert Witnesses*

[296] Bayer presented the evidence of the following expert witnesses:

a) **Dr. Shen Luk**. Dr. Luk's qualifications are discussed above. His mandate was to determine whether the Zarah tablets contain about 2 mg to 4 mg of drospirenone particles, and whether at least 70% of the drospirenone dissolves within 30 minutes according to the standard dissolution protocol described in claim 31. Dr. Luk offered no opinion on the results of his testing, which were interpreted by Dr. Davies.

b) **Dr. Martyn Christopher Davies**. His qualifications are discussed above. Dr. Davies was asked to provide an opinion on whether the Zarah tablets fall within the scope of claims 31, 48 and 49. He also provided his opinion on the formulation details of the Zarah tablets.

[297] Cobalt presented the evidence of the following expert witnesses:

a) **Dr. Graham Buckton** of Hampshire, United Kingdom. He is an emeritus professor of pharmaceutics at the University College London School of Pharmacy. He also provides consultancy in the areas of development and formulation of products to industrial companies. Dr. Buckton is an expert in pharmaceutical formulation and pharmaceutical material science, including the use of materials characterization techniques. Dr. Buckton provided evidence on the manufacturing process of the Cobalt product, the interpretation of the patent, and whether the Cobalt product infringes the patent.

b) **Dr. Mary Miller** of Duluth, Georgia. She is an executive director at MVA Scientific Consultants [MVA], an analytical consulting and testing service laboratory located in Duluth, Georgia. She is an expert in analyzing small particles and products using spectroscopic methods. MVA conducted confocal Raman experiments on the Cobalt product, which Dr. Miller supervised.

c) **Dr. Simon Webster** of Leeds, United Kingdom. He is the Founder and Managing Director of Artos Innovation Limited, which provides analytical and diagnostic technology development to developers and sellers, and Iguana Innovation Limited, which provides business and technical support services for investors. Dr. Webster is an expert in Raman spectroscopy, including the use of Raman spectroscopy to characterize and image pharmaceutical products and their composition. His mandate was to respond to the opinions expressed by Drs. Luk and Davies with respect to Juniper's testing of the Cobalt product, and contrast the work described in Dr. Miller's report with the testing performed by Juniper.

C. *The Evidence – Experimental Testing*

(1) Experiments conducted by Bayer

[298] As in the Apotex proceedings, Bayer retained Juniper to conduct confocal Raman spectroscopy and dissolution testing on Cobalt's Zarah tablets. Juniper did not conduct FT Raman spectroscopy on the Zarah tablets, because Cobalt has never alleged that its Zarah tablets contain drospirenone in the form of a molecular dispersion.

(2) Experiments conducted by Cobalt

[299] MVA performed confocal Raman spectroscopy experiments to determine whether the Zarah tablets are comprised of drospirenone particles.

D. *General Observations Regarding the Evidence*

[300] I found the expert witnesses who were called to testify by both parties regarding Bayer's allegation of infringement against Cobalt to be generally credible. The sole exception is Dr. Buckton, whose evidence I found to be inconsistent with that of all other expert witnesses, and with his own testimony in prior litigation.

E. *Further Observations Regarding Construction of the Claims*

[301] Bayer and Cobalt do not agree on the meaning of "drospirenone particles" in claim 31. Bayer asserts that the meaning has previously been settled by this Court and the Federal Court of Appeal, and in both instances the term "drospirenone particles" was held to include all drospirenone particles that rapidly dissolve in the manner described in the claim.

[302] Dr. Buckton testified that, as a consequence of the tabletting process undergone by the Zarah product, the sprayed-on drospirenone and other materials rearrange and bond together. According to Dr. Buckton, a tablet is formed by the application of an enormous force to a mixture of pharmaceutically active ingredients and excipients that are held in the die of a tabletting machine. The force initially causes the particles to consolidate, move past each other, and fragment to a small extent, until no further movement is possible and a tablet is produced: "[d]uring the tabletting process, brittle materials will fracture instantaneously, move and rebond, whereas plastic materials will flow and thus intermingle between, join and bond with the other particles".

[303] Dr. Buckton characterized the contents of a tablet as a "bonded mass" (*i.e.*, comprising bonded materials but not free-standing particles). As a result of fracturing and flowing, the materials put into the die of the tabletting machine do not emerge unchanged:

> … But undoubtedly the particle of [redacted], which is oozed and flowed under the pressure, will not be the particle of [redacted] that it started with. The particle of [redacted], which is fractured and rebonded, will not be the particle of lactose it started with. And equally, drug particles, if they fractured or flowed – and drugs can be brittle or can be plastic, different drugs are brittle or plastic or some can be both – they will not be the same material they started with either. So there will be a movement and change of materials as they flow, break and rebond and form new things in the tableting process.

