Federal Court  Cour fédérale

Date: 20090629

Docket: T-161-07
Docket: T-1161-07

Citation: 2009 FC 676

BETWEEN:

SANOFI-AVENTIS CANADA INC.,
SANOFI-AVENTIS DEUTSCHLAND GmbH and
SCHERING CORPORATION

Plaintiffs

and

APOTEX INC.

Defendant

AND BETWEEN:

APOTEX INC.

Plaintiff by Counterclaim

and

SANOFI-AVENTIS CANADA INC. and
SCHERING CORPORATION
SANOFI-AVENTIS DEUTSCHLAND GmbH and
RATIOPHARM INC.

Defendants by Counterclaim

Docket: T-1161-07

BETWEEN:

SANOFI-AVENTIS CANADA INC.,
SCHERING CORPORATION and
SANOFI-AVENTIS DEUTSCHLAND GmbH

Plaintiffs

and

NOVOPHARM LIMITED

Defendant

AND BETWEEN:

NOVOPHARM LIMITED

Plaintiff by Counterclaim

and

SANOFI-AVENTIS CANADA INC.,
SCHERING CORPORATION and
SANOFI-AVENTIS DEUTSCHLAND GmbH

Defendants by Counterclaim

REASONS FOR JUDGMENT

SNIDER J.

I. Introduction

[1] Sanofi-Aventis Canada (Sanofi Canada) sells a drug in Canada with the trademark of ALTACE, which is used primarily in the treatment of high blood pressure and cardiac insufficiency. The active ingredient in ALTACE is ramipril. With some exceptions, Sanofi Canada purchases ramipril from its affiliate, Sanofi-Aventis Deutschland GmbH (Sanofi Deutschland) who manufactures ramipril in Germany. Ramipril is included in Canadian Patent No. 1,341,206 (the '206 Patent), a patent that was issued March 20, 2001 and held by Schering Corporation (Schering). Each of Sanofi Canada and Sanofi Deutschland are licensees under the '206 Patent.

[2] In January, 2007, Apotex Inc. (Apotex) commenced sales of a generic version of ALTACE – Apo-Ramipril – in Canada. Similarly, Novopharm Limited (Novopharm) began selling Novo-Ramipril in Canada in May, 2007. Apotex and Novopharm became authorized to sell a ramipril

product in face of an existing patent following the conclusion of a series of proceedings brought under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 (the *NOC Regulations*) which I will detail later.

[3] In 2007, Sanofi Canada, Sanofi Deutschland and Schering commenced two actions claiming infringement of the '206 Patent. The defendant in the first action (Court File T-161-07) is Apotex and the defendant in the second (Court File T-1161-07) is Novopharm. Each of the two Defendants responded to the Statement of Claim filed against it with a Statement of Defence and Counterclaim, asserting that the '206 Patent was invalid on a number of grounds. The counterclaims of Novopharm and Apotex joined Ratiopharm Inc. (Ratiopharm) as a defendant by counterclaim in each of the actions. The portions of the counterclaims affecting Ratiopharm were stayed under the provisions of s. 50(1) of the *Federal Courts Act*, R.S.C. 1985, c.F-7 by Order of Justice Roger Hughes dated September 12, 2007. There is no further reference to Ratiopharm in these Reasons.

[4] Since the patent in question, the issues raised by the parties and much of the evidence is common to both actions, the two were heard together. These Reasons for Judgment apply to both actions.

[5] The combination of the two actions in this manner resulted in great efficiencies in the trial process. The 37-day trial, which involved complex issues on both patent validity and damages, took place within two years of the filing of the first Statement of Claim. The efficiencies and timeliness of the trial were only possible due to the great degree of cooperation amongst the four sets of

counsel involved and to the effective case management of Prothonotary Milczynski. I thank them all sincerely.

[6] For the reasons expressed in these Reasons for Judgment, I have concluded that Apotex and Novopharm have infringed certain claims of the '206 Patent. However, I have also found that Claims 1, 2, 3, 6 and 12 of the '206 Patent are invalid. In very general terms, the key determination leading to this result is my finding that, on a balance of probabilities, the inventors of the '206 Patent could not soundly predict, as of October 20, 1981, that all of the eight compounds of Claim 12 of the '206 Patent would have the utility promised by the patent. Claims 1, 2, 3 and 6 include the same compounds as are covered by Claim 12. Accordingly, it follows that Claims 1, 2, 3, 6 and 12 of the '206 Patent are invalid and the claims of Schering and Sanofi will be dismissed.

[7] If I am wrong in this conclusion, and the claims were based on a sound prediction, it follows – on the particular facts of this case – that the same prior art that would form the basis of a sound prediction would render the relevant claims of the '206 Patent obvious as of the appropriate date for assessing obviousness.

[8] The Defendants have raised other grounds of invalidity. In light of my finding of invalidity on the basis of lack of utility, it is not strictly necessary for me to rule on these other grounds. However, if I were required to do so, I would conclude that:

- The '206 Patent is not invalid for obviousness double patenting;

- For the '206 Patent, there is no requirement that the patentee disclose the "best mode" for producing the patented compounds;

- The *Gillette* defence is unavailable to the Defendants on these facts; and

- Apotex's argument that Schering was not the first to invent the subject matter of the '206 Patent fails.

[9] The application leading to the '206 Patent was filed in Canada on October 20, 1981. According to s. 78.1-78.2 of the present *Patent Act* (R.S.C. 1985, c.P-4), patent applications filed before October 1, 1989 are to be dealt with under the provisions of the *Patent Act* as they read immediately before that date. Accordingly, references the *Patent Act* in these Reasons will, unless specifically noted otherwise, be to the *Patent Act* as it stood immediately prior to October 1, 1989.

[10] Finally, I note that the trial of these actions was not bifurcated. Sixteen days of evidence and two days of final argument were devoted to the remedies phase of this matter. Because of my dismissal of the actions, there is no need to consider these issues. Nevertheless, I will retain my notes from the second phase of the trial. In the event that it becomes necessary, I could be available to hear further updates to the evidence and submissions and make determinations on the appropriate damages and remedies.

II. Table of Contents

[11] To assist the reader, the following sets out a Table of Contents for these Reasons with paragraph numbers for each heading:

III. Witnesses

A. *Introduction*

[12] During the 31-day evidentiary phase of this trial, many witnesses appeared, both as expert and fact witnesses. Fifteen days of the trial consisted of evidence dealing with the infringement and validity issues. The balance of the trial was spent considering possible remedies should the plaintiffs be successful in their claims. As noted above, I have concluded that the '206 Patent is invalid. Accordingly, there is no need (at this time) to assess the evidence presented by the many capable witnesses who appeared in the damages phase of the trial.

[13] In the following, I will provide a brief overview of the expert and fact witnesses who appeared during the infringement and validity portion of the trial and the areas to which they testified. For the expert witnesses, I have set out a very short description of their education and experience in the areas for which this court found each of them to be qualified. More detailed references to the experts' evidence are contained in the appropriate sections of these reasons.

[14] The experts produced by both the Plaintiffs and Defendants were very helpful to the Court. I would comment, however, that there was considerable overlap and repetition in their evidence.

B. *Plaintiffs' Expert Witnesses*

(1) Dr. Paul A. Bartlett

[15] After completing his Ph.D. studies in Organic Chemistry, Dr. Paul A. Bartlett began an impressive academic career in 1973 with University of California, Berkley. From 1996 to 2000, he was Chair of the Department of Chemistry. Dr. Bartlett is, at present, a Professor Emeritus of Chemistry at the University of California, Berkley. He has extensive consulting and research experience in fields of relevance to the issues before me in this case. I accepted his qualifications as an expert in medicinal chemistry and synthetic organic chemistry. During his appearances and in his expert reports, on behalf of Schering, Dr. Bartlett provided opinions on the issues of claims construction, infringement, utility, sound prediction and obviousness.

(2) Dr. André Charette

[16] Dr. Charette is a professor at the University of Montreal, Department of Chemistry. He holds the Canada Research Chair in Stereoselective Drug Synthesis of Bioactive Molecules as well as the NSERC, Merck Frosst and Boehringer Ingelheim Industrial Chair on the same topic. He was qualified as an expert in the areas of organic chemistry relating to stereochemistry and stereoselective synthesis.

[17] On behalf of Sanofi, Dr. Charette gave opinions directed to the methods of synthesis of the compounds included in Claims 1, 2, 3, 6 and 12 of the '206 Patent. He reviewed and opined on the experimental techniques used by Dr. Bihovsky, Dr. Mariampillai and Dr. Lautens in their attempts to follow the directions of Example 20 of the '206 Patent. His evidence and testimony also touched on whether the compounds covered by Claim 12 could be prepared using methods known in the art, other than that given by Example 20.

(3) Dr. Arthur Patchett

[18] Dr. Patchett has had a lengthy and distinguished career in pharmaceutical chemistry. He joined Merck & Co. (Merck) as a research chemist in 1957, remaining with that company in various capacities until 2002. Dr. Patchett is a co-inventor of the ACE inhibitors enalapril and lisinopril. Of particular relevance to this trial is the role that he played in Merck's disclosure of its work in the design of enalapril and lisinopril at a lecture at Troy, New York in June 1980. Dr. Patchett was

qualified as a medicinal chemist with experience in the design and development of ACE inhibitors. Since his retirement in 2005, Dr. Patchett has been retained as a consultant for Schering-Plough.

[19] On behalf of Schering, Dr. Patchett provided his opinions on the issues of sound prediction and obviousness. Although there was a certain level of repetition between the evidence of Dr. Patchett and Dr. Bartlett, Dr. Patchett's experience at Merck brought a unique experience to the Court that was very helpful.

(3) Dr. Wendel Nelson

[20] Dr. Nelson is a professor in the Department of Medicinal Chemistry, University of Washington. He has been in academia since 1965 and served for 19 years (from 1989 to 2007) as a senior editor for the Journal of Medicinal Chemistry. He was qualified as an expert in the area of medicinal chemistry.

[21] On behalf of Sanofi, Dr. Nelson provided his opinions on the issues of patent construction, utility, sound prediction and obviousness. To a large degree, his opinions were confirmatory and repetitive of those of Dr. Bartlett.

