Federal Court Cour fédérale

Date: 20190508

Docket: T-739-17

Citation: 2019 FC 616

Ottawa, Ontario, May 8, 2019

PRESENT: Mr. Justice Roy

BETWEEN:

LES LABORATOIRES SERVIER
and
SERVIER CANADA INC.

Applicants

and

APOTEX INC.
and
MINISTER OF HEALTH

Respondents

JUDGMENT AND REASONS

I. Overview

[1] This application, pursuant to section 6 of the *Patented Medicines (Notice of compliance) Regulations*, SOR/93-133 as amended [the *NOC Regulations*], seeks an order from this Court in the nature of a writ of prohibition for the purpose of preventing the Minister of Health from

issuing a Notice of Compliance to Apotex Inc. [Apotex] for its APO-PERINDOPRIL/AMLODIPINE consisting of orally administered tablets containing 3.5/2.5 mg, 7/5 mg and 14/10 mg perindopril/arginine/amlodipine.

[2] Les Laboratoires Servier and Servier Canada [Servier], the applicants, are innovators in the pharmaceutical industry who have obtained regulatory approval from the Minister of Health concerning a pharmaceutical product known as VIACORAM® for an angiotensin-converting enzyme (ACE) inhibitor, a drug used primarily for the treatment of hypertension and heart failure.

[3] The patent which grants a monopoly to the applicant is Canadian Patent No. 2,423,825 [the '825 Patent or '825]. It is with respect to the "Nouveau sel de périndopril et les compositions pharmaceutiques qui le contiennent" ([TRANSLATION] "New Perindopril salt and pharmaceutical compounds containing it").

[4] A generic manufacturer, like Apotex Inc., who wishes to market a generic version of a drug must file a submission (here, it is an abbreviated new drug submission) with the Minister of Health; the submission makes specified comparisons between the generic drug and the innovator drug in order to obtain a Notice of Compliance [NOC] for its own generic drug.

[5] In effect, the generic drug manufacturer who wants to market a drug already protected by a patent has two options: either the generic manufacturer waits until the expiration of the patent to obtain the Minister's approval or it alleges through a Notice of Allegation [NOA] that the

patent is invalid and, therefore, would not be infringed if a Notice of Compliance were to be issued. This is the case here. The NOA includes a detailed statement of the legal and factual basis for the allegation (subparagraph 5(3)(b)(ii) of the *NOC Regulations*, SOR/93-133). The NOA constitutes the framework within which the debate must take place. It frames the proceedings: an allegation not included in the NOA cannot be raised in the proceedings.

[6] Here, the NOA concerns the invalidity of the '825 Patent owned by Servier. There is no allegation of non-infringement.

[7] In its NOA of April 4, 2017, Apotex Inc., a generic manufacturer, alleged invalidity of the '825 Patent on the basis of a number of grounds: double-patenting and improper selection, insufficiency, obviousness, inutility, overbreadth, and anticipation.

II. Introduction

[8] Fundamentally, this case is concerned with a patent relating to perindopril, the active pharmaceutical ingredient (API) that is used in the treatment of hypertension and heart failure. But this case is not about getting a monopoly for perindopril. Servier was successful in obtaining a patent in Canada for a compound, the perindopril molecule, and its pharmaceutically acceptable salts (Patent 1,341,196, referred hereafter as ['196 or '196 Patent]).

[9] The application for what became '196 was dated October 10, 1981, but for reasons that never emerged in this case, the '196 Patent was issued close to 20 years later, on March 6, 2001.

As a result, Servier enjoyed a monopoly on the drug used in the treatment of hypertension until March 2018.

[10] The drug was commercialized in Canada since 1994 (obviously well before the '196 Patent was issued) under the name "COVERSYL®". Servier chose to commercialize the perindopril with one of its pharmaceutically acceptable salts. The said salt is designated as the erbumine salt of perindopril or tert-butylamine salt of perindopril. Erbumine is the accepted abbreviation for the tert-butylamine salt.

[11] Servier sought to patent a different salt than erbumine, in association with perindopril, through its application for a New Perindopril Salt and the Pharmaceutical Compositions containing it. Filed in March 2003, ten years after it started commercializing perindopril in the form of its erbumine salt, the application was successful and was issued on February 21, 2006. If valid, it provides Servier with a monopoly specific to a particular salt, the arginine salt of perindopril, a salt that is different from the erbumine salt of perindopril but which constitutes a subset of the "pharmaceutically acceptable salts" covered by the '196 Patent. In other words, both the erbumine and the arginine salts are said to be subsets of the '196 Patent, but they are different in that the arginine salt is said to provide better stability in environments of higher temperature and humidity. The new patent, the one in suit, bears the number 2,423,825.

[12] In essence, Apotex contends that Servier extends its monopoly illegally by patenting a salt that had been the subject of the '196 Patent as one of the pharmaceutically acceptable salts. The '825 Patent is invalid, says Apotex. Apotex is free to commercialize its version of the tert-

butylamine salt of perindopril, and does, as the '196 Patent has expired in Canada. Furthermore, as was confirmed during the hearing of this case, Apotex can certainly develop a different salt of perindopril as the '825 Patent is limited to the arginine salt. Nevertheless, Apotex challenges the arginine salt of perindopril that is commercialized by Servier.

[13] The '825 Patent claims a priority date from French Patent No. 02.04847 filed on April 18, 2002.

III. The '825 Patent

[14] '825 is a short document of merely five pages, the fifth page showing the five claims. It pertains to the invention of the arginine salt of perindopril, its hydrates and pharmaceutical compositions containing it. The '825 Patent is not concerned with perindopril as such but rather with a new salt. Perindopril exists in the overall neutral state as a zwitterion (an overall neutral molecule with acidic and basic components, where these components are negatively and positively charged) where its carboxylic acid is negatively charged and its amine is positively charged. As already indicated, perindopril and its “pharmaceutically acceptable salts” was the subject of Canadian '196 Patent.

[15] The '825 Patent’s disclosure notes that it has proven difficult to find a pharmaceutically acceptable salt that will provide good bioavailability with adequate stability such that it will be suitable for the preparation and storage of pharmaceutical compositions. It was considered that the tert-butylamine salt was not the complete solution to the problems encountered in relatively high heat and humidity environments. Thus, the tert-butylamine salt must be protected with

additional packaging in some countries and its shelf-life is limited to two years. Although the tert-butylamine salt was adequate for the development of the product containing perindopril, the '825 Patent is presented as being an improvement.

[16] These constraints are somewhat remedied with the new arginine salt, which has “the entirely unexpected advantage over all the other salts studied and, more specifically, over the tert-butylamine salt of perindopril” ('825 Patent, p. 2).

[17] The problem posed to which the '825 Patent offered a solution was the volatility of the erbumine salt of perindopril, which is susceptible to degradation by the formation of diketopiperazines and by hydrolysis at the ester, triggered by high heat and high humidity. Liquid chromatography tests at Servier confirmed that perindopril is inherently unstable and the erbumine salt did not remedy the chemical stability issues. The '825 Patent refers, at page 2, to the consequences of this instability, namely the necessity for “tropicalized” PVC/foil blister packaging for the perindopril erbumine tablets and the restrictive 2-year shelf-life. The tablets must be stored at a temperature of less than 30 degrees.

[18] The reader is advised that numerous salts customarily used in the pharmaceutical industry were studied and were rejected as being unusable. The disclosure insists that, unexpectedly, the arginine salt of perindopril showed advantages over the other salts studied.

[19] Although the invention is said to relate to the arginine salt of perindopril, its hydrates and to pharmaceutical compositions containing it, the '825 Patent speaks in terms of “the arginine salt

of perindopril is preferentially the salt of natural arginine (L-arginine)" (p. 2). The only other place the reader will find a reference to the L-arginine salt is to be found at page 4 of the specification where are presented the results of a study comparing the volatility of the new salt to that of the tert-butylamine salt. The Patent states that "(t)he arginine salt used in this study is the L-arginine salt". The L-arginine salt is found in nature, but there also exist other configurations: D-arginine and the racemate D-L.

[20] There are many pharmaceutical compositions that are mentioned, such as nasal administration, suppositories, creams, ointments, and tablets or dragees. The '825 goes on to say that the "pharmaceutical composition according to the invention will preferably[1] be immediate release tablet". As we shall see when the claims are examined, the third claim refers specifically to a pharmaceutical composition claimed, that of an immediate-release tablet.

[21] Similarly, the '825 shows also a preference for a dosage between 1 and 10 mg of the arginine salt of perindopril (p. 3), yet it claims a dosage from .2 to 10 mg at claim 4. Evidently, this time the '825 Patent claims more than the preference expressed in the disclosure. Thus, the disclosure speaks of these preferences:

a) one about the pharmaceutical composition, which translates into claim 3 which is about the preferred composition in the form of an immediate release tablet;

b) another about the preferred dosage of 1 to 10 mg of the arginine salt of perindopril, which does not translate into any claim, as the fourth claim ends being for a dosage from .2 to 10 mg of the arginine salt;

c) finally the preference for the salt of natural arginine, the so-called L-arginine, is only referenced with respect to the comparative study between the arginine salt and the erbumine salt found in the disclosure. Two things are notable. First, the '825 states that "(t)he arginine salt used in the study is the L-arginine salt". Second, the Patent never claims anything other than arginine salt of perindopril and its hydrates; the claims do not specify that only L-arginine is sought.

[22] The '825 Patent offers little information on how the L-arginine salt was prepared other than "according to a classical method of salification of organic chemistry" (p. 4). This will be read with the information provided to the reader on how the study was conducted. One reads at the bottom of page 3:

> The study was carried out using immediate-release tablets containing either 2.4 mg of the arginine salt of perindopril or 2.0 mg of the tert-butylamine salt of perindopril (each of the two tablets containing 1.7 mg of perindopril). The tablets were assayed 6 months after the start of storage of the tablets at different temperatures and different relative humidities (% R.H.).

The study's results are reproduced herein. As can be seen, at 40ºC, with relative humidity of 75%, the erbumine salts degrades quite significantly more than the arginine salt in that significantly less perindopril erbumine salt (loss of close to 1/3) remains according to the study in conditions of high humidity and high temperature:

Conditions 6 months	**tert-Butylamine salt of perindopril Percentage remaining (%)**	**Arginine salt of perindopril Percentage remaining (%)**
25ºC 60% HR	101.0	99.5
30ºC 60% HR	94.4	98.1
40ºC 75% HR	67.2	98.6

The '825 clamours the "very great stability of the arginine salt compared to the tert-butylamine salt" (p. 4). Hence, the disclosure declares that the new product requires less constraint with respect to packaging and allows obtaining a shelf-life of at least three years.

[23] The three inventors listed on the '825 Patent are Gérard Damien, who offered an affidavit and was cross-examined, François Lefoulon and Bernard Marchand. Perindopril arginine was first produced in 1984 by Mr. Marchand.

[24] The '825 Patent makes five claims. Claim 1 of the '825 claims an arginine salt of perindopril and its hydrates. Claim 2 claims a pharmaceutical composition containing the arginine salt of perindopril and its hydrates in combination with one or more non-toxic and pharmaceutically acceptable excipients. Claim 3 claims the pharmaceutical composition of claim 2 in the form of an immediate-release tablet. Claim 4 claims a pharmaceutical composition of claims 2 or 3, containing 0.2 to 10 mg of perindopril arginine. Claim 5 refers to the usefulness of the pharmaceutical composition according to any of claims 2 to 4 for the treatment of hypertension and heart failure.

IV. Issue

[25] The issue before this Court is whether Servier has demonstrated that the allegations of invalidity made by Apotex in its Notice of Allegation are unjustified. The grounds of invalidity raised concerning the '825 Patent are:

- invalidity;
- insufficiency;
- overbreadth;
- obviousness;
- double-patenting;
- anticipation.

V. The Witnesses

A. Fact witnesses

[26] The parties have submitted affidavits from four fact witnesses: Denise Pope and Gérard Damien for Servier; and Lisa Ebdon and Duane Terrill for Apotex. Denise Pope is a paralegal at Norton Rose Fulbright LLP, counsel for the applicant. Lisa Ebdon is a paralegal/law clerk at Goodmans LLP, counsel for the defendant. Duane Terrill, is Associate Director, Regulatory Affairs for Apotex Inc. Because the affidavits provided by Denise Pope, Lisa Ebdon and Duane Terrill served the primary purpose of submitting exhibits, these witnesses were not cross-examined.

[27] Gérard Damien was the only fact witness to be cross-examined. Mr. Damien is one of the named inventors on the '825 Patent. He holds a degree in Chemical Engineering from the *Institut*

National des Sciences Appliquées de Lyon. From February 1970 to November 1974, he worked as a researcher in organic chemistry at les Laboratoires Égic. He subsequently began his 34-year career at Les Laboratoires Servier in December 1974 as Manager of the Analytical Development Department at the Centre for Pharmaceutical Development. He remained in this role until 1987, when he became Assistant Director and, subsequently, Director of the Centre in 1992 (Damien affidavit at paras 8-10). He also explored and determined the cause of the instability of the perindopril erbumine tablets, conceived of the arginine salt of perindopril as a solution to the problem, investigated and confirmed its stability as compared to perindopril erbumine.

[28] Mr. Damien provided the history of the Patent. In 1982, Mr. Damien began development work on perindopril in its erbumine salt form, which he had received from the synthesis research team at Servier. Servier's goal was "to develop a pharmaceutical formulation containing the perindopril erbumine salt that was stable enough to be launched on the market quickly, preferably in tablet form" (Damien affidavit at para 22). Mr. Damien's specific role was to "put in place appropriate analytical methods to analyze the perindopril erbumine salt, study the purity of batches of the perindopril erbumine salt used in developing the pharmaceutical composition, and undertake stability studies on the active ingredient itself as well as on the pharmaceutical composition of the perindopril erbumine salt" (Damien affidavit at para 25).

[29] At the time, Mr. Damien was "concerned (as was [his] team) about the possibility that the perindopril erbumine salt could lead to stability issues given the initial stability results of the experimental formulations" (Damien affidavit at para 26). Subsequent liquid chromatography studies and structural analyses revealed that perindopril itself could degrade via two different

pathways: first, hydrolysis of the ester function at high relative humidity; and second, intramolecular cyclization leading to the formation of lactam-type compounds at high temperatures. Thus, finding a formulation of the perindopril erbumine that limited the rate of degradation of the perindopril proved to be a challenge (Damien affidavit at paras 27-28). The formulation that was achieved, that was marketed as COVERSYL®, was stable at low to moderate temperatures and at low to moderate humidity, but it became less stable at higher temperatures and high relative humidity.

[30] In order to bring perindopril to market quickly, Servier chose to use perindopril erbumine salt and proceed with direct compression instead of its preferred wet granulation to avoid the loss of perindopril.

[31] In his affidavit, Mr. Damien recalled a discussion with his colleague, Bernard Marchand, in the mid-1980's, during which an arginine salt of perindopril was suggested as an alternative formulation. The issue was that erbumine was understood to be a relatively volatile product when used in the salification of perindopril. The solution became optimal packaging that would be resistant to heat and humidity, what has been referred to as a type of "tropicalized" packaging. That brought Mr. Damien and his team to discuss the possibility of a different salt. The conversation then turned to the use of other amino acids (Damien affidavit at para 44). Mr. Damien recalled his experience at Égic where he worked with lysine, a natural amino acid. No lysine was available at Servier at the time. However, "the natural form of arginine, i.e. L-arginine" (Damien affidavit at para 46) was available. Neither Mr. Damien nor Mr. Marchand was aware of the L-arginine salt having been used to form a salt of an active ingredient.

However, they did know that the L-arginine salt had been used on its own in some pharmaceutical preparations (Damien affidavit at para 46).

[32] In 1984, Mr. Damien and Mr. Marchand succeeded in synthesizing the perindopril arginine salt. The process was not optimized to manufacture the perindopril arginine salt. Non-salified perindopril and L-arginine were brought together in stoichiometric quantities in an aqueous medium. The solution was then vacuum dried. This method was considered a standard procedure at the time (Damien affidavit at para 47). At this stage, substantial progress had already been made in the development of the perindopril erbumine salt tablets and Management at Servier had strong reservations about spreading the research efforts too thin. Further, Management wanted to bring their existing perindopril erbumine product to market as quickly as possible and the instability of the tablets could be alleviated by the use of tropicalized packaging for hot and humid countries (Damien affidavit at para 49).

[33] Between 1990 and 1993, Mr. Damien's team continued to support Servier's efforts to bring to market the perindopril erbumine salt. In addition, Mr. Damien conducted a few tests to confirm his hypothesis that the stability problems with perindopril erbumine were linked to the volatility of erbumine. Mr. Damien confirmed this hypothesis, which renewed his interest in finding the most stable salt of perindopril (Damien affidavit at paras 50-54).

[34] Mr. Damien subsequently supervised the comparative stability testing of five perindopril salts: sodium, hydrochloride, maleate, arginine, and erbumine. The active ingredients were tested in powder form. The results demonstrated that perindopril arginine salt and the perindopril

erbumine salt were both stable at high temperature (100 degrees Celsius) for 48 hours when the container was sealed. However, when the perindopril erbumine salt was heated to 100 degrees Celsius for 48 hours in an open container, total degradation of the perindopril molecule was observed. In contrast, when perindopril arginine was heated to 100 degrees Celsius for 48 hours in an open container, the arginine salt did not degrade (Damien affidavit at paras 56-59). Hence, perindopril arginine tablets could be packaged in ordinary pill bottles, in contrast to the tropicalized packaging that was required for the perindopril erbumine tablets. However, at that stage, it would have been necessary to manufacture perindopril arginine salt tablets to fully evaluate their stability. That was not a priority for Servier at that time. Servier continued to use different packaging according to the region where the tablets were marketed. However, the tropicalized packaging was more expensive and required new equipment and additional steps.

[35] In 1998, Mr. Damien convinced Management at Servier to reopen the topic of alternative perindopril salts. Further to having conducted more advanced stability testing comparing the stability of perindopril erbumine with that of perindopril arginine, it was concluded that perindopril arginine salt tablets demonstrated greater stability than the perindopril erbumine salt tablets and that they could be packaged in a pill bottle with a desiccant. It also became clear to Mr. Damien during these studies that in the presence of humidity, the arginine salt would be able to form hydrates. Based on Mr. Damien’s results, Servier decided in late 2002 to develop and market the perindopril arginine salt (Damien affidavit at paras 67-74).

B. The Expert Witnesses

[36] The parties have also submitted affidavits from five expert witnesses, all of whom were cross-examined. Servier's expert witnesses are: Dr. Stephen Byrn, Dr. Allan Mark Evans and Dr. Naïr Rodriguez-Hornedo. Apotex's expert witnesses are: Mr. Richard J. Bastin and Dr. Michael J. Zaworotko.

(1) Dr. Stephen Robert Byrn, PhD

[37] Dr. Byrn is a renowned expert in pharmaceutical development and, specifically, formulation development, stability and salt selection. He is the Charles B. Jordan Professor of Medicinal Chemistry at Purdue University and holds a PhD in Chemistry from the University of Illinois, with post-doctoral work at UCLA. Dr. Byrn is a prolific author of peer reviewed publications and has co-authored the leading book in the field of solid state chemistry of pharmaceuticals. He also founded SSCI, Inc. (SSCI), a research and information company in 1991, with 100 employees specialized in analytical research with respect to polymorph and salt studies. The company was sold in 2006. Dr. Byrn had conducted, supervised or controlled over 100 salt screens and over 200 polymorph screens as of April 2002.

[38] The expert has testified on numerous occasions in patent cases, including being retained by innovators mainly, but also by generic pharmaceutical companies.

[39] Dr. Byrn was an expert witness retained by Servier in the Australian case *Apotex Pty Ltd v Les Laboratoires Servier* [2013] FCA 1426 (Justice Rares) in the Federal Court of Australia, a

case about a patent quite similar to our patent in suit. In that case, Dr. Byrn set out his opinion regarding (1) how he would attempt to solve the instability problem of tert-butylamine perindopril when exposed to heat and humidity and (2) Apotex Pty Ltd's allegation of obviousness (Byrn affidavit at para 21).

[40] Dr. Byrn was assigned a number of mandates which he addressed in his affidavit:

a) he provided a scientific background in which he described the knowledge of a researcher in the field and the development of pharmaceutical compounds as of April 2002, with a focus on the stability of the product and the formation of salts;

b) once the first mandate completed, Dr. Byrn was given the English version of the '825 Patent. He was asked to discuss the qualifications of the POSA, the common general knowledge of that person, the understanding such a person would have of the 825 claims and what the inventive concept is;

c) following mandate #2, Dr. Byrn was advised of the allegations of invalidity made concerning the '825 Patent. Responding to questions provided by counsel, he addressed first the issue of obviousness;

d) the fourth mandate related to anticipation. He was provided with two patents for the purpose of examining the allegation of anticipation: United States Patent No. 4,508,729 and Canadian Patent No. 1,341,196, to which reference was made earlier;

e) Dr. Byrn was then asked if the disclosure in '825 was sufficient for a person of skill in the art (POSA) to understand the nature of the invention and how to practice the invention as of October 18, 2003;

f) he was then asked to opine on an allegation of overbreadth, i.e. whether the subject of the invention is broader than the invention described in '825;

g) Dr. Byrn then addressed the issue of the utility of the invention;

h) it is argued that the claims of the '825 Patent and the '196 Patent are for the same invention. The expert was asked whether the claims of '825 are “patentably distinct” from those of the '196 Patent;

i) finally, Dr. Byrn reviewed an Apotex letter of January 19, 2017 which contains allegations about '825; he was asked to comment to the extent the allegations affected or altered his opinion relating to the previous mandates.

[41] With respect to the scientific background, which includes the development and evaluation of stable pharmaceutical compounds and composition, Dr. Byrn provided a description of the knowledge that a researcher in the field of formulation and development of pharmaceutical compounds would have been endowed with as of April 2002. To that end, Dr. Byrn also describes the POSA as being someone with “a bachelor’s or higher degree in Pharmacy (with a focus on chemistry), or in Chemistry, Biochemistry or a related area … and a minimum of 1 to 2 years of experience working in the field” (Byrn affidavit at para 163).

[42] Dr. Byrn insists on the requirement of stability of pharmaceutical compounds because it is one of the most important criteria for safety and efficacy. Chemical and physical stability are evaluated and assessed. Packaging may be a solution in solving stability issues if the method of manufacture of the product (e.g. wet granulation or compression) leaves the issue not adequately addressed. Crystal formation is said to be a potential strategy, but it is unpredictable according to the witness. Dr. Byrn affirms that a scientist “would be aware that salts, like all solids, may absorb water from their surroundings”. However, “there was, and still is, no way to predict

which hydration states a salt has, if any" (para 97). The unpredictability, together with the effort and time required to search for crystal forms, make the strategy "secondary".

[43] As for salts that can be isolated, Dr. Byrn states that "there is no correlation between the properties of salts and the properties of the acids and bases from which they are derived" (para 113). They have unpredictable physical properties (para 118). That results in a process of trial and error in the search for a suitable salt form without being able to predict the result.

[44] The affiant is not leaving the reader under the impression that the wheel must be re-invented every time a scientist seeks to perform a salt screen for a pharmaceutical product. There was, at the time, literature, which would be part of the common general knowledge of the person of skill. That would be consulted to identify what has worked in the past: there are lists of salt formers that have even been approved by regulators. The publications of Berge[2] and Bighley[3] are referenced. However, "the ability to make a salt with one salt former is not predictive of the ability to make a second salt with the same salt former in conjunction with a different compound" (para 126). Dr. Byrn states that not only are these lists of acids and bases that can be put to contribution, but often variables include different solvents, different temperatures, different cooling rates and different concentrations. Even today, solid form screening and salt screening is done empirically, by hand.

[45] Dr. Byrn summarizes the process of looking for another salt of perindopril as:

a) select salt formers from 10-12 classic salt formers because they have been used with many important and well-known drugs;

b) select solvents, concentrations, temperatures and crystallization conditions;

c) if the products are unstable, the scientist could use other, less common salt formers, already listed in the literature in order to avoid the scrutiny of regulators.

The results are not guaranteed.

[46] Dr. Byrn notes that in April 2002, the state of the art was not very advanced in terms of addressing stability issues, formulation chemistry and solid state chemistry of drugs. As such, the 1977 Berge publication would have been the main foundational document that a POSA would have used to understand salts. Furthermore, at the time, a number of ACE inhibitors were already on the market and the POSA would have had access either to the formulations or the tablets of the drugs. A POSA would also have been aware of the USP 2000 list of common excipients listed in the Handbook of Excipients, 3rd Edition. Finally, the POSA would have been aware of the key documents pertaining to these technologies, including two publications by Berge and Gould[4] and other publications co-authored by Dr. Byrn[5] himself. He opines that the POSA would readily conclude that it is a difficult exercise to find a suitable salt because it is not predictable and it requires experiments: “the POSA would view the development of a stable product a major issue that the '825 Patent solved” (para 169). As part of the common general knowledge (CGK) of the time, a POSA would have had knowledge in the field of solid chemistry of drugs, including crystallography, analytical methods and ways to determine the stability of drug compounds (paras 165-187).

[47] Dr. Byrn then proceeds to construe the claims of the '825 Patent. Dr. Byrn posits that the POSA would understand that claim 1 pertains to the L-arginine salt of perindopril. Dr. Byrn also notes that use of the term "and its hydrates" would connote to the POSA that the L-arginine salt could contain some water. Based on the data in the Patent, the POSA would also know that at high humidity levels, the L-arginine salt of perindopril is stable and could therefore take on water without degrading. The fundamental inventive concept is similarly the L-arginine salt of perindopril that may potentially form hydrates. The other claims are dependent on claim 1.

[48] With respect to obviousness, Dr. Byrn observes succinctly that the difference between the "state of the art" in April 2002 and "the inventive concept of the claims of the '825 Patent is the L-arginine salt of perindopril, which may pick up water" (para 209). Furthermore, Dr. Byrn contends that a POSA would have attempted to improve the stability of perindopril erbumine before considering the search of a new salt form of perindopril (paras 210-217). In searching for a new salt, the POSA would look to numerous other choices before resorting to L-arginine (para 221) which was not a salt former for a commercial product, much less an ACE inhibitor, at the time. Finally, even if the POSA were to successfully synthesize the arginine salt of perindopril, it would not have been known whether this salt would have been characterized by increased stability. In fact, a POSA would not think that it was more or less self-evident that attempting to form an arginine salt with perindopril would lead to a solid, much less that it would have the stability properties sought (para 230). In view of the state of the art, there would have been many other choices the POSA would have selected before resorting to arginine. A POSA would not have come directly and without difficulty to the arginine salt of perindopril. Moreover, it was not self-evident that what was being tried ought to work: it was not obvious to try to form an

arginine salt with perindopril because of the numerous avenues of solution for the stability problem and the properties of salts were, and are, unpredictable. Indeed, "(a) POSA would believe that arginine salt is unlikely to work" (para 233).

[49] With respect to anticipation, Dr. Byrn finds that neither the previous Canadian 1,341,196 Patent claiming perindopril and "pharmaceutically acceptable salts" nor the U.S. Patent No. 4,508,729 disclose the arginine salt (para 255). Dr. Byrn did not discuss enablement in view of his conclusion that the patents did not even satisfy the disclosure requirement.