[304] Cobalt's position, based on Dr. Buckton's evidence, is that even if Cobalt's [redacted] produces discrete particles, the tabletting process will cause these drospirenone particles to bond together to form a region of drospirenone on the surface of the carrier particles by virtue of the enormous compression force applied. Cobalt maintains that, as a result of the tabletting process, the contents of its product no longer fall within the claims in issue.

[305] According to Dr. Buckton, drospirenone [redacted] forms a "composite" or "construct" with the carrier. Dr. Buckton admitted the terms "composite" and "construct" have no special scientific meaning; they simply refer to two things brought together in the literal sense, in this case drospirenone and the carrier. Dr. Buckton did not dispute that the drospirenone [redacted] may exist in particulate form, but he nevertheless maintained that those particles would not be encompassed by claim 31.

[306] Bayer submits that Dr. Buckton's interpretation is "contrary to prior judicial findings, contrary to the opinions of other experts in these proceedings, contrary to his own testimony in the United Kingdom, and contrary to science in general". Dr. Buckton previously provided expert evidence in a case involving the equivalent to the '426 patent in the United Kingdom. In that proceeding, he acknowledged that the [redacted] was known to "increase the rate of dissolution, since upon drying the solvent off, a large number of very small API [active pharmaceutical ingredient] particles would be [redacted] particles".

[307] I accept Bayer's assertion that Dr. Buckton's testimony stands alone. I prefer the evidence of Drs. Parr, Webster and Davies, all of whom defined the term "particle" as a solid state, non-dissolved form of matter.

F. *Analysis*

(1) Cobalt's Manufacturing Process

[308] Bayer argues that Cobalt's manufacturing process inherently produces drospirenone particles. According to the Cobalt ANDS, the manufacturing process for Zarah tablets may be divided into [redacted]:

[redacted]

[309] Dr. Davies noted that Cobalt's formulation does not [redacted], and the drospirenone in the Zarah tablet therefore cannot exist as a molecular dispersion. Dr. Cima agreed that if drospirenone [redacted], then the result must be drospirenone particles. In the words of Dr. Cima, "that's the only thing they can be". While Dr. Cima expressed this view in the context of Bayer's allegation of infringement against Apotex, counsel for Cobalt acknowledged that scientific information provided by expert witnesses at a general level could be considered in both cases.

[310] Dr. Buckton conceded that the [redacted] used to manufacture Zarah tablets is the same as the one described in the '426 patent. Although his evidence was not entirely consistent

on this point, he also acknowledged that drospirenone particles may result from the [redacted].

(2) Bayer's Confocal Raman Spectroscopy Experiments

[311] On behalf of Bayer, Juniper obtained cross sections of two Zarah tablets and subjected them to confocal Raman spectroscopy. Survey area maps were then prepared, which indicated where drospirenone was located within the area scanned. Ten smaller areas were selected from each survey area map to obtain higher resolution Raman maps for each Zarah tablet.

[312] Dr. Davies testified that the result of Juniper's confocal Raman spectroscopy tests confirmed the presence of discrete particles of drospirenone in the Zarah tablets. He concluded that the Raman survey maps revealed the presence of isolated drospirenone particles in the Zarah tablets.

[313] The higher resolution Raman maps also showed drospirenone as discrete particles and clusters of particles in the Zarah tablets. Based on the confocal Raman experiments, Dr. Davies concluded that Zarah tablets contain 3 mg of drospirenone particles. He found no evidence of drospirenone in non-particulate form, and he therefore formed the opinion that all 3 mgs of drospirenone in the Zarah tablets is particulate.

[314] Dr. Webster cautioned that Juniper had sampled only a very small fraction of the total tablet. He described this as a methodological constraint, rather than a criticism of Juniper's test results.

[315] Dr. Davies countered that the process used by Cobalt to manufacture its Zarah tablets yields a homogenous distribution of drospirenone particles throughout the tablet, and the samples analyzed by Juniper were therefore representative of the drospirenone particles contained in the tablet as a whole. Dr. Luk explained that, given Cobalt's admission that its tablet contains 3 mg of drospirenone, and the absence of a molecular dispersion, it follows that this amount of drospirenone must all be particulate.

(3) Cobalt's Confocal Raman Spectroscopy Experiments

[316] MVA conducted confocal Raman spectroscopy experiments on two Zarah tablets. One tablet was not processed prior to scanning, and a Raman intensity map was generated of the tablet's outer surface. The other tablet was cross-sectioned. An area comprising 1 mm by 1 mm was scanned to obtain a high resolution Raman map. The Raman map of the tablet cross-section had a lower resolution than the Raman map of the tablet surface.