(4) Dr. James D. Wuest

[22] Dr. James D. Wuest is a Professor of Chemistry at the University of Montreal, where he has been a full professor since 1986. Prior to joining the University of Montreal, he was an Assistant Professor of Chemistry at Harvard University and Harvard Medical School. Since 2001, Dr. Wuest has held the Canada Research Chair in Molecular Materials. He was qualified as an expert in synthetic organic chemistry.

[23] On behalf of Sanofi, Dr. Wuest commented on the experimental work of Dr. Bihovsky, as well as that of Drs. Mariampillai and Lauten, with respect to Example 20. He also provided his opinion on whether the compounds covered by Claim 12 could be prepared using methods known in the art, other than that given by Example 20. There was considerable overlap and repetition between his opinions and those offered by Dr. Charette and Dr. Roach.

(5) Dr. Mark Lautens

[24] Dr. Lautens is the AstraZeneca Professor of Organic Synthesis at the University of Toronto, where he has been a full professor since 1995. Dr. Lautens was qualified as an expert in synthetic organic chemistry.

[25] On behalf of Sanofi, Dr. Lautens carried out the synthesis described in Example 20 of the '206 Patent.

(6) Dr. Zola Horovitz

[26] Dr. Zola Horovitz was qualified as an expert in pharmacology with particular experience in the area of hypertension and ACE inhibition. Dr. Horovitz worked for almost 35 years in pharmacological research at the Squibb Institute for Medical Research (Squibb). Since his retirement from that post in 1994, he has been a consultant to the biotechnology and pharmaceutical industries, including various companies that develop products in the cardiovascular field. Dr. Horovitz gave evidence on obviousness, sound prediction and utility.

[27] As with Dr. Patchett, Dr. Horovitz's opinions overlapped to some extent with that of other witnesses. However, Dr. Horovitz brought a unique perspective to the trial because of his pharmacological experience in industry.

(7) Dr. Braden Roach

[28] Dr. Braden Roach has been involved in research, for over 20 years, in areas of chemical synthesis research, in both academic and industry settings. Dr. Roach was qualified as an expert in the synthesis of organic compounds. He was asked by counsel for Schering to opine on the work of each of Dr. Lautens and Dr. Bihovsky in their attempts to follow the synthesis of Example 20. There was considerable overlap and repetition between his opinions and those offered by Dr. Charette and Dr. Roach.

C. *Plaintiffs' Fact Witnesses*

[29] Schering presented two fact witnesses to the Court. Dr. Bernard Neustadt is employed by Schering as a research fellow serving as a medicinal chemist in the company's discovery effort. He has been an employee with Schering since 1969. He is one of the inventors of the subject matter of the '206 Patent. The other fact witness was Dr. Elizabeth Smith, who has been an employee at Schering since 1972. She is a one of the inventors of the subject matter of the '206 Patent.

D. *Defendants' Expert Witnesses*

(1) Dr. Eugene Thorsett

[30] Dr. Eugene Thorsett is a synthetic organic chemist with 33 years of experience in the pharmaceutical industry. Of particular interest in this case, Dr. Thorsett was a researcher at Merck from 1975 to 1988, including during the early stages of the development of ACE inhibitors, including enalapril and lisinopril. Dr. Thorsett was qualified as an expert in medicinal and synthetic organic chemistry with particular knowledge in pre-clinical drug development, especially those related to pharmacology, such as pharmacokinetics and the absorption, distribution, metabolism and excretion of a pharmaceutical compound within an organism, and in the area of lead drug candidate optimization, and in the design and development of enzyme inhibitors, including ACE inhibitors. His testimony and reports, on behalf of Apotex, were directed to the issues of claims construction, utility, sound prediction and obviousness.

(2) Dr. Mario Ehlers

[31] Dr. Ehlers is a physician-scientist with 11 years of experience in academic research and 8 years of biopharmaceutical industry experience in drug development, diagnostic product development, and central lab services. He was qualified as a biochemist with academic and industry experience in structure function studies on ACE and ACE inhibitors and the design and synthesis of new ACE inhibitors. On behalf of Novopharm, Dr. Ehlers provided his opinion on patent construction and sound prediction.

(3) Dr. Christopher John Moody

[32] Since 1979, Dr. Moody has been in academia. At present, he is the Sir Jesse Boot Professor of Chemistry at the University of Nottingham, United Kingdom. Of particular interest, Dr. Moody was employed, from 1977 to 1979, as a senior research chemist by Roche to work on a project involving the design and synthesis of ACE inhibitors as potential medicines for hypertension. Dr. John Moody was qualified as an expert in organic chemistry with experience in heterocyclic chemistry. He spoke to the issues of claims construction and the process used by Schering and Novopharm to synthesize ramipril.

(4) Dr. Robert Allan McClelland

[33] Dr. McClelland is Professor Emeritus of the University of Toronto. From 1983 to June 2005, he was Professor of Chemistry at the University of Toronto. Dr. McClelland was qualified as an expert in the area of physical organic chemistry, especially reactive intermediates generated in nucleophilic substitution and addition reactions, and in the area of biological and medicinal chemistry, especially the properties of heterocyclic drugs and synthesis of new analogues.

[34] On behalf of Apotex, Dr. McClelland provided his expert opinion and replied to certain opinions of the Plaintiffs' experts in the following areas: a comparison of the claims of the '087 Patent with those of the '206 Patent; a comparison of the Apotex manufacturing process of ramipril with that claimed in Canadian Patent No. 1,187,087 (the '087 Patent); Example 20 of the '206 Patent; and the Schering research work in respect of the '206 Patent.

(5) Dr. Ian Fleming

[35] Dr. Fleming is a Professor Emeritus of Chemistry at the University of Cambridge and an Emeritus Fellow at Cambridge's Pembroke College. From 1965 to 2002, he held various academic posts at Cambridge, his last position being that of Chemistry Professor from 1998 to 2002. He was qualified as an expert in synthetic organic chemistry.

[36] On behalf of Apotex, Dr. Fleming provided his expert opinion in the following areas: Example 20; a comparison of the claims in the '087 Patent and the '206 Patent; and, a comparison of the Apotex manufacturing process of ramipril with that claimed in the '087 Patent.

[37] While Dr. Fleming was a highly competent and knowledgeable expert, I question whether his opinions were necessary to the understanding of the Court, given that his mandate was almost identical to that of Dr. McClelland. It seems to me that one or the other of these two experts would have been adequate.

(6) Dr. Timothy J. Ward

[38] Dr. Ward is the Associate Dean of the Sciences and a Professor in the Department of Chemistry at Millsaps College in Jackson, Mississippi. Dr. Ward worked for Dionex Corporation and Syntex Pharmaceuticals between 1987 and 1990, when he entered academia. He was qualified as an expert in separation science, including chromatography. On behalf of Apotex, he provided his expert opinion on the science of chromatography and separation. In particular, Dr. Ward opined on the separation methodology needed for the compounds of Claim 12 of the '206 Patent and on the work done by Schering in separating compounds within the scope of Claim 12.

(7) Dr. Clayton Heathcock

[39] Dr. Heathcock is a chemist with over 45 years of academic experience in organic chemistry and medicinal chemistry. He is currently Professor Emeritus at the University of California at

Berkeley and Chief Scientist of the Berkley branch of the California Institute for Quantitative Biosciences. Dr. Heathcock was qualified as a synthetic organic chemist.

[40] On behalf of Novopharm, Dr. Heathcock provided his opinion on whether the subject matter of the '206 Patent would have been obvious to a person skilled in the art. In light of the evidence of Dr. Thorsett, I question whether Dr. Heathcock added materially to the Court's knowledge in this area.

(8) Dr. Ron Bihovsky

[41] Dr. Bihovsky is a scientist with over 20 years of experience in chemistry, including in academia and private industry. In 2001, he founded Key Synthesis LLC, an organic chemistry lab that performs contract synthetic projects for pharmaceutical and biotechnology companies, process research and consulting work. Dr. Bihovsky was qualified as an expert in organic synthesis.

[42] Dr. Bihovsky was retained on behalf of Apotex to attempt to reproduce the synthesis described in Example 20 of the '206 Patent and to provide his opinion on the ability of a person skilled in the art to carry out the chemical reactions of Example 20.

E. *Defendants' Factual Witnesses*

[43] Apotex presented two factual witnesses to the Court. Dr. Stephen Horne is the vice president of research and development at Apotex Pharmachem. His testimony related to a sample of a

compound known as “Ram 85” that was provided to Dr. Bihovsky. Dr. Gabriela Mladenova testified as to her laboratory work in or around 2003. At that time, Dr. Mladenova performed some experiments, under the direction of Dr. Lee-Ruff, in which she unsuccessfully attempted to reproduce the synthesis described in Example 20 of the '206 Patent.

IV. **Background to the '206 Patent**

A. *Introduction*

[44] The '206 Patent is entitled “Carboxyalkyl Dipeptides, Processes for Their Production and Pharmaceutical Compositions Containing Them”. Some background information on the subject matter and history of the patent and the relevant chemical principles may be helpful.

B. *Chemical Principles*

[45] The experts did not disagree on the organic chemistry and biochemistry applicable to these proceedings. What follows is a very brief outline of that evidence.

(1) Stereochemistry

[46] An understanding of the basic principles of stereochemistry is necessary to understand the nature of the invention as claimed in the ‘206 Patent.

[47] Stereochemistry is the study of the three dimensional spatial orientation of compounds of atoms in molecules and the consequences of such arrangements. Molecules having exactly the same chemical composition (and molecular formula) as well as the same molecular structure (i.e. the same connectivity of atoms) may differ in their spatial arrangement in three dimensions. Such compounds are referred to as "stereoisomers".

[48] The term "chiral centre" or “stereocentre”, as it appears in stereochemistry, is used to describe carbon atoms that have four different function atoms or groups attached to it. A chiral compound is one that exists in two mirror image forms that are not superimposable—like a person’s hands.

[49] In order to describe the stereochemistry of molecules having chiral centres, chemists have devised a system whereby a chiral centre is described as being in either the R or S configuration, depending on the exact spatial arrangement of atoms around the chiral centre.

(2) ACE Inhibitors Generally

[50] Amino acids are the basic building blocks from which living matter is constructed. By combining various numbers and groups of these acids in various configurations, larger structures known as peptides are formed. The bonds between these acids are known as peptide bonds. Larger groups known as proteins may be formed from such acids.