[50] With respect to sufficiency of disclosure, Dr. Byrn contends that the '825 Patent "discloses everything that the POSA would need to understand what the invention is (the L-arginine salt of perindopril), make it, and put it into practice" (para 258). Further, "a POSA would also know how to formulate a pharmaceutical composition (and make a tablet) which contains the L-arginine salt of perindopril" (para 261). It is a simple exercise for a POSA as the patent discloses the use of "a standard method of salification", with which a POSA would be familiar.

[51] The formulation of a tablet would also be a straight forward exercise for a POSA who would identify the excipients used in the COVERSYL tablets, which are commonly incorporated in immediate release tablets (claim 3).

[52] I note that Dr. Byrn refers to the formation of hydrates which, he explains, would be understood by the POSA as suggesting that the L-arginine salt of perindopril is not less stable if it picks up water (which may or may not happen) (para 271).

[53] With respect to overbreadth, Dr. Byrn maintains that each of the 5 claims in the '825 Patent pertains to what has been described in the specification. Notably, Dr. Byrn contends that claim 1 is "limited to the L-arginine salt of perindopril, whether or not it contains water" (Byrn affidavit at para 279), which corresponds to the specification.

[54] With respect to utility, Dr. Byrn finds that the POSA would conclude that the subject matter of each of the claims in the '825 Patent is capable of a practical purpose (paras 285-287). The new salt is more stable to heat and humidity: that allows for a different packaging and less limitation on its shelf-life and storage conditions.

[55] The POSA would find in the data provided at page 4 of the '825 Patent the utility in that the data show that the new salt is more stable than the tert-butylamine. Furthermore, the testing conducted by Mr. Damien and his team confirms the better stability of the L-arginine salt of perindopril, thus confirming the utility of the new salt.

[56] The expert was critical of the testing conducted by Apotex:

- tablets were not tested, but rather the testing was in bulk form;

- the packaging used meant that the products were essentially sealed and designed to avoid degradation. This is obviously counter-productive if one seeks to assess instability and hydration;
- the testing did not include excipients, which may affect stability.

[57] With respect to double-patenting, Dr. Byrn states in no uncertain terms that the claims of the '825 Patent and the earlier '196 Patent do not pertain to the same invention and, further, that a POSA would find that the claims of the '825 Patent are patentably distinct from the claims of the '196 Patent (paras 301 and 303).

[58] For Dr. Byrn, the '196 Patent includes a very general reference to “pharmaceutically acceptable salts”. “The Patent is directed to the perindopril molecule. It is not a patent directed to salt forms of perindopril” (para 302).

[59] Because the '196 Patent speaks in general terms of “pharmaceutically acceptable salts”, it would not be suggesting of including the arginine salt of perindopril. Arginine salt was not a salt form of an approved product in 2002 and 2003. Claim 1 of the '825 Patent is therefore patentably distinct. In fact, the '196 Patent presents example salts (ammonium, maleate, sodium, acetate, trifluoroacetate and bistie trifluoroacetate), that are not amino acids like the L-arginine; none of these examples would suggest L-arginine (para 306).

[60] Finally, Dr. Byrn finds a number of perceived contradictions in Apotex’s Letter of Allegation. Chiefly among them, he sees a tension between allegations of obviousness and the claim that there was insufficient specification in the '825 Patent (paras 313 and 314).

(2) Dr. Allan Mark Evans, PhD

[61] Dr. Evans is an expert in pharmaceutics and pharmaceutical sciences. He holds a PhD in Clinical and Experimental Pharmacology from the University of Adelaide, Australia. Dr. Evans has over 26 years of experience in conducting research in clinical pharmacology including pharmacokinetics and biopharmaceutics. He is presently Provost & Chief Academic Officer at the University of South Australia.

[62] Dr. Evans was also an expert witness for the Servier in Australian case *Apotex Pty Ltd v Les Laboratoires Servier*, (*supra*). Dr. Evans supplied two individual affidavits and two joint expert reports with the other expert witnesses retained in the Australian proceeding. He also testified in open court before Justice Rares (Evans affidavit at para 22).

[63] In his affidavit, Dr. Evans was asked to comment on a plethora of issues some of which overlap with the ground covered by Dr. Byrn. First, he provides a general comment on pharmaceutical compounds as well as the '825 Patent. Following the completion of his comment on the '825 Patent, he was advised by counsel for the applicant that there were allegations of insufficiency of disclosure with respect to the '825 Patent. He was then instructed to answer a series of questions regarding the '825 Patent that the applicant’s counsel advised him would allow the Court to come to a finding on whether or not the '825 Patent provided sufficient disclosure. The same process was repeated to enable him to answer questions pertaining to overbreadth and utility. He did not discuss obviousness.

[64] Dr. Evans was then given the English translation of Mr. Damien's affidavit and asked whether anything therein altered his opinions of the aforementioned allegations of invalidity. The same process was repeated with a series of literature references. Finally, counsel for the applicant gave Dr. Evans a copy of "a letter from Apotex Inc. dated January 19, 2017" which contained allegations about the '825 Patent. Dr. Evans was asked to comment on this letter. (paras 27-46)

[65] First, Dr. Evans comments generally on the criteria to develop an active pharmaceutical ingredient for a commercial drug product, strategies for improving stability and questions pertaining to salt synthesis. Stability is at the forefront of the concerns in the development of the active pharmaceutical ingredient (API). Accelerated stability studies (where the product is subjected to extreme conditions of relative humidity and heat) are commonly used. In the end stability improves shelf-life, but also patient safety and therapeutic efficacy. From a commercial benefits standpoint, the expert identifies a number of advantages:

- the manufacturing environment need not be as carefully controlled;
- larger remaining shelf-time;
- large individual batches can be produced, thus reducing the frequency of production;
- wider range of packaging options will not be required; different packaging for the same product brings a range of complexities.

[66] Dr. Evans' evidence is consistent with that of Dr. Byrn as to how a POSA would get to identify a suitable salt, starting with salt forming agents of a limited number. That is because the task is difficult and time-consuming. Typically, scientists will use formulations most likely to succeed because they have been used commercially with success in the past. There is no

guarantee of success: indeed other variables factor in, such as the solvent, concentration and temperature. This is not a straightforward process.

[67] Dr. Evans seems to be in broad agreement with Dr. Byrn in terms of the nature of the skilled person, the POSA. In his words: “The POSA to whom the 825 Patent is addressed is a scientist in the pharmaceutical field or industry, knowing how medications are made, evaluated and regulated” (para 126) and the person may “have at least a bachelor’s degree in industrial/pharmaceutical chemistry or chemical engineering … as well as a minimum of two (2) years of experience working in a pharmaceutical company” (para 127). Dr. Evans lists a series of journals and textbooks which the POSA would have been familiar with as of April 2002 (paras 130-131). Dr. Evans notes that in 2002, a POSA would have likely been aware of perindopril as an ACE-inhibitor and also aware that any development program for perindopril would need to take into account premature degradation of the active pharmaceutical ingredient (paras 133-134). In order to resolve stability issues, the POSA would have started by modifying the existing product formulation and exploring changes to the packaging which would be simpler than searching for an alternative salt form of perindopril. In selecting salts for testing, the POSA would focus on approved commercial drugs in salt form, consulting lists of salts in publications such as those co-authored by Bighley (paras 143-148).

[68] Dr. Evans construed the claims in the '825 in much the same way as Dr. Byrn (paras 150-159). Thus, the “classical method of salification” is truly well known by the POSA as leading to salt formation. His understanding of claim 1 is that the POSA would recognize that L-arginine is the naturally occurring form of arginine, making it the form that would be readily approved by

regulators as it is found in the body. Dr. Evans also noted that the salt in claim 1 retains water or not, and was in a hydrate form; it may pick up and incorporate water without degrading.

[69] Dr. Evans acknowledges that there exist L-arginine, D-arginine and a racemic mixture. However, the disclosure of '825 refers to "(t)he arginine salt of perindopril is preferentially the salt of natural arginine (L-arginine)". The data produced at page 4 of '825 deals with the stability of the L-arginine. That would confirm in the mind of the POSA that the invention does not refer to the other forms of arginine. There is also a technical reason why the racemic mixture cannot be considered. Paragraph 154 reads:

> Another reason why the POSA would understand that arginine in claim 1 is not referring to a racemic mixture of L-arginine and D-arginine is because perindopril is a chiral molecule having five stereogenic centres with particular configurations. Combining a racemic mixture of arginine with perindopril would result in a mixture of diastereomeric salts with different physical properties such as solubility and melting point. Such a mixture of salts without uniform properties would be undesirable from both a production and a regulatory perspective.

[70] Claims 2 to 5 are read the same way as read by Dr. Byrn.

[71] With respect to sufficiency of disclosure, Dr. Evans maintains that the specification of the '825 Patent provides sufficient information to the POSA with common general knowledge to prepare the L-arginine salt of perindopril using a classical method of salification, and prepare pharmaceutical compositions thereof as claimed in the Patent (para 161). The POSA would know about the classical method of salification. In essence, the POSA can't predict that a stable salt can be produced, but once told that it can in fact be done, the POSA would be able to arrive at

the salt. Similarly, the POSA would know how to formulate a tablet of L-arginine perindopril using '825 and the information available in the public domain. Indeed “the 825 patent does not claim a particular formulation, much less an optimized formulation” (para 174).

[72] With respect to overbreadth, Dr. Evans maintains that the claims of the '825 Patent are no broader than the invention of the '825 Patent (para 182). Since claim 1 refers to L-arginine salt of perindopril, which may pick up water, and the tested tablets are tablets of L-arginine perindopril, the inventors made the invention claimed. The other claims follow naturally.

[73] With respect to utility, Dr. Evans concludes that the POSA would know that the L-arginine salt of perindopril is useful because of its increased stability in the face of high heat and humidity. Indeed the subject matter of every claim is capable of practical purpose because of the improved stability. Such utility was demonstrated, as the data displayed at page 4 of '825 shows. Furthermore, the L-arginine salt of perindopril is a compound known for the treatment of arterial hypertension and heart failure.

[74] Finally, none of Dr. Evans’ opinions changed following his reading of the affidavit of Mr. Damien, various references or Apotex’s Letter of Allegation (paras 52-54).

(3) Dr. Naïr Rodriguez-Hornedo, PhD

[75] Dr. Rodriguez-Hornedo is an expert in pharmaceutical development, pre-formulation science and dosage form optimization, including salts. She teaches pharmaceutical sciences at the University of Michigan, Ann Arbor. She holds a PhD. in Pharmaceutics from the University

of Wisconsin-Madison. Dr. Rodriguez-Hornedo has been teaching and researching in the pharmaceutical field for over 30 years, with a focus for the last ten years on pharmaceutical multi-component crystals and cocrystals. She has published many articles on issues relevant to this case, such as pharmaceutical compounds, pharmaceutical formulations, salts, crystallization and cocrystals. It is the first time she is retained by Servier.

[76] Dr. Rodriguez-Hornedo was given the same nine-point mandate and instructions as Dr. Byrn, although she was asked to comment on anticipation before obviousness and double-patenting before utility.

[77] As with Dr. Byrn and Dr. Evans, the scientific background of the skilled person would essentially be the same as April 2002 and October 2003, according to Dr. Rodriguez-Hornedo. The expert provided a long scientific tutorial on basic concepts relevant to this case and her affidavit. In particular, Dr. Rodriguez-Hornedo provided explanation about stability, crystallinity, cocrystals, hydratation/hydrates, acids and bases, salts and hygroscopicity.

[78] The affidavit considers basically the same steps a scientist would follow in search of greater stability: packaging, manufacturing process, excipients, chemical structure of the API. Searching for other solid state forms constitutes another avenue.

[79] The expert identifies a series of textbooks and papers that a scientist would consult, including of course those of Stephen Berge, Lyle Bighley and Donald Monkhouse, which contain a list of salts found in US Food and Drug Administration (FDA) approved, and non-

approved, commercially marketed products, as well as a list of salt forms reported to have been made but not commercialized. Dr. Rodriguez-Hornedo reports that salt screens were done manually at the time, with the various combinations of variables making the process lengthy and the likelihood of success unknown (paras 113 and 116).

[80] Dr. Rodriguez-Hornedo would appear to require marginally higher academic qualifications and experience to be an adequate POSA. If the person does not hold a PhD or master's degree in pharmaceutical science (with a chemistry focus) with a year or two of industrial experience in the pharmaceutical industry, a bachelor's degree in chemistry or biochemistry, together with 3 to 5 years of experience in the field would be acceptable.

[81] As for the claims in '825, Dr. Rodriguez-Hornedo says that the POSA would expect the arginine in claim 1 to be the one found in nature, the L-arginine: the POSA would expect to be told if the arginine referred to is a non-natural one. Furthermore, naturally occurring compounds are preferred by regulators as more likely to be safe. The '825 disclosure would confirm that the L-arginine is the one contemplated at claim 1 because page 2 speaks in terms of "(t)he arginine salt of perindopril is preferentially the salt of natural arginine (L-arginine)" and the only testing, found at page 4 of the disclosure, compares L-arginine to tert-butylamine salt of perindopril. The reference to "hydrates" in claim 1 means "the L-arginine salt of perindopril which has water molecules associates with the solid. Moisture uptake can lead to the formation of hydrates" (para 149). The expert notes that is not possible to know the hydration state until the hydrate has been discovered.

[82] Claim 2, which deals with excipients, simply addresses the L-arginine salt, regardless of water, but with non-toxic and pharmaceutically acceptable excipients. Claim 3 is concerned with a tablet, said tablet having an immediate release rather than a modified or sustained release. Claim 4 covers the same scope as claims 2 and 3, but adds limitations to the amount of arginine salt of perindopril. Finally, claim 5 adds the element of treating hypertension and heart failure. The invention is therefore the L-arginine salt of perindopril and its hydrates.

[83] Dr. Rodriguez-Hornedo is largely in agreement with Dr. Byrn on the points of anticipation, obviousness, overbreadth and double-patenting.

[84] The expert found that the criteria for anticipation were not met. Considering the '196 Patent and the US '729 Patent No. 4,508,729, neither one discloses the arginine salt of perindopril. Dr. Rodriguez-Hornedo concludes:

> A POSA would understand the references in the 729 and the 196 Patents to "a pharmaceutically-acceptable inorganic or organic base", "a pharmaceutically-acceptable inorganic or organic acid" and "their pharmaceutically acceptable addition salts" to do no more than point in a general way to the possibility that either a basic or acidic salt might be formed using an organic or inorganic salt former. The number of possible salt formers covered by the claim is at least in the hundreds. …
>
> (Rodriguez-Hornedo affidavit at para 170)

[85] On obviousness, Dr. Rodriguez-Hornedo states forcefully that "(p)rior to being retained as an expert in this litigation matter, I had not read any literature on pharmaceutical products using arginine salts" (para 174). Arginine would not have been a candidate to form a salt with perindopril. The differences between the common general knowledge and the prior art, and the

inventive concept involve many steps that would not have been obvious. Inventive skill and effort are needed. There was no indication that L-arginine salt of perindopril could be made or that it could be more stable than the tert-butylamine salt.

[86] Further references to more prior art did not prove to be more successful. Dr. Rodriguez-Hornedo classified references in eight categories, none of which would be considered to be of assistance:

- references describing general approaches;
- references describing arginine as a potential salt former;
- references involving ACE inhibitors;
- references describing perindopril and its salts;
- references providing examples of arginine salts;
- references listing arginine as a potential salt of a compound or class of compounds without specific examples;
- references describing the use of perindopril to treat medical conditions;
- references describing pharmaceutical products containing hydrates.

[87] Was the invention of '825 obvious to try? Not according to the expert. There were many avenues of exploration to solve the stability issue, but there were not a finite number of solutions, with the L-arginine salt of perindopril not being a predictable solution. Large amounts of time and effort would be required: it follows that “skill and judgment is required to narrow down the choices of variables, such as the salt former, concentrations of perindopril and salt formers, solvents, pH, and temperatures” (para 230). Stability testing alone could take at least 6 months. Indeed, nothing in the prior art would have motivated a POSA to try to form an L-arginine salt of perindopril.

[88] With respect to sufficiency of specification, Dr. Rodriguez-Hornedo meticulously details the steps involved in the preparation of perindopril arginine using the specification of the '825 Patent (paras 239-256). Her conclusion is ultimately that the information contained within the '825 Patent is sufficient to allow the POSA to produce the invention using only the instructions contained in the disclosure. Notably, she mentions that while the '825 Patent does not describe a particular process, it does refer to a classical method of salification. One such classical method of salification would be to "combine perindopril and the L-arginine in a solvent, and then to collect the salt that precipitates. While a change in solvent, concentration or pH may be required, this would be no more than routine experimentation for a POSA" (para 243). Essentially, the view expressed by Dr. Rodriguez-Hornedo is consistent with the demonstration made by Dr. Byrn (Byrn affidavit at paras 259 and 260).

[89] The expert contends that '825 is not overbroad. None of the claims is broader than the invention as invented or as described in the Patent. I note in particular on this reading, that claim 1 would be understood by the POSA as the hydration state not limiting the invention, which is simply the L-arginine salt of perindopril. The invention remains the same.

[90] The expert also addressed the allegation of double-patenting. '825 and '196 are for different inventions. They are patentably distinct because the arginine salt of perindopril is not included in the scope of the '196 claims, as arginine is neither disclosed nor described in the specification of '196. The claims of '825 are distinct from '196 "because inventive skill and effort would be required to arrive at the invention in the claims of the 825 patent" (para 268).

[91] With respect to utility, Dr. Rodriguez-Hornedo is in agreement with Dr. Byrn but also adds that the utility was demonstrated on the basis of the data contained within the '825 Patent itself. The increased stability serves a practical purpose. The data at page 4 of '825 makes the case. Further, even if the utility had not been demonstrated by the '825 Patent, the data provided therein proves a factual basis to soundly predict the utility of the invention (para 56). The further data provided by Mr. Damien confirm the testing results concerning the invention.
Dr. Rodriguez-Hornedo later contends that Apotex was unsuccessful in showing lack of utility in their Letter of Allegation. She identifies two important differences between Apotex's bulk testing and that which was carried out and reflected in the Patent. First, Apotex used the API as opposed to the pharmaceutical tablets. Second, the Apotex testing used packaging that was not representative of how perindopril erbumine would have been marketed. (paras 290-291). Hence, the results of the defendant's testing were skewed and are not useful.

(4) Mr. Richard J. Bastin

[92] Richard J. Bastin is one of two experts retained by Apotex. He is a consultant who worked in the pharmaceutical industry from 1983 to 2013 in the fields of drug formulation and process development. He is less of an academic, and more of a practitioner. He holds a M.Sc. in Chemistry from the University of Manchester and an MBA from Open University. Out of the five experts in this case, he is the only one who does not hold a PhD in the relevant field. He has, however, extensive experience in the industry.

[93] As with the experts retained by Servier, Mr. Bastin was directed to offer his opinion in a series of steps, one following the other:

a) work undertaken by the average pharmaceutical development scientist;

b) review of the '825 Patent;

c) being provided with some 18 documents, from the Berge, Bighley and Monkhouse paper of 1977 and its 1996 update, to Mr. Bastin's own Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical entities[6] of 2000, Mr. Bastin was asked if the POSA would have needed ingenuity to arrive at the inventive concepts of the '825 Patent. He also considered the Damien affidavit in answering the question;

d) are the properties of perindopril arginine unique compared to the properties possessed by any other members of the group of pharmaceutically acceptable salts of perindopril;

e) Mr. Bastin then reviewed the '196 Patent in order to opine on whether claim 5 overlaps with the subject matter of the claims in '825;

f) the next step concerned the disclosure found in '825 and whether it allows the invention to be put in practice by the skilled person;

g) the expert then opined on a comparison between '825 and the invention made;

h) Mr. Bastin reviewed the Summary Basis of Decision for COVERSYL to offer views on storage requirements and shelf-life of the product;

i) he also opined on the testing of the arginine salt and the erbumine salt conducted by Apotex;

j) Mr. Bastin commented on the reports supplied by the experts retained by Servier.

[94] Mr. Bastin was asked: "what work would the average pharmaceutical development scientist have done (and why) in April 2002 if he/she was instructed to overcome a stability issue

relating to the marketed perindopril tert-butylamine (erbumine) product?" (Bastin affidavit at para 10). In providing his answer, Mr. Bastin was asked to assume certain facts that would have been known in April 2002. He was given the chemical structure of perindopril, access to several foreign patents, and the information that perindopril was marketed in its erbumine salt form. Finally, he was told that the tablets were marketed with additional packaging measures for certain countries and had a two-year shelf-life (Bastin affidavit at para 11).

[95] Mr. Bastin replied that an average pharmaceutical development scientist would consider 4 approaches to solving the stability issue in respect of perindopril erbumine: alternative packaging, altering the formulation, using a different salt of perindopril or selecting a more stable crystalline form of perindopril erbumine. The preferable path would depend on the source of the instability. Where the instability is the result of the interaction between the active ingredient and one of the excipients, a change in the formulation, to use a more suitable excipient, would have been a preferred choice (paras 12-16).

[96] The work to be undertaken by the POSA faced with a stability issue is not much different from views offered by the experts retained by Servier. What was significantly different was the insistence Mr. Bastin put on the possibility of discovering a different salt of perindopril, using a structured salt screen, or a different crystalline form of perindopril tert-butylamine. Mr. Bastin insists on the use of structured salt screens, which he describes in great details.

[97] With respect to the '825 Patent, Mr. Bastin noted, much like the experts for Servier, that the POSA would be someone with experience in chemistry, preformulation, formulation and

conducting stability studies. This person would have a PhD in chemistry or a related field with 1-2 years of relevant experience, or a M.Sc. in the same disciplines with 3-5 relevant experience. The POSA would understand as of October 2003, that the “essence” (para 40) of the '825 Patent is perindopril arginine and its hydrates. A POSA would also understand the increased stability of perindopril arginine compared to perindopril erbumine in high heat and relative humidity. It would be understood that the '825 Patent relates to pharmaceutical compositions of perindopril arginine and its hydrates would be useful to the treatment of hypertension and heart failure (para 40).

[98] Mr. Bastin seems to read the '825 Patent in a way similar to the scientists retained by Servier. The Patent is about perindopril arginine and its hydrates; it is useful for the treatment of hypertension and heart failure. He identifies the utility as being the stability to heat and humidity compared to erbumine perindopril, together with the treatment of hypertension and heart failure.

[99] There are however some nuances bordering on differences. Having reviewed the '825 Patent, Mr. Bastin opines that “the salt of the invention also relates to salts prepared with L-arginine and D-arginine, and presumably, racemic (D,L) arginine” (para 102). He notes that the excipients are not identified in the specification. He seems to take issue with the stated “very great stability” of the new salt as he is not satisfied with the data supplied, which do not include bulk material (only on immediate release tablet). Mr. Bastin claims also that the POSA would not understand the phrase “classical method of salification of organic chemistry”, yet he offers a method (para 108). His criticism relates to the contention that the Patent does not offer a particular method. It is not clear why there should be a method identified as the specification is

content to refer to the arginine salt being “prepared according to a classical method of salification of organic chemistry”. In fact, Mr. Bastin describes a method very similar to what was offered by the other experts.

[100] Tellingly, the expert retained by Apotex claims that the statement in '825 that the results were unexpected would not be shared by the POSA because the structured salt screen method would have identified a salt with greater stability. It is noteworthy that the expert limits himself in his paragraph 111 to a general statement that a structured salt screen would have produced, with a very high degree of probability, a salt of perindopril more optimal than the one marketed up to now, i.e. erbumine perindopril. He does go so far as concluding that arginine perindopril would have been produced.

[101] Crucially, Mr. Bastin claims that the POSA would not have required inventive ingenuity to arrive at the subject matter/inventive concept in the '825 Patent. In his view, the skilled person would have prepared perindopril arginine as part of any structured salt screen that would have been conducted when seeking to identify an optimal salt form of perindopril (para 199). Further, the skilled person would have been able to prepare pharmaceutical compositions of perindopril arginine, including immediate release tablets, without difficulty using standard pharmaceutical excipients and routine methods of preparation (para 200). While the '825 Patent states that numerous salts were studied, it is clear, in the view of Mr. Bastin, that the inventors studied merely a few salts and they did not even come close to being in a position to determine that all salts customarily used in the pharmaceutical sector were unusable (para 234). After having read the affidavit of Mr. Damien, his mind was unchanged (paras 43-44).

[102] Mr. Bastin's thesis is that a structured salt screen will produce a better salt. Over a great number of paragraphs, Mr. Bastin explains in great detail how a structured salt screen would produce the L-arginine salt because he would expect the POSA to include L-arginine as one of the salt formers to be used (para 180). To be sure, the process presented by Mr. Bastin contains many variables to be accounted for. Thus, Mr. Bastin states at paragraph 172 that the only difference between the prior art, which he reviews, and is considerable, and the inventive concept of '825 "is that there is not a specific description of perindopril arginine or its hydrates having actually been made in the documents I have reviewed. Likewise, there is not a specific description of a pharmaceutical composition containing perindopril arginine or its hydrates in the treatment of hypertension or heart failure". In other words, there is not a significant step between the state of the act, which includes the new techniques of salt screening and the relatively simple arginine salt of perindopril, the inventive concept.

[103] For the expert, it would appear that the method leads to the solution. In fact, he discounts the evidence of Mr. Damien, who testified that the properties of perindopril arginine and its hydrates are unique among the pharmaceutically acceptable salts of perindopril. He is not satisfied with the demonstration (para 242). He notes that a very limited number of salts were tested by Servier over a period of 20 years: sodium, hydrochloride, maleate and tert-butylamine. Early on, the Servier scientists settled on tert-butylamine, before perindopril arginine was discovered in 1984.

[104] Further, Mr. Bastin also claims that the content of the '825 Patent overlaps with that of the patent claiming perindopril and pharmaceutically-acceptable salts, the '196 Patent. Mr. Bastin

repeats that prior to April 2002, arginine would have been a well-known salt former to the POSA, contrary to the view expressed by the Servier experts, which would make it a pharmaceutically acceptable salt of perindopril (paras 246-247). The expert does not discuss that it is perindopril that is patented in '196.

[105] In addition, Mr. Bastin is of the view that, assuming the perindopril arginine would not have been found through a structured salt screen, the '825 Patent did not describe its invention in a manner that would have allowed the skilled person to successfully use routine methods to identify suitable conditions to prepare perindopril arginine. Having read the '825 Patent, this skilled person would not know, *inter alia*, whether the inventors prepared and used hydrated, assuming it could be prepared, or non-hydrated forms of perindopril arginine and the method used by the inventors to prepare perindopril arginine. The POSA would not know the ingredients used in the immediate release tablets and how to prepare them. Moreover, the expert questions what is meant by "classical method of salification of organic chemistry". The expert seems to acknowledge that the method followed by the inventors could be used, but he prefers another one (para 255-256). In fact, he expressed a preference for a controlled crystallization.