[317] For each tablet, Raman intensity maps were generated to show the distribution of the primary ingredients contained in the Zarah tablets: drospirenone, [redacted]. A Raman intensity overlay map was then produced for each tablet from the individual intensity maps of drospirenone, [redacted].

[318] Dr. Webster observed that the drospirenone in the MVA Raman maps appeared to be more widely distributed than in the Juniper maps, which in his view suggested Juniper may have failed to detect some non-particulate drospirenone. He attributed this to the longer exposure time and shorter wavelength of the laser light used by MVA. Dr. Webster identified additional factors

which he suggested may have affected the relative sensitivities of the testing conducted by MVA and Juniper, but offered no definitive conclusions.

[319] Dr. Miller characterized the distribution of drospirenone, [redacted] in the Zarah tablets as "intimately mixed". She stated that spectra collected from points in the overlay of the Raman intensity maps that appeared to correspond to only one ingredient in fact showed the presence of all three ingredients mixed together.

[320] Bayer acknowledged that Juniper's drospirenone Raman intensity maps tended to show a greater incidence of discrete particles of drospirenone when compared to the more continuous drospirenone signal in the MVA maps. However, Bayer argued this was likely due to the higher resolution of Juniper's Raman analysis. Dr. Luk suggested the drospirenone in the MVA Raman intensity maps may have been detected from outside the confocal plane, *i.e.*, outside the region intended to be examined. The apparent "continuous distribution of drospirenone" detected in the MVA Raman intensity maps may therefore have resulted from the detection of drospirenone in multiple planes of the sampling volume.

[321] I prefer the evidence of Drs. Luk and Davies. I accept their analysis of Cobalt's manufacturing process, and their conclusion that this necessarily produces drospirenone in the form of particles. I also accept the results of Juniper's testing, which confirmed that all of the drospirenone in Cobalt's tablets is particulate. Finally, I find that the assertion that the "intimate mixing" that is said to be demonstrated by MVA's test results is not in fact possible, because Cobalt's manufacturing process would not cause [redacted] to be present in the same

location. A more plausible theory, in my view, is that the comparatively poor resolution of MVA's images, and the possibility that drospirenone may have been detected from outside the confocal plane, caused the results and conclusions of Cobalt's witnesses to be unreliable.

[322] Cobalt did not suggest that its tablets do not meet the dissolution profile described in claim 31 of the '426 patent, nor was this asserted in its pleadings. None of Cobalt's experts conducted dissolution testing. Dr. Buckton accepted that Cobalt's product would likely meet the dissolution profile, saying that he would be "amazed if the Cobalt product didn't hit that dissolution".

G. *Conclusion*

[323] I am satisfied that Bayer has discharged its burden of demonstrating, on a balance of probabilities, that Cobalt's Zarah tablets infringe claim 31 and dependent claims 48 and 49 of the '426 patent. Both tablets contain drospirenone that is at least 90% in the form of particles; the amounts of the pharmaceutically-active ingredients fall within the parameters of the claims in issue; and they meet the dissolution profile described in claim 31 of the patent. The Zarah tablet is also exposed to the gastric environment upon dissolution. The Zarah tablets therefore meet these and all other essential elements of claims 31, 48 and 49.

XII. Remedies

[324] Bayer seeks the following relief in its statements of claim against Apotex and Cobalt: declarations as to validity; declarations as to infringement; an injunction; delivery up or destruction under oath; damages or an accounting of profits as they may elect; pre- and post-judgment interest, compounded; costs and other relief.

[325] Bayer is entitled to a declaration that claims 31, 48 and 49 of the ‘426 patent are not invalid based on any of the asserted grounds of obviousness, anticipation, overbreadth, insufficiency or ambiguity of the specification, or inutility.

[326] Bayer is entitled to a declaration that claims 31, 48 and 49 of the ‘426 patent have been infringed, either directly and/or by inducing infringement, by Apotex’s sale, importation, offering for sale and manufacture of its 3 mg drospirenone / 0.03 mg ethinylestradiol products marketed as “Zamine 21” and “Zamine 28” and its 3 mg drospirenone / 0.02 mg ethinylestradiol product marketed as “Mya”.

[327] Bayer is entitled to a declaration that claims 31, 48 and 49 of the ‘426 patent have been infringed, either directly and/or by inducing infringement, by Cobalt’s sale, importation, offering for sale and manufacture of its 3 mg drospirenone / 0.03 mg ethinylestradiol products marketed as “Zarah 21” and “Zarah 28”.