[51] Enzymes are organisms present in the body that facilitate the conversion of materials such as proteins and peptides into other material. The enzyme that is of interest in this case is the

angiotensisn-converting enzyme (ACE). ACE can bind with a compound known as angiotensin I to produce angiotensin II. This conversion increases blood pressure by constricting blood vessels.

[52] Ramipril, along with other drugs mentioned in these reasons, are all "ACE inhibitors". ACE inhibitors bind with ACE to prevent the conversion of angiotensin I to angiotensin II; the result is lower blood pressure.

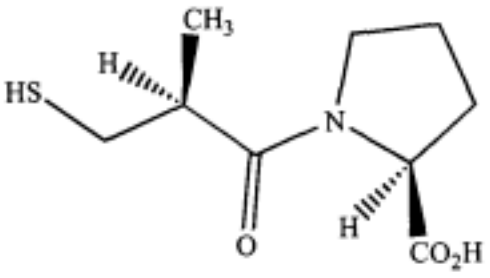
C. *History of ACE Inhibitors*

[53] A number of the experts in this trial were present at various critical times during the history of ACE inhibitors and provided very useful evidence. A number of the articles produced in evidence were also helpful. I summarize this evidence in the following paragraphs.

[54] Dr. Horovitz, who became Director of Pharmacology at Squibb in 1967, provided an excellent summary in his report of the early history of ACE inhibitors. The story begins in the late 1960s, when scientists began studying the venom of the *Bothrops jararaca*, an indigenous Brazilian snake, because it was known to reduce blood pressure. Scientists at Squibb isolated the active compound and synthesized a compound known as teprotide, a peptide. Teprotide was first tested on humans in 1973 and proved to be an effective antihypertensive agent in humans. However, teprotide was only effective through intravenous administration.

[55] The transformation of teprotide into an orally-effective ACE inhibitor occurred as a result of work done by a team of scientists working for Squibb, including Drs. Miguel Ondetti and David

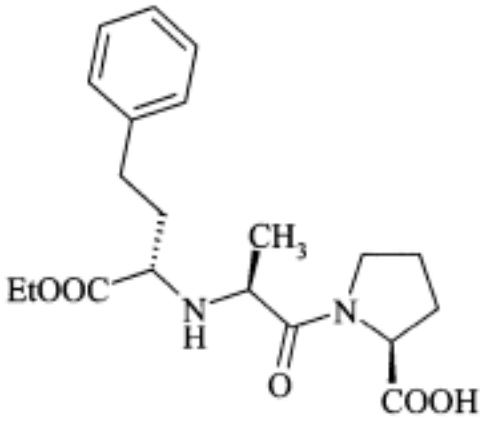
Cushman. Although the precise structure of ACE was not known at the time, the Squibb scientists developed some hypotheses about a model in the human body for ACE, relying upon what was known about another enzyme known as carboxypeptidase A. According to Dr. Horovitz, one of the first steps taken by the Squibb scientists was to include a carboxyl group (HO_2C) at the terminal of the teprotide molecule based on prior art in relation to carboxypeptidase A. They then added a CH_2 to the backbone. Next, the scientists introduced a sulfhydryl (SH) group in the terminal position instead of the carboxyl group. This was captopril, the first small molecule, orally-effective ACE inhibitor. As stated by Dr. Horovitz, "[a]fter almost ten years of work at Squibb, and the testing of thousands of compounds, Squibb finally had a drug that could be used for the treatment of hypertension and was orally active". The structure of captopril is set out below:



Captopril

[56] While captopril was a tremendous innovation in the development of ACE inhibitors, the presence of the sulphur atom was responsible for serious side effects in some people. The next major advancement came from Merck. In response to the problem of the side effects, the Merck scientists (including Dr. Thorsett and Dr. Patchett) focused on removing the sulfhydryl (SH) group (also referred to as a thiol group or thiol moiety). The replacement of the thiol group with a carboxylic acid (COOH) moiety resulted in enalapril. While enalapril lacked the sulphur moiety present in captopril, it retained the proline unit or five-membered ring structure at the C-terminus of

the compound. This new ACE inhibitor had three stereocentres, all of which were in the S configuration. The structure of enalapril is set out below:



Enalapril

[57] On June 18, 1980, at a medicinal chemistry conference in Troy, New York (the Troy conference), Dr. Patchett presented Merck's new ACE inhibitor. The disclosure made by Merck at the Troy conference was widely anticipated by the ACE inhibitor community. During his appearance at this trial, Dr. Patchett testified that there were at least several hundred – maybe more – attendees for his lecture . Many of those in attendance were scientists at a number of pharmaceutical companies who had been carrying out research to develop new ACE inhibitor drugs. Dr. Elizabeth Smith of Schering was one such scientist. As discussed below, Dr. Smith had carried out some preliminary work that, she hoped, could build on or incorporate the Merck disclosure.

D. *Schering's Work on ACE Inhibitors*

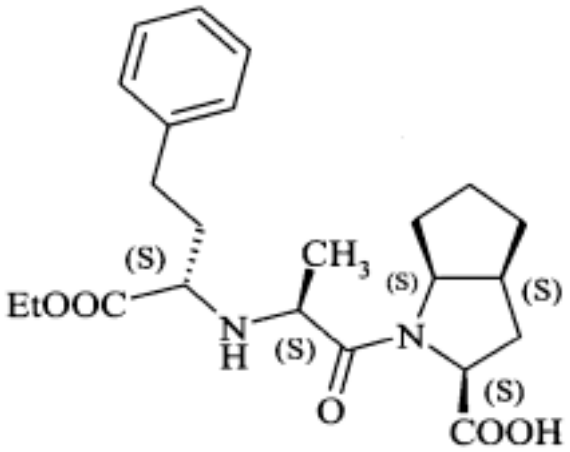
[58] Although more will be said further on in this decision about the development work done by Schering during the late 1970s and early 1980s, it is helpful at this point to provide an overview of the nature of the research work that was being done by Schering leading up to the application for what would become the '206 Patent and the compound ramipril. In this respect, the evidence of Dr. Smith and Dr. Neustadt was helpful.

[59] Prior to the Merck announcement at the Troy conference in June of 1980, scientists at Schering, including Dr. Smith, were trying to develop an antihypertensive compound that would be more effective than captopril. While Merck's work involved the removal of the thiol group, Schering's work focused on a different aspect of the captopril molecule - that is, the proline unit. By late 1979 or early 1980, Dr. Smith and her colleagues had found that the replacement of the proline in captopril with certain fused ring or spirocyclic moieties resulted in active compounds.

[60] As a result of the Merck disclosure at the Troy conference, the Schering scientists decided to try to create compounds combining the Merck disclosure with the work that they had already been working on in relation to the proline end of the molecule. That is, Schering's scientists decided to try using various spirocyclic and bicyclic ring structures in place of the proline on an enalapril-type molecule. This proposed work was documented in an invention disclosure report dated June 20, 1980. According to Dr. Smith, this report shows the conception of the generalized structure of the compounds in what ultimately became the '206 Patent.

[61] On October 23, 1980, Schering filed US Application No. 199,886. The subsequent Canadian patent application claimed priority from this U.S. patent application.

[62] On October 20, 1981, Schering filed Patent Application 388,336 (the '336 Application) in Canada. The Canadian application ultimately resulted in the issuance of the '206 Patent in March of 2001. The '206 Patent Claims 1, 2, 3, 6 and (subject to some disagreement) 12 cover the molecule known as ramipril, a very successful commercialized compound. The structure of ramipril is set out below:



Ramipril

E. *The Conflict Proceedings*

[63] As noted, Schering filed the '336 Application in Canada on October 20, 1981. Other claimants also applied for the issuance of patents covering certain compounds. Of specific interest, ADIR filed Application 387,093 (the '093 Application) and Hoechst Aktiengesellschaft (Hoechst), a predecessor to Sanofi Deutschland, filed Patent Application 384,787 (the '787 Application). As

provided for in the *Patent Act*, certain of the claims in the '336 Application were placed into conflict with claims in the other applications.

[64] The conflict proceedings continued until December 12, 2000 when the three parties to the conflict consented to an Order of Justice Marc Nadon, which Order provided for an allocation of the claims in conflict. As a result, the '206 Patent finally issued on March 20, 2001.

V. Prior Litigation

[65] These actions are not the first litigation involving the '206 Patent and ramipril. All of the earlier cases involved applications brought pursuant to the *NOC Regulations*. The legislative scheme of the *NOC Regulations* is complex. Simply stated and of particular relevance to this litigation, a party such as Apotex or Novopharm (referred to in the *NOC Regulations* as a "second person") may seek authorization (in the form of a Notice of Compliance (NOC)) from the Minister of Health to market a drug, in spite of the fact that the drug may be the subject of a patent. Once a party has declared its intentions to seek an NOC, it must address all patents that might affect its proposed product. A patent holder or other "first person" may apply to the Federal Court for an Order of Prohibition preventing the Minister from issuing the necessary authorization to the "second person".

[66] There is no doubt that the applications brought under the *NOC Regulations* involve allegations of infringement and invalidity. However, at the end of the proceeding, the judge hearing the application is not tasked with making a final determination of infringement and validity. Rather,

the judge must determine whether the allegation by the second person is "justified". The distinction is a fine one, which is based, to a large degree, on the "summary" nature of the NOC hearing (see, for example, *Pharmacia Inc. v. Canada (Minister of Health and Welfare)* (1994), 58 C.P.R. (3d) 209 at paras. 13-14 (F.C.A.); *AB Hassle v. Apotex Inc.*, 2006 FCA 51, [2006] 4 F.C.R. 513 at para. 2 [*AB Hassle*]). An NOC proceeding is conducted on a "paper record" of affidavit evidence and on the limited written and oral submissions of counsel. There is no opportunity for *viva voce* evidence from the experts who might provide further guidance and clarification to the hearing judge. So, even though these "summary" proceedings involve thousands of pages of affidavit evidence, extensive cross-examination and many hundreds of hours of work by all parties concerned (and the applications Judge), the result does not provide a determinative finding on the patent's validity. A patent holder who fails to obtain an Order of Prohibition may still commence a patent infringement action. Conversely, a generic company against whom a Prohibition Order has been made may bring an action to impugn the patent. Given this situation, I can sympathize with the frustration expressed by Dr. Bernard Sherman who, during his testimony, expressed the following views:

> It may well be that some didn't turn his mind adequately to what happens afterwards and maybe no one even considered the possibility that there would be subsequent litigation.
>
> But the regime doesn't make sense if generic manufacturers are going to do the research, litigate for years, win under the regulations and then be unable to launch; particularly if there is no undertaking for damages, the industry can't survive.