[106] Mr. Bastin also opined on whether the '825 claims are consistent with the invention made and described. The subject matter of the '825 Patent is of course the arginine salt of perindopril and its hydrates. For the expert, no work done by the inventors was identified to show that they actually prepared a hydrate of perindopril arginine: they could not have known that a hydrate "could actually be formed" (para 262).

[107] Quite obviously, the expert takes a view of what a "hydrate" is. Thus, he states at paragraph 263 that "(s)imply because a compound absorbs water, it does not mean that the compound will form a hydrate". He would consider only the "bound water" to form part of the compound's crystal lattice, leading to a change in the crystalline lattice of the perindopril arginine. Mr. Bastin continues by stating that "if the inventors had identified a change in the crystalline form of perindopril arginine following exposure to increased humidity during the stability studies, this would indicate that the perindopril arginine initially prepared was not physically stable" (para 263). Without a hydrate, as defined by the expert, being prepared, the stability of a composition of a hydrate of perindopril arginine could not be ascertained either factually or following a line of reasoning to predict improved stability to heat and humidity.

[108] The expert also notes that the claims refer to arginine, not specifically L-arginine. Mr. Bastin argues that "(w)hile it would be reasonable for inventors to expect that D-arginine or racemic arginine would form a salt with perindopril, that the salt would crystallise, and that the salt would not exhibit the same instability issues as perindopril tert-butylamine since these forms of arginine would also be known to be volatile, the skilled person would not be able to predict whether these forms of perindopril arginine would be able to form a hydrate, and whether these forms of perindopril arginine would exhibit very great stability to that and to humidity when compared to perindopril *tert*-butylamine" (para 269).

[109] Finally, the inventive concept of claim 1 is the perindopril arginine (and not only the salt of natural arginine) and hydrates of perindopril arginine, while the pharmaceutical composition is understood to be the inventive concept of claims 2 to 4. Claim 5 is simply that the various

compositions of claims 2 to 4 are useful to treat hypertension and heart failure. It does not appear that there is a dispute as to the utility of the invention (if it is an invention): greater stability to heat and humidity.

(5) Dr. Michael J. Zaworotko, PhD

[110] Dr. Zaworotko holds a PhD. in Chemistry from the University of Alabama. He is the Bernal Chair of the Crystal Engineering and Science Foundation of Ireland and Research Professor at the University of Limerick, in Ireland. He has authored some 390 papers, most of which relate to crystallization. He is currently an associate editor of the journal *Crystal Growth & Design*. Dr. Zaworotko has done some consulting work for pharmaceutical companies in the United States and Europe.

[111] Dr. Zaworotko was immediately given the '825 Patent and he was not asked to comment on obviousness. Dr. Zaworotko was instructed in much the same way as Mr. Bastin, except that he was given a narrower mandate than that of Mr. Bastin. The expert was asked to opine on the following areas:

- who is the POSA and what would be understood of the '825 Patent, its subject matter and that of its claims, and its utility;
- having reviewed the affidavit of Mr. Damien, Dr. Zaworotko was asked to consider:
    - how was perindopril arginine prepared and what would the POSA consider to be “a classical method of salification of organic chemistry”;
    - what were the solid forms of perindopril arginine prepared by the inventors;

- was the disclosure in '825 sufficient to arrive at the same perindopril arginine;
- does the work carried out by the inventors show that bulk perindopril arginine has "very great stability" to heat and to humidity compared to the tert-butylamine salt;
- the nature and amount of effort to arrive at perindopril arginine;
- whether the claimed invention is consistent with that disclosed in the Patent and made by the inventors.

[112] Although the expert would suggest that the POSA has an advanced degree in Chemistry (he did not allude to the bachelor degree) with two years' experience, Dr. Zaworotko is in substantial agreement with the other experts on the definition of the POSA. He also agrees on the subject matter of the '825 Patent. He notes that while the '825 Patent does not expressly identify a utility for perindopril arginine, upon reviewing the description in the patent, a POSA would understand that perindopril arginine, its hydrates and the pharmaceutical compositions containing them would be more stable in the face of high heat and relative humidity, compared to perindopril erbumine. He notes however that the POSA "would not know of the solid form of perindopril arginine used, the composition of the tablet or the packaging used to obtain this result" (para 96). Furthermore, perindopril arginine could be used to treat hypertension and heart failure (para 34).

[113] Dr. Zaworotko seems to believe that the POSA would understand that the "classical method of salification of organic chemistry" to involve the isolation of a salt, but following standard crystallization procedures (para 91) such as cooling the solution, evaporation or adding a solvent in which the salt is not soluble.

[114] It is interesting to note that Dr. Zaworotko takes issue with the statement in the '825 disclosure that the results of the stability studies (p. 4 of the '825 Patent) was “entirely unexpected” and “could not have been deduced from, or suggested by, the tracking of the literature of this product”, but he seems to do so on a rather different basis. Evidently, the statement refers to perindopril, yet the criticism speaks in terms of “preparing and identifying salts of a drug molecule to select a salt with acceptable stability (in addition to other properties) was a common, routine practice for pharmaceutical scientists well before 2002” (para 94). He accepts that it is not possible to precisely predict in advance which salt will be most stable however: he can, at best, say that the POSA would be confident that a salt of perindopril with “acceptable stability” would be located.

[115] It is somewhat surprising to read that Dr. Zaworotko would consider that the reference, at page 4 of '825, to “less onerous constraints” with respect to packaging would prove to be a challenge for the POSA (para 95). The original French version speaks of “contraintes moins lourdes” ([TRANSLATION] less weighty constraints) and the disclosure refers to these onerous constraints as relating to packaging, these constraints having to do with organizational complexities and costs. Indeed, the disclosure refers specifically to the intrinsic fragility of the API, perindopril, which has required protection with additional packaging measures.

[116] Looking at the '825 claims, Dr. Zaworotko reads the word “and its hydrates” in claim 1 as being “hydrated crystal forms of perindopril arginine”. Furthermore, the claim is not limited to L-arginine, which would make the POSA understand that the salt could be prepared with D-arginine or racemic arginine. For the expert, “hydrates” means that water molecules are part of

a crystal lattice; they are absorbed into that crystal lattice (para 101). Claim 2 would be understood to mean that the pharmaceutical composition could be in any common form, while the pharmaceutical composition is an immediate-release tablet according to claim 3. The excipients used would not function to delay or prolong the release of the API. Claim 4 specifies the dose of arginine salt of perindopril while claim 5 speaks of using the product for treatment of hypertension and heart failure – the POSA would know that the product is useful because of the API, not because of the salt.

[117] Upon reading the affidavit of Mr. Damien, Dr. Zaworotko opined that a POSA would not consider the inventors' work to be a "classical method of salification of organic chemistry". In his view, the classical method of salification of organic chemistry is "the isolation of a salt following standard crystallization procedures, *i.e.* cooling of the solution, evaporating some of the solvent or adding an anti-solvent to reduce the solubility of the salt" (para 118). Freeze-drying to isolate a salt would not be considered to be a standard method. A POSA, following the directions provided in the '825 Patent could not be expected to arrive at the same solid forms of perindopril arginine as prepared by the inventors (paras 122-125). The inventors used freeze-dried an aqueous solution while the skilled person would have isolated a salt by following what he calls the standard crystallization (using a solution of the salt that is cooled, then evaporating some of the solvent and adding an anti-solvent to reduce the solubility of the salt).

[118] Dr. Zaworotko took issue with the testing conducted by Servier to obtain the L-arginine salt of perindopril. The stability testing is acknowledged to show better stability in favour of perindopril arginine (open flask for 48 hours at 100ºC), yet the expert discounts such result

because these conditions are “irrelevant to real-world conditions and industry regulatory standards for stability testing” (para 128). Unfortunately, there is no discussion of accelerated testing to which other experts referred. In the end, it seems that the criticism is limited to the use of the words “very great stability” which, presumably, is considered by the expert as unwarranted hyperbole.

[119] The expert notes that the arginine salt absorbs more water under high humidity conditions than perindopril tert-butylamine. He does not discuss the fact that '825 is concerned with finding a remedy to the loss of the API, perindopril, in high heat and high humidity, requiring the “tropicalized packaging”. In fact, the Patent addresses degradation of the product in that the API is reduced in various conditions. Servier was looking for the stability of a compound where there is less of a loss of the API.

[120] In the view of Dr. Zaworotko, there was not a significant effort involved in arriving at the invention. He seeks to dissect the various tests conducted over time to conclude that it consists of the work that would be performed by a POSA (para 145).

[121] Finally, the expert expressed the view that the invention claimed in the '825 Patent is not consistent with the invention disclosed in the Patent. This time, the criticism is centered on the inclusion of hydrates. The expert notes that the Patent provides no specific information regarding characterisation of the solids that were isolated. The Damien affidavit is not more instructive. Dr. Zaworotko would have liked to be told “whether any water associated with the material was absorbed surface water or whether the water was absorbed to form part of the crystal lattice”

(para 149). He claims that a change in the crystalline form of the perindopril arginine "would be a further indication that perindopril arginine exhibits lower physical stability when compared to perindopril *tert*-butylamine" (para 149). It is unclear why Dr. Zaworotko focused some attention on the physical stability. As indicated earlier, the stability that the inventors were looking for was with respect to the loss of perindopril in conditions of high heat and high relative humidity, its chemical stability.

[122] Dr. Zaworotko is critical of Mr. Damien who stated at paragraph 74 of his affidavit that the studies conducted showed that "it became clear that the perindopril arginine salt was absorbing water". That made Mr. Damien conclude that the salt could form hydrates. For the expert, that reasoning is "fundamentally flawed" because, in his view, a hydrate requires that water molecules be part of or within the crystal lattice. Merely absorbing water (pick up water) does not form a hydrate, according to his definition of the term. That makes him conclude that without testing, "it would be scientifically unsound to conclude that a hydrate was formed" (para 150). Dr. Zaworotko did not comment on the last sentence of paragraph 74 of the Damien affidavit where he concludes that the absorption of water had proven to be irrelevant ("Nevertheless, the absorption of water by the perindopril arginine salt did not pose a problem because there was no impact on the stability of the perindopril tablets").

[123] In essence, the perindopril arginine salt absorbed more water than the perindopril erbumine salt, yet there was less of a loss of perindopril in the former compared to the latter. In the end, the expert concludes that the invention is not consistent with the invention described or

made because it does not have “very great stability” to heat and humidity compared to perindopril erbumine salt.

C. Witnesses: admissibility and weight of evidence

[124] Apotex sought in this case to challenge the credibility, indeed to impugn the integrity of Dr. Byrn, one of the experts retained by Servier to enlighten the Court in this case. The initial complaint concerned the fact that Dr. Byrn has testified numerous times in favour of innovators. However, the Supreme Court noted that the concepts of independence, impartiality and freedom from bias which anchor the duty of experts owed to the courts at common law “must be applied to the realities of adversary litigation. Experts are generally retained, instructed and paid by one of the adversaries” (*White Burgess Langille Inman v Abbott and Haliburton Co.*, 2015 SCC 23, [2015] 2 SCR 182, at para 32). The mere fact that an expert has been retained does not undermine these underlying concepts.

[125] Apotex did not seek to have Dr. Byrn declared inadmissible as an expert, yet the charge based on having testified where he was retained as an expert by innovators was severe. As I understand it, the allegation is that Dr. Byrn has testified so often for innovators that he has become an advocate for the pharmaceutical industry. In my view the attack was unwarranted. Reading the cross-examination of Dr. Byrn, it is clear that he is an experienced witness who is fully aware of the evidence he has given in his affidavit; he will defend the opinion given. It is what is expected, within limits, of an expert witness after all. The quality of the evidence is to be assessed by the trier of fact.

[126] The Court did not have the benefit of observing Dr. Byrn testifying, contrary to the Australian Court in the case dealing with perindopril arginine. Nevertheless, there was nothing on the record to suggest that Dr. Byrn did not acquit himself in the fashion expected of experts in Canada. There is evidently a very good reason why Apotex did not attempt to have him ruled inadmissible. The test is a high one:

> [106] … For expert testimony to be inadmissible, more than a simple appearance of bias is necessary. The question is not whether a reasonable person would consider that the expert is not independent. Rather, what must be determined is whether the expert's lack of independence renders him or her incapable of giving an impartial opinion in the specific circumstances of the case (D. M. Paciocco, "Unplugging Jukebox Testimony in an Adversarial System: Strategies for Changing the Tune on Partial Experts" (2009), 34 *Queen's L.J.* 565, at pp. 598-99). A challenge to a trial judge's decision to qualify an expert witness, like a challenge to a finding that the expert is independent and impartial, requires consideration of, *inter alia*, the substance of the expert's opinion.
>
> (*Mouvement laïque québécois v Saguenay* (City), 2015 SCC 16, [2015] 2 SCR 3).

[127] The Court would not find that the weight to be afforded to his evidence would be less because Dr. Byrn has testified for innovators in the past, thereby somehow showing a bias of some sort. More would be needed. We do not know, for instance, how many times experts refuse mandates, or are not used in litigation. If Dr. Byrn has been retained as often as Apotex claims, it may as well be because of his stellar résumé and expertise. Indeed the experience accumulated over the years allows him to anticipate questions coming from an accomplished cross-examiner. That was on display in this case.

[128] Apotex insisted that Dr. Byrn was caught being completely inconsistent during the cross-examination on his affidavit. I ruled during the hearing that such inconsistency had not been shown, the witness not having been asked properly about the alleged inconsistency in a way to, first, establish the allegation and, second, allow an opportunity to explain.

[129] The cross-examination was concerning the meaning of “its hydrates” in claim 1 of the '825 Patent. During a phase of the cross-examination in the morning, many attempts were made to suggest that hydrates occur when molecules of water are incorporated into the crystal form, the resulting compound will be a hydrate. Every time such an attempt would be made, using different formulation but trying to get the expert to agree that a hydrate must be in a crystal structure, Dr. Byrn responded that the proposition put to him by the cross-examiner was true for crystalline hydrates. But there are non-crystalline hydrates, which did not seem to satisfy the cross-examiner (cross-examination of Dr. Byrn, questions 568 to 579 and questions 599 to 605).

[130] After lunch, the cross-examination resumed with a return to crystalline hydrates, with the cross-examiner asking the same leading question as before. The witness was steadfast: there are hydrates that are crystalline, and some that are not (questions 612 to 615). It is at this stage that the cross-examiner pulled one affidavit, out of dozens of affidavits sworn in Canadian litigation over the years by Dr. Byrn. He directed the attention of the witness to one sub-paragraph 26 c) of his affidavit which reads:

> 26. Many pharmaceutically important materials exist as solids. When in the solid form, a number of different forms may be available. Some of the terms that may be used to describe theses different forms of these compounds include amorphous, hydrates, anhydrate, polymorphs, and solvates. As a particular chemical compound may exist in any number of these different forms, it is

> necessary to identify the particular form to understand the reference to the compound. It is therefore useful to define these terms:
>
> (a) "Amorphous" forms are non-crystalline solids.
>
> (b) "Polymorphs" exist when two forms have the same chemical composition but different crystal structures.
>
> (c) "Hydrates" exist when a form, in addition to containing molecules of a given substance also contain molecules of water regularly incorporated into the crystal structure.
>
> (d) "Anhydrates" exist when there is no solvent incorporated into the structure. Different anhydrous forms are termed polymorphs. These compositions however may still have variable amounts of water present, in an unbound form. An anhydrate can contain a certain amount of unbound water.
>
> (e) "Solvates" exist, when solvents, such as alcohols like ethanol or isopropanol, or compounds such as acetonitrile, or acetone are incorporated into the crystal structure.

Without asking any question about the paragraph, the cross-examiner moved on.

[131] Servier took issue with any use Apotex would seek to make of the exchange based on the well-known rule of fairness, more than 125 years old, enunciated by the House of Lords in *Browne v Dunn* ((1893), 6 R. 67):

> Now, my Lords, I cannot help saying that it seems to me to be absolutely essential to the proper conduct of a cause, where it is intended to suggest that a witness is not speaking the truth on a particular point, to direct his attention to the fact by some questions put in cross-examination showing that that imputation is intended to be made, and not to take his evidence and pass it by as a matter altogether unchallenged, and then, when it is impossible for him to explain, as perhaps he might have been able to do if such questions had been put to him, the circumstances which it is suggested indicate that the story he tells ought not to be believed, to argue that he is a witness unworthy of credit. My Lords, I have always understood that if you intend to impeach a witness you are bound,

> whilst he is in the box, to give him an opportunity of making any explanation which is open to him; and as it seems to me, that is not only a rule of professional practice in the conduct of a case, but is essential to fair play and fair dealing with witnesses. Sometimes reflections have been made upon excessive cross-examination of witnesses, and it has been complained of as undue; but it seems to me that a cross-examination of a witness which errs in the direction of excess may be far more fair to him than to leave him without cross-examination, and afterwards to suggest that he is not a witness of truth, I mean upon a point which it is not otherwise perfectly clear that he has had full notice beforehand that there is an intention to impeach the credibility of the story which he is telling. …
>
> [pp. 70-71]

This passage from Lord Herschell's speech is even reinforced by Lord Halsbury :

> … To my mind nothing would be more absolutely unjust than not to cross-examine witnesses upon evidence which they have given, so as to give them notice, and to give them an opportunity of explanation, and an opportunity very often to defend their own character, and, not having given them such an opportunity, to ask the jury afterwards to disbelieve what they have said, although not one question has been directed either to their credit or to the accuracy of the facts they have deposed to. …
>
> [p. 76]

[132] The confrontation, if the witness is to be impeached, must take place as he is testifying. It did not occur here.

[133] There will of course be cases where it will be so clear "that notice has been so distinctly and unmistakably given, and the point upon which he is impeached, and is to be impeached, is so manifest, that it is not necessary to waste time in putting questions to him upon it" (Lord Herschell, p. 71). But such is not the case here.

[134] It is clear that the cross-examiner was not interested in getting an explanation from the witness if there was an inconsistency. As conceded during the hearing, sub-paragraph 26 (c) does not state that hydrates only exist where water is incorporated in a crystal lattice. In fact, the only other page the Court has from the affidavit suggests that the case in which the affidavit is produced centered on crystal structure. Context matters. Quite clearly, the witness in that case was saying that hydrates exist when molecules of water are regularly incorporated into the crystal lattice. It is far from clear that Dr. Byrn was defining hydrates as being only where there is a crystalline form, for the water to be incorporated into the crystal structure. If such was the contention of counsel, the issue ought to have been put to the witness.

[135] It was not at all manifest that there was an inconsistency between the testimony being given in this case and the sub-paragraph in a case litigated many years previous. If there was a contradiction or inconsistency, counsel ought to have followed the guidance of *Browne v Dunn*. The rule of general application (*R. v Lyttle*, [2004] 1 SCR 193, 2004 SCC 5, at para 65), although certainly not absolute, must be applied in this case because fairness so commands. As a matter of fact, Dr. Byrn's re-examination established that the case in which the affidavit was made "was about 17 dihydrochloride monohydrate, a crystalline hydrate" (question 1021). Had the opportunity been afforded, the witness could have explained the context in which the affidavit was sworn. Counsel chose not to pursue the matter. The credibility of Dr. Byrn cannot be impugned on the basis of some affidavit which, on its face, does not appear to be contradictory and on which he has not been properly cross-examined.

[136] Furthermore, the assertion made by Apotex that the definition given by Servier's experts is "entirely inconsistent" with publications of Dr. Byrn and Dr. Rodriguez-Hornedo is unsupported. Both recognize that hydrates may form in the crystal lattice, but both assert that there may be another form. While Dr. Zaworotko was critical of both Dr. Byrn and Dr Rodriguez-Hornedo (he had their affidavit when he prepared his), he recognized at paragraph 163 of his own affidavit that Dr. Rodriguez-Hornedo stated in her own Encyclopedia of Pharmaceutical Technology[7] that "a solid with water incorporated into the "interstitial voids or part of the crystal lattice" " constitute hydrates. His affidavit was focused on crystals and crystallization. I am satisfied that the experts retained by Servier provided persuasive evidence on what constitutes a hydrate. Dr. Zaworotko asserted that "(t)he skilled person would understand the reference to "hydrates" in claim 1 to refer to crystalline forms of perindopril arginine in which water molecules are part of, or absorbed into, the crystal lattice" (para 101). The evidence tends to show that it is only one of possible hydrates.

[137] Apotex was also critical of the evidence supplied by Dr. Rodriguez-Hornedo. The contention is that the witness could not have produced her evidence in the short period of time Apotex claims was spent by the expert with Servier Canadian counsel. The contention is meritless. I read her cross-examination and Dr. Rodriguez-Hornedo responded fully to the allegation. Not only were her contacts with counsel more frequent than what was asserted, but she had to work on her own and the area of chemistry covered by her testimony is very well known by her.

[138] Servier contended that Dr. Byrn and Dr. Evans were deemed credible by the Australian Court where issues similar to those of the Canadian case were in play. Both witnesses testified before the Australian Court. The Australian case was a trial. A NOC case is largely a "paper exercise" without witnesses appearing in Court. More importantly perhaps, having testified in a companion case, where the law actually differs, may cut both ways. A witness who has expressed an opinion before may not be prone to change his mind in a subsequent case. Even if instructed, as these two witnesses were instructed, by the applicant's counsel, the fact remains that they know the issues and the claims by the time they testify in the Canadian proceedings. The fact that they may have been found credible in Australia is in my view irrelevant in the Canadian case where they never appear before this Court. The cogency of their evidence is assessed on the basis of the record, understanding that they have offered evidence in proceedings that are more or less similar.

[139] On the other hand, Servier argued that Dr. Zaworotko, as a specialist in crystal engineering, was less useful to the Court. I agree. It seemed that Dr. Zaworotko saw the case through the prism of crystals. His evidence did not have the breadth of that offered by Mr. Bastin.

[140] Contrary to the contention of Servier that Mr. Bastin evidence was the result of results-oriented analysis performed under the control of counsel for Apotex, I found the evidence of Mr. Bastin to be useful and relevant. His "blinded" evidence was impressive and added to the weight of the evidence. I note in particular that he did not know about perindopril, or the '825 Patent, before 2017.

[141] In the end, the evidence of each expert has to be assessed with respect to the issues that need to be decided, without excluding off the bat the opinion given on the issues of the case.

VI. Person of skill in the art (POSA or POSITA)

[142] There is no significant daylight between the positions of the parties as to the qualities and skills of the mythical person of skill in the art. It is constituted by a person, or team of persons, with training and experience in pharmaceutical sciences, chemistry, formulation, which includes the properties of a drug and its stability.

[143] A person with a successful 10th grade chemistry class will not do. I accept Servier's suggestion, which is fundamentally supported by the experts retained by Apotex, that the POSA has typically an advanced degree in chemistry or biochemistry that will be complemented by suitable experience. Someone with a bachelor's degree and adequate experience would also qualify. The information in the patent specification is addressed to the POSA. The Supreme Court in *Consolboard Inc. v MacMillan Bloedel (Sask.) Ltd.*, [1981] 1 SCR 504 [*Consolboard*] described the POSA in the following fashion:

> The persons to whom the specification is addressed are "ordinary workmen", ordinarily skilled in the art to which the invention relates and possessing the ordinary amount of knowledge incidental to that particular trade. The true interpretation of the patent is to be arrived at by a consideration of what a competent workman reading the specification at its date would have understood it to have disclosed and claimed.
>
> [p. 523]

The person must have sufficient qualifications to perform the task of helping with the interpretation of the patent. As put by Binnie J. in *Whirlpool Corp. v Camco Inc.*, 2000 SCC 67, [2000] 2 SCR 1067 [*Whirlpool*], "(r)ocket science patents may only be comprehensible to rocket scientists" (para 71). An advanced degree with some experience or a bachelor's degree with considerable experience is required.

VII. Burden of Proof

[144] A patent is presumed to be valid (ss. 43(2) of the *Patent Act* (R.S.C., 1985, c. P-4)) [the Act]. Accordingly, the party alleging invalidity in NOC proceedings has the initial burden, an evidential burden, of advancing evidence capable of establishing invalidity; that has the effect of rebutting the legal presumption. At that stage, the burden shifts and it is for the applicant to establish that each allegation of invalidity is not justified (*Eli Lilly Canada Inc. v Apotex Inc.*, 2018 FC 736; *Laboratoires Servier v Canada (Health)*, 2015 FC 108, at paras 46 to 49). In other words, once the issue of invalidity has been put into play because it has an air of reality, the burden shifts.

[145] It is not a matter of dispute between the parties in this case that it is Servier's burden to prove that the allegation of invalidity of its '825 Patent are unjustified. The standard applicable in civil matters, the balance of probabilities, is that which applies.

VIII. Claims construction

[146] I have reviewed in some detail the evidence led in this case. Controversy over perindopril is not new. The decision of this Court, confirming the validity of claims 1, 2, 3 and 5 of the '196 Patent in *Laboratoires Servier, Adir, Oril Industries, Servier Canada Inc. v Apotex Inc.*, 2008 FC 825, 332 FTR 193; 67 CPR (4th) 241 [*Laboratoires Servier*], appeal dismissed, 2009 FCA 222, 75 CPR (4th) 443, provides a glimpse into the tortuous litigation that took place in the 80's and 90's (paras 63 to 66) in Canada. Fortunately, this case does not have those complications.

[147] The '825 Patent is relatively speaking a simpler document than most pharmaceutical patents. The '825 does not claim as an invention perindopril. That was done in Canada through '196. It is rather a particular salt that is alleged to be an improvement over the salt used originally to market perindopril that is the subject matter of '825. Before addressing infringement or invalidity issues, the Court must consider the construction to be given to the claims. It is of course a matter for the Court to determine with the assistance of experts. I have already described the persons of skill in the art (the parties agree generally on the characteristics of such person). I have also described the Patent in suit in some details. The claims construction is made as of the date of publication of '825, October 18, 2003.

[148] However, before embarking on the construction of '825 itself, it is important to keep in mind the rules of construction which apply to claims construction. A patent is interpreted without considering any allegation of invalidity (it is understood in this case that if '825 is valid, it would be infringed by Apotex's products). It has been said that "(c)laims construction is antecedent to

consideration of both validity and infringement issues". It cannot become a results-oriented interpretation (*Whirlpool*, *supra*, at para 43).

[149] Being a question of law, it is an issue for the Court, but with the assistance of the skilled person because the patent is addressed to such a person. In *Burton Parsons Chemicals, Inc. v Hewlett-Packard (Canada) Ltd.*, [1976] 1 SCR 555, the task is described as:

> While the construction of a patent is for the Court like, that of any other legal document, it is however to be done on the basis that the addressee is a man skilled in the art and the knowledge such a man is expected to possess is to be taken into consideration.
>
> [p. 563]

[150] Nevertheless, the Court must approach the construction task from the perspective of the purposive construction as opposed to a literal approach favoured by many. The following passage from Lord Diplock in *Catnic Components Ltd. v Hill & Smith Ltd.*, [1982] RPC 183 [*Catnic*] was cited approvingly in *Whirlpool* at paragraph 44:

> My Lords, a patent specification is a unilateral statement by the patentee, in words of his own choosing, addressed to those likely to have a practical interest in the subject matter of his invention (i.e. "skilled in the art"), by which he informs them what he claims to be the essential features of the new product or process for which the letters patent grant him a monopoly. It is those novel features only that he claims to be essential that constitute the so-called "pith and marrow" of the claim. A patent specification should be given a purposive construction rather than a purely literal one derived from applying to it the kind of meticulous verbal analysis in which lawyers are too often tempted by their training to indulge. The question in each case is: whether persons with practical knowledge and experience of the kind of work in which the invention was intended to be used, would understand that strict compliance with a particular descriptive word or phrase appearing in a claim was intended by the patentee to be an essential requirement of the invention so that *any* variant would fall outside

> the monopoly claimed, even though it could have no material effect upon the way the invention worked.
>
> [Emphasis in original.]