[328] Bayer is entitled to an order enjoining Apotex and Cobalt (and any subsidiary and affiliated companies, franchisees, officers, directors, employees, agents, licensees, successors, assigns and any others over whom they exercise lawful authority) from manufacturing, using, offering for sale and/or selling to others for their use oral contraceptive tablets that infringe claims 31, 48 and 49 of the ‘426 patent and otherwise infringing or inducing infringement of claims 31, 48 and 49 of the ‘426 patent.

[329] Bayer is entitled to an order directing Apotex and Cobalt to deliver up to Bayer, or destroy under oath, all articles in its possession, power or control, the use of which would offend the injunction described above, or that fall within the scope of claims 31, 48 and 49 of the ‘426 patent.

[330] Prothonotary Milczynski’s Bifurcation Order in the case against Apotex dated February 11, 2014 provided that the question of Bayer’s entitlement, if any, to an accounting of profits would be dealt with in the context of the liability phase of the proceedings in T-1468-13. The same direction was made with respect to the proceedings in T-1368-14 in an Order dated January 15, 2015.

[331] Prothonotary Milczynski’s Bifurcation Order in the case against Cobalt dated January 23, 2014 (T-1379-13) provided that the issue of Bayer’s entitlement to an accounting of profits and Bayer’s election between Bayer’s damages and Cobalt’s profits would be addressed in the “Infringement Quantification phase”.

[332] None of the parties addressed the question of Bayer's entitlement, should it be the successful party, to elect between damages and an accounting of profits. I will therefore give the parties thirty (30) days from the date of this Judgment and Reasons to make written submissions, not exceeding ten (10) pages, regarding this matter.

[333] Bayer's entitlement to pre- and post-judgment interest will be dealt with once damages and/or an accounting of profits have been determined.

XIII. Costs

[334] Prior to the issuance of these Reasons, the parties were directed to make submissions regarding the disposition and/or quantum of costs respecting the validity and infringement portions of these proceedings. To their credit, the parties were able to reach agreement on many aspects of a proposed costs framework in the event that the claims of the '426 patent in issue were held to be valid and infringed. This agreement is reflected in the Judgment that follows.

[335] In light of my conclusions that claims 31, 48 and 49 of the '426 patent are valid and infringed by Apotex's and Cobalt's tablets, it is unnecessary to resolve the parties' disagreement regarding entitlement to costs if claims 31, 48 and 49 of the '426 patent were found to be valid but not infringed, or invalid but infringed. The remaining areas of dispute are:

a) Travel, accommodation and related expenses by counsel in respect of meetings with fact witnesses and meetings with clients;
b) Expenses relating to discovery and trial fact witnesses;
c) Costs relating to interpreter services in respect of discovery and at trial;

d) Costs relating to the translation of documents in respect of discovery and at trial; and

e) Adjustments to the successful party's costs award based on that party's conduct of the proceedings.

[336] Bayer is the sole successful party in these proceedings. The question of any adjustment that should be made to the successful party's costs award based on any party's conduct therefore applies only to Bayer.

[337] Apotex says that Bayer's costs award should be reduced to reflect the following:

a) On the first day of trial, Bayer abandoned its reliance on numerous claims of the '426 patent, specifically claims 1, 2, 4, 5, 6, 7, 30 and 52; and

b) In closing argument, Bayer abandoned its reliance on K-means clustering analysis in relation to its claim of infringement against Apotex.

[338] Cobalt says that Bayer's costs award should be reduced to reflect the abandonment of its reliance on claims 1, 2, 4, 5, 6, 7, 30 and 52 of the '426 patent. In addition, Cobalt maintains that Bayer should be entitled to only one set of costs arising from the issue of validity following September 3, 2015, the date on which Cobalt indicated to the Court that it would be bound by the validity determination in the Apotex actions.

[339] Bayer seeks increased costs on the grounds that Apotex and Cobalt lengthened the proceedings by conducting discoveries in relation to matters that they did not pursue at trial, and

by demanding disclosure of irrelevant documents. Bayer also says that Apotex abandoned numerous defences at trial, served its notices of experimental testing after the applicable deadline, conducted experimental testing late, and served its expert reports less than two weeks before the trial began. Bayer maintains that Cobalt failed to admit facts that it should have admitted, brought improper motions to amend its pleadings, and advanced defences that were not disclosed in its pleadings. Bayer also takes issue with the timing of Cobalt's notices of experimental testing and the delivery of its expert reports.