[67] However, until and unless Parliament sees fit to address the scheme of the *NOC Regulations*, the situation will arise where a party to an NOC proceeding is exposed to the risk of patent infringement or impeachment proceedings, as applicable.

[68] This was the background against which the earlier ramipril litigation was conducted and against which I must consider such jurisprudence.

[69] In the case of *Aventis Pharma Inc. v. Pharmascience Inc*., 2005 FC, 340, [2005] 4 F.C.R. 301, [referred to as *Ramipril I (FC)*)], Aventis Pharma Inc. (a predecessor to Sanofi Canada) sought an Order of Prohibition, under the *NOC Regulations*, to prevent the Minister of Health from issuing an NOC to Pharmascience Inc. in respect of ramipril. At that time, three different patents were listed for ALTACE on the register maintained by the Minister pursuant to *NOC Regulations*: the '206 Patent; Canadian Patent 1,187,087 and Canadian Patent 1,246,457 (the '457 Patent). In the Notice of Allegation served by Pharmascience in relation to its ramipril capsules, Pharmascience alleged that claims 1, 2, 3, 6 and 12 of the '206 Patent were invalid because they covered subject matter that is not patentably distinct from the subject matter of the claims of the '087 Patent and the '457 Patent. In other words, Pharmascience argued that the '206 Patent was invalid on the basis of "double patenting", an argument that is raised in the case now before me, by both Apotex and Novopharm. On the evidence before me in that application, an Order of Prohibition was issued.

[70] My overall conclusion in *Ramipril I (FC)* was affirmed in *Pharmascience Inc. v. Sanofi-Aventis Canada Inc.*, 2006 FCA 229, [2007] 2 F.C.R. 103 [*Ramipril I (FCA)*]. Specifically, the Court of Appeal rejected Pharmascience's arguments that the '206 Patent was invalid for obviousness or double patenting.

[71] In *Aventis Pharma Inc. v. Apotex Inc*., 2005 FC 1283, 278 F.T.R. 1 [referred to as *Ramipril II (FC)*], Justice Anne Mactavish dismissed an application by Aventis Pharma Inc. to

prohibit the Minister of Health from issuing an NOC to Apotex. The basis of Justice Mactavish's decision was that Apotex's allegation of the absence of sound prediction for the claims in question was justified. The result of this decision was that the Minister of Health issued an NOC to Apotex, permitting Apotex to market Apo-Ramipril. The decision of Justice Mactavish was affirmed by the Court of Appeal in *Aventis Pharma Inc. v. Apotex Inc.*, 2006 FCA 64, 265 D.L.R. (4th) 308 [*Ramipril II (FCA)*].

[72] In *Sanofi-Aventis Canada Inc. v. Novopharm Ltd*., 2007 FCA 163, [2008] 1 F.C.R. 174 [*Ramipril III*], another case dealing with NOC proceedings in respect of the '206 Patent, the majority of the Court of Appeal found it to be an abuse of process within the meaning of the *NOC Regulations* for a patent holder to relitigate an allegation of invalidity against a generic, if the allegation had been held to be well founded in an earlier proceeding against a different generic. Subsequently, Novopharm was also issued an NOC, permitting it to market Novo-Ramipril.

[73] The final decision involving ramipril and the '206 Patent was *Sanofi-Aventis Inc. v. Laboratoire Riva Inc.*, 2007 FC 532, 58 C.P.R. (4th) 109 [*Ramipril IV (FC*)]. Justice Sean Harrington followed the Court of Appeal decision in *Ramipril III* and dismissed the application by Sanofi-Aventis et al. Because of the prospect of a successful appeal to the Supreme Court of Canada in *Ramipril II (FCA)* – which did not come to pass – Justice Harrington continued on to express his views on the substantive issues before him. While he agreed with Justice Mactavish's conclusions on the issue double patenting in *Ramipril II (FC)*, he would have come to different conclusion on the question of sound prediction. Justice Harrington, based on the evidence before him, would have

concluded that there was a sound basis for Schering's prediction of ACE inhibition by the compounds of the relevant claims of the '206 Patent.

VI. Validity, Presumption and Burden

[74] The Plaintiffs bear the burden of demonstrating that the Defendants have infringed the '206 Patent. Once infringement has been established, the burden shifts. Under s. 43(2) of the *Patent Act*, a patent is presumed valid in the absence of evidence to the contrary. The Defendants have the onus of demonstrating that the '206 Patent is not valid. The Defendants do not disagree with this burden. The parties differ, however, with respect to one aspect of the appropriate evidentiary burden on the Defendants.

[75] The Plaintiffs point to Supreme Court jurisprudence that teaches that the burden is on the Defendants to show that the Commissioner of Patents erred in allowing the '206 Patent (see *Schmeiser v. Monsanto Canada Inc.*, 2004 SCC 34, [2004] 1 S.C.R. 902 at para. 24 (*Schmeiser)*; *Apotex Inc. v. Wellcome Foundation Ltd*., 2002 SCC 77, [2002] 4 S.C.R. 153 at paras. 42-44 [referred to as *Wellcome AZT (SCC)*]). Further, the Plaintiffs submit that I should review the Commissioner's decision on a reasonableness standard, as one would do in the context of an application for judicial review of the decision by the Commissioner to issue the '206 Patent.

[76] In my view, the burden on the Defendants in this patent infringement action is not one that can easily be defined by judicial review standards. The focus of the Court in this litigation is s. 43(2) of the *Patent Act*, which directly places the burden on the Defendants to rebut the presumption of

validity. For the most part, the decision of the Commissioner is simply not relevant to the determination before me. Having said that, this does not mean that I cannot have any regard for the Commissioner's decision. Subject to weight, some determinations of the Commissioner may be of assistance.

[77] The evidentiary burden is that of a civil burden of proof. The Defendants can meet their burden if they can persuade me, on a balance of probabilities, either that: (a) they have not infringed the '206 Patent; or (b) the claims at issue are invalid on any one of the grounds advanced by them.

[78] In this case, the Defendants do not contest all of the claims of the '206 Patent; issue is taken only with respect to Claims 1, 2, 3, 6 and 12. Accordingly, a finding that Claims 1, 2, 3, 6 and 12 are invalid would invalidate only those claims and not the entire '206 Patent.

VII. Claims Construction

A. *Principles of Claims Construction*

[79] The first step in a patent suit is to construe the claims, in accordance with principles that were clearly stated in *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67, [2000] 2 S.C.R. 1067 [*Whirlpool*] and many other cases. This jurisprudence teaches that claims are to be interpreted in a purposive way in order "to achieve fairness and predictability and to define the limits of the monopoly" (*Dimplex North America Ltd. v. CFM Corp.*, 2006 FC 586, 292 F.T.R. 38 at para. 49, aff'd 2007 FCA 278, 60 C.P.R. (4th) 277 [*Dimplex*]). Where necessary, the whole of the patent, and

not only the claims, should be interpreted (*Eli Lilly Canada Inc. v. Apotex Inc*, 2008 FC 142, 63 C.P.R. (4th) 406 at para. 25; *Eli Lilly Canada Inc. v. Novopharm Ltd*., 2007 FC 596, 58 C.P.R. (4th) 214 at para. 103).

[80] Construction of the claims is a matter for the Court to determine. The Court is called on to determine, on an objective basis, what a hypothetical skilled person would have understood the inventor to mean (*Whirlpool,* above, at paras. 45, 53). Where a patent is of a highly technical nature, the person skilled in the art will be someone possessing a high degree of expert scientific knowledge and skill in the particular branch of the science to which the patent relates (*Ramipril II (FC)*, above, at para. 64; *Apotex Inc. v. Syntex Pharmaceuticals International Ltd*., [1999] F.C.J. No. 548 at para. 38 (C.A.) (QL)).

[81] The Court should construe the claims in light of the description in the specification, assisted, where necessary, by experts as to the meaning of technical terms, if they cannot be understood by the Court from reading the specification (*Shire Biochem Inc. v. Canada (Minister of Health)*, 2008 FC 538, 328 F.T.R. 123 at para. 22 [*Shire*]; *Whirlpool,* above, at para. 45).

[82] It is also important to recognize that purposive construction should be directed at the points at issue between the parties. To quote Justice Hughes in *Shire,* above, at paragraph 21:

> The Court, however is not to construe a claim without knowing where the disputes between the parties lie. To quote Justice Floyd of the England and Wales High Court (Patent Court) in *Qualcomm Incorporated v Nokia Corporation* [2008] EWHC 329 (Pat) at paragraphs 7 to 11, who in turn quoted the late Justice Pumfrey (as he then was) in *Nokia v Interdigital Technology Corporation* [2007] EWHC 3077 (Pat), "it is essential to see where the shoe pinches so that one can concentrate on the important points".

[83] Lastly, as the '206 Patent was issued under the old *Patent Act*, all claims at issue are to be construed as of the date of issue and grant of the patent (*Pfizer Canada Inc. v. Canada (Minister of Health)*, 2005 FC 1725, 285 F.T.R. 1 at para. 36).

[84] With these overarching principles in mind, I turn to the patent in question.

B. *Person Skilled in the Art*

[85] Having reviewed the submissions of the parties and the expert evidence on the qualifications of a skilled person, I am satisfied that there is no material difference amongst the positions of the parties or their experts. In short, I am satisfied that the skilled person is an individual holding a Master's or Ph.D. degree in synthetic organic chemistry, medicinal chemistry, pharmacology or another area of biochemistry or biology and having at least a few years of experience in either industry or academia.

C. *Description of the '206 Patent*

[86] As noted, claims should be construed in light of the specification offered in the patent. A brief review of the description of the '206 Patent would therefore be useful at this time.

[87] The '206 Patent is entitled “Carboxykyl Dipeptides, Processes for Their Production and Pharmaceutical Compositions Containing Them”. The introductory first paragraph of the description gives a broad description of the invention and sets the stage for the skilled reader’s understanding of the claims:

> The present invention relates to carboxyalkyl dipeptides which are useful as inhibitors of angiotensin-converting enzyme and as antihypertensive agents.