[151] The Court is looking for what has been allegedly invented, the identification "of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention" (*Whirlpool*, at para 45). We are looking for what the inventor objectively intended to communicate by his claims. As my colleague Justice Robert Barnes puts it in *Alcon Canada Inc. v Apotex Inc.*, 2012 FC 410 at paragraph 27:

> [27] … the law is clear that a purposive approach requires the Court to examine claim language in the sense that the patentee is presumed to have used it and not through the lens of strict literalism. Even a term that appears to be plain and unambiguous may, when read in the context, reasonably support a different meaning. …

But then the question becomes what was intended by the inventor when the words used to fence the invention were chosen?

[152] The skilled person is an important player in a field that is technical in nature. But the skilled person does not decide the issue. At the end of the day, it is the Court that decides, taking into consideration the knowledge that the skilled person is expected to possess and the evidence offered by experts.

[153] As stated in *Whirlpool*, at paragraph 49, the purposive construction is consistent with "being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public" *(Consolboard,* at p. 520). Indeed, Dickson J. cited with approval Duff C.J.C. in *Western Electric Co., Inc., et al. v Baldwin International Radio of Canada,* [1934]

SCR 570 finding that "where the language of the specification, upon a reasonable view of it, can be so read as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction". Dickson also referred to the oft-quoted passage from Sir George Jessel in *Hicks & Son v. Safety Lighting Company*, (1876), 4 Ch. D. 607 who concluded that a patent is to be considered "with a judicial anxiety to support a really useful invention".

[154] Nonetheless, the purposive construction will not allow a construction not consistent with the language used by the inventor. In *Free World Trust v Électro Santé Inc.*, 2000 SCC 66, [2000] 2 SCR 1024 [*Free World Trust*], the Supreme Court confirmed that "(t)he primacy of the claims language was already rooted deeply in our jurisprudence and should , I think, be affirmed again on this appeal" (para 40). The balance may be found at paragraph 51 of *Free World Trust:*

> … The involvement in claims construction of the skilled addressee holds out to the patentee the comfort that the claims will be read in light of the knowledge provided to the court by expert evidence on the technical meaning of the terms and concepts used in the claims. The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used *provided* the words used are interpreted fairly and knowledgeably.
>
> [My emphasis, except for the word "provided", in italics in the original]

[155] In the end, a Court is not to redraft claims; it can only interpret them (*Eli Lilly & Co. v O'Hara Manufacturing Ltd.*, 26 CPR (3rd) 1 [*O'Hara*]). But the nature of the invention is to be

ascertained through a consideration of the whole specification (claims and disclosure), if the words of the claim are ambiguous (*Consolboard*, p. 520; *Whirlpool*, at para 52).

[156] To conclude on the rules of construction, the fundamental rule, the so-called "orthodox rule", continues to be that as articulated in *Lister v Norton Brothers and Co*, (1886), 3 RPC. 199, and endorsed in *Whirlpool* (at para 49), that a patent "must be read by a mind willing to understand, not by a mind desirous of misunderstanding". That obviously applies to the skilled person. As stated by Binnie J. in *Whirlpool*, "(a) "mind willing to understand" necessarily pays close attention to the purpose and intent of the author" (para 49). The Court in *Free World Trust* endorsed the same idea at paragraph 44 as it quotes *The Canadian Law and Practice Relating to Letters Patent for Inventions*, 4th ed., Carswell 1969 (Fox), where, speaking of the skilled person, it is said that "(h)e is assumed to be a man who is going to try to achieve success and not one who is looking for difficulties or seeking failure". That, it seems to me, is in contradistinction to a skilled person who would try to find fault with every word or would look at the patent from his point of view limited by a particular expertise.

[157] There are five claims that need to be constructed. The first one refers to the subject matter of the alleged invention: the arginine salt of perindopril and its hydrates. The other claims depend on the first one and they are more limiting than claim 1, but are construed consistently with the larger claim. Thus, claim 2 adds to the salt and its hydrates pharmaceutically acceptable excipients (one or more that are non-toxic). The arginine salt and its hydrates, together with non-toxic and pharmaceutically acceptable excipients, are then characterized in claim 3 as being presented as an immediate-release tablet. Claim 4 takes the composition of claim 2 or the

immediate-release tablet of claim 3 and specifies that it contains from 0.2 to 10 mg of the arginine salt of perindopril. The pharmaceutical composition of claims 2 to 4, which all include the arginine salt of perindopril and its hydrates, is useful for the treatment of hypertension and heart failure.

[158] There are some contentious issues, "where the shoe pinches so that one can concentrate on the important points" (*Nokia v Interdigital Technology Corporation* [2007] EWHC 3077, as quoted by Snider J. in *Laboratoires Servier*, at para 98, the perindopril case). Here, the shoe pinches in two spots: what is the arginine salt of perindopril and what is meant by "its hydrates". Both pinches stem from claim 1, as was to be expected.

[159] Servier takes the position that the arginine salt of perindopril is the L-arginine. It became clear during the hearing that Servier considered the term as unambiguous, such that the Court should not have to resort to the whole specification in arriving at its construction.

[160] The disclosure identifies the arginine salt of perindopril as being preferentially the salt of natural arginine, the L-arginine ('825 Patent, p. 2) and reveals that the arginine salt used in the study at page 4 is the L-arginine salt. Neither D-arginine nor a racemic form of arginine is natural. Dr. Rodriguez-Hornedo testified that a skilled person would "expect to be told if a reference to arginine is intended to refer to a non-natural form" (Rodriguez-Hornedo affidavit at para 147). The witness also stated that the naturally occurring form of arginine will be more readily approved by regulators as it is found in common foods (para 147). Dr. Byrn concurred with Dr. Rodriguez-Hornedo, adding that the POSA would know that the inventor meant

L-arginine because it is not toxic (since it exists in the body) and it would obviously be the most economical variant. He states that "the POSA would understand that the claim pertains to the L-arginine stereoisomer" (Byrn affidavit at para 189). Contrary to L-arginine, the D stereoisomer is not a naturally occurring amino acid, which suggests that the POSA would be reinforced in the thinking that the claims refer to L-arginine. The witnesses did not state in their affidavits how these outside considerations would be relevant to "fence" the monopoly. The *Free World Trust* Court referred with approval to this passage taken from *Minerals Separation Corp. v Noranda Mines Ltd.*, [1947] Ex. C.R. 306 at p. 352:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.

How do issues like more economical variant or easier acceptance by a regulator impact the scope of a monopoly? There is nothing stopping our inventor from commercializing that which is more economical or easier to find, but still protecting the monopoly by claiming the whole of arginine.

[161] Servier sought to find further support for its position through the cross-examination of the two experts retained by Apotex. In the case of Mr. Bastin, he was questioned about what constitutes a pharmaceutically acceptable salt and he seemed to agree that a salt former, like arginine, would be pharmaceutically acceptable because used and tested in the past, with the result that it has been determined to have acceptable characteristics. Asked if that was accurate, he answered:

> A. Yes. So the arginine isn't natural so you would not use it, you would use the natural form, L-arginine, that would be pharmaceutically acceptable.
>
> [AR volume 27, p. 7436]

In the case of Dr. Zaworotko, when shown the entry in the *Merck Index*, an encyclopedia of chemicals, drugs and biologicals published in 1996 as the 12th edition[8], he accepted that the entry 817 for arginine never refers to D-arginine. In fact, it refers to L-arginine.

[162] Accordingly, Servier refers to the cannon of interpretation of patents in support of its view that the claims would be interpreted speaking of L-arginine: a purposive construction considering the evidence of skilled person willing to understand and not one looking for difficulties or seeking failure.

[163] Apotex, on the other hand, argues that "arginine" in claim 1 must include L-arginine, but also D-arginine and racemic arginine. Mr. Bastin states in his affidavit (paras 102 and 114) that because the disclosure speaks of arginine salt of perindopril being preferentially the natural L-arginine, that implies that the salt of the invention can be prepared with D and "presumably" racemic arginine. Dr. Zaworotko made the same argument (Zaworotko affidavit at para 100).

[164] Apotex's experts relied heavily on the claims and the disclosure to testify that claim 1 cannot be limited to L-arginine. The disclosure makes the difference between arginine and L-arginine, making the latter a preference (Bastin affidavit at paras 283-284) and stating that the tests conducted were on l-arginine. On cross-examination, Dr. Byrn, Dr. Rodriguez-Hornedo and Dr. Evans all acknowledges that arginine takes different forms (L, D and racemic), all known at

the time. Dr. Rodriguez-Hordeno resisted the suggestion that "preferentially" must mean something (questions 561 to 574). In the end, she had to concede:

> 575 Q. How do you then explain the fact that the author of this patent indicated that L-arginine was but a preference?
>
> A. I think it's for the sake of clarity, so that the term is not ambiguous.
>
> Q. Well, does't the language on page 2 then tell us that the claim can cover more than the L-arginine, with l-arginine being the preference? That's the clarification.
>
> A. M'hm.
>
> 577 Q. Do you agree with that?
>
> A. Yeah, the way it's written.
>
> 578 Q. Thank you.

In my view, the position taken originally by the witness was difficult to maintain and Dr. Rodriguez-Hornedo had to concede in the end.

[165] The same can be said of the position taken by Dr. Byrn during his cross-examination. I reproduce in its entirety the portion of the cross-examination which deals with the preference for L-arginine expressed in the disclosure but not reproduced in the claims:

> 556 Q. What does the word preference mean to you?
>
> A. Preferred.
>
> 557 Q. Okay, for something to be preferred does there have to be a comparator?
>
> A. There should, there would be, yes.

558 Q. Okay, so in this case the L-arginine is said to be preferred over something necessarily, is that right?

A. It is saying it is preferred, correct.

559 Q. And the things it has to be preferred over in this sentence are the racemate or the D, is that right?

A. That is correct.

560 Q. Do you understand the difference being something being a preference as opposed to a requirement; do you have that understanding?

A. I have that understanding but I think this is of extremely strong preference; that is what I was trying to capture in paragraph 189 and 190.

561 Q. You understand the difference between an extremely strong preference and a requirement?

A. Of course, it is a gradation.

562 Q. Okay, and this patent does't speak to – it speaks to the L-arginine as being – even to take your words, an extremely strong preference, right?

A. I mean, I…

563 Q. Right?

A. Correct, because…

564 Q. Okay, Over…

A. …I had paragraphs 189 and 190.

565 Q. Over the other salts, the D and the racemate?

A. Correct.

566 Q. And when we get to Claim 1, it uses the language 'an arginine salt of perindopril', right?

A. Correct.

567 Q. Which is like the words we see at the start of the sentence on page 2 that we have looked at?

A. It is; those two words are the same.

[My emphasis.]

Whether the preference is extreme or simpliciter, the point of the matter is that the '825 Patent makes the difference between natural arginine and arginine writ large. And the necessary implication is that when using one the patentee knows the difference.

[166] Apotex took issue also with the meaning to be ascribed to “its hydrates” in claim 1. While Drs. Byrn, Rodriguez-Hornedo and Evans are of the view that a hydrate requires that there be incorporation of water, in the sense that the molecule picks up, or absorbs, water, Dr. Zaworotko seems to require that a hydrate must be a crystalline hydrate (Zaworotko affidavit at para 61). Mr. Bastin takes the same view at para 114 of his affidavit. Dr. Zaworotko argues that the water is incorporated in the crystal lattice. It is not disputed by the experts retained by Servier that a hydrate could be formed with water incorporated in the lattice of a crystal; it is rather that it is not the only form of hydrate. It does not have to be a hydrate as water incorporated in a compound that is not a crystal would be a hydrate.

[167] In my view the evidence of Dr. Rodriguez-Hornedo is the most cogent. Her affidavit recognizes the existence of a hydrate with a crystal lattice, but, “(a)lterntively, the term “hydrate” may also be used and understood to denote a compound that has picked up water from the surrounding environment” (para 77). She goes on to state how the amount of water can be measured in either case, for a crystal but also when it is not a crystal. Under cross-examination, the questioner, as he did with Dr. Byrn, repeatedly suggested that a hydrate was a crystal hydrate. Each time, Dre Rodriguez-Hornedo corrected the questioner. At Q. 330, there was again the

suggestion that a hydrate was crystalline. She was clear that "(a) hydrate need not be a crystal. Hydrate can be a solid that is or is not crystalline, and therefore water need or need not be part of that crystal lattice".

[168] Dr. Evans, who offered the same opinion on hydrates was asked on cross-examination on his affidavit if he had read the Byrn and Rodriguez-Hornedo affidavits prior to swearing in his own affidavit. Not only he had not read theses affidavits earlier, but at the time of his cross-examination, he still had not read them.

[169] There is no doubt that Dr. Zaworotko is an expert in crystals and crystallization. In fact, he dedicates 22 paragraphs of his affidavit on background information on crystals and crystallization. He equates hydrates in claim 1 with hydrated crystal forms at paragraph 101 of his affidavit. No one disputes that hydrates can take a crystal form. In fact, Dr. Byrn agreed many times during his cross-examination. It is just that there are other compounds that may absorb water.

[170] Finally, the '825 Patent does not signal in any way that the hydrates referred to have to have a crystal form.

[171] Counsel for Servier urged the Court to limit its construction of claim 1 to the words of the claim. The argument is to say that there is no ambiguity that would require a reference to the specification.

[172] I cannot agree with this argument. The simple fact that the claim speaks of "an arginine salt of perindopril", which Servier would like to read as the "L-arginine" salt, proves the existence of an ambiguity as it shows that the word is "able to be interpreted in more than one way", that it has "a double meaning … caused by inactness of expression" (the Canadian Oxford Dictionary). What may appear to be plain and unambiguous may not be. Here, the mere fact that words used are, in the view of some experts, to mean something other than the plain words in view of considerations falling outside the specification (easier approval of regulators, non-toxic, found in common foods and body, most economic variant of arginine), but also considerations coming directly from the disclosure ("preferentially" meaning that the patentee was considering exclusively L-arginine, and the testing was conducted solely on L-arginine), signals ambiguity that must be resolved through an examination of the disclosure.

[173] When the specification is considered in its entirety, it is inescapable that the patentee uses throughout the specification "the arginine salt of perindopril". Over the span of less than 3 pages (out of four), I was able to count eight times where the patentee speaks of "the arginine salt of perindopril" or "the arginine salt". More importantly, the patentee refers to L-arginine only twice. Each time, it is directly in relation, and in contradistinction, to the arginine salt of perindopril in the same sentence. In other words, the arginine salt of perindopril includes the salt of natural arginine, the L-arginine, but there are clearly other forms. Indeed, each expert acknowledged that the skilled person would know about the other forms of arginine.

[174] I reproduce the two sentences where the two are found together:

- The arginine salt of perindopril is preferentially the salt of natural arginine (L-arginine) ('825 Patent, p. 2).

- The arginine salt used in this study is the L-arginine salt ('825 Patent, p. 4).

There cannot be any doubt that the patentee made the difference between the salt of natural arginine and the arginine salt. The purposive construction of claims calls for finding the intent of the patentee. What are the boundaries the patentee wishes to put around the claimed invention, thus warning against trespassing on the property thus claimed.

[175] Furthermore, the patentee uses on two more occasions a "preference". Once where a preference for "immediate-release tablets" is identified and once where the amount of arginine salt is said to be "preferentially from 1 to 10 mg" (p. 2). In both cases, the claims refer back to the preference: once to claim the form of an immediate-release tablet (claim 3) and once to claim a pharmaceutical composition with 0.2 to 10 mg of the arginine salt of perindopril (claim 4). I draw two inferences from this. First, the inventor claims when he wants to what has been presented as preferential; second, the inventor also claims more than what has been identified as the preferential quantity of arginine salt. That makes this difficult to suggest that the inventor was not conscious of the use of "preferential". When he wants to claim, he does.

[176] As Lord Diplock put it in *Catnic*, the "Patent specification is a unilateral statement by the patentee, in words of his own choosing, addressed to those likely to have a practical interest in the subject matter of his invention (i.e. "skilled in the art"), by which he informs them what he claims to be the essential features of the new product or process for which the letters patent grant him a monopoly" (pp. 242-243). I have not been convinced that Servier used the broad,

expansive language with a view to limiting the scope of its claimed monopoly. Indeed the language of the patent and the evidence point in a different direction.

[177] Servier's experts defended the reading of claim 1 as being limited to L-arginine because that would be that to which a POSA would be thinking where seeing a reference to arginine, largely because it is formed in nature. The problem with that is that it does not account for the words used. As the Supreme Court stated in *Free World Trust*, "(t)he primacy of the claims language was already rooted deeply in our jurisprudence and should, I think, be affirmed again on this appeal" (at para 40). Servier's experts were in the end of little assistance to the Court. They refused for a time to acknowledge the words of the specification, relying instead on extrinsic considerations to read down the claims. A purposive construction of the claims requires an explanation for why a claim should be read more narrowly than has been written by the patentee to claim a monopoly. The cross-examination of Dr. Byrn and Dr. Rodriguez-Hornedo was indicative of a lack of explanation, scientific or otherwise. It is clear from these experts that if they had to practice the invention, they would go to L-arginine. This is perfectly understandable. But there was no explanation for why the patentee would monopolize only one form of arginine, unless there was a mistake, leaving open the possibility that other forms of arginine could be used.

[178] I wondered aloud during the hearing of this case if the use of "arginine salt of perindopril", instead of "the salt of natural arginine" could have been an error, perhaps an egregious error. Servier would not concede that it would be such an error. It took the position that "arginine salt of perindopril" in claim 1 is unambiguous and meant "L-arginine" the natural

form of arginine. Thus, there was no need to resort to the rest of the specification and explain away the two sentences reproduced at para 174. With respect there is ambiguity. At any rate, the Court cannot redraft the claims. In *Eli Lilly & Co. v O'Hara Manufacturing Ltd.* (1989), 26 CPR (3^{rd}) 1, the Federal Court of Appeal considered that the words used by the patentee must be taken to have significance. Pratte J.A., for the Court, wrote:

> 20. … A court must interpret the claims; it cannot redraft them. When an inventor has clearly stated in the claims that he considered a requirement as essential to his invention, a court cannot decide otherwise for the sole reason that he was mistaken. …

Where the inventor explicitly stipulates that it is the arginine salt that he wishes to monopolize, a court has to give effect. In *Free World Trust*, we read:

> 51 This point is addressed more particularly in *Whirlpool Corp. v. Camco Inc.*, [2000] 2 S.C.R. 1067, 2000 SCC 67 (CanLII) and *Whirlpool Corp. v. Maytag Corp.*, [2000] 2 S.C.R. 1116, 2000 SCC 68 (CanLII), released concurrently. The involvement in claims construction of the skilled addressee holds out to the patentee the comfort that the claims will be read in light of the knowledge provided to the court by expert evidence on the technical meaning of the terms and concepts used in the claims. The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used *provided* the words used are interpreted fairly and knowledgeably.
>
> [Italics in original.]

[179] Accordingly, the Court concludes that claim 1 of the '825 Patent must claim the arginine salt of perindopril, and not only its natural form. There is simply no evidence leading in a

different direction. The inventor's intention was to claim the arginine salt. He knew the difference with L-arginine. As for "its hydrates", the Court concludes that they are not limited to crystal hydrates. For a hydrate to occur, the molecule of water is removed from the environment: the hydrate incorporates the water according to the evidence. The water does not stay on the surface. I agree that there is nothing in the disclosure that would suggest a different definition of a hydrate.

IX. Analysis

[180] A number of grounds were advanced by Apotex in support of its allegation that the '825 Patent is invalid: they are obviousness, sufficiency, overbreadth, utility and double-patenting. Anticipation, which had been announced in its Notice of Allegation, was abandoned and will not be addressed by the Court.

[181] Some of those grounds of invalidity can be dealt with more easily and summarily. The Court will deal with them first. There is utility to the '825 Patent and the disclosure is sufficient for the person of skill to practice the Patent. On the other hand, '825 suffers from overbreadth and, while there may have been originally a creative spark when a small amount of perindopril arginine salt was synthesized in 1984, and was found to be more stable than perindopril erbumine later by April 18, 2002 (the priority date), the preponderance of the evidence on this record in this case is that the advancements in salt forming were such that, for the arginine salt of perindopril, the skilled person equipped with the common general knowledge, and considering the prior art in accordance with Canadian Patent Law, would have arrived at a solution for a

better stability of the API. The information available to the public in Canada and elsewhere made obvious the subject matter and inventive concept defined by claim 1.

A. Utility

[182] It is no great secret that for an invention to exist, it must be useful art or useful improvement in any art (s. 2 of the Act).

[183] Recently, the Supreme Court of Canada addressed squarely the issue of utility in *AstraZeneca Canada Inc. v Apotex Inc.*, 2017 SCC 36, [2017] 1 SCR 943 [*AstraZeneca*]:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2, courts should undertake the following analysis. First, courts must identify the subject-matter of the invention as claimed in the patent. Second, courts must ask whether that subject-matter is useful — is it capable of a practical purpose (i.e. an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized — a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (*AZT*, at para. 56).

[184] Thus, a scintilla of utility suffices, as long as it is related to the nature of the subject matter. At least as far back as 1982, the Supreme Court agreed that unrecognized properties of known compounds can be the subject matter of a patent (*Shell Oil Co. v Commissioner of Patents*, [1982] 2 SCR 536) [*Shell*]. The invention in that case was described as "the surprising discovery that compounds having a specific chemical structure have useful properties in respect of the regulation of the growth of plants" (p. 538).

The *Shell* Court found, at page 549:

> I think the word "art" in the context of the definition must be given its general connotation of "learning" or "knowledge" as commonly used in expressions such as "the state of the art" or "the prior art". The appellant's discovery in this case has added to the cumulative wisdom on the subject of these compounds by a recognition of their hitherto unrecognized properties and it has established the method whereby these properties may be realized through practical application. In my view, this constitutes a "new and useful art" and the compositions are the practical embodiment of the new knowledge.

The Court had no difficulty establishing the difference with *Commissioner of Patents v Farbwerke Hoechst Aktiengesellschaft Vormals Meister Lucius & Bruning*, [1964] SCR 49 where the "invention" was anti-diabetic composition consisting of anti-diabetic compounds diluted by a carrier. There was nothing new and useful since the patentee already had a patent for the compound. As the Court said, "the addition of an inert carrier, which is a common excipient to increase bulk, and so facilitate measurement and administration, is nothing more than dilution and does not result in a further invention over and above that of the medicinal itself" (p. 53).

[185] *Wellcome Foundation* (*Apotex Inc. v Wellcome Foundation Ltd*., 2002 SCC 77, [2002] 4 SCR 153 [*Wellcome Foundation*]) goes in the same vein. Was ruled to be patentably distinct the new use of a compound that was not novel. There was evidently a use for the old compound. In the case at bar, we are dealing with a new compound, not an old one for which a new use was discovered, the arginine salt of perindopril and its salts. The salt was found for the express purpose of reducing the instability to heat and humidity compared to the pharmaceutical product already marketed by Servier. The specification could hardly have been more explicit and the results of the test displayed at page 4 of '825 leave no doubt that there was more than a scintilla

of utility as the arginine salt of perindopril does not degrade at 30ºC and relative humidity of 60 %, and even more so at 40ºC and relative humidity of 75 % (after 6 months). According to the study featured in the '825 Patent, after six months at 40ºC and relative humidity of 75 %, the perindopril erbumine had degraded by some 33 % while the arginine salt of perindopril had barely degraded. The greater stability translates into less onerous constraints in terms of packaging. As the Supreme Court put it in *Teva Canada Ltd. v Pfizer Canada Inc.*, 2012 SCC 60, [2012] 3 SCR 625 [*Teva*], "(u)tility can be demonstrated by, for example, conducting tests, but this does not mean that there is a separate requirement for the disclosure of utility" (para 40). Here, the '825 Patent discloses tests as was done in *Teva:*

> [41] In any event, Pfizer disclosed the utility of sildenafil by disclosing that tests had been conducted. Sildenafil was found to be useful before the priority date, which means that the requirement in *AZT* is met. Further, "[e]vidence as to utility may be found in the reception of the invention by the public. Enthusiastic reception by those to whom it is directed will tend to indicate that the invention is useful": Perry and Currier, at §7.12.

[186] Given that the subject matter of claim 1 is an arginine salt of perindopril and its hydrates, its utility must be established, but a single use, capable of a practical purpose, what the Supreme Court designated in *AstraZeneca* as "an actual result" (para 54), has been amply shown. The invention is not speculative, fanciful or inoperative. The evidence of utility was uncontradicted.

[187] Claims 2, 3, 4 and 5, which relate back to the arginine salt of perindopril and its hydrates do therefore have utility. Claim 2 adds excipients; claim 3 presents the pharmaceutical composition in the form of immediate release tablets; claim 4 makes claim 2 and 3 with 0.2 to 10

mg of arginine salt of perindopril; claim 5 makes arginine salt of perindopril and its hydrates useful for the treatment of hypertension and heart failure. As a result, every claim is useful.

[188] Apotex's assertion on utility is not easy to follow. The very point of the invention is to allow the use of perindopril without the constraints of special packaging. In its Memorandum of fact and law, Apotex contends that the difference in stability between perindopril arginine and perindopril erbumine "is dependent on the conditions of the test. Apotex's testing showed that, in the proposed packaging for storage of the bulk materials, perindopril erbumine and perindopril arginine had equivalent stability" (para 84). However, Apotex's testing was done using sealed and protective packaging which is designed to avoid degradation in heat and high relative humidity. Dr. Byrn described the packaging thus at paragraph 295 of his affidavit:

> 295 I note that Apotex's testing was carried out on the API for the *tert*-butylamine and the arginine salts of perindopril, and not on tablets containing these perindopril salts. This is consistent with the containers used. The perindopril *tert*-butylamine was stored in polyethylene/poly-foil bags contained in a mini fibre drum, and the L-arginine salt of perindopril was packed in an inner antistatic polyethylene bag sealed with a cable tie encased within a heat sealed aluminum foil composite outer bag under nitrogen within an HDPE container. These types of packaging are those used for bulk storage of API at a warehouse.
>
> [Italics in original.]