[340] I agree with Apotex and Cobalt that Bayer's costs award should be reduced to reflect Bayer's abandonment of its reliance on claims 1, 2, 4, 5, 6, 7, 30 and 52 of the '426 patent, and the abandonment of its reliance on K-means clustering analysis in relation to its claim of infringement against Apotex. While this approach is imperfect, in the interests of simplicity and efficiency, I will reduce Bayer's costs award by disallowing its claims for costs in respect of the matters enumerated in subparagraphs 335(a) to (d), above, and by disallowing its claims for increased costs based on the manner in which Apotex and Cobalt conducted the proceedings.

[341] I agree with Cobalt that Bayer should be entitled to only one set of costs and disbursements arising from the issue of validity following September 3, 2015.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. Claims 31, 48 and 49 of the '426 patent are valid and infringed by Apotex and Cobalt;

2. Apotex and Cobalt (and any subsidiary and affiliated companies, franchisees, officers, directors, employees, agents, licensees, successors, assigns and any others over whom they have control) are enjoined from manufacturing, using, offering for sale and/or selling to others for their use oral contraceptive tablets that infringe claims 31, 48 and 49 of the '426 Patent;

3. Apotex and Cobalt shall deliver up to Bayer, or destroy under oath, all articles in its possession, power or control, the use of which would offend the injunction described in paragraph 2, above, or that fall within the scope of claims 31, 48 and 49 of the 426 patent;

4. The parties may, within thirty (30) days of the date of this Judgment, make written submissions, not exceeding ten (10) pages, regarding Bayer's entitlement to elect between damages and an accounting of profits;

5. Bayer's entitlement to pre- and post-judgment interest will be dealt with once damages and/or an accounting of profits have been determined;

6. Bayer is entitled to the following costs from Apotex and Cobalt:

    a. Bayer may claim reasonable counsel fees at the upper end of column IV, Tariff B of the *Federal Courts Rules*, including fees for up to one "first counsel" (at 100% of the Tariff) and for one "second counsel" (at 50% of the Tariff, if present) in respect of:

        i. preparation of pleadings;

        ii. documentary and oral discovery;

        iii. meeting with testifying experts, provided that travel time for counsel (regardless of whether first or second counsel) be reduced by 50%;

        iv. preparation of expert reports and reply reports for those experts who appeared at trial;

        v. preparation of witnesses who appeared at trial;

        vi. attendance at *inter partes* testing;

        vii. preparation and attendance at pre-trial conferences; and

        viii. services after judgment not otherwise specified (Tariff Item 25).

b. Bayer may claim counsel fees at mid-level of column III, Tariff B of the *Federal Courts Rules* for one "first counsel" for preparation and attendance on motions.

c. Bayer may claim counsel fees at the upper end of column IV, Tariff B of the *Federal Courts Rules*, including fees for up to two "first counsel" (at 100% of the Tariff) and for one "second counsel" (at 50% of the Tariff, if present) in respect of preparation for and attendance at trial, and for the preparation of written submissions (Tariff Items 13-15).

d. Bayer may claim the following disbursements:

    i. reasonable travel, accommodation and related expenses for up to two counsel in relation to *inter partes* testing and meeting with testifying experts (business class airfare shall be reimbursed for travel to Europe);

    ii. photocopying at a rate of 10 cents per page;

    iii. stenography services (discovery and trial); and

    iv. reasonable fees and disbursements for testifying experts (including travel expenses to testify) at an hourly rate less than or equal to the hourly rate charged by senior counsel. There shall be no

entitlement to fees and disbursements for non-testifying experts, assistants, law clerks, and students.

e. Bayer may claim only one set of costs and disbursements arising from the issue of validity following September 3, 2015.

"Simon Fothergill"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKETS:	T-1379-13, T-1468-13 AND T-1368-14
DOCKET:	T-1379-13
STYLE OF CAUSE:	BAYER INC. AND BAYER PHARMA AKTIENGESELLSCHAFT v COBALT PHARMACEUTICALS COMPANY
AND DOCKETS:	T-1468-13; T-1368-14
STYLE OF CAUSE:	BAYER INC. AND BAYER PHARMA AKTIENGESELLSCHAFT v APOTEX INC.
PLACE OF HEARING:	TORONTO, ONTARIO
DATE OF HEARING:	JANUARY 11-14; 18-22; 25-28 FEBRUARY 1-5; 8-11; 17-19
PUBLIC JUDGMENT AND REASONS:	FOTHERGILL J.
CONFIDENTIAL JUDGMENT AND REASONS AND PUBLIC JUDGMENT AND REASONS DATED:	SEPTEMBER 7, 2016

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