[88] The patent description then sets out that the compounds of the invention are compounds of a very general formula (referred to as Formula I). Formula I covers a huge class of compounds as it identifies numerous variable substituents and includes all possible stereochemistry and all pharmaceutically acceptable salts.

[89] In 18 pages of the description, various configurations of Formula I are described and further formulae set out. Embodiments including bicyclic rings and spiral rings are listed and some compounds are described as “preferred” or “more preferably” or even “most preferably” (see page 14, for example). Of particular note is the fact that, beyond these bare allegations of relative effectiveness, there is no information on how these designations were arrived at and no experimental data to assist the reader in making such determinations.

[90] Furthermore, throughout the patent, the compounds are described as including “all possible stereoisomers” (see, for example, page 16). The only statement that appears to limit stereochemistry is on page 17 where the inventors state the following:

> In general . . . the aminoacid part-structures . . . of Formula I are preferred in the configuration most similar to that of natural L-amino

> acids. Usually, natural L-aminoacids are assigned the S-configuration. A notable exception is the natural amino acid L-cysteine which is assigned the R-configuration

[91] These descriptions are all so broad as to be of little use in interpreting the claims of the patent.

[92] Beginning on page 18, the description turns to the making of the compounds, stating that:

> The compounds of the present invention can be produced by one or more of the methods and subroutes depicted in the following equations. Reactive groups not involved in the condensations described below such as amino, carboxy, mercapto, etc., may be protected by methods standard in peptide chemistry prior to the coupling reactions and subsequently deprotected to obtain the desired products. In other words, in the formula of the following description of the processes R, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above for Formula I, including suitable protection.

Following these introductory words, the writers describe processes A to E by which a compound of Formula I can be obtained. Once obtained, a compound "obtained by any one of processes A to E can be transformed into another compound of formula I by methods known in the art" (p. 22). The first mention of diastereomers and mixtures of compounds and the need to separate them is found at page 23, where it is stated that:

> In the compounds of Formula I, the carbon atoms to which R^1, R^3 and R^5 are attached may be asymmetric. The compounds accordingly exist in disastereoisomeric [sic] forms or in mixtures thereof. The above described syntheses can utilize racemates, enantiomers or diastereomers as starting materials. Enantiomeric intermediates may be obtained by resolution methods known in the art. When diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods.

[93] With respect to the making of the compounds of Formula I, I can see no limiting language. That is, while the description sets out some ways to obtain the compounds, I read this to mean that there may be other processes that could be used. The experts do not disagree with this interpretation. For example, during his appearance, Dr. Fleming agreed that "the teaching of this patent is that bicyclic ring is either a known compound and/or can be prepared according to known methods". Applying this finding to the claims, I would not construe the patent claims to require that the claimed compounds result from any particular synthesis route.

[94] Beginning at page 26 of the '206 Patent, the description sets out 67 examples which "illustrate the preparation of the compounds of the present invention". The authors state that any diastereomers prepared by any of the methods "may be isolated by column chromatography or fractional crystallization". Of particular interest in this litigation is Example 20, which sets out the method for making 1-[N-(1-carboethoxy-3-phenylpropyl) – (S)-alanyl] octahydrocyclopenta [b] pyrrole-2(S)-carboxylic acid:

> A. Substitute octahydrocyclopenta [b] pyrrole (prepared by reduction of 2-ketooctahydrocyclopenta [b] pyrrole in tetrahydrofuran with lithium aluminum hydride) for octahydroisoindole in Example l8A to obtain octahydrocylo-penta [b] pyrrole-2-carboxylic acid.
>
> B. Use ethyl octahydrocyclopenta [b] pyrrole-2-carboxylate (prepared by esterification with the ethanol of the acid prepared as described in paragraph A) in place of ethyl octahydroindole-2-carboxylate in the procedure described in paragraphs B through E of Example 1 to give the title compound.

[95] Example 20A, in turn, relies on Example 18A which is as follows:

> 2-[N- (l-carboethoxy-3-phenylpropyl) - (S) -alanyl] octahydroisoindol -1(S) - carboxylic acid
>
> Heat cis-octahydroisoindole (prepared by reduction of cis-hexahydrophthalimide in tetrahydrofuran with lithium aluminum hydride) and mercuric acetate in 10% aqueous acetic acid under reflux for twenty hours to give cis-hexahydro-Δ^1-isoindole. Dissolve this compound in water and treat with potassium cyanide followed by 2N hydrochloric acid at 0° for two hours and at room temperature for twenty hours to give l-cyano-cis-octahydroisoindole. Heat this cyano compound in 6N hydrochloric acid under reflux for 6 hours followed by concentration of the reaction mixture and absorption of the residue on an XAD-2 resin column. Elute with methanol to obtain cis-octahydroisoindole-l-carboxylic acid.

[96] Following the examples, at pages 72 to 97, a lengthy list of compounds is provided, which compounds, according to the inventors "exemplify the compounds of formula I, which can be prepared according to the described processes".

[97] Finally, beginning at page 97, the description sets out sample formulations that are "illustrative of the present invention" and notes that:

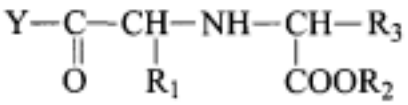
> It will be apparent to those skilled in the art that many modifications, both of materials and methods, may be practiced without departing from the purpose and intent of this disclosure.

[98] With the perspective given by this lengthy disclosure, I turn to the construction of the claims at issue, beginning with Claims 1, 2, 3 and 6.

D. *Construction of Claims 1, 2, 3 and 6*

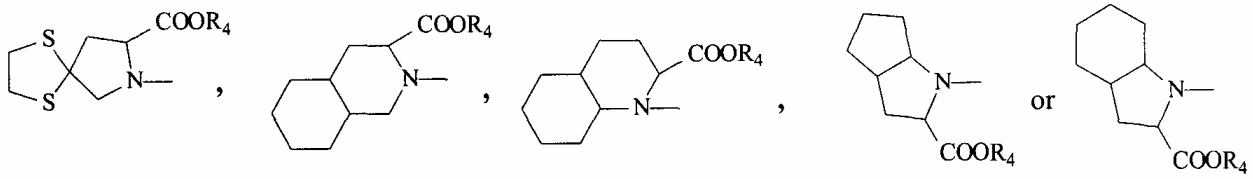
[99] There is no material controversy over the proper construction of Claims 1, 2, 3 and 6. Those claims state as follows:

1. Compounds having the general formula:



wherein:

Y is selected from:



R_4 is selected from hydrogen and C_{1-4} alkyl;

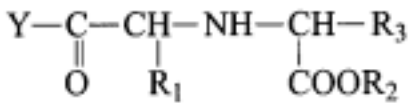
R_1 is selected from C_{1-4} alkyl which may be substituted with amino;

R_2 is selected from hydrogen and C_{1-4} alkyl;

R_3 is selected from phenyl—C_{1-3} alkyl and $(CH_2)_{1-2}$—X—C_{1-4} alkyl wherein X is S or NH; and

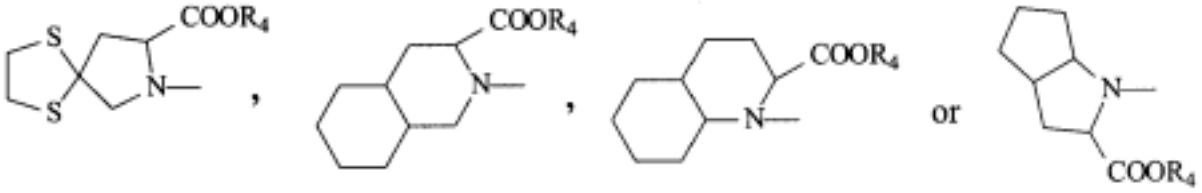
their pharmaceutically acceptable salts.

2. Compounds having the general formula:



wherein:

Y is selected from:



R_4 is selected from hydrogen and C_{1-4} alkyl

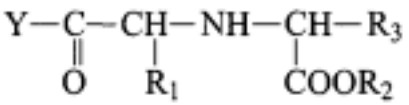
R_1 is selected from C_{1-4} alkyl which may be substituted with amino;

R_2 is selected from hydrogen; and C_{1-4} alkyl;

R_3 is selected from C_{1-9} alkyl, phenyl—C_{1-3} alkyl and $(CH_2)_{1-2}$—X—C_{1-4} alkyl wherein X is S or NH; and

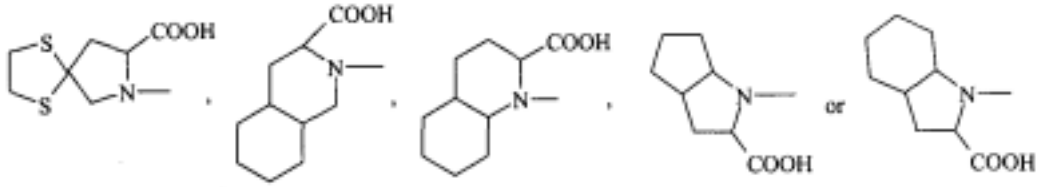
their pharmaceutically acceptable salts.

3. Compounds having the general formula:



wherein:

Y is selected from:



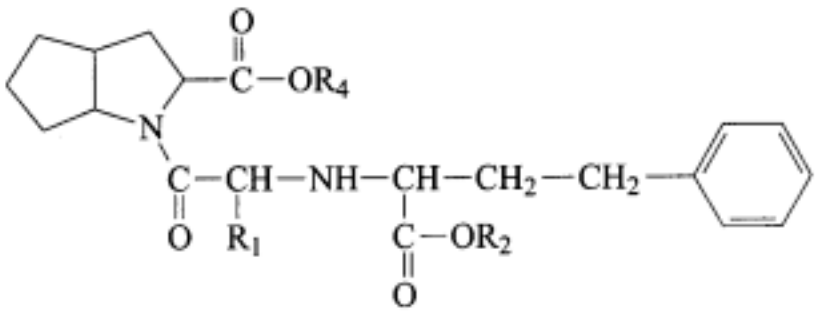
R_1 is selected from C_{1-4} alkyl which may be substituted with amino;

R_2 is selected from hydrogen and C_{1-2} alkyl;

R3 is selected from phenyl – C_{1-1} alkyl;

and their pharmaceutically acceptable salts.