One would have thought that such testing defeats the purpose of testing for high heat and high humidity if the product is to be protected against heat and humidity, in order to avoid degradation. For its sole defence, Apotex claims that its testing used standard protocols which "dictate that testing must be conducted in the proposed packaging" (Memorandum of fact and law, para 85). But the point of the matter was that the new product would not need very special

packaging, what has been called the "tropicalized variety". In support of that statement, Apotex offers paragraph 413 of Mr. Bastin who concludes therein:

> 413. … However, based on the information provided in the Damien Affidavit, the instability observed in perindopril *tert*-butylamine tablets is not caused by any interaction with excipients. Rather, in certain forms of packaging, *tert*-butylamine is lost from the formulation when stored at higher temperatures. This instability is caused by the volatility of *tert*-butylamine. As I have discussed, the stability tests conducted by Apotex show that, under standard stability conditions, perindopril *tert*-butylamine and perindopril arginine API have equivalent stability in standard commercial packaging. If differences in stability are observed in other forms of packaging (whether as API or a formulated product), this shows that any improvement in stability is dependent on the packaging used.
>
> [Italics in original.]

That is the point that is indeed driven home by the further testing conducted by Mr. Damien and discussed at some length by Dr. Byrn at paragraphs 291 to 297 of his affidavit. I accept his evidence, which is completely consistent with that of Dr. Evans and Dr. Rodriguez-Hornedo. The utility of the '825 Patent is in my view unassailable on the record before the Court. Servier quipped during its presentation on utility that Apotex wants to sell the invention of claim 1. It must be because it has at least a scintilla of utility. That was perhaps having in mind paragraph 41 of *Teva* (reproduced at para 185 of the reasons) where the Supreme Court accepts the view of Perry and Currier that "(e)nthusiastic reception by those to whom it is directed will tend to indicate that the invention is useful". At any rate, even without the "enthusiastic reception", the utility of the invention was established on a balance of probabilities.

B. Sufficiency

[189] Apotex contends that the '825 Patent is invalid for insufficiency. The Act requires, at subsection 27(3), that the patentee disclose the invention for which a monopoly is granted by law for a period of time (s. 44 of the Act for a patent filed on or after October 1, 1989). Subsection 27(3) reads:

(3) The specification of an invention must	**(3)** Le mémoire descriptif doit:
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	**a)** décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
(b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;	**b)** exposer clairement les diverses phases d'un procédé, ou le mode de construction, de confection, de composition ou d'utilisation d'une machine, d'un objet manufacturé ou d'un composé de matières, dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l'art ou la science dont relève l'invention, ou dans l'art ou la science qui s'en rapproche le plus, de confectionner, construire, composer ou utiliser l'invention;
(c) in the case of a machine, explain the principle of the machine and the best mode in which the inventor has contemplated the application of that principle; and	**c)** s'il s'agit d'une machine, en expliquer clairement le principe et la meilleure manière dont son inventeur en a conçu l'application;

(d) in the case of a process, explain the necessary sequence, if any, of the various steps, so as to distinguish the invention from other inventions**.**	**d)** s'il s'agit d'un procédé, expliquer la suite nécessaire, le cas échéant, des diverses phases du procédé, de façon à distinguer l'invention en cause d'autres inventions

As can be seen, the disclosure requirement is made more stringent in the case of a machine where the Act calls for "the best mode in which the inventor has contemplated the application of that principle". The "best mode" requirement is not present for other types of invention, including obviously a pharmaceutical patent.

[190] The disclosure requirement stems from the grand bargain at the heart of our patent system: in exchange for a valuable monopoly, the inventor discloses the invention. There exists a long list of statements where the proposition is articulated. The Supreme Court in *Teva* (*supra*), referring to *Wellcome Foundation* (*supra*), described again the *quid pro quo* recently:

> [32] The patent system is based on a "bargain", or *quid pro quo*: the inventor is granted exclusive rights in a new and useful invention for a limited period in exchange for disclosure of the invention so that society can benefit from this knowledge. This is the basic policy rationale underlying the Act. The patent bargain encourages innovation and advances science and technology. Binnie J. explained the *quid pro quo* as follows in *AZT*, at para. 37:
>
> > A patent, as has been said many times, is not intended as an accolade or civic award for ingenuity. It is a method by which inventive solutions to practical problems are coaxed into the public domain by the promise of a limited monopoly for a limited time. Disclosure is the *quid pro quo* for valuable proprietary rights to exclusivity which are entirely the statutory creature of the *Patent Act*.
> >
> > [Italics in original.]

[191] However, the required disclosure is not that which will make the ordinary person on the street "get it". It is rather to the skilled person to whom the patent is addressed is the person who will benefit from the disclosure that will be found in the specification. In *Consolboard* (*supra*), the Court endorsed this passage from Lord Halsbury in *Tubes, Ld. v Perfecta Seamless Steel Tube Company, Ld.* (1902), 20 RPC 77, at pages 95-96:

> … if one has to look at first principles and see what the meaning of a Specification is … why is a Specification necessary? It is a bargain between the State and the inventor: the State says, "If you will tell what your invention is and if you will publish that invention in such a form and in such a way as to enable the public to get the benefit of it, you shall have a monopoly of that invention for a period of fourteen years." That is the bargain. The meaning which I think, in my view of the Patent Law, has always been placed on the object and purpose of a Specification is that it is to enable, not anybody, but a reasonably well informed artisan dealing with a subject-matter with which he is familiar, to make the thing, so as to make it available for the public at the end of the protected period.
>
> [Emphasis in the original.]

The same passage was quoted in *Teva*. But adequate disclosure must be a pre-requisite to having a valid patent if the bargain is to have any meaning.

[192] It follows that the adequate disclosure will allow a person skilled in the art, equipped with the common general knowledge, to produce the invention. On the other hand, what is asked of the skilled person in this case is not to come up with a product that will have a better stability than the perindopril erbumine. That was the business of the inventor. Rather, the point is that the skilled person must be able to produce the arginine salt of perindopril using the Patent in suit. With the specification in hands, will the skilled person know what the invention is and "(t)he description must be such as to enable a person skilled in the art or the field of the invention to

produce it using only the instructions contained in the disclosure" (*Pioneer Hi-Bred Ltd. v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 [*Pioneer Hi-Bred*], at p. 1638).

[193] As already pointed out, the matter must be approached with a mind willing to understand. Apotex argues that '825 does not sufficiently teach how to make perindopril arginine. Referring to the Patent Rules, it reminds the Court that the description must set forth at least one mode for carrying out the invention. In fact, the Patent states, at page 4, that the arginine salt "has been prepared according to a classical method of salification of organic chemistry". Servier says that the person skilled will know what to do based on that reference in '825. Apotex disagrees.

[194] Apotex relies to some extent on the Australian case which considered the equivalent Australian patent to the Canadian '825 Patent (*Apotex Pty Ltd. v Servier Laboratories (Aust) Pty Ltd.*, *supra*). The difficulty with relying on a foreign case is of course that their legal requirements may very well be different from Canadian requirements. For instance, Australia appears to be interested in Australian prior art while section 28.3, with respect to obviousness, speaks of information that "became available to the public in Canada or elsewhere". As for disclosure, Australian law requires that the best method be described in the specification, a requirement that is not unknown to Canadian patent law but that exists only with respect to a machine (para 27(3)(c) of the Act).

[195] It is therefore in a very particular context in which the Australian case must be considered. At the hearing, Apotex referred specifically to paragraph 179:

> 179. I am of opinion that the expert evidence revealed that the mere reference to utilising a classical method of salification was

> wholly inadequate to describe the best method, or any substantive content of any particular classical method that the patentee knew of performing the invention. The generalised and unspecific description of the method in the complete specification left too much to chance for a skilled addressee to select from in order to perform the invention. While the patentee need not disclose the best method of *making* an article provided that the complete specification describes its design, and hence performance, the patent for an article ordinarily will illustrate and provide detail of that design from which a skilled addressee will be able to deduce how to manufacture the invention: *Firebelt* 51 IPR at 544 [49]-[50]. The bare description "a classical method of salification" does not allow the skilled addressee to follow a routine process of deduction from that description because it leaves open too many variables.
>
> [Italics in original.]

However, the colour of this paragraph is better revealed when it is read in context. For that purpose, I reproduce paragraphs 178 and 180 of the Australian decision. They show, in my view, that the Australian Federal Court was concerned that the mere reference in the Patent to a classical method of salification could not satisfy the test of the "best method".

> 178. I do not accept Servier's arguments that, *first*, the complete specification described the best method of performing the invention known to it simply because it referred to preparation using a classical method of salification and, *secondly*, the opinion of the six experts that the variety of choice as to methods parameters available to a skilled addressee for selection classical salification was merely a hypothetical, but unproven, lacuna in the disclosure made in the complete specification of the best method.
>
> 180. Servier's argument was that because the patentee disclosed in the complete specification a method of performing the invention and that method, by its generality, included both of the actual methods it used in 1986 and 1991, Apotex had the onus of proving that those methods were better than the general one. That argument was syllogistic. <u>The mere fact that a complete specification described a method for performing the invention so that sufficient information was conveyed to a skilled addressee to enable him or her to work it, does not necessarily satisfy the patentee's additional obligation to describe the best method he, she or it knows</u>. Mr Damien did not know, and was indifferent to, whether the 1986

> or 1991 methods created a hydrate or not. But he did know that, those methods created the arginine salt in a useable form, and as a person skilled in the art, he knew that there were many alternatives available from which to choose and that some were likely not to be as good as others.
>
> [Italics in original and my emphasis.]

That made Justice Rares conclude that "the very general description of one method (classical) of salification that itself afforded many possible means of performance that could involve considerable trial and error is not the same as a description of the best method that Servier knew" (para 182). Servier could have done better, and did not. But such is not the test under Canadian Patent Law.

[196] The other argument offered by Apotex is that the method actually used by Servier involved freeze drying an aqueous solution (lyophilisation); that method, say Apotex experts, is not a classical method of salification.

[197] Thus, the issue is to determine if the description enables the skilled person to produce this invention (*Pioneer Hi-Bred*, (*supra*)). The Federal Court of Appeal has found in *Teva Canada Limited v Leo Pharma Inc.*, 2017 FCA 50 that the sufficiency of the disclosure is to be measured by "what the skilled person would consider sufficient to enable it to work the invention" (para 44), a question of fact to be resolved with the assistance of experts in the field. Moreover, the Court of Appeal decided that limited testing is permitted (para 59), as "some non-inventive trial and error may be required to put a properly disclosed invention into practice" (para 59). The same view was asserted again in *Bombardier Recreational Products Inc. v Arctic Cat, Inc.*, 2018

FCA 172, at paras 78 to 80: “A disclosure will still be enabling if it does not require undue efforts” (para 78).

[198] Turning to the expert evidence in this case, I accept the evidence of the Servier experts that using a classical method of salification will require some trial and error, but it does not fall in the category of undue efforts.

[199] Dr. Zaworotko did not seem to encounter much difficulty in identifying a classical method (affidavit at para 91). As for lyophilisation, he expressed some surprise (at para 115) and would not consider it to be a classical technique to isolate a salt or for crystallisation. Mr. Bastin expressed a similar view: the method described by Mr. Damien (in his exhibit GD-4) would not be a classical method. Under cross-examination, he explained why, but also indicated what in his view would be a classical method. At pages 163, 164 and 165 of the cross-examination, we read:

> Q. Okay. Let’s have a look at paragraph 363. Could you have a look at the patent that you’re discussing in your paragraph 363, please? This is US Patent No. 4,425,355.
>
> A. Yes, okay.
>
> Q. I need you to pull that for us.
>
> A. Do you know what number that is? DR. CHONG: Yes. It’s number 6.
>
> **THE WITNESS**: Number 6. Yes, Okay. I have it.
>
> BY MR. DALEY:
>
> Q. Okay. And I want you to go to the top of the patent and confirm for me that this patent was issued in 1984.
>
> A. Yeah.

Q. Now, if you could turn to column 7 and read the entire paragraph that begins on 21 - -

A. Claim 7, did you say?

Q. Colum 7.

A. Colum 7.

Q. Line 21. I'll read it out to you. "The salts are formed in conventional manner by reacting the free acid form of the product with one or more equivalents of the appropriate base providing the desired cation in a solvent or medium in which the salt is insoluble, or in water and removing the water by freeze drying". Do you see that?

A. Yes.

Q. Freeze drying is another way of saying by lyophilization?

A. Yes.

Q. Does this suggest to you that lyophilization was considered to be a conventional method of salification at the time this patent was drafted?

A. No.

Q. Why not?

A. Because it is a quick technique for isolating salts that will give you some output but it would not give you material with typical properties. So people would prefer to use a conventional method of re-crystallization which would be a re-crystallization from a solvent system.

Q. You nonetheless accept that the inventors used the term "conventional method" when mentioning lyophilization. Correct?

A. Well, I would just say, in terms of what is conventional, are you referring to the dissolving of the salt and counter ion to form a salt in solution or is conventional that plus how you isolate the salt form from that solution? So I would not say that - - lyophilization is a method of preparing salts and for a drug to go in a product would not be a conventional method. I know, from my experience, people preparing salts for a patent often lyophilize them. It's a very quick way of preparing different forms with relatively low effort.

> Q. Okay. And that's something that they might have done as early as 1984, according to this patent. Is that right?
>
> A. Yes, possibly, yes.
>
> [My emphasis.]

Not only lyophilisation was known to form salts in 1984, but there would also be the method presented as the "solvent system". After all, what '825 was stating is that, once perindopril arginine has been "invented", all that the person of skill has to do is practice the invention using a classical method of salification. It appears that the mind willing to understand would know about lyophilisation and solvent method.

[200] But Mr. Bastin was pushed further on cross-examination. At page 166, Mr. Bastin states without hesitation that "a POSA should know how to make perindopril arginine without undue effort". The following pages confirm that once you know where you are going, the person of skill will get there without much effort.

[201] That is consonant with the views expressed by the experts retained by Servier. Dr. Byrn states that making the L-arginine salt of perindopril is a simple exercise for the skilled person. He explains in details what a classical method of salification would be, including that "one such method is to mix equimolar amounts of the pharmaceutical compound (perindopril) and the salt former (L-arginine) in a common solvent (typically water or a mixture of water and an organic solvent), and either cool the solution to evaporate the solution to allow crystals to form" (para 259). These are routine exercises that the skilled person learns as an undergraduate. I note that Dr. Byrn goes on to explain how a tablet would be formulated (paras 264 to 269).

[202] Dr. Evans reached the same conclusion as did Dr. Byrn. He describes the same method at paragraph 162 of his affidavit where the liquid evaporates until the solid precipitates. His views on formulation are similar. It should be noted that Dr. Evans disagreed with Dr. Zaworotko, in his reply affidavit, about his suggestion that freeze drying (lyophilisation) is not a classical technique for salification. A difference must be made between "isolating a salt" and "crystalizing a salt": they are not one and the same. Having noted that the freeze drying issue had not even been alleged in the Apotex NOA (which would explain why it was not addressed originally), he goes on to state:

> 21 To be clear, while I agree that freeze drying is not a standard method of crystallization, freeze drying is a standard method of isolating salts, and was among the salt isolation techniques known to the POSA prior to April 18, 2002. As a pharmaceutical scientist I have used freeze drying (and evaporation under vacuum) as efficient method of isolating salts in the laboratory and am aware that others in the field were doing so prior to 2002.
>
> 23 Both freeze drying and evaporation involve the removal of water to yield a more pure material, usually in solid form. The POSA would know that freeze drying may be more suited to organic drug molecules that may be temperature sensitive as evaporative methods may require the use of elevated temperatures that could degrade the drug.

[203] The affidavit of Dr. Rodriguez-Hornedo was equally impressive on this issue. She too refers to collecting the salt that precipitates (para 243). I note in particular her observations on the formulation of tablets:

> 252. To ensure that the only variable in the comparative stability study is the salt of perindopril used, the POSA would formulate tablets containing the L-arginine salt of perindopril using the same excipients in the same quantities as those containing the *tert*-butylamine salt. Therefore, the POSA would reduce the weight of the filler, lactose monohydrate, by a total of 0.4 mg to account for the increased weight of the L-arginine salt, which is due to the

> difference in molecular weight caused by the heavier L-arginine. A POSA would know that such a small adjustment to the quantity of the fillers would not affect the characteristics of the tablet.
>
> [Italics in original.]

[204] I have accepted that the method used to obtain the evidence of the experts was appropriate. There is no evidence that they have consulted each other in arriving at the view they have expressed. The evidence of the Servier experts is consistent among them. The classical method of salification of organic chemistry referred to a method well known by the person of skill. Furthermore, with the explanation provided by Dr. Evans about freeze drying not being a standard method of crystallization, there may not even be any day-light between Dr. Zaworotko and the experts retained by Servier. Finally, Mr. Bastin agreed that once one knows where she is going, she will get there without much effort. The real difference has to do whether there was a need for an inventive concept to arrive at the invention of perindopril arginine, not how that salt is produced. Accordingly, the disclosure in the '825 Patent is not insufficient. The allegation is not justified on this record.

C. Overbreadth

[205] The principle is simple enough on its face. A patent cannot validly claim more than has been invented. The claims may not be broader than the invention (*Schering-Plough Canada Inc. v Pharmascience Inc.*, 2009 FC 1128). As usual, Professor Vaver captures in a few words what is at stake in his *Intellectual Property Law*, Irwin Law, 2nd Edition (2011):

> The game for patent holders, especially in highly competitive industries, is to reveal as little and to claim as much as possible. The less disclosed, the more that can be retained as competitive edge. The wider one claims, the tougher it is for imitators and

> competitors. But the specification must stay clear of the known and the obvious. It must demonstrate and claim only something over and above existing technology. Much patent drafting involves trying simultaneously to achieve these aims. Along the way several obstacles must be avoided, lest the claims or the whole patent end up invalid.
>
> [p. 346]

The '825 discloses little, but, as already found, in my view it discloses enough. But the patent holder claimed as much as possible by claiming the arginine salt of perindopril and its hydrates and not only the salt of natural arginine. In so doing claim 1 is accused of being broader than the invention, as are the other four since they are dependent on claim 1; they incorporate the arginine salt of perindopril and its hydrates in every claim.

[206] Apotex challenges the validity of the '825 on the ground that its claims are broader of the invention in two aspects: first, Servier claimed the arginine salt of perindopril, which includes the D-arginine and the racemate arginine salt of perindopril; second, Servier claimed the hydrates of perindopril arginine. In both cases, Apotex argues that there is no evidence in this whole record that Servier made the D-arginine or the racemate arginine salt of perindopril or that Servier made a hydrate of perindopril arginine.

[207] If either one of those obligations is accepted, it will be fatal to the validity of '825.

(1) Arginine salt of perindopril

[208] The dilemma to which Prof. Vaver referred is often present in patent drafting. An inventor can claim a monopoly or less than has been invented, or everything new, ingenious or

useful that has been disclosed in the specification. As Binnie J. put it in *Whirlpool*, "(t)he usual rule is that what is not claimed is considered disclaimed" (para 42).

[209] In the case at bar, the claims construction revealed that the patentee chose to claim as much as possible, knowing that there existed other forms of arginine. The patentee expresses a preference for the salt of natural arginine, the L-arginine ('825 Patent, p. 2) and is specific that the "arginine salt used in this study is the L-arginine salt" ('825 Patent, p. 4). The claims construction can only lead, in my view, to the conclusion that the five claims refer to arginine: L, its natural form, D and the racemic arginine salt of perindopril. That is what was claimed.

[210] The experts retained by Servier did not elaborate very much in answering their sixth mandate dedicated to overbreadth. That is probably because they relied on their view of claim 1 in their claims construction.

(a) *Dr. Byrn*

[211] In his expert report, Dr. Byrn indicates that "Pasteur determined that the salt came in two forms – dextrorotatory and levorotary (or "D" and "L")" (para 185). At paragraphs 189 and 190, he explains his preference for the "L" configuration:

> 189 The POSA would know that arginine is a naturally occurring amino acid and that it exists in the body in the "L" configuration. The POSA would know that the L-arginine, being a natural amino acid and existing in the body, is not toxic. Upon reading Claim 1, the POSA would understand that the claim pertains to the L-arginine stereoisomer.
>
> 190 The "D" stereoisomer is not a naturally occurring amino acid. This would reinforce for the POSA that the L-arginine salt of perindopril is what Claim 1 pertains to. The POSA would also

> understand that L-arginine is the most economical variant as it can be readily obtained from natural sources.

Far from denying the existence of “D” or a mixture of “D” and “L”, he makes the preference for “L” found in the specification to be an argument that the skilled person would read the claims as claiming less than what appears on the page. In effect, claim 1 is limited to the “L” configuration because it is a natural amino acid and it exists in the body, not because it is the only form of arginine.

(b) *Dr. Evans*

[212] Dr. Evans follows the same approach. Having found that claim 1 refers to L-arginine, he readily concludes that what was invented, the L-arginine salt of perindopril, is what was claimed, (Evans affidavit at paras 183 to 185). Since the testing was conducted on the L-arginine salt of perindopril, the argument goes, the patentee must have claimed only L-arginine.

[213] The reasoning for limiting the claims to L-arginine is somewhat puzzling. The patentee would have limited his monopoly because the naturally occurring form of arginine would make the approval by regulatory agencies easier (para 152). However, there is nothing that would prevent a patentee from marketing the L-arginine salt once the monopoly over L, D and the racemate has been obtained. Also puzzling is the argument that the disclosure speaks of a preference for L-arginine and the studies conducted on stability were done on L-arginine. No explanations are offered for having stated that is claimed an arginine salt of perindopril, not the L-arginine which is recognized by the expert as being one configuration. Indeed, he contends that the skilled person would recognize only L-arginine for some chemistry reason (para 154).

But again, this expert conflates the monopoly as claimed with what he considers to be "a mixture of salts without uniform properties … undesirable from both a production and a regulatory perspective" (para 154).

(c) *Dr. Rodriguez-Hornedo*

[214] As with respect to her two colleagues, the overbreadth issue is quickly disposed of if one accepts that the claims are limited to L-arginine as the "POSA would understand this to mean that this salt has been synthetized by the inventors" (para 259). For Dr. Rodriguez-Hornedo, the understanding of the skilled person that the claims are limited to L-arginine stems from the fact that L-arginine "is the naturally occurring form of arginine that is found in common foods" (para 147). She also contends that naturally occurring compounds receive approval from regulators more easily. Finally, she too found support on the reference in '825 to L-arginine as a preference and having been used for testing.

[215] As I have tried to show in the section of these reasons dealing with claims construction, claim 1 is ambiguous and there is a need to resort to the disclosure. Counsel was urging the Court to be satisfied with the evidence of its experts. From the moment one has to argue that the words have to mean something else, a sub-set of the category, it seems to me that there is ambiguity. As can be seen, these experts relied in fact on the disclosure to support their view that the skilled person would understand that the patentee intended to claim only L-arginine in spite of what is stated in claim 1. They have to rely on the disclosure because, on its face, claim 1 claims as much as can be by making the arginine salt of perindopril the claimed invention. These experts know of the other possible configurations. In order to contend that the arginine salt of

claim 1 is the L-arginine configuration, they have little choice but to seek to find support in the disclosure or explain a choice that is not self-evident. The argument that it is inappropriate to consider the disclosure cannot be sustained.

[216] But relying on the disclosure poses its own challenges. That is because the disclosure refers to L-arginine for limited purposes, which cannot be ignored. In fact, the justification presented by the experts for their limitation of the monopoly sought to L-arginine offers considerations that the Court finds not particularly relevant. To say that the inventor, in spite of the words chosen to define the fence he creates around his invention, would have meant something narrower because of the availability of L-arginine and regulatory concerns is less than convincing.

[217] The argument seems to be that the claims should be under-read because the disclosure neglects to address the other configurations which would have the effect of turning the proposition on its head: the claims are to be under-read in order to meet the invention that has been otherwise presented as being “preferentially” L-arginine. In a somewhat bootstrapping effort, Servier seeks in effect to limit *ex post facto* its claimed monopoly to that which has been presented as a preference. Moreover, the disclosure says what it says: a preference is expressed for L-arginine. It does not say “preferably” but rather “preferentially”. That necessarily implied the existence of other configurations. When read in a purposive way, the inventor’s intention appears to be to protect against the use of arginine in its other configurations. The protection was for the arginine salt which had been found to have properties that improved the stability of perindopril. An analogy with the '196 Patent may perhaps be apposite. In '196, it was perindopril

that was the invention and, as pointed out by Servier's counsel, it would have been ridiculous to monopolize perindopril for that monopoly to be for naught as soon as a salt of perindopril was to be found. Thus, the protection was for perindopril and its pharmaceutically acceptable salts. Here, what good is it to be granted a monopoly for L-arginine if there are other configurations that may be synthesized during the length of the statutory monopoly? Surely Professor Vaver has a point when he says that "(t)he wider one claims, the tougher it is for imitators and competitors" (Vaver, *supra* at p. 346).

[218] The Supreme Court in *Free World Trust* did not do away with the language of the claims (para 31 and 40). On the contrary, it noted at paragraph 51 that "(t)he involvement in claims construction of the skilled addressee holds out to the patentee the comfort that the claims will be read in light of the knowledge provided to the court by expert evidence on the technical meaning of the terms and concepts used in the claims". Here, the skilled person would have recognized that there exist other configurations of arginine: we know from their expertise that the technical meaning of arginine includes many configurations. That preference is based on the presence of arginine in nature (the *Merck Index* refers to L-arginine under its reference to arginine in one of its catalogs), the approval from regulators that would be made easier and the fact that the invention has expressed a preference for L-arginine and has tested L-arginine for stability.

[219] One is hard pressed to explain how the easier acceptance by regulators can help define the scope of a claim for monopoly. As for the existence of L-arginine in nature, that makes the configuration attractive for commercial purposes initially, but that does not protect against imitations and competitors who may find an incentive to develop other configurations if they are

not fenced out. It is equally difficult to accept that a mere preference expressed in the disclosure, which has translated into the only testing conducted on the natural form of L-arginine, can be turned into the only form of arginine monopolized: the tail does not wag the dog. The less tortured evidence of Mr. Bastin is in my view more convincing. He notes that claim 1 of '825 is not limited to L-arginine as the skilled person would know of D and racemic arginine. Because the disclosure states a preference for the salt of natural arginine, "the use of "arginine" in claim 1was not intended to be limited to L-arginine only" (Bastin affidavit at para 269). In the view of Mr. Bastin, "claim 1 would be understood by the skilled person to encompass perindopril salts prepared with L-arginine, D-arginine and racemic arginine". Because the only invention made by the patentee was L-arginine, the patentee should not have included other arginine salts in its claims. But they did.

[220] The Court does not re-write claims: it interprets them (*O'Hara*). Unfortunately for the patentee, if claiming arginine was a mistake, this is not a mistake that can be corrected by the Court on the basis of a preference expressed by experts on bases that are largely irrelevant to defining the scope of the monopoly claimed. The Court takes it that "if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used provided the words used are interpreted fairly and knowledgeably" (Free World Trust, *supra*, para 51).

[221] I do not mean to suggest that a mistake was made in claim 1. Indeed, as indicated earlier, counsel for Servier took the position that the claims are not ambiguous in spite of the clear reference to arginine, as opposed to L-arginine. That was probably the only way to avoid a

reference to the disclosure which, from the Servier point of view, can be problematic. As I have pointed out before, all the experts agree that arginine encompasses L, D and racemic arginine which makes the use of "arginine salt of perindopril" an ambiguous expression, if one tries to limit it to one configuration. In fact, claim 1 is not ambiguous if it is acknowledged that it encompasses the three. It is rather that, as said by Professor Vaver, one claims as much as possible. The purpose of the inventor was to claim arginine salt of perindopril as its invention. That was the fence, the boundary. In *Minerals Separation North American Corporation v Noranda Mines Limited* (1947) Ex. C.R. 306, President Thorson wrote:

> By his claims the inventor puts fences around the fields of his monopoly and warns the public against trespassing on his property. His fences must be clearly placed in order to give the necessary warning and he must not fence in any property that is not his own. The terms of a claim must be free from avoidable ambiguity or obscurity and must not be flexible; they must be clear and precise so that the public will be able to know not only where it must not trespass but also where it may safely go.
>
> [p. 352]

The burden was on Servier to satisfy the Court that the claims are not broader than the invention in order for the allegation made by Apotex to be unjustified. It has not been successful. In my view, the claims are clear examples of "overclaiming". Justice Harrington famously said in *Biovail Pharmaceuticals v Canada (Ministry of National Health and Welfare*), 2005 FC 9: "To overclaim is to lose everything".

[222] If Servier meant to circumscribe its monopoly, it should have done so with clear language. Instead, it has found itself in the unfortunate position of having to argue that it meant something different than what was clearly stated. In my estimation, no purposive construction of

the claim can save it from its language. The "(i)ntention is manifested in words, whose meaning should be respected, but words themselves occur in a context that generally provides clues to their interpretation and a safeguard against their misinterpretation." (*Whirlpool*, *supra*, para 49). The uncertainty thus created would run counter to our patent system. In *Free World Trust*, the Supreme Court said this in the context of the adherence to the language of the claims:

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

The '825 Patent is invalid because its claims are broader than the invention.

(2) And its hydrates

[223] The '825 Patent is invalid because it seeks a monopoly for "sel d'arginine de périndopril", in spite of having invented a salt of natural arginine. That suffices to render the whole Patent invalid. However, Apotex also argued that the '825 Patent is overbroad because it claims "ainsi que ses hydrates" ([TRANSLATION] "and its hydrates").

[224] I have been perplexed by the discussion around “its hydrates”. The '825 Patent uses the term twice. Once in claim 1 and once in the disclosure where the inventor presents the invention as relating “to the arginine salt of perindopril, its hydrates and to pharmaceutical composition containing it”. Both the “official” French version and the excellent English version must be understood to indicate that “the pharmaceutical composition containing it” are the pharmaceutical compositions containing the arginine salt of perindopril. It is less than clear what is the hydrate the Patent refers to and what is actually being claimed. The Patent itself is of little assistance.

[225] The evidence of the inventor, Mr. Damien, was also of little assistance. It is limited to one paragraph, the penultimate paragraph in a 75 paragraph affidavit. It reads:

> 74. During those studies, it became clear that the perindopril arginine salt was absorbing water. I therefore came to the conclusion that in the presence of humidity the arginine salt would be able to form hydrates. Nevertheless, the absorption of water by the perindopril arginine salt did not pose a problem because there was not impact on the stability of the perindopril tablets.

There is no indication in either the Patent or Mr. Damien’s affidavit as to what constituted his observation that perindopril arginine “absorbed” water. It is equally obscure how in the presence of humidity hydrates would form. There is no definition offered by the inventor of what constitutes a “hydrate” or what he meant by “hydrate”. Finally, one can perhaps infer that if observations show that the perindopril arginine salt “absorbs” water, the tests conducted to assess its stability would tend to those that the perindopril arginine salt was stable at high temperatures and high humidity which would explain the comment that the absorption of water did not impact the stability.

[226] The overbreadth of claim 1 concerning “its hydrates” having been put into play, it became Servier’s burden to show on a balance of probabilities that the second half of its claim 1 was not overbroad. The Court is not satisfied that the burden has been discharged on the record put before it.

[227] The debate between the experts as to whether hydrates exist only where the water finds its way into the crystal lattice, as argued in particular by Dr. Zaworotko, has largely become a red-herring. As indicated before, the weight of the evidence in this case is that it does not matter whether a person of skill would understand that hydrates may be crystalline or non-crystalline. What counts is that the water is absorbed, that is that water ends up in the lattices of a crystal or makes it way in the interstitial void of a non-crystalline, as argued by Dr. Byrn and Dr. Rodriguez-Hornedo.

[228] I wondered whether Servier was in fact claiming the hydrates. Its expert, Dr. Byrn, stated at paragraph 279, under the title “Sixth Mandate: Overbreadth”, that the first claim “itself is limited to the L-arginine salt of perindopril, whether or not it contains water”. In the end there was never any suggestion that the hydrates are not claimed. Presumably they are claimed for the purpose of avoiding allowing a competitor to patent a hydrate of an arginine salt of perindopril. But then, it is for Servier to show that it invented a hydrate or, at the very least that, through sound prediction, their existence is predicted.

[229] The evidence in this case did not disclose that a hydrate of perindopril arginine was ever made. At its highest, the Servier evidence is limited to paragraph 74 of Mr. Damien’s affidavit. It

"became clear", he said, "that the perindopril arginine salt was absorbing water". No detail whatsoever is offered to substantiate what became clear, and how it became clear. Mr. Damien goes on to elliptically say that he came "to the conclusion that in the presence of humidity the arginine salt would be able to form hydrates". As indicated before, the absorption of water does in the view of the experts imply water in lattices of crystal form or in the interstitial voids of a non-crystal form, and not water on the surface.

[230] On the evidence in this case, there is no proof that Servier ever made a hydrate. Indeed, Dr. Evans agreed under cross-examination that for a compound such as perindopril, there would be no certainty that a hydrate could be formed at all (cross-examination, questions 496 and 497). The uncertainty about the formation of hydrates was confirmed by Dr. Byrn (Byrn affidavit at paras 97 and 98, although in the context of crystals) and Dr. Rodriguez-Hornedo (Rodriguez-Hornedo affidavit at para 149). Dr. Zaworotko is more virulent, calling Mr. Damien's reasoning "fundamentally flawed": he expresses the view that, "without conducting any testing on the material prepared, it would be scientifically unsound to conclude that a hydrate would be formed". As for Mr. Bastin, he opines that even if water is absorbed, it does not necessarily follow that a compound will form hydrates. He could not find any study performed by Mr. Damien and his group that examined the absorption of water leading to the formation of a hydrate (Bastin affidavit at para 263). That conclusion appears to be confirmed by paragraph 74 of Mr. Damien's affidavit where he declares that he came to the conclusion that hydrates may form on the basis of some observation that the arginine salt of perindopril was absorbing water.

[231] Apotex argues that there does not exist on the record before the Court any basis for claiming hydrates. To the extent that hydrates are claimed, I agree. On the evidence in this case, there is nothing to support a claim to "its hydrates" has been invented by Servier. There has been no testing. Contrary to what Servier asserted, the issue is not so much that it is faulted for not having tested all hydrates as it has not shown that it has tested one. In view of the evidence of its experts, hydrates do not appear magically: there is no certainty that a hydrate could be formed at all. Without any evidence that the inventor actually invented something, there cannot be a valid claim to that invention.

[232] Apotex suggests that Servier is relying on the law of sound prediction to salvage the claims against the allegation of overbreadth. Apotex says that, from its Notice of Allegation, Servier has known that Apotex claimed that there was no hydrate made. Its only defence has been that perindopril arginine salt absorbs water which may convert into a hydrate. That, says Apotex, is invoking the law of sound prediction.

[233] The doctrine of sound prediction permits to establish utility even where the utility has not been fully verified as of the filing date. In *Wellcome Foundation*, *supra,* the Supreme Court explained the policy reason behind the doctrine:

> 66 The doctrine of "sound prediction" balances the public interest in early disclosure of new and useful inventions, even before their utility has been verified by tests (which in the case of pharmaceutical products may take years) and the public interest in avoiding cluttering the public domain with useless patents, and granting monopoly rights in exchange for misinformation.

[234] In order to be successful, the patentee will have to meet three conditions

1) there must be a factual basis for the prediction;

2) the inventor must have an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and

3) there must be proper disclosure.

(*Wellcome Foundation*, *supra*, at para 70; *Bell Helicopter Textron Canada Limitée v Eurocopter*, 2013 FCA 219, 120 CPR (4th) 394, at para 134).

[235] Applying these conditions for sound prediction in the context of an overbreadth allegation, the Court must find that they are not met on this record. It is clear from the evidence adduced in this case that there is overbreadth simply because the inventor offers no support for his alleged invention. As Hughes and Woodley on Patents (LexisNexis, 2nd Ed, loose-leaves) plainly state at § 29, "(a) claim is not overly broad if its scope is supported by the disclosure". It "must not be broader than the invention disclosed, or broader that (sic) the inventor's discovery entitles him/her to receive". The statements of Mr. Damien in his affidavit do not rise above the level of speculations. The '825 Patent only refers to hydrates without saying anything about them. The affidavit of Mr. Damien is limited to his conclusion that, because it became clear that there was water absorption (we don't know why or how), the perindopril arginine salt "would be able to form hydrates".

[236] The Court in *Wellcome Foundation* showed a willingness to allow the doctrine to be used beyond a narrow ambit, yet re-asserted that "Parliament intended to get something more than speculation in exchange for the grant of a patent monopoly" (para 69). Here, I have not been able to see anything more than speculations, without any kind of testing performed to establish that hydrates form. "If the claims are soundly predicted and there has been sufficient disclosure of

how to make the invention, then there is no overbreadth of the claims" (Hughes and Woodley on Patents, *supra*, § 29). Here there was no disclosure.

[237] I am of course concerned not to bring back inadvertently the promise of the patent, a doctrine that was ruled to be unsound in *AstraZeneca Canada Inc. v Apotex Inc.*, 2017 SCC 36, [2017] 1 SCR 943. In *Apotex Inc. v Abbott Laboratories, Limited*, 2018 ONSC 5199, the Ontario Superior Court refused to allow amendments to a reply and defense to counterclaim in what the case management judge called "protracted litigation" between the parties. It appears that Apotex sought to turn overpromising into other grounds of invalidity. The Superior Court put the argument thus:

> [8] However, rather than considering the mischief of "overpromising" solely in the context of a patent's utility, Apotex argues that the Supreme Court effectively kept that doctrine alive by determining that any false or unfulfilled promises in a patent specification *should instead* be addressed when assessing *other* established grounds of invalidity. The other established grounds, which Apotex seeks to expand by these pleadings amendments, are "over-breadth and insufficiency" (i.e., failure to comply with s. 27 of the *Act*), and "the making of wilfully misleading statements" in the petition or specification (i.e., failure to comply with s. 53 of the *Act*.
>
> [Italics in the original.]

Finding support in decisions of this Court, the Superior Court concluded:

> [27] There is superficial attraction to Apotex's position, based on the arguably permissive language of the two references quoted above from *AstraZeneca* and *Eli Lilly*. Upon further more careful reflection, however, I have rejected Apotex's position, taking specific account of the reasoning in the subsequent decisions of the Federal Court that have rejected the repackaging of "Promise Doctrine" based pleadings to satisfy the invalidity grounds set out in ss. 28 and 53. I side with the conclusions reached consistently since *AstraZeneca* by the specialist bench of the Federal Court, and I regard Laskin J.'s comments in *Eli Lilly* as case specific and

> simply a gloss on the language of the Supreme Court in the context of the circumstances of that case. Having specifically overruled the Promise Doctrine as bad law, it is not evident and indeed is counterintuitive that the Supreme Court intended that promise based arguments would simply be imported into claims of overbreadth or misrepresentation under those sections.
>
> [28] I find extensive support of that position, not only in the significant pushback of the Federal Court in a number of cases decided since *AstraZeneca*, and specifically the decision of Manson J. in *Apotex Inc. v. Pfizer Canada Inc.*, but also in the academic commentary of Professor Siebrasse, that we should "whack the zombies dead once and for all."[9] The five decisions of the Federal Court all support the proposition that "the zombies really are dead", that is, that a party cannot change what was really a promise based pleading into one that could result in invalidity under s. 27 or 53, even though the Supreme Court recognized that there are "mischiefs" that could fall under those heads.
>
> [Footnote omitted.]

[238] Manson J., in *Apotex Inc. v Pfizer Canada Inc.*, 2017 FC 951, noted the decision of Brown J. in *Pfizer Canada Inc. v Apotex Inc.*, 2017 FC 774 which he summarized as to the application of the Promise Doctrine to other grounds of invalidity:

> [42] Justice Brown recently decided in Pfizer *Canada Inc v Apotex Inc*, 2017 FC 774 [*Pfizer*] that not only was the Promise Doctrine not good law in terms of utility but also overbreadth of claims and insufficiency of patent specifications, as the SCC did not specifically endorse the Promise Doctrine with respect to construing section 27(3) of the Patent Act and would have done so if that was the Court's intention.

[239] There is an argument to keep the promise of the patent doctrine, which has now been debunked, from being incorporated into other grounds of invalidity, such as insufficiency, overbreadth or false representations. The sound prediction doctrine is related to the utility of the

patent in that the utility can be soundly predicted. In *Wellcome Foundation* (*supra*), the Court wrote:

> 56 Where the new use is the *gravamen* of the invention, the utility required for patentability (s. 2) must, as of the priority date, either be demonstrated or be a sound prediction based on the information and expertise then available. If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, *per* Pigeon J. in *Monsanto Co. v. Commissioner of Patents*, 1979 CanLII 244 (SCC), [1979] 2 S.C.R. 1108, at p. 1117, the prediction at the date of application was not sound, or, irrespective of the soundness of the prediction, "[t]here is evidence of lack of utility in respect of some of the area covered".
>
> [Italics in original.]

Thus, if, through the use of the sound prediction doctrine, the respondent attempts to bring the promise of the patent into overbreadth of claims, I would be reluctant to entertain the argument.

If sound prediction may be used more broadly in order to examine if a claim is too broad in view of the disclosure, as was the issue in *Monsanto Company v Commissioner of Patents*, [1979] 2 SCR 1108 [*Monsanto*], and not as a disguise for the promise of the patent, the use of the doctrine of sound prediction may be of assistance. The Court cites with approval this paragraph of *Olin Mathieson Corporation v Biorex Laboratories Ltd*, [1970] RPC 157, a decision of the English Chancery Division:

> Where, then, is the line to be drawn between a claim which goes beyond the consideration and one which equiparates with it? In my judgment this line was drawn properly by Sir Lionel when he very helpfully stated in the words quoted above that it depended upon whether or not it was possible to make a sound prediction. If it is possible for the patentee to make a sound prediction and to frame a claim which does not go beyond the limits within which the prediction remains sound, then he is entitled to do so. Of course, in so doing he takes the risk that a defendant may be able to show that his prediction is unsound or that some bodies falling within the

> words he has used have no utility or are old or obvious or that some promise he has made in his specification is false in a material respect: but if, when attacked, he survives this risk successfully, then his claim does not go beyond the consideration given by his disclosure, his claim is fairly based on such disclosure in these respects, and is valid.
>
> [p. 193]

[240] The Court in *Monsanto* disagreed with the Commissioner of Patents and the Patent Appeal Board that having tested only three compounds out of a vast number of compounds, there could not have been a reasonable prediction. The Court was more generous than the Commissioner. It found that the reasons for being dissatisfied with only three tests were unsatisfactory: "In the instant case, the Board, in spite of a complete absence of any evidence of *unsoundness* of the prediction, deny the claims and would in the end limit them to the area of *proved utility* instead of allowing them to the extent of *predicted utility*" (p. 1121). For the Court it cannot be that the patentee must test and prove all its claimed compounds:

> Under that section the Commissioner is instructed to refuse the patent when "satisfied that the applicant is not by law entitled" to it. Here what he has said in approving the decision of the Board is in effect "I am not satisfied you are entitled to it". In my opinion the Commissioner cannot refuse a patent because the inventor has not fully tested and proved it in all its claimed applications. This is what he has done in this case by refusing to allow claims 9 and 16 unless restricted to what had been tested and proved before the application was filed. If the inventors have claimed more than what they have invented and included substances which are devoid of utility, their claims will be open to attack. But in order to succeed, such attack will have to be supported by evidence of lack of utility. At present there is no such evidence and there is no evidence that the prediction of utility for every compound named is not sound and reasonable.

[241] It is not completely clear that Servier invoked the doctrine of sound prediction to justify the hydrates being included in claim 1. Apotex relies on a short passage in Servier's

Memorandum of fact and law where it says, at paragraph 62, "(t)his is consonant with the perindopril L-arginine made under the direction of Mr. Damien, which was hygroscopic, and that he concluded would form hydrates in the presence of humidity". Not only is that statement different than what Mr. Damien wrote in his affidavit at paragraph 74, where he merely said that he "came to the conclusion that in the presence of humidity, the arginine salt would be able to form hydrates", but this cannot be a sound prediction as none of the three required conditions is met. In the circumstances of this case, the doctrine of sound prediction could only be attractive to Servier. But the conditions were not met.

[242] As a result, the Court must find that claims 1 to 5 are overbroad because they claim more than what has been invented. Servier did not discharge its burden of showing that the allegation is not justified.

D. Obviousness

[243] The parties also discussed at some length whether or not the arginine salt of perindopril, whose utility is to improve the stability of perindopril in heat and high humidity over the tert-butylamine salt of perindopril, was obvious to the skilled person. In spite of the conclusion reached on overbreadth, the result of which is that a prohibition order will not be granted, I have chosen to examine the allegation of obviousness. The Court concludes that the claims are invalid for obviousness in the particular circumstances of the claim.

[244] It may have been that, in the mid-80's, Mr. Damien and Mr. Marchand had a flash of genius when they decided to seek to, faced with the lack of stability of the perindopril erbumine,

consider a different salt former. As Mr. Damien puts it in his affidavit, “we came across a number of elements that suggested that the cyclization reaction was aided by the fact that erbumine, used in the salification of perindopril, is a relatively volatile product and the loss of erbumine as the temperature rises could release perindopril in its non-salified form, which cyclizes more easily” (para 38). The discussion, at the time, of possible non-volatile bases turned to the use of an amino acid, which led to thinking of using lysine, which Mr. Damien had used in the past.

[245] Lysine not being available at Servier at the time, Mr. Damien and colleagues turned to the natural form of arginine. Mr. Damien declares that the L-arginine salt had never been used to form a salt of an active ingredient (para 46). That was in 1984. The '825 Patent would be filed some twenty years later, with a priority date of April 18, 2002. Mr. Marchand and Mr. Damien were successful in synthesizing the perindopril salt in 1984, using conventional laboratory techniques. The complete evaluation of the new salt would have to wait as Servier had decided to market its perindopril erbumine, the formulation of which having proven to be a challenge already. But Mr. Damien never looked back to identify a different salt. He wanted to test his arginine salt of perindopril against the three salts already discarded at the time Servier chose tert-butylamine in the early 80’s (sodium, hydrochloride and maleate salts). What was proven to be synthesizable in the mid-80’s would be tested more systematically in the 90’s.

(1) The obviousness framework

[246] There does not appear to be daylight between the parties as to what is the state of the law on obviousness in view of the Supreme Court decision in *Apotex Inc. v Sanofi-Synthelabo*

Canada Inc., 2008 SCC 61,[2008] 3 SCR 265 [*Sanofi*]. It is section 28.3 of the *Act* that requires that the subject-matter claimed not be obvious on the claim date. Here it is April 18, 2002, the priority date. Section 28.3 reads:

28.3 The subject-matter defined by a claim in an application for a patent in Canada must be subject-matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to	**28.3** L'objet que définit la revendication d'une demande de brevet ne doit pas, à la date de la revendication, être évident pour une personne versée dans l'art ou la science dont relève l'objet, eu égard à toute communication :
(a) information disclosed more than one year before the filing date by the applicant, or by a person who obtained knowledge, directly or indirectly, from the applicant in such a manner that the information became available to the public in Canada or elsewhere; and	**a)** qui a été faite, plus d'un an avant la date de dépôt de la demande, par le demandeur ou un tiers ayant obtenu de lui l'information à cet égard de façon directe ou autrement, de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs;
(b) information disclosed before the claim date by a person not mentioned in paragraph (a) in such a manner that the information became available to the public in Canada or elsewhere.	**b)** qui a été faite par toute autre personne avant la date de la revendication de manière telle qu'elle est devenue accessible au public au Canada ou ailleurs.
1993, c. 15, s. 33.	1993, ch. 15, art. 33.

[247] As everyone knows, the definition of "invention" in the *Act* requires that there be something new (as well as useful). While anticipation, which is not raised in this case, is concerned with a lack of novelty, obviousness addresses more directly the lack of inventiveness.

As the Federal Court of Appeal pointed out in *Ciba Specialty Chemicals Water Treatments Limited's v SNF Inc.*, 2017 FCA 225 [*Ciba*], "(o)bviousness is not concerned with novelty as a stand-alone ground of invalidity; on the other hand, if a patent does not contain something new, there can be no invention" (para 48).

[248] In *Sanofi*, the Supreme Court adopted the framework in *Pozzoli SpA v BDMO SA*, [2007] EWCA Civ 588 where Lord Jacob restated the framework to be used in the obviousness inquiry developed in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59. The framework is adopted and reproduced by the Supreme Court at paragraph 67 of *Sanofi*:

> In the result I would restate the *Windsurfing* questions thus:
>
> (1) (a) Identify the notional "person skilled in the art";
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?
>
> [Emphasis added in original.]

[249] Care must be taken to apply the test as developed. In *Ciba* (*supra*), the Court of Appeal noted that step 3 involves the difference between the state of the art and the inventive concept or the claim as construed. The common general knowledge should not be substituted for the state of

the art (para 47). The Court of Appeal had already a few months earlier helpfully drawn the difference between the two in *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc.*, 2016 FCA 119, [2017] 2 FCR 280 [*Mylan Pharmaceuticals*]:

> **A. Prior art and common general knowledge**
>
> [23] Prior art is the collection of learning in the field of the patent at issue. It comprises any publically available teaching, however obscure or not generally accepted.
>
> [24] The common general knowledge, in contrast, is the "knowledge generally known by persons skilled in the relevant art [skilled persons] at the relevant time": *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61, at para. 37, [2008] 3 S.C.R. 265. Unlike the prior art, which is a broad category encompassing all previously disclosed information in the field, a piece of information only migrates into the common general knowledge if a skilled person would become aware of it and accept it as "a good basis for further action": *General Tire & Rubber Co. v. Firestone Tyre & Rubber Co.*, [1971] F.S.R. 417, (1972) R.P.C. 457 at 483 (C.A.).
>
> [25] Prior art is used for specific purposes in patent law, such as to found an allegation that prior art anticipated the invention or rendered it obvious. The common general knowledge informs the way in which the claims and specifications are read, because it is to the skilled person that the patent is addressed. Any inquiry in patent law that is performed from the perspective of a skilled person will import the common general knowledge.
>
> [My emphasis.]

In effect, the common general knowledge is narrower than the prior art. As the *Ciba* Court noted, "(t)he common general knowledge is merely a subset of the prior art" (para 50). Any publicly available teaching, even if it is obscure, will be considered in the obviousness analysis. However, obviousness will not be determined based on the prior art at large. The allegation of obviousness

brings with it the elements of the prior art that will make the "invention" obvious. It follows that the choice of those elements is left to the party alleging obviousness (*Ciba*, *supra*, para 60).

[250] *Ciba*, *supra*, also warns against introducing into step 4 of the framework a reference to "self-evident". The Court points out that the "Skilled Person can have recourse to their common general knowledge supplemented by those pieces of prior art which could be discovered by a reasonably diligent search" (para 62). This is not a distinction without a difference as the Court goes on to conclude that this inquiry goes beyond asking whether the relevant differences are self-evident or not: step 4 speaks of requiring any degree of invention. In a word, the examination can be more probing than requiring that the differences be more or less self-evident. It seems that strict adherence to the test is to be preferred. If the difference between the state of the art and the inventive concept, or the claim as construed, is constituted by steps that would have been obvious to the skilled person that will make the alleged invention obvious. Conversely, if those steps require any degree of invention, the invention will not be obvious.

(2) The experts

[251] Professor Vaver describes in a colourful fashion the contest between the parties at page 329 of his *Intellectual Property Law* (*supra*):

> Instead, the field is dominated by debating points. Challengers minimize what the inventor has accomplished as the sort of thing any fool could have done. They say the invention has no creative spark or ingenuity about it. They allege that what looks obvious now must also have been obvious when the invention was made. In reply, the patent holder says that, if any fool could have made the invention, how come no other fool – including the challenger – had?[309] Moreover, no creative spark or ingenuity is required: patient plodders deserve their reward too.[310] The final flourish is to

> deny the relevance of 20/20 hindsight, as Milton said of Satan's invention of gunpowder: "So easy it seemed, once done, / Which yet undone most would have thought, impossible."[311]
>
> [Footnotes omitted.]

What is unusual, in my view, is that the alleged invention was for all intents and purposes "discovered" in 1984, with the ability for the new compound to resist degradation established a few years later. There was not a long process involved in putting perindopril and arginine together and there was no effort thereafter to confirm diligently that which had already been discovered. Instead. Mr. Damien's testimony is that Servier compared arginine salts to other salts already discarded at the time tert-butylamine was selected (1982) as it was considering the beneficial performance of the arginine salt of perindopril.

[252] Patents often speak in terms of "surprising" or "unique". '825 is no exception as it speaks of results being "entirely unexpected" (p. 4) and "entirely unexpected advantages" (p. 2). That is in spite of the fact that Messrs. Marchand and Damien thought of arginine in 1984 as a potential solution for the instability of perindopril arginine and, indeed, synthesized arginine salt of perindopril in 1984 (Damien affidavit at paras 44 and 47). There may have been that spark of ingenuity at that time, especially in view of the prior art, but to say that the results were entirely unexpected may be in the nature of some exaggeration. The evidence is that they tried arginine because they thought it might work.

[253] The general difficulty with the product developed by Servier in this case is that the definition of what can constitutes prior art in Canada is broad. In the words of the Court of Appeal in *Mylan Pharmaceuticals* (*supra*), "(i)t comprises any publically available teaching,

however obscure or not generally accepted." (para 23). It appears to be broader than what is accepted in some jurisdictions. More importantly perhaps, the prior art concerning salts and salt forming evolved significantly between 1984, when Servier synthesized the perindopril arginine salt, and the priority date of April 2002. As Mr. Damien states in his affidavit, to his knowledge "the L-arginine salt had never been used to form a salt of an active ingredient" (para 46). He conceded that, as is readily evident from the evidence, "(a)t the time, there was no systematic salt selection process at Servier" (para 20). The erbumine salt of perindopril was selected because the research team had been able to synthesize it and the compound was relatively pure. The same three salts that were tested against the arginine salt (sodium, maleate and hydrochloride) had been tested at the time the erbumine salt was selected; (obviously) they were rejected.

[254] It is somewhat surprising that the two experts retained by Servier who opined on obviousness focused their attention on a skilled person who, at step 4 of the *Sanofi* analysis, would not be arriving at the arginine salt of perindopril without much difficulty, but without considering fully the evolution of science in salt forming. In 1982, Servier did not have a salt selection process. The common general knowledge was quite different twenty years later and there was more prior art to consider.