6. Compounds having the general formula:



wherein:

R_1 is selected from C_{1-4} alkyl;

R_2 is selected from hydrogen and C_{1-4} alkyl; and

R_4 is selected from hydrogen and C_{1-4} alkyl; and

their pharmaceutically acceptable salts.

[100] Each of Claims 1, 2, 3 and 6 is what is known as a "*Markush*" claim. (*Markush* claims were named after Eugene Markush, the first inventor to use them successfully in a U.S. patent (see *Ex parte Markush*, 1925 Dec. Comm'r Pat. 126, 128 (1924)). A *Markush* claim is expressed as a chemical formula with multiple "functionally equivalent" chemical entities allowed in one or more parts of the compound. In very general terms and as described by Schering in its final argument, each of Claims 1, 2, 3 and 6 claims a class of compounds containing various ring moieties, which are coupled with a "backbone" taught in the earlier Merck enalapril patent.

[101] Claims 1, 2 and 3 describe subclasses of compounds which can cover the following analogues of enalapril:

- octahydroindole (which can be referred to as "6,5-saturated bicyclic ring");
- perhydroquinoline and perhydroisoquinoline (which can be collectively referred to as "6,6-saturated bicyclic ring);
- octahydrocyclopenta[b]pyrrole (which can be referred to as "5,5-saturated bicyclic ring"); and
- 1,4-dithia-7-azaspiro[4.4]nonane (which can be referred to as "spirocyclic").

[102] Because of the multiple variations of substituents described in each of Claim 1 and 2 and the existence of unspecified chiral centres, the number of compounds encompassed is vast. For example, Dr. McClelland estimated that Claim 1 would cover about 29 million compounds. Claim 2 is even larger (about 228 million compounds). Claim 3 is slightly narrower (about 215,424 compounds), according to the evidence of Dr. McClelland.

[103] Claim 6 is limited to 5,5-saturated compounds, where R_1, R_2 and R_4 have the options described in the claim. The structure drawn in Claim 6 contains five asymmetric carbon atoms; the claim does not specify chirality at any of the five asymmetric carbon atoms or stereocentres. According to Dr. McClelland, Claim 6 would include about 28,800 compounds.

[104] It was accepted by all of the experts that ramipril is one of the compounds covered by Claims 1, 2, 3 and 6.

E. *Construction of Claim 12*

[105] Insofar as Novopharm is concerned, the "shoe pinches" in the construction of Claim 12 of the '206 Patent. Claim 12 is as follows:

> 12. The compound 1- [N- (l-carboethoxy-3-phenylpropyl) – (S) - alanyl] octahydrocyclopenta [b] pyrrole-2 (S) -carboxylic acid and its pharmaceutically acceptable salts thereof.

[106] As written, Claim 12 specifies the stereochemistry at only two stereocentres: (S)-alanyl and 2(S)-carboxylic acid at the 2-position of the bicyclic ring structure. As noted, those are set in the S configuration; the others are not specified. Yet, as agreed by all of the experts and accepted by me, the skilled person would know that the described structure would have five stereocentres or chiral centres. Since the Claim does not exclude any possible diastereomers for the unspecified three stereocentres, Claim 12 includes eight possible compounds. Each compound would have two centres designated in the S configuration, with the other three in either an R or S configuration. When all stereocentres are in the S configuration, the compound is ramipril.

[107] With respect to the construction of Claim 12, the question that has arisen is whether it claims each of the eight individual diastereomers, as submitted by Schering and Sanofi, or only a mixture of the eight – and not to the individual diastereomers – as asserted by Novopharm. Initially, both Apotex and Novopharm claimed that Claim 12 was a claim to a mixture. In final argument, only Novopharm pursued this argument. The question is important because, if Novopharm is correct, Claim 12 cannot be construed to cover ramipril.

[108] Except for two Novopharm expert witnesses, all of the experts accepted that Claim 12 is a claim to eight individual diastereomers, one of which is ramipril. Specifically, the testimony of Drs. Bartlett, Patchett, Nelson and Wuest for the Plaintiffs and Drs. Thorsett, Fleming and McClelland for Apotex was consistent with this construction of Claim 12. Novopharm's experts, Dr. Ehlers and Dr. Moody, were the only experts to differ. I turn to a consideration of the arguments for the "mixture construction" advanced by Novopharm and its two experts.

[109] Briefly stated, the arguments of Novopharm can be summarized as follows:

- In Claim 12, the patentee uses the singular word "compound". In contrast, the plural word "compounds" is used in claims 1, 2, 3 and 6, each of which include many compounds.

- Dr. Ehlers opined that chemists often do not resolve and characterize diastereomers; the product of a reaction will often be referred to as "the compound", even where it is a mixture of diastereomers.

- In the disclosure, the word “compound” is used to describe mixtures of diastereomers. By way of example, Example 20B states that the process described will give “the title compound”; the title compound in Example 20 is a mixture of diastereomers. Importantly, since the compound named in Example 20 is the “compound” claimed in Claim12, this means that the claim refers to a single compound.

- As acknowledged by Dr. Bartlett, the majority of the examples in the '206 Patent are for a compound which consists of a mixture of diastereomers.

- The use of the word “compound” to describe a mixture is consistent with the common use of the word; even Dr. Patchett referred to a mixture as a compound in the scientific paper published in *Nature Magazine* that disclosed enalapril.

[110] I am not persuaded that the construction proposed by Novopharm should prevail.

[111] The first problem that I have with the submissions relates to the comparison of Claim 12 to Claims 1, 2, 3 and 6. Claim 12 differs fundamentally from the earlier claims in that it describes only one chemical formula. In contrast, claims 1, 2, 3 and 6 are *Markush* claims. As such, the plural “compounds having the general formula” is used because the alternative—writing each of the names of the compounds covered—would be a tedious and unnecessary exercise. Thus, it is logical to refer to Claims 1, 2, 3 and 6 as “compounds”, while using the term “compound” to describe the sole chemical formula given by Claim 12. The construction that I have adopted finds further support

in a review of all of the claims of the '206 Patent, which discloses that the word "compounds" is used for all of the *Markush* claims and the word "compound" where a general formula is not used. Therefore, I do not believe that any deeper inference should be drawn from the use of "compounds" in Claims 1 to 7 and "compound" in Claims 8 to 13.

[112] When I review the format of the claims in the context of the entire patent, I am satisfied that the use of the word "compound" in Claim 8 was never intended to apply to only a mixture. Rather, it appears to me that the word was used only as a means to differentiate the later claims from the earlier *Markush* claims. Novopharm's interpretation of the word "compound" in isolation from the balance of the '206 Patent ignores this difference.

[113] With respect to some of the other arguments of Novopharm, I am not in disagreement. Dr. Ehlers is no doubt correct that scientists may sometimes refer to a mixture as a "compound". Nevertheless, I do not believe that one can draw from this a conclusion that every reference to a "compound" is to a mixture or that the use of the word "compound" precludes use of the word to describe more than one compound.

[114] Novopharm also submits that its interpretation of Claim 12 is consistent with the fact that Schering had not, as of the Canadian filing date, made any of the diastereomers of Claim 12 as a single compound, but only as mixtures. Thus, Novopharm argues, Schering did not have sufficient information to claim each compound on its own.

[115] The basic flaw in this argument is that, on these facts, it is illogical. Novopharm is correct that Schering had not made the individual compounds. However, it also never made a mixture of all eight compounds included in the Claim 12 description. The application of Novopharm's reasoning would lead to the absurd conclusion that Claim 12 cannot cover either the individual compounds or a single mixture of all eight. The more serious problem with Novopharm's submission is that Schering was not required to make each of the individual compounds claimed, provided that there was a sound prediction that the claimed compounds of Claim 12 would be useful. Therefore, the fact that each of the eight compounds claimed in Claim 12 has not been made has no bearing on the proper construction of that claim. The question of sound prediction is addressed later in these reasons.

[116] The notion of Claim 12 as a mixture was unequivocally rejected by most of the experts. Dr. Bartlett's testimony on this question was particularly helpful. When asked in direct examination about his view of the construction of Claim 12, Dr Bartlett noted that chemists will "use the term compound when what we are talking about is a conceptual structure". He also pointed out aspects of the '206 Patent that would lead a skilled reader to interpret Claim 12 as a claim to eight individual compounds. One such point is that the patent teaches separating mixtures of compounds to obtain individual stereoisomers, thereby inferring that individual stereoisomers are the claimed products. Even Dr. Moody, in cross-examination, agreed that the patent teaches to separate mixtures by known methods such as conventional chromatographic separation or fractional crystallization. If Novopharm's construction is correct and the claims refer only to mixtures, then why would the inventors instruct the skilled reader on how to separate such mixtures?

[117] Dr. Bartlett also referred to Claim 8, a claim not in dispute but which is described as a "compound". With no stereochemistry identified, there are 32 possible compounds. On Novopharm's interpretation, Claim 8 would be a mixture of all 32 compounds. This, as Dr. Bartlett opined, would lead to an absurdity since Example 67 of the '206 Patent illustrates the preparation of an all-S configuration compound that would be included in Claim 8. Why would an inventor explicitly describe the preparation of a compound in the specification and then claim the compound only as a mixture with 31 others?

[118] In sum, I prefer the evidence of Dr. Bartlett and the other experts for Sanofi, Schering and Apotex over that of Dr. Ehlers and Dr. Moody. As taught by *Whirlpool*, above, at paragraph 49, claims "must be read with a mind willing to understand". In my view, a skilled reader would not embark on a dry, linguistic interpretation of this patent but would read the claims in the context of the specification and having regard to the inventor's purpose. Reading Claim 12 as proposed by Novopharm is not a reading by a mind willing to understand but by a mind seeking to distort the logical meaning that flows from a reading of the claims in their context. I find that a person skilled in the art would construe Claim 12 as a claim to eight individual compounds. One of those compounds is ramipril.

F. *The "Promise" of the '206 Patent*

[119] A serious disagreement exists between the experts for the Defendants and the Plaintiffs on the question of whether claims should be construed to include an inherent promise that the compounds are useful as both ACE inhibitors and as antihypertensive agents. The experts for

Apotex and Novopharm construe the patent such that the compounds claimed would have utility in both ACE inhibition and reduction of high blood pressure. In contrast, the experts for Schering and Sanofi are of the view that the claims do not include a promise of antihypertensive reduction.

[120] The place to begin is the '206 Patent specification. What meaning can be drawn from the words used by the inventors to describe their invention?

[121] As noted, the '206 Patent opens with a simple declaration that:

> The present invention relates to carboxyalkyl dipeptides which are useful as inhibitors of angiotensin-converting enzyme and as antihypertensive agents. [Emphasis added]

[122] A key statement is made on p. 24 of the patent specification, where the inventors state that

> The compounds of this invention have useful pharmacological properties. They are useful in the treatment of high blood pressure. The compounds of the present invention can be combined with pharmaceutical carriers and administered in a variety of well known pharmaceutical forms suitable for oral or parental administration to provide compositions useful in the treatment of cardiovascular disorders and particularly mammalian hypertension. [Emphasis added]

[123] There is absolutely no language on p. 23-25 of the patent description that places any limitation on the usefulness of any of the compounds. There is nothing in the words that can be read to indicate that only some of the compounds will be useful or that only some of them will work as either ACE inhibitors or antihypertensive agents.

[124] When these provisions at pages 23-25 of the patent are read in light of the assertion that the compounds “are useful in the treatment of high blood pressure”, I believe that the skilled reader

would assume that the inventors were alleging that all of the compounds covered by Formula I would be useful in treating hypertension. Of course, the compounds claimed in the patent are subsets of those included in Formula I. Thus, if the patent is interpreted such that it asserts that all of the compounds will be useful in the treatment of hypertension, it follows that the inventors are also asserting that all of the claimed compounds of Claim 12 (and the other claims) would have such use.

[125] This interpretation of the promise of the patent was accepted by a number of the experts for the Defendants, including Drs. Thorsett, Moody, Patchett and Ehlers.

[126] Dr. Bartlett was the key expert witness for the Plaintiffs on this aspect of the '206 Patent. Specifically, his view of the promise of the patent, as contained in his expert report, is as follows:

> In my opinion, the person of ordinary skill would understand the logical linkage between ACE inhibition and antihypertensive activity . . . ; that is, that the compounds of the patent have activity as ACE inhibitors and that the utility of ACE inhibitors in medicine is as potential antihypertensive agents. The person of ordinary skill would not believe that every compound that has ACE inhibitory activity would possess all of the other properties necessary to exert an in vivo antihypertensive effect.

[127] In criticizing the experts who disagreed on this point, Dr. Bartlett stated that:

> In suggesting that every individual stereoisomer of every structure covered by the 206 Patent will possess the panoply of properties that is required for a drug to be effective in the treatment of a disease, Drs. Thorsett, Freidinger [who did not testify], and Ehlers are setting the bar too high. Indeed, at the time a patent is applied for, it is simply not possible for the inventors to have carried any compound covered far enough into commercial development to be able to assess whether it possesses all the properties, including lack of side effects or toxicity, that would enable it to be used to treat a disease like high blood pressure. Such an interpretation would be inconsistent with the understanding of a person skilled in the art with respect to a large number of other patents in the field of ACE inhibition and in other

> fields of medicinal chemistry where the activity of a compound can be linked to a means of treating a disease.

[128] This passage demonstrates that Dr. Bartlett has not construed the claims in light of the promised utility; rather he has modified or read down the promise of the patent to suit his understanding of the claims. I cannot accept this reasoning. Such an approach to the question of the promise of the patent excuses the inventors from any requirement of precision in their claims or in the patent specification. If a patentee promises a particular result, he should be held to that promise. In expressing this view, I am not requiring commercial success or a certain level of commercial development to have taken place. As noted, a "mere scintilla of utility" would be sufficient. Schering could have claimed only those compounds for which it had obtained some level of *in vivo* activity and those other compounds "more or less closely related", (*Monsanto Co. v. Commissioner of Patents* (1979), 42 C.P.R. (2d) 161 at 175 (S.C.C.) [*Monsanto*]), where it could reasonably infer some factual basis for concluding that activity could be predicted. Instead, Schering chose to claim a huge class of compounds; they should be construed in light of the promised utility described in the patent.

[129] I have another problem with the testimony of Dr. Bartlett. As was drawn to the attention of Dr. Bartlett and the Court, Dr. Bartlett's evidence in *Laboratoires Servier v. Apotex Inc.*, 2008 FC 825, 332 F.T.R. 193 [*Perindopril*] was inconsistent with his position before this Court. During cross-examination of Dr. Bartlett on this point, Dr. Bartlett expressed the opinion that the promise in Canadian Patent No. 1,341,196 (the '196 Patent) (the patent considered in *Perindopril*) was the

same promise as that found in United States Patent No. 4,105,776 (Squibb) and United States Patent No. 4,374,829 (Merck):

> Q. And you would agree with me that this Merck patent would be an example of something that would be contrasted to the '196 Patent and its promise?
> A. The wording is different. I think that one of skill in the art would understand that all of the patents in this field rest on the same scientific basis which I outline in my report; that is, people understand that inhibition of angiotensin-converting enzyme in vivo leads to an antihypertensive effect and, therefore, the utility of ACE inhibitors is as potentially antihypertensive agents.
>
> I think although the wording of the French patent is different from the wording of these English language patents, I think a person of ordinary skill in the art would take [the '196 Patent and the '206 Patent] as the same art and the same purpose and the same teachings in that sense. [Emphasis added]

[130] This is in stark contrast to his opinion in the *Perindopril* litigation in which Dr. Bartlett suggested that, unlike the *Perindopril* patent, the same Squibb and Merck patents and other patents in the field were promising both antihypertensive and ACE inhibition activity. The following are paragraphs from Dr. Bartlett's *Perindopril* report that were read into the record during his cross-examination in this proceeding:

> An antihypertensive effect of the compounds is not expressly promised by the '196 Patent. However, it was understood by the 1980s, and certainly by the publication date, that inhibition of angiotensin-converting enzyme in vivo leads to a lowering of arterial blood pressure. It was thus understood by one of skill in the art that the utility of an angiotensin-converting enzyme inhibitor is as a potential antihypertensive agent.
>
> The explicit promise of the '196 Patent is that the compounds disclosed are inhibitors of ACE, a promise that is less encompassing than that of other issued patents in the field. Merck's patents [e.g., the '829 Patent] that cover the carboxyalkyl dipeptide class of ACE inhibitors stated that the compounds are useful as converting-enzyme inhibitors and as antihypertensives. …. and as antihypertensives. . . . The patents from the Squibb Research Group [e.g., the '776 Patent]

> which cover a variety of ACE inhibitors classes state . . . [Emphasis added]

[131] The difficulty that I have with how Dr. Bartlett has interpreted the promise of the '206 Patent together with his inconsistent testimony as between the *Perindopril* action and this litigation leads me to question his objectiveness and to reduce the weight that his evidence on this point should be accorded.

[132] On this question, I prefer the opinion of Dr. Thorsett and Dr. Ehlers, each of whom concluded that the '206 Patent promises that all of the compounds will have utility as both ACE inhibitors and antihypertensives.

[133] My conclusion of a dual promise is consistent with existing jurisprudence on the promised utility of this and other ACE inhibition patents.

[134] Although the decision of Justice Mactavish in *Ramipril II (FC)*, above, may not be binding, I observe that Justice Mactavish was faced with the same question of the promise of the '206 Patent. Her conclusion was that the '206 Patent had a two-fold promise: "that is, the patent promises that the compounds claimed by the patent will have utility as both ACE inhibitors and as anti-hypertensive agents" (*Ramipril II (FC)*, above, at para. 280). Similarly, Justice Harrington in *Ramipril IV (FC)*, above, at paragraph 45, stated that "The promise was simply that the compounds claimed by the patent would have utility as both ACE inhibitors and anti-hypertensive agents".

[135] My assessment of the promise of the '206 Patent is also consistent with the determination of Justice Elizabeth Heneghan in *Pfizer Canada Inc. v. Apotex Inc.*, 2005 FC 1205, 43 C.P.R. (4th) 241 [*Pfizer Quinapril (FC)*]. In that case, Justice Heneghan was asked to examine the utility of claims of Canadian Patent No. 1,341,330 ('330 Patent), which patent covers another drug in the general class of ACE inhibitors. Pfizer argued that a purposive construction of the relevant claims, including reference to the specifications, discloses that the invention of the '330 Patent relates to ACE inhibition. On the other hand, Apotex argued that all of the claims of the '330 Patent promise compounds useful in reducing or relieving hypertension, which is distinct from ACE inhibition. With reference to the specification of the '330 Patent, Justice Heneghan concluded that the claims of the '330 Patent would be read by a person skilled in the art as referring to compounds useful for the relief of hypertension (*Pfizer Quinapril (FC)*, above, at para. 64). It appears clear that she reached this conclusion on the basis of specific words in the '330 Patent. The abstract of the patent stated that: "The compounds of the invention, their salts and pharmaceutical compositions thereof are useful as antihypertensive agents" [Emphasis added]. Another example of this direct promise could be seen in the sentence in the specification that read:

> Thus by the administration of a composition containing one or a combination of compounds of formula I or pharmaceutically acceptable salts thereof, hypertension in the species of mammal suffering therefrom is alleviated (*Pfizer Quinapril (FC)*, above, at para. 65).

[136] Although this decision was reversed in the Federal Court of Appeal, the Court of Appeal concluded that Justice Heneghan's characterization of the promise of the '330 Patent "is reasonable in light of the passage cited above and the overall [tenor] of the disclosure" (*Pfizer Canada Inc. v. Apotex Inc.*, 2007 FCA 209, 60 C.P.R. (4th) 81 at para. 121 [*Pfizer Quinapril (FCA)*]. The words of the specification for the '330 Patent and those contained in the '206 Patent are similar.

[137] In contrast, I observe the promise expressed in the words of the '206 Patent as compared to those of the '196 Patent considered in *Perindopril*, above. In *Perindopril*, the patent at issue related to a large class of compounds all of which were promised to have utility as ACE inhibitors. Apotex, in that case, argued that the patent made a two-fold promise; that is, the '196 Patent promised that all of the compounds would have utility as both ACE inhibitors and as antihypertensive agents. In rejecting that argument, I noted that "there is no statement in the '196 Patent, as there was for the '330 Patent, that the compounds of the invention . . . are useful as antihypertensive agents". (*Perindopril*, above, at para. 292). In the case now before me, there is such an explicit statement.

G. *Summary on Construction*

[138] In sum, the key aspects of the construction of Claims 1, 2, 3, 6 and 12 are as follows:

- Each of Claims 1, 2, and 3 claims a class of compounds all of which contain various ring moieties coupled with a "backbone" taught in the earlier Merck enalapril patent. The various bicyclic moieties encompass the following:

  — octahydroindole (which can be referred to as "6,5-saturated bicyclic ring");

  — perhydroquinoline and perhydroisoquinoline (which can be collectively referred to as "6,6-saturated bicyclic ring");

— octahydrocyclopenta[b]pyrrole (which can be referred to as "5,5-saturated bicyclic ring"); and

— 1,4-dithia-7-azaspiro[4.4]nonane (which can be referred to as "spirocyclic ring").

- Claim 6 is limited to compounds with a 5,5-saturated bicyclic ring structure.

- Claim 12 is a claim to 8 individual stereoisomers – all with a 5,5-saturated bicyclic ring structure – as described in the stated formula.

- Inherent in Claims 1, 2, 3, 6 and 12 is the utility of the compounds in inhibiting ACE and reducing hypertension.

VIII. Infringement

[139] A patent grants to the patentee, for the term of the patent, "the exclusive right, privilege and liberty of making, constructing, using and vending" (*Patent Act*, s.44). The question to be asked by the Court in determining infringement is: did the defendant by his acts or conduct, deprive the inventor, in whole or in part, directly or indirectly, of the advantage of the patented invention? (*Schmeiser*, above, at para. 44)

[140] In December 2006, Apotex received an NOC from Health Canada allowing it to market and sell ramipril capsules under the trade name of Apo-Ramipril. In May 2007, Novopharm received an NOC to market and sell ramipril capsules under the trade name of Novo-Ramipril. The evidence is clear that the sale of Apo-Ramipril and Novo-Ramipril constitutes an infringement of Claims 1, 2, 3, 6 and 12 of the '206 Patent. Infringement has been proved by the Plaintiffs.

[141] In the event that I were to find that the '206 Patent was infringed and valid, the only question that would remain is whether all ramipril product handled by the Defendants should be characterized as infringing product. Since I conclude, for the reasons that follow, that the claims in issue are not valid, there is no need to examine whether some volumes of product manufactured or in the possession of the Defendants should be exempted from liability. However, should it become necessary to do so I would begin with the exemption from liability pursuant to s. 55.2(1) of the *Patent Act* (as it now applies) or because of relevant common law principles.

IX. Utility

A. *General Principles*

[142] The *Patent Act* defines an invention as something that is "new and useful" (*Patent Act*, s. 2). From this comes the concept of "utility".

[143] A number of principles associated with the law of utility are well established through the jurisprudence. To begin, the overarching concept is that, as of the relevant date, there must have been a demonstration of utility of the invention or, lacking that, a sound prediction of utility based on the information and science available at the time of the prediction (see, for example, *Merck & Co. v. Apotex Inc.*, 2005 FC 755, 41 C.P. R. (4th) 35 at para. 121; *Pfizer Canada Inc. v. Apotex Inc.*, 2007 FC 26, 306 F.T.R. 254 at paras. 36-40, aff'd 2007 FCA 195, leave to appeal to S.C.C. refused, [2007] S.C.C.A. No. 371).

[144] As with the other questions of validity, the Defendants bear the burden. To demonstrate lack of utility, the Defendants must show "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do" (*Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.* [1981] 1 S.C.R. 504 at 525 [*Consolboard*]). As stated in *Wellcome AZT (SCC)*, above, at paragraph 56:

> If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, per Pigeon J. in Monsanto Co. v. Commissioner of Patents, [1979] 2 S.C.R. 1108, at p. 1117, the prediction at the date of 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".

[145] Beyond these general statements of the law, there are a number of other guiding posts:

- Where the specification does not promise a specific result, no particular level of utility is required - a "mere scintilla" of utility will suffice (H.G. Fox, *Canadian Law and Practice Relating to Letters Patent for Inventions*, 4th ed. (Toronto: Carswell, 1969) at 153). However, as stated in *Consolboard*, above, where the specification

sets out an explicit "promise", utility must be measured against that promise (see also *Pfizer Canada Inc. v. Canada (Minister of Health)*, 2008 FCA 108, 67 C.P.R. (4th) 23 at para. 53 [*Pfizer Atorvastatin (FCA)*]);

- Utility does not depend upon marketability (*Consolboard*, above, at 525; *Ramipril II (FC)*, above, at paras. 271-272). In other words, in assessing whether an invention has utility, the issue is not whether the invention is sufficiently useful as to be able to support commercialization, unless commercial utility is specifically promised;

- The relevant date has been held to be the filing of the Canadian patent application (*Ramipril II (FC)*, above, at paras. 88-96); and

- Where a claim is to a class of compounds, lack of utility of one or more of the compounds will invalidate all of the compounds of that particular claim (*Ramipril II (FCA)*, above, at para. 26).

[146] The doctrine of sound prediction can be relied upon by an inventor to justify patent claims whose utility has not actually been demonstrated, but can be soundly predicted based upon the information and expertise available (*Wellcome AZT (SCC)*, above, at para. 56). At paragraph 70 of *Wellcome AZT (SCC)*, above, the Supreme Court of Canada articulated a three-part test that must

be satisfied in order to establish that a sound prediction has been made by the an inventor. The three elements of the test are:

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.

[147] To be sound, a prediction does not need to amount to a certainty, as it does not exclude the risk that some compounds within the area claimed may, at some later time, prove to be devoid of utility. With these principles in mind, I turn to the '206 Patent and the evidence before me.

[148] As of the Canadian filing date – that is, October 20, 1981 – Schering had not made and tested all of the compounds that are included in the claims in dispute. While Schering had carried out some testing and obtained some positive results, it is evident that the efficacy of most of the compounds of the '206 Patent was based on a prediction. In other words, Schering – supported by Sanofi – asserts that the prediction of utility of all compounds included in the claims of the '206 Patent was sound.

[149] The Defendants are not asserting that there is evidence of lack of utility. Rather, they submit that the prediction at the date of application was not sound.

[150] I will focus first on the eight compounds of Claim 12. If the defendants are successful in their arguments with respect to any one of the compounds of Claim 12, they have met their burden. Since Claims 1, 2, 3 and 6 all encompass Claim 12, they will also fail if Claim 12 fails.

B. *Sound Prediction: Factual Basis and Articulable and Sound Line of Reasoning*

[151] The question of sound prediction is one of fact (*Wellcome AZT (SCC)*, above, at para.71). The inventors must be able to show that, at the relevant time, they were in possession of a factual basis upon which they could articulate the desired result. It is important to note that the perspective being examined at this stage is a subjective one. In assessing sound prediction, we are not confined to examining the invention through the eyes of a person skilled in the art. Rather, the knowledge, activities and endeavours of the inventors themselves must be considered.

[152] As noted, the first two prerequisites for sound prediction are that the inventors had: (a) a factual basis for their conclusion; and (b) an articulable line of reasoning from which the desired result can be inferred from the factual basis. In this case, the two prongs of the test work in tandem. The Plaintiffs submit that their sound prediction rests on a combination of Schering's research program into ACE inhibitors and the publicly-available literature and other information, from which they could infer utility of those compounds not yet tested. In other words, they argue that the actual research work of the Schering scientists, together with knowledge in the public domain, would have given Schering a factual basis and an articulable line of reasoning to soundly predict, as of October 20, 1981, that all of the compounds of Claim 12 of the '206 Patent would have utility.

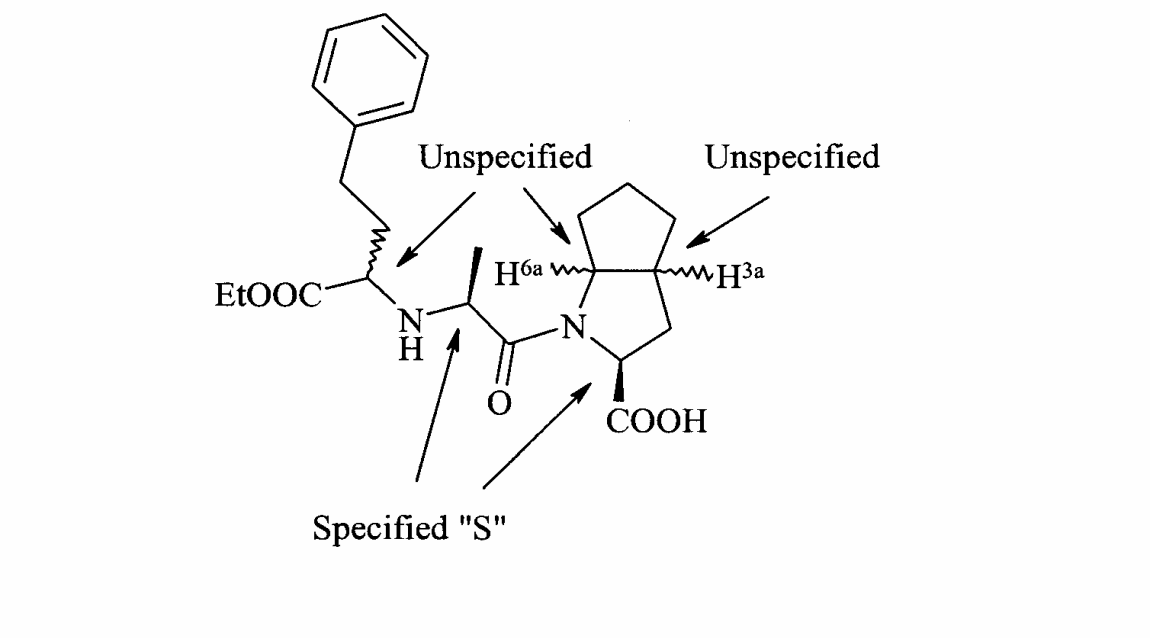
[153] Keeping in mind that utility is measured against the promise of the '206 Patent, the question before me is: did Schering have a factual basis for predicting that all eight compounds of Claim 12 would have utility as ACE inhibitors and antihypertensives?

[154] In responding to the question of sound prediction, I was