[255] Thus, Dr. Byrn acknowledges that the skilled person would find inspiration in the scientific literature, yet he refers to Berge, Bighley and Gould, papers done in 1977 (and updated in 1996) and in the 80's and 90's, which lag behind the latest developments. He says at paragraph 223 of his affidavit that the "POSA would view the list of Berge (1977) as a starting point". Dr. Byrn concludes quickly that arginine would not be a candidate for a new salt because

it was a salt identified as a salt in the Table III of Berge which is simply a list of potentially useful salts. There is no meaningful discussion of techniques developed closer to 2002 that systematically address the issue of salt forming. When asked to consider if it was more or less self-evident that the POSA should try to form a new salt of perindopril, Dr. Byrn finds that it is not possible to predict if solutions are viable. The skilled person would believe that the arginine salt is unlikely to work. In fact he returns to the Berge nomenclature and its three tiers: "identifying and isolating a tier 2 or tier 3 salt of a given compound is unpredictable" (para 234). He seems to require certainty. Finally he states that there is no finite or closed group of potential solutions.

[256] Dr. Byrn does not ignore the existence of salt screens, but he calls the process long and arduous. "Each individual test conducted in the context of a salt screen may be considered as routine, but the collective of the tests and the balancing of the data obtained from these tests is not routine" (Byrn affidavit at para 236). They are routine, but they are not routine. No explanation is supplied.

[257] Reading Dr. Byrn's evidence, one is left with the impression that he was advocating for a position, the position he had already exposed in the Australian case. Hence, it was not completely surprising that, once he was asked to consider a list of references, he simply declared that they would not be instructive to a POSA attempting to resolve the instability of the tert-butylamine perindopril. His opinion would not have changed. While on two occasions in the preceding paragraphs of his affidavit the expert had stated that arginine had not been used as a salt former for a commercial product (para 211) and that he had never been involved in a salt

study that moved to the Berge Table III (where arginine would be) (para 226), he had to acknowledge that references given to him by counsel gave arginine as a salt former. Dr. Byrn discounted these in the following fashion:

> 248 Many of the references do in fact refer to arginine as an option to form a salt. These references will typically include a list of various salt formers, arginine being one of the salt formers in the list. I note that these lists look fairly similar and a POSA would think of these as "laundry lists" with no particular direction to any one of the members. None of the references include any stability data for any arginine salt form. It is unclear in the case of many of the references whether or not the arginine salt form was even synthesized.

Without any elaboration, the Court is left largely with peremptory statements. Although clear, they have the disadvantage of being of limited assistance as they are limited to claiming a lack of predictability of salt forming and the need to use salt formers for approved and marketed products, assuming more than demonstrating that, in 2002, arginine was not that kind of a salt former.

[258] Dr. Rodriguez-Hornedo showed more engagement than her colleague. She refers to the Stahl[9] textbook that summarizes the literature on the preparation, selection and use of salt of active pharmaceutical ingredients. As I understand it, it is not so much prior art itself as it reports on the prior art and recent developments.

[259] Arginine (and L-arginine) is mentioned on many occasions and is included in a list of common pharmaceutical salt formers. Dr. Rodriguez-Hornedo takes issue with that characterization as she complains that "(t)here is no explanation of the criteria used to determine

whether a salt former is "common" " (Rodriguez-Hornedo affidavit at para 182). Surely that must mean at least that it is not uncommon. She goes on to say that "I am unsure why arginine is included in that list because it does not appear on the list of most common salts in other references". It is a surprising comment in view of the fact that the references are the Berge tables of 1977 (as updated by Bighley in 1996) and "preformulation" in Michael E. Aulton ed., *Pharmaceutics: The Science of Dosage Design Form 1988*[10], some 14 years earlier.

[260] Considered as a whole, the chapter on obviousness from the two Servier experts who testify directly on obviousness appears more like an attempt to discourage the use of arginine as a salt former, invoking repeatedly the structural differences between perindopril and arginine salts when success was attained with other active pharmaceutical ingredients. There is seemingly always a reason for why arginine would not work with perindopril, yet Mr. Damien did not have much difficulty in 1984 in synthesizing the perindopril arginine salt. References describing general approaches to solving the stability problem are rejected as setting out general consideration for searching for suitable pharmaceutical salts, not with solving the specific problem with perindopril. References describing arginine as a potential salt former are discounted because "the POSA would not have come directly and without difficulty to the L-arginine salt of perindopril in light of the CGK" (Rodriguez-Hornedo affidavit at para 209). References involving ACE inhibitors do not fare any better. Although arginine is listed as a possibility in a list of potential salt formers, the witness argues that no arginine salt of the ACE inhibitors was made and that they have different chemical structure than the perindopril. References providing examples of arginine salts are accused of having "been chosen in hindsight in view of perindopril arginine being the subject-matter of the invention described in the 825

Patent" (Rodriguez-Hornedo affidavit at para 220). It is not clear why this prior art should be faulted. The expert disposes of those references by stating at the end of paragraph 220:

> … None of these references would have allowed the POSA to know (i) if the L-arginine salt of perindopril could be formed and isolated; (ii) the conditions for the preparation of the L-arginine salt of perindopril; and (iii) if the L-arginine salt of perindopril would be suitably stable.

[261] In other words, Dr. Rodriguez-Hornedo appears to want a solution on a silver platter for the purpose of the obviousness analysis. Nowhere do we see any attempt at mosaicking (*Wenzel Downhole Tools Ltd. v National-Oilwell Canada Ltd.*, 2012 FCA 333, [2014] 2 FCR 459, at para 87), even in a rudimentary fashion, in view of the prior art. This is not anticipation. The approach taken is rather to identify issues with the prior art to conclude that none leads inexorably to the solution in the form of arginine salt of perindopril in 2002 (and not in 1984). There is no attempt at considering the cumulative effect of the prior art.

[262] When considering the "obvious to try" possibility at step 4 of the obviousness framework, Dr. Rodriguez-Hornedo concludes that there was a large number of salt formers to choose from, with none of the solutions being predictable. The POSA would have known that "the experimentation may require a large amount of time and effort. It would require many experiments to test all the combinations of variables for a salt screen, many of which may not produce a solid salt" (para 230). In effect, Dr. Rodriguez-Hornedo was very negative, as is her prerogative.

[263] In my view, Apotex made a convincing case that, on the facts of this case, it is more likely than not that the alleged invention was obvious. To put it another way, Servier did not discharge its burden of showing that the allegation of obviousness was not justified with the evidence that was presented. To be sure, not every new salt for a known active pharmaceutical ingredient will be obvious. But in this case routine experiments, given the common general knowledge and the prior art in April 2002, would have generated the invention, the arginine salt of perindopril.

(3) Applying the obviousness framework

[264] The analytical framework has already been identified in *Sanofi*. The skilled person of step 1 has been identified as has been the relevant common knowledge. There is no dispute over this. The inventive concept is also the subject of consensus among the experts. For claim 1, the perindopril arginine and its hydrates is the inventive concept (Dr. Byrn and Dr. Rodriguez-Hornedo would define arginine as L-arginine, a difference that is not material in the obviousness analysis). The inventive concepts of claims 2 to 4 relate to the pharmaceutical compositions (excipients, immediate-release tablet, and quantity of arginine salt of perindopril) which contain the arginine salt of perindopril and its hydrates. The inventive concept of claim 5 is that the pharmaceutical compositions (which all contain the arginine salt of perindopril and its hydrates) are useful in the treatment of hypertension and heart failure. The only concept that requires attention is the arginine salt of perindopril which, according to Servier, required inventive ingenuity in 2002, as opposed to ingenuity in 1984 when Mr. Damien decided to synthesize it.

[265] I note in passing that the Court in *Ciba* (*supra*) noted the confusion generated by the undefined notion of an "inventive concept". Justice Pelletier would reduce that uncertainty "by simply avoiding the inventive concept altogether and pursuing the alternate course of construing the claim" (para 77). The "unnecessary satellite debate" about what constitutes the undefined "inventive concept" that often ensues did not take place in this case because the experts agreed on an inventive concept that is consonant with the general construction of the claims.

[266] That accounts for steps 1 and 2. Step 3 and 4 require that if there are differences between the state of the art and the inventive concept, here the arginine salt of perindopril and its hydrates, "do these differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?" (*Sanofi*, para 67).

[267] It is at the stage where the gap between the state of the art and the inventive concept that the *Sanofi* Court introduced the "obvious to try" considerations that are said to be particularly relevant with regard to inventions in the pharmaceutical industry:

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

[268] Recently this Court captured in a few words the essence of the exercise. In *Teva Canada Limited v Janssen Inc.*, 2018 FC 754, Justice George Locke, then of this Court, found:

> [259] Because the 146 Patent concerns an area of endeavour "where advances are often won by experimentation, where there may be numerous interrelated variables with which to experiment", it is appropriate to apply the "obvious to try" test. As indicated in paragraph [83] above, a finding that an invention was "obvious to try" requires evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention.

[269] This is our situation. It is not that an "obvious to try" is the be-all and end-all, but it is an approach that could be helpful. The *Sanofi* Court provided factors that should be considered at the fourth step:

> ii. "Obvious to Try" Considerations
>
> [69] If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> 3. Is there a motive provided in the prior art to find the solution the patent addresses?

There is no need to have certainty that the "try" in the obvious to try will be successful. It is rather that is more or less self-evident that the "try" ought to work in view of the common general knowledge and the prior art; a mere possibility will not suffice but an amount of uncertainty is allowed in the obvious-to-try analysis. It would not be obvious to try if certainty was required.

[270] As was seen when the Court reviewed the evidence on obviousness offered by experts retained by Servier, they stressed the unpredictability of salt forming. Indeed they conveyed the impression that certainty was required. They did not see fit to consider the mosaic constituted by the prior art. In *Laboratoires Servier, Adir, Oril Industries, Servier Canada Inc. v Apotex Inc.*, 2008 FC 825 at para 254 (see also *Biovail Corporation v Canada (Health)*, 2010 FC 46 at para 84; *AstraZeneca Canada Inc. v Teva Canada Limited*, 2013 FC 246 at para 34 and *Laboratoires Servier v. Canada (Health)*, 2015 FC 108 at para 182), Snider J. said:

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

The various elements of the prior art, together with the common general knowledge, would be enough, argues Apotex, to try: the prospects of success were sufficient to try.

[271] In the case of *Amgen Canada Inc. v Apotex Inc.*, 2015 FC 1261 involving bio-similars, Hughes J. considered the difficulty and the risk of failure. At paragraph 98, he reproduced a part of Amgen's factum:

> [98] Amgen stresses the difficulty and inherent risk of failure in the processes it undertook. I repeat a part of its Counsel's brief at trial on this point:
>
> > *(a) The process from going to a prior art protein preparation to a functional recombinant polypeptide was inherently unpredictable. The PSA did not know*

> *that what was to be tried was going to work until experiments were performed and obtained the result.*
>
> *(b) There was a variety of available techniques confronting the PSA that might be employed to try to successfully complete a recombinant cloning program. These various techniques ranged in their level of activity.*
>
> *(c) There was no guidance for which methods or techniques could be applied with an expectation of success. A skilled person would have been required to select from the multitude of available techniques, methods, etc. to design a program that they hoped would work.*
>
> *(i)* A skilled person would recognize that techniques that had been successful for previous researchers could not be expected to be successful for them.
>
> *26. There was a genuine possibility that the program might have been cut short, due to failure, at any number of steps along the way. The failure (or success) of many important aspects of any project are dictated by nature and are simply not amenable to any level of prediction (much less constituting a reasonable prospect of success) in advance.*
>
> [Italics in original.]

The opposing view stressed that skill is expected of the skilled person and that some risk of failure is expected.

[272] The Court agreed. Skilled work is not creative work:

> [101] There was a high degree of skill required and risk involved in what Amgen undertook. The steps were routine in the sense that they were carried out by skilled persons operating with the science as it was known at the time. This amounts to what is termed "*skilled work*" on the Robot Curve previously reproduced, and not to the "*creative work*" necessary to deserve patent protection. …
>
> [Italics in original.]

Furthermore, an assurance of success is not required. Hughes J. quoted with approval Mustill L. J. in *Genentech Inc's Patent* [1989] RPC 147, at page 281 commenting on a most difficult project that "It cannot, in my judgment, be assumed that inventiveness must have been involved somewhere, just because a wager on success could have been placed at long odds".

[273] There is also case law with respect to the selection of salt forms which supports the view that some salts, using salt screening, do not require inventiveness. They are the product of routine experimentation even if many steps are required. In *Ratiopharm Inc. v Pfizer Limited*, 2009 FC 711, Hughes J. found:

> [167] In the present case, unlike *Sanofi*, we are presented with a situation where the inventors were given a task, to look at amlodipine maleate and see if they could make it work sufficiently so as to pass it on for final formulation for regulatory approval. They quickly determined that there were two problems, stability and stickiness, only the first of which is mentioned in the patent. They tried adjusting formulations, a routine task. In fact, a suitable formulation for maleate was eventually found but not mentioned in the patent except as a besylate formulation. They also tried other salts through a well known process, salt screening. They tried a number of salts, including sulphonates, of which besylate is one. While besylate would not be everyones' first choice, it was not an unreasonable choice.
>
> [168] In proceeding through a salt screen, the besylate as well as other sulphonates, seems to work well enough so as to pass them along to others for final formulation and seek regulatory approval.
>
> [169] <u>All of this is routine for a person skilled in the art at the time. In the first set of salts screened the inventors found a few salts, particularly the sulphonic acid salts, including besylate, good enough, so they stopped there, why bother testing more.</u>
>
> [My emphasis.]

The case supports the proposition that salt screening is routine and that it may produce an obvious result. But that may not be the case. It all depends on the facts, including of course the prior art.

[274] In *Gilead Science Inc. v Canada (Health)*, 2013 FC 1270 [*Gilead*], Barnes J. was dealing with "the superior qualities of the fumarate salt of tenofovir disoproxil for use in pharmaceutical formulation" (para 70). The Court found that salt screening was a routine foundation:

> [80] *Teva cites Ratiopharm Inc v Pfizer Ltd*, 2009 FC 711, [2009] FCJ No 967 aff'd 2010 FCA 204, [2010] FCJ No 968 [*Amlodipine*], for the premise that salt selection is a routine procedure. In Amlodipine, Justice Hughes considered the validity of a patent claiming the besylate salt of the compound amlodipine. The Canadian filing date for the patent in that case was April 2, 1987. Therefore, the date to assess the knowledge of the person of skill in that case is approximately a decade earlier than the knowledge of the person of skill in the present application. Justice Hughes found the patent to be invalid by reason of obviousness. He made factual findings with respect to the motivation of the person of skill to try specific salt formers and the predictability of success (at paragraph 170). Most relevant to this application, he described salt screening to be a "well-known" and "routine pre-formulation procedure" for the person of skill (at paragraphs 155 and 167).
>
> [My emphasis.]

Barnes J. commented that if salt selection was routine in 1987, it was certainly not less routine ten years later. The same observation can be made for salt selection in 2002. The Court in *Gilead* addressed the argument, not dissimilar to the argument in this case, that there may be multiple choices facing the skilled person:

> [82] Gilead argues that there were multiple choices available to person of skill in developing a suitable salt for tenofovir disoproxil such that there was no clear pathway to fumaric acid. The fact that there were multiple pathways available to the person of skill does not necessarily lead to the result that a claimed invention was non-

> obvious: see *Hoffman-La Roche Ltd v Apotex Inc*, 2013 FC 718, [2013] FCJ No 844 at paras 316-341. Although a person of skill may not have predicted with a high degree of certainty that fumaric acid could be used to produce an acceptable salt formulation for tenofovir disoproxil, there would still be an expectation that, with routine screening of a handful of acidic salt formers, one or more acceptable compounds would emerge. The idea that fumaric acid was an unlikely candidate is belied, in part, by the fact that Gilead included only one other acid in its screening, that being citric acid. According to Dr. Myerson, the person of skill would have known at that time that citric acid was likely to be unstable (Applicants' Record, Volume 23, Tab 190 at pp 6944-6945).
>
> [My emphasis.]

Similarly, in our case Mr. Damien thought in terms of lysine and arginine in 1984, at a time where the use of arginine was much more limited compared to the evidence available in 2002. But the similarities do not end there.

> [83] In this case it is noteworthy that, despite its assertion that the choice of fumaric acid was counterintuitive and that its success as a useful salt former was unpredictable, Gilead presented no evidence of the inventive history behind the 059 Patent. Specifically, Gilead produced no evidence to show that it unsuccessfully screened numerous promising acidic salt formers and only resorted to fumaric acid as a last resort. It seems to me that if historical evidence of the sort produced by Gilead in support of the 619 Patent is to receive meaningful consideration, the absence of such evidence may well lead to an opposite inference (see *AstraZeneca Canada Inc v Teva Canada Ltd*, 2013 FC 245, [2013] FCJ No 241 at para 64).
>
> [84] In the face of an obviousness attack, the absence of evidence uniquely in the possession of Gilead leads me to conclude that the development of TDF was routine and not the end product of an onerous or inventive process of discovery. On the evidence before me, the choice of a salt form for tenofovir disoproxil that met Gilead's needs and that was shown by a routine screen to be better than the free base and one other salt form of questionable value is neither surprising nor inventive.
>
> [My emphasis.]

[275] In the case at hand, it is clear that Servier would not be able to show that the development of the arginine salt of perindopril was unpredictable because it was produced in 1984 and its utility to address instability problems with its perindopril erbumine was promising came well before 2002. Nevertheless, I would not draw a negative inference in the particular circumstances of this case based on a lack of evidence. I am not confident that there is evidence in the possession of Servier and it would have been artificial, perhaps, to prove how difficult it was for the skilled person to produce the arginine salt of perindopril in 2002, in spite of how easy it was in 1984. Servier relied on the evidence of its two experts. That is all that it has. It remains nevertheless that there is no evidence other than general statements that the inventor engaged in arduous and difficult experimentation while the evidence on the Apotex side is that the work would be routine. As I will endeavour to show, the evidence offered by Servier is amply superior on the obviousness issue.

[276] Still more recently, Mactavish J. confirmed yet again that salt forming can be a routine operation. In *Bristol-Myers Squibb Canada Co v Teva Canada Limited*, 2016 FC 580, there existed a free base of atazanavir which had good anti-viral activity; however its bio-availability was poor in solid form and it was relatively insoluble. A salt of atazanavir was developed which was more soluble and had better bioavailability. The case bears some resemblance with the case at hand as it was known that an atazanavir salt could be made (perindopril erbumine was on the market in Canada since 1994), and the improved solubility of the salt was not claimed as part of the inventive concept (the inventive concept of '825 Patent is simply the arginine salt of perindopril and its hydrates, without including the improved stability). The parties agreed

creating a salt form by using an acid in a salt screen was a well-known technique. Our Court concludes at paragraphs 501 and 502.

> [501] In conducting a salt screen of atazanavir, the POSITA would, therefore, have come directly and without difficulty to the bisulfate salts of atazanavir. Standard techniques for characterizing the properties of these salts would then have disclosed the existence of Type-I and Type-II atazanavir bisulfate salts and the properties of each form, including the anhydrous non-hygroscopic crystallinity and solid state stability of the Type-I bisulfate salt form. While the POSITA would not have known in advance what the properties of each of the bisulfate salts would be, I do not understand the applicants to suggest that there was anything inventive about the techniques used to identify the characteristics of the Type-I atazanavir bisulfate salt.
>
> [502] That the POSITA would have come directly and without difficulty to the Type-I bisulfate salt of atazanavir is confirmed by what actually happened in this case. It will be recalled Mr. Lindrud's evidence was that rather than wasting time and money going down blind alleys, the BMS team succeeded in making atazanavir salts (including the Type-I atazanavir bisulfate salt) on the *very first day* of their drug development project. Using routine techniques, it then took the team approximately six weeks or so to characterize both Type-I and Type-II atazanavir bisulfate salts insofar as matters such as their solubility, crystallinity, melting points, hygroscopicity and short-term solid state stability were concerned. I do not consider this process to have been either prolonged or arduous.
>
> [Italics in original and my emphasis.]

[277] Servier did not comment on that case law and it did not seek to distinguish it. I have reached the conclusion that it is not a body of law that can easily be ignored or dismissed, where the issue is salt forming. As stated herein above, I prefer the evidence of Mr. Bastin because of its cogency coming through the details he supplies in his testimony of salt forming. I shall review his evidence in some details, as I seek to fulfil step 3 of the four-step approach in identifying the gap between the state of the art and the inventive concept. As structured salt screens are part of the prior art in 2002, the gap between prior art and the inventive concept will not be as wide as it

used to be in 1984. Furthermore, the use of arginine is more prevalent in 2002 than it was in 1984.

[278] It will not be a surprise to anyone that perindopril was known. Perindopril and its acceptable pharmaceutical salts were patented in Canada since 2001 and perindopril erbumine, a salt of perindopril, had been marketed in Canada since 1994.

[279] The instability of compounds was not a new issue either and a skilled person would know of the options available to address the issue. Mr. Bastin offered at paragraph 59 of his affidavit a number of options to address instability, with the selection of an alternative salt being prominently featured.

[280] Well before 2002, the physiochemical properties of a drug were improved through salt formation. Mr. Bastin states at paragraph 62 of his affidavit that "(b)y April 2002, it had become common practice for a pharmaceutical development scientist to conduct a structured salt screen by forming and characterising a number of salts using pharmaceutically acceptable salt formers to identify the salt or salts of a drug that have the most favourable properties". As we know, Servier did not have a "systematic salt selection process" in 1982 (Damien affidavit at para 20). Mr. Bastin goes on to explain in great details the use of salts in drug development (Bastin affidavit at paras 143 to 148). The evolution had reached the point that in 2002, a skilled person would commonly conduct what Mr. Bastin called a "structured salt screen" early in the development of a drug with the goal of discovering the most optimal salt. The prior art includes the papers of Gould (1986), Morris (1994)[11] and Bighley (1996), but also a paper, authored by

the witness, of the two main approaches used as structured salt screen; the tiered approach, advocated by the witness, has prevailed over the decision-tree approach. Nevertheless, both are improvements in that they allow for a smaller number of salt formers to be considered, making the effort at finding appropriate salts a routine kind of endeavour.

[281] The tiered approach tests on "a group of salts in tiers, with only the salts possessing the most favourable properties from a first tier of testing being progressed to the next tier of testing" (Bastin affidavit at para 155). The method is further explained at paragraph 156:

> 156. In Morris, the Tiered Approach is outlined through a case study describing the use of the approach in the salt selection for an acidic drug, BMS-180431, which contains a carboxylic acid group that was used to form salts with a number of basic salt formers. Initially, salts were prepared using a variety of basic salt formers from different classes, and the seven crystalline salts isolated (five metals (sodium, potassium, calcium, zinc and magnesium) and two amino acids (arginine and lysine)) were subjected to tier 1 testing for hygroscopicity.[51] Following tier 1 testing, three of seven salts (magnesium, arginine and lysine) were determined to have low hygroscopicity, and were then evaluated using tier 2 testing to assess whether changes in crystal structure occurred under extremes of humidity conditions using a combination of XRPD and thermal analysis techniques, and for aqueous solubility. The two salts with acceptable properties in the tier 2 testing (arginine and lysine) were then subject to a third tier of testing involving accelerated thermal stability and photostability screening, as well as drug-excipient compatibility. In the example of a structured salt screen provided by Morris, both of the salts (arginine and lysine) assessed in tier 3 were determined to have suitable properties for further development, and the arginine salt was selected for progression. Using this Tiered Approach, the more rigorous and time consuming testing, such as stability testing, is not conducted until the final tier where fewer candidates will be present.
>
> [Footnote omitted and my emphasis.]

Mr. Bastin refined some more the tiered approach in 2000:

> 158. As I described above, a further rational or structured approach to salt selection is provided in Bastin. Like the method reported by Morris, the approach in Bastin also utilised a range of salt formers from different classes instead of the older approach of starting with hydrochloric acid, [54] and gradually working through the mineral acids, sulfonic acids and organic acids until a suitable salt form was identified. However, the approach in Bastin assessed additional properties, such as solubility, intrinsic dissolution rate, morphic form, microscopy and particle size, at an earlier stage than Morris. In addition, Bastin also described the use of a microplate or well technique, which allowed for the crystallisation of salts from a wider range of solvent systems using only small amounts of material. This capability was added to the screen in order to minimise the likelihood that a salt was overlooked because an initial crystallisation was not successful. For salt formers where a product is isolated, larger amounts of the salt are prepared so that its properties can be assessed and compared.
>
> [Footnote omitted.]

[282] The tiered approach presented by the witness is said to be significantly superior to that advocated by Dr. Byrn. Mr. Bastin writes:

> 342. At paragraphs 121 and 122 of his affidavit, Dr. Byrn has set out the approach that he believes a skilled person would follow when preparing salts. In general, Dr. Byrn's approach is consistent with what the skilled person would have done in the 1970s and early 1980s. However, by April 2002, Dr. Byrn's approach was out of date. The skilled person had progressed to using structured salt screens, such as those described in Morris and Bastin.
>
> 343. While the approach described by Dr. Byrn, which follows the approach outlined in Bighley, could still be used with success, it may take longer to identify a suitable salt. Notably, in the approach described by Dr. Byrn, the skilled person makes one salt at a time, studies the salt, and then proceeds to make a second salt if the properties are not acceptable. As well, this approach proceeds by testing all the salt formers in a given class (for example, the sodium salt, then other metallic salts, and then organic salts for acidic drugs, or the hydrochloride salt followed by other mineral acids and then organic salts for basic drugs). In contrast, a structured salt screen simultaneously looks at multiple salt formers from different classes at the same time to minimise the amount of salts that need to be prepared, and the amount of time required for their preparation.

[283] At step 4 of the four-step approach to the obviousness inquiry, the gap between the inventive concept and the prior art, which will have been identified at step 3 as including a robust availability of methods to use salt screens, is examined to determine if the difference between the two is obvious or there is any degree of invention. Mr. Bastin must be right that the difference is that "there is not a specific description of perindopril arginine or its hydrates having actually been made in the documents I have reviewed" (para 172). That is equally true of a specific description of a pharmaceutical composition that contains perindopril arginine and its hydrates, and the use of the composition in the treatment of hypertension or heart failure. Such is the gap that Apotex argues can be bridged with the help in 2002 of the salt screening approach known as the tiered approach.

[284] The skilled person would have known in 2002 that perindopril erbumine had stability issues: the packaging and labelling told the story. The motivation of Mr. Damien to find a solution would be present in the skilled person. The difference however would be that the 2002 skilled person has the benefit of a methodology Mr. Damien did not have in 1984. That constitutes a strong motive existing in the art to find the solution of developing the arginine salt of perindopril. The skilled person identifies the problem and is motivated to solve it. The POSA knows that a structured salt screen is available, which constitutes a motive in the prior art to find a solution through a salt screen. That skilled person would have been looking for a different salt since the problem was with the molecule, not the packaging or other crystalline forms of perindopril erbumine:

> 175. Since three crystalline forms of perindopril *tert*-butylamine that were stated to exhibit valuable characteristics for formulation were published in 2001, the skilled person would expect that the easily identified, and that attempts to identify further alternative

> crystalline forms may not be successful using routine methods. Therefore, as of April 18, 2002, the skilled person would be motivated to identify an alternative salt form of perindopril to address the stability problem associated with perindopril *tert*-butylamine.[60]
>
> [Footnote omitted.]

It is noteworthy that two persons of skill, Mr. Damien and Mr. Marchand, did exactly that in 1984: let's find a different salt than the product which was showing instability.

[285] In my view, the skilled person would have found it obvious to try the salt screen that is better structured, such as the tiered approach which was by then part of the prior art if not included already in the common general knowledge. By 2002, it was more or less evident that if a salt screen ought to be tried. I accept Mr. Bastin's evidence when he states at paragraph 321 of his affidavit:

> At paragraph 134 of his affidavit, Dr. Byrn acknowledges that the concepts of a salt screen are basic, but then suggests that carrying out an actual salt screen is anything but straight forward. Professor Evans also states that salt screening is not straight forward at his paragraph 102. I disagree. As I have discussed above (see paragraphs 62 to 74 and 151 to 162), by April 2002, salt screening had become a routine part of the preformulation studies carried out by skilled persons on drug substances. While there is not a 100% guarantee of success there is a very high expectation of success for the majority of drugs when suitable salt formers are assessed. The skilled person would only have a lower expectation of success in cases where the drug is very weakly acidic or basic, the drug has a poorly ionisable group, the drug has extreme solubility issues, or there is steric hindrance surrounding the ionisable group of the drug that may obstruct salt formation. These situations represent exceptions to the general expectations of the skilled person, and are usually identified before the salt screen is initiated.
>
> [My emphasis.]

Thus it is more or less evident that what is being tried ought to work.

The experts also identified a number of salt formers that could be used to form perindopril salts, based on the pKa of perindopril. There is therefore a finite number of predictable solutions known to the POSA. Mr. Bastin made a demonstration.

[286] Mr. Bastin testified that he created his affidavit by being provided with tranches of information, one at a time. Thus, he opined that instability issues with perindopril erbumine could be addressed in four different ways: packaging, different formulation, different salt or select a more crystalline form of perindopril erbumine. Even without being supplied the '825 Patent, but being aware of the instability issues of the perindopril erbumine, the expert identified arginine as being a candidate for a salt former that would address the instability problem of perindopril erbumine. Although rather technical, it is worth reproducing paragraphs 76 and 77 of Mr. Bastin's affidavit where he explains why arginine would have been a strong candidate as a salt former for perindopril:

> 76. Owing to the pKa values for perindopril at 5.66 and 3.5, the pharmaceutical development scientist would identify perindopril as having stronger acidic properties than basic properties. With a pKa of 3.5, the carboxylic acid of perindopril would be considered a weak acid. However, it would still be expected to form a salt with commonly used cationic salt formers (bases), which would all have pKa values above 5.5 (2 or more pKa units above a pKa of 3.5). With a pKa of 5.66, the secondary amine of perindopril would be considered a very weak base. As a result, it would only be expected to form salts with strongly acidic anionic salt forms (acids), which would have pKa values below 3.7 (2 or "more pKa units below a pKa of 5.66).
>
> 77. For an initial salt screen, it is my opinion that the pharmaceutical development scientist would select a few salt formers from among the commonly used classes of basic salt formers: organic amines, metallic bases and cationic amino acids.

> The likely salt formers that would be selected in an initial salt screen would be as follows:

Salt Former Class	Expected First Round Salt Formers
Organic Amines (4)	Meglumine
	Diethanolamine
	Triethanolamine
	Choline
Metallic Bases (3)	Sodium[35]
	Potassium
	Calcium
Cationic Amino Acids (2)	Arginine
	Lysine

I note that an explanation of what constitutes the pKa value is found at footnote 20 (para 54) of Mr. Bastin's affidavit:

> [20] The pKa or the acid dissociation constant, of a compound is a measure of its strength as an acid or base in solution, and its ability to ionise. A lower pKa value (for example, -6.0 for hydrochloric acid) indicates a highly ionisable or "strong" acid, while a higher pKa (for example, 4.76 for acetic acid) indicates a less ionisable or "weak" acid. Conversely, for a basic compound, the lower the pKa the weaker the base, and the higher the pKa the stronger the base. Since pKa is a logarithmic value, a pKa difference of 1 represents a 10-fold difference in acid/base strength.

Apotex rightly stressed that the short list of salt formers was arrived at without having had access to the '825 Patent. The expert arrived at the short list without knowing that arginine was the solution found by the inventor. In fact, he did not know about perindopril before 2017 when he was retained. It just happens that the two cationic amino acids arrived at for the purpose of trying

(lysine and arginine) through routine work by a person of skill, who follows a more rigorous method, are the two acids identified early on by the inventors.

[287] In a nutshell, Mr. Bastin's evidence is that a skilled person would in 2002 arrive at arginine being a salt former for perindopril. In fact, he did. Counsel for Apotex insisted of the hearing of this case that the result was arrived at with their expert being completely blind to the issues of the case. I would not conclude from that technique used to create affidavit evidence that it is so superior as to exclude from consideration all other evidence; but it certainly adds weight to the evidence, especially where the method is practiced, and if it is not countered. In my estimation, the reply affidavits of Dr. Byrn and Dr. Evans do not provide any meaningful counterweight.

(a) *Servier's counter to obviousness argument*

[288] Servier is right to point out that obvious to try must be approached with caution. But "the obvious to try" assists in the obviousness analysis especially where progress is achieved by experimentation. After all, "obviousness is largely concerned with how the skilled worker would have acted in the light of the prior art" (*Sanofi*, para 70*)*. Nevertheless prudence commands that the wisdom of hindsight does not creep in.

[289] The Court does not accept Servier's contention that Mr. Bastin was "blinkered", being led to some preordained destination. The issues to be resolved are in the view of Servier whether a skilled person would find obvious to try to form a new salt to improve the stability of perindopril and, if so, whether arginine would be one such salt given all possible salt formers. I

have reached the conclusion that such was the case, as the issue of the preparation of the arginine salt of perindopril is conceded as being without difficulty, as is the testing to determine the stability of perindopril arginine.

[290] In my view, the Servier's "blinkered argument" was met by the blinding approach followed by Apotex. Indeed, while Servier contends that the fact that Mr. Bastin did not know about perindopril before 2017 is a weakness, I find that to be a strength. By applying a method (the tiered approach to salt screening), Mr. Bastin arrived at a small number of salt formers that would be considered in an initial screening, two of which are lysine and arginine. This does not constitute a research project. This is routine work for the skilled person.

[291] Servier's argument about the inadequacy of the prior art and the common general knowledge fell short of the mark. Not only "(o)bviousness is not determined by reference to the prior art at large" and "(t)he choice of those elements of prior art is entirely in the hands of the party alleging obviousness" (*Ciba*, para 61), but Servier never showed what other prior art was missing such as to make a difference. Mr. Bastin's testimony is to the effect that, in 2002, a skilled person who would have been confronted to the instability of perindopril erbumine, not an unusual problem and not a particularly difficult problem; the skilled person would have looked at a number of solutions, including having a different salt of perindopril. The arginine salt of perindopril would have been arrived at using a routine methodology perfected by experts in the field such that the search for an appropriate salt former would be reduced to a small number of potential salt formers. Mr. Bastin even made a demonstration in this case of identifying arginine as a salt former from a small group of salt formers, not a universe of possibilities. It was for

Servier to expose difficulties in the testimony of Mr. Bastin. I have read his (long) affidavit on numerous occasions and his entire cross-examination twice: none was exposed.

[292] Contrary to Drs. Byrn and Evans who already knew about perindopril and the arginine salt of perindopril through their involvement in the Australian case 6 years ago, Mr. Bastin was truly blind. His testimony speaks of a methodology perfected in 2000. On the other hand, Servier's experts rely largely on the Berge paper of 1977, updated in 1996, to exclude arginine from consideration because it would not have been used in US Federal Drugs Administration (FDA) approved drugs and the pKa values do not tell the whole story. But the Bastin's tiered approach, considering such pKa values, would have produced, without difficulty and routinely, the arginine as one of a few salt formers. Moreover, by 2002, arginine had already been used as a salt former for approved drug products. Indeed, ADIR, an affiliated company of Servier, obtained numerous patents in the 1990's where arginine was presented as a suitable salt former. In 13 such patents (US 5,084,452; US 5,395,834; US 5,639,902; US 5,686,477; US 5,703,118; US 5,712,294; US 5,712,312; US 5,714,495; US 5,721,276; US 5,731,352; US 5,843,986; US 5,889,003; US 6,063,804), arginine is listed among pharmaceutically acceptable bases which may be used to form a salt arginine; often arginine is listed with tert-butylamine.

[293] In that same vein, Servier chose not to engage meaningfully with the teachings of Morris and Bastin, on salt selection methodology. In his case study, Morris selected seven salt formers, two of which are lysine and arginine. Bastin lists commonly used salt formers, including arginine designated as cationic salt former, which would be the first choice in the case of perindopril, owing to the pKa values of perindopril.

[294] The textbook, *The Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, by Stahl and Wermuth, should not be ignored if only because it summarizes the literature already in existence as of April 2002 (Rodriguez-Hornedo affidavit at paras 103 and 107). It refers on numerous occasions to arginine as a common salt former. The evidence in this case is significantly favourable to the conclusion that arginine was not an unknown in 2002 and the practice of conducting a salt screen had evolved to the point of being routine in a number of situations. It may well be that, for some problems it would not produce in a routine fashion a positive result or solution. These must be examined on a case-by-case basis: there is not a "one model fits all".

(b) *History of the invention*

[295] In *Sanofi*, the Supreme Court recognized the relevance of the history of the invention:

> [70] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.
>
> [71] For example, if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that may be evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person. Their course of conduct would suggest that a skilled person, using his/her common general knowledge and the prior art, would have acted similarly and come up with the same result. On the other hand, if time, money and effort was expended in research looking for the result the invention ultimately provided before the inventor turned or was instructed to turn to search for the invention, including what turned out to be

> fruitless "wild goose chases", that evidence may support a finding of non-obviousness. It would suggest that the skilled person, using his/her common general knowledge and the prior art, would have done no better. Indeed, where those involved including the inventor and his or her team were highly skilled in the particular technology involved, the evidence may suggest that the skilled person would have done a lot worse and would not likely have managed to find the invention. It would not have been obvious to him/her to try the course that led to the invention.

In this case, there was of course no such time, money and effort expended in 1984, and even later when the testing was conducted. Nevertheless, it is difficult in my view to put much weight on the history of the invention given the peculiarity of this case. That is because the prior art and common general knowledge were quite limited in 1984, compared to 2002. Mr. Damien may have had a flash of genius in 1984, but his invention, if that was an invention, was not patented then. As the *Sanofi* Court notes, "obviousness is largely concerned with how the skilled worker would have acted in light of the prior art" (para 70). This is assessed in 2002. It was Servier's burden to fill that 18-year gap. It is perhaps odd that there would be 18 years between the discovery of a compound and the decision to seek to patent it. Invariably there will have been major changes in the common general knowledge and the state of the art, especially in the pharmaceutical industry. Here the 18-year gap makes it difficult to treat the history of the invention as an important element to weigh. Nevertheless, the history of the invention tends at least to show that the preparation of perindopril arginine was made without difficulty, as was the testing in 1991 and in 1998-2000.

(c) *Pfizer Canada Inc. v Apotex Inc., 2017 FC 774 [Pfizer] (Brown J.)*

[296] Servier relied on *Pfizer* for the proposition that not all salts are obvious, a proposition that the Court accepts. It remains that previous case law of this Court already examined in these reasons found obviousness in the selection of some salts. The *Pfizer* decision, which had concluded that the Apotex obviousness allegation was not justified, was appealed by Apotex. The Federal Court of Appeal decision came after our case was heard: *Apotex Inc. v Pfizer Canada Inc.*, 2019 FCA 16. Apotex relied in their appeal in *Pfizer* on two Federal Court of Appeal decisions where the Court confirmed two decisions of this Court discussed herein above where the selection of salt forms was found to be obvious (*Pfizer Limited v Ratiopharm Inc.*, 2010 FCA 204, 87 CPR (4th) 185 [*Ratiopharm*] concerning "amlodipine", and *Bristol-Myers Squibb Canada Co. v Teva Canada Limited*, 2017 FCA 76, 146 CPR (4th) 216 [*Bristol-Myers*] concerning atazanavir). Apotex argued in *Pfizer* that the first judge, my colleague Justice H. Brown, ought to have followed the appellate lead in *Ratiopharm* and *Bristol-Myers*. I have reviewed the two Court of Appeal decisions (there is a companion case: *Teva Canada Limited v Pfizer Canada Inc.*, 2019 FCA 15). They confirm the trial judge decision(s) because each case must be decided on its facts. Brown J. had already adverted to the issue where he wrote at paragraph 289:

> [289] … Both parties cited cases where, on the accepted evidence in a particular case, various courts came to conclusions on obvious to try. While of relevance, each case in this connection has been decided on facts particular to it, having regard to the submissions of the experts and counsel. Although Apotex pressed hard, it remains that none say that all salt screens are obvious to try, or involve only matters of routine experimentation. Nor do any say that all polymorph or crystal screen research is obvious to try or merely entails routine experimentation. None do and of course none could. Ultimately the proper characterization of each case is a

> question of applying the law of obvious to try as set out in *Sanofi* to the evidence before the Court.

Contrary to the wish expressed by Apotex, not every salt is obvious. But it is also true that not every salt is non-obvious. The Court of Appeal said that much at paragraph 41 of *Pfizer*:

> [41] … There is no question that *Atazanavir* and *Amlodipine* as well as other past cases can provide helpful illustrations of the obviousness inquiry; however, contrary to what Apotex appears to urge, *Atazanavir* and *Amlodipine* cannot be used to force a given conclusion on obviousness based on broad factual similarities to the detriment of otherwise significant differences in a given case. However trite, each case is to be decided on the basis of the specific evidentiary record put before a judge.

[297] The Court of Appeal went on to conclude that there were no palpable and overriding errors in the fulsome analysis conducted by the first Judge. "The Federal Court Judge is entitled to deference on his appreciation of the evidence, including the weight given to competing evidentiary submissions" (para 36). Brown J. was of the view that the work undertaken in his case was not routine and was rather akin to a research project, on the basis of the record before him and the arguments that were presented. The guidance that can be derived from *Pfizer* in the Court of Appeal is that each case involving salts is not the "slam dunk" hoped for by Apotex and other generic manufacturers. It is rather a matter of facts and evidence to be weighed on a case-by-case basis. As the Court of Appeal says at paragraph 55 when considering the distinction between salts and crystals, "(w)hile a judge could come to a different conclusion in another case where a novel crystal forms part of the inventive concept, in the present case, the Federal Court Judge did not err in distinguishing between salts and crystals".

[298] The case at bar appears to be singularly simpler than the *Pfizer* case. One has a sense for the complexity of the invention when we read paragraph 256 and 275 of Brown J.'s reasons:

> [256] The inventive concept of claims 43 and 44 is a sustained release dosage form comprising the new crystalline Form I ODV succinate that has specific pharmacokinetic characteristics namely a peak blood plasma level of less than 225 ng/ml and (sic), and therefore reduces the incidence of certain side effects that would otherwise result from oral administration of ODV succinate.
>
> [275] While the prior art disclosed that sustained release formulations of other drugs including EFFEXOR XR had been both made and used to ameliorate blood plasma concentrations generated by immediate release administration, the prior art contained no application of this general principle to ODV, nor to ODV succinate nor to Form I ODV succinate. The evidence establishes that it would not have been obvious to the Skilled Person that ODV succinate had any stable, solid crystal form at all, let alone one that could be formulated into a sustained release formulation. Nor was it obvious or predicted or predictable that Form IODV succinate would have the appropriate stability, solubility, permeability and bioavailability characteristics for oral formulation development as identified by the experimentation entailed in its development. It was not known, predicted or predictable that any such sustained release formulation of ODV succinate would result in blood plasma levels below 225 ng/ml while maintaining therapeutic concentrations as per both Claims 43 and 44.

Many more passages could be presented to make the same point. On the other hand, '825 is about the arginine salt of perindopril made to address a single issue, stability. Brown J. concluded, based on the record and the arguments, that a research program was needed: nothing routine here:

> [321] On balance, and in my respectful view, the actual course of conduct in this case entailed more than routine experimentation; in my view it was a research program. This confirms my earlier finding that the Skilled Person looking at the prior art and common general knowledge would see a research program in terms of finding a compound suitable for drug development that had the

> necessary properties including solid state stability at ambient temperatures and relative humidity, solubility, permeability and bioavailability.

As I have tried to demonstrate, the facts of this case are completely different.

[299] Therefore, I must conclude that the *Pfizer* decision is of no assistance to either party. Apotex cannot claim that every salt is obvious: Servier cannot make the analogy between the facts in *Pfizer* and the facts in this case.

(d) *The Australian case*

[300] The Federal Court of Australia dealt with an Australian Patent that is the equivalent of the '825 Patent. In the case of *Apotex Pty Ltd v Les Laboratoires Servier*, (*supra*), the Court addressed a number of grounds in support of allegations of invalidity. It was a trial that lasted 15 days with Mr. Damien, Dr. Byrn and Dr. Evans appearing before the Court. It preferred the evidence of Dr. Byrn in particular. But that is neither here nor there.

[301] Reading the decision at trial, as well the FCA Full Court on appeal ([2016] FCAFC 27), it is apparent that the law varies between the two countries. One significant difference that appears from reading the decision is that the skilled person is equipped with the common general knowledge in Australia. That manifests itself through a discussion in the reasons for judgment of whether the Berge paper was common general knowledge in Australia or whether it would have been introduced in Australia through an Australian text book. It appears that the Morris paper was also discussed in the context of salt selection, with Dr. Byrn apparently accepting “that the

Morris study described one intelligent and tenable salt selection process". But Dr. Byrn "never tried arginine in any salt-screens he conducted, preferring instead to work with counter-ions in Table 1 of the Berge paper that he consider appropriate for the particular compounds with which he was trying to make salts" (para 119). Evidently, there is no indication that the Federal Court of Australia was exposed to the Bastin paper or the Stahl book (and its content).

[302] I am satisfied that I should not rely on the findings specific to a case in decisions of foreign courts concerning patents that may be comparable. The records vary, the arguments vary, and the applicable law varies. I share the view to that effect expressed by my colleague Justice Fothergill in *Apotex Inc v Shire LLC,* 2018 FC 637.

[303] In the end, I must conclude that Apotex's allegation of obviousness of the claims of the '825 Patent is justified. Servier has not discharged its burden that the allegation is not justified on this record

E. Double-Patenting

[304] In view of my conclusion on obviousness, I see no need to deal with the obviousness-type double-patenting advanced by Apotex. As pointed out by Rennie J.A. in *Mylan Pharmaceuticals*, the " "same-invention" double-patenting" occurs when the claims are outright identical or coterminous. A double-patenting argument can be made even if the claims are not identical "when the second patent is not identical to the first, but is nonetheless not "patentably distinct" from the first" (para 27). I would have found, had I have to, that the claim 5 in '196 Patent was not identical to the claims of '825. The fact that claim 5 speaks of perindopril and its

pharmaceutically acceptable salts does not capture the arginine salt. I agree with my colleague Justice Brown in *Pfizer* (para 397). That would have left obviousness-type double-patenting.

[305] Clearly obviousness and obviousness double-patenting are different. But they lead to the same point. Obviousness double-patenting has a different policy objective: the prevention of evergreening an existing patent. However by finding a patent invalid as no invention exists because it is obvious, the same result is attained: there will not be evergreening. In *Mylan Pharmaceuticals*, Rennie J.A. identifies the advantage of seeking invalidity for obviousness:

> [29] In an obviousness challenge, any piece of prior art, including a collection of works, can be cited as rendering the impugned patent obvious and therefore not patentable: *Sanofi-Synthelabo* at paragraphs 67-71. By contrast, in an obviousness-type double-patenting challenge, only the earlier patent can be cited as rendering the impugned patent not patentably distinct; any other prior art is only relevant insofar as it contributes to the common general knowledge of the skilled person.

But, again, the outcome is the same.

[306] Conversely, there may be an advantage of operating under obviousness double-patenting:

> [30] Finally, in an obviousness challenge, subsection 28.3(a) of the *Patent Act* provides that any information disclosed by the patentee within a year prior to the filing cannot be cited as prior art that renders the patent obvious. This effectively gives the patentee a one-year grace period before filing in which it can make disclosures without worrying that those disclosures will be the basis of an obviousness attack. Double-patenting is not subject to subsection 28.3(a), which is what allows the earlier patent to be cited if it was published within a year of the filing date of the impugned patent.

That was not an issue in this case.

[307] The obviousness double-patenting focusses on whether there is ingenuity, something new in the second patent, the same as in the obviousness analysis. Rennie J.A. noted the resemblance at paragraph 36 of *Mylan Pharmaceuticals*:

> [36] The Supreme Court of Canada in *Whirlpool* indicated that the substance of a double-patenting inquiry – like obviousness – is whether there is "invention" or "ingenuity" in the move from the first patent to the second: *Whirlpool* at paras. 66-67. Moreover, because the doctrine exists to prevent the evergreening of patents with uninventive additions, examination of whether the changes in the second patent are or are not inventive is directly linked to the policy considerations that underlie the doctrine. Finally, while not dispositive, the use of the label "obviousness" for this type of double-patenting indicates that a similar analytical process is appropriate.

Thus, once it has been determined that the '825 Patent is invalid for obviousness, there is no point, in my estimation, in pursuing further obviousness-type double-patenting.

I should not be taken as suggesting that there is no distinction between the two. There is:

> [37] This, in execution, requires consideration of the claims of the second patent against the claims of the first patent. The distinction from an obviousness inquiry is nuanced, but doctrinally important. As noted by Hughes J. in *Merck v. Pharmascience*, at para. 124:
>
> > What is important to keep in mind is that the exercise required in the inquiry as to whether there is double patenting is that the claims of the earlier patent owned by the same patentee as the latter must be compared with the claims of the latter to see if they are "identical or co-terminus", or whether the latter is "obvious" in view of the former. Therefore, the exercise is somewhat different than that of dealing with obviousness of a

> patent having regard to the art that would have been known to a person skilled in the art as of the relevant time. The exercise respecting double patenting is to present the notional person skilled in the art with the claims of the first patent and inquire whether what is claimed in the second patent was "identical or co-terminus" with the first or would have been obvious in light of the earlier patent. The inquiry must not bother with any inquiry as to whether the earlier patent would have come to the attention of the notional person skilled in the art. Nor does the inquiry extend to the validity or otherwise of the claims of the earlier patent. Nor does the inquiry extend to "prior art" beyond the earlier patent, as Binnie J. wrote at paragraph 67 of *Whirlpool*, the inquiry is whether a second patent can be justified unless the claims exhibit "novelty or ingenuity" over the first patent.
>
> [Emphasis in original.]

It is rather that those distinctions do not make a difference in the case at hand which is decided on the basis of obviousness.

X. Conclusion

[308] The allegation of invalidity of the '825 Patent on account of lack of utility and insufficiency of disclosure are not justified.

[309] The allegations of invalidity for overbreadth and obviousness are justified.

[310] The allegation of invalidity by reason of anticipation was not asserted. As for the allegation of invalidity by reasons of double-patenting, the Court declined to consider it further in view of its conclusion on obviousness.

[311] It follows that the application for an order of prohibition sought by the first person, Servier, must be dismissed, with costs in favour of the second person, Apotex.

[312] On the issue of costs, the parties suggested, and the Court concurred, that they should reach an agreement on what is to be included in the bill of costs. The parties are invited to communicate with the Court for a direction in case they cannot reach an agreement.

JUDGMENT in T-739-17

THIS COURT'S JUDGMENT is:

1. The application by Les Laboratoires Servier and Servier Canada Inc. to prohibit the Minister of Health from issuing a Notice of Compliance to Apotex Inc. for its APO-PERINDIPRIL/AMLODIPINE, orally administrated perindopril arginine/amlodipine tablets (3.5 mg/2.5 mg, 7mg/5 mg and 14 mg/10 mg strengths) until the expiry of Canadian Patent No. 2,423825 is dismissed; and

2. Costs are awarded to Apotex Inc. If the parties are unable to agree on costs, they may seek directions from the Court for a way to proceed.

"Yvan Roy"
Judge

ANNEX

Footnote Table

Footnote #	Short Form (if applicable)	Long Form	Footnote placed at para # and found thereafter at other paras #
1		I note that the translation of the Patent, issued in French, probably ought to have used the word "preferentially" as the original French version uses "à titre préférentiel". Indeed, the French is consistent in its use of "préférentiel" and not "préférable", which may have a slightly different connotation where "préférable" is said, in Le Petit Larousse illustré, to refer to what deserves to be preferred, what suits better, as opposed to being a mere preference.	20
2	Berge & Bighley, 1977	Stephen M Berge, Lyle D Bighley & Donald C Monkhouse "Pharmaceutical Salts" (1977) 66:1 Journal of Pharmaceutical Sciences 1.	44, 46, 79, 93, 255, 259, 280, 292
3	Bighley & Berge, 1996	Lyle D Bighley, Stephen M Berge & Donald C Monkhouse "Salt Forms of Drugs and Absorption" in James Swarbrick & James C Boylan, eds, *Encyclopedia of Pharmaceutical Technology*, vol 13 (New York: Marcel Dekker, 1996).	44, 46, 79, 93, 255, 259, 292
4	Gould	Philip L Gould, "Salt Selection for Basic Drugs" (1986) 33 International Journal of Pharmaceutics 201.	46, 255, 280
5	Bym	Stephen R Bym, Ralph R Pfeiffer & Joseph G Stowell, *Solid-State Chemistry of Drugs*, 2d ed (West Lafayette, Indiana: SSCI, Inc, 1999); Stephen R. Bym et al, "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations" (1995) 12:7 Pharmaceutical Research 945.	46
6	Bastin	R J Bastin, M J Bowker, M.J & B J Slater, "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities" (2000) 4 Organic Process Research & Development 427.	93, 301

Footnote Table

7	Rodriguez-Hornedo	K R Morris & N. Rodriguez-Hornedo, "Hydrates" in *Encyclopedia of Pharmaceutical Technology* vol 7, J Swarbrick and J. C. Boylan, eds, (New York: Marcel Dekker, 1993)	136
8	The Merck Index	Susan Budavari, ed, *The Merck Index*, 12th ed (Whitehouse Station, 2001).	161
9	Stahl	P Heinrich Stahl & Camille G Wermuth, eds, *Handbook of Pharmaceutical Salts: Properties, Selection and Use* (Weinham: Wiley, 2002).	258, 294, 301
10	Aulton	M.E Aulton, ed, *Pharmaceutics: The Science of Dosage Form Design* (Edinburgh: Churchill Livingstone, 1988).	259
11	Morris	K R Morris et al, "An Integrated Approach to the Selection of Optimal Salt Form for a New Drug Candidate" (1994) 105 International Journal of Pharmaceutics 209.	280, 293

FEDERAL COURT

SOLICITORS OF RECORD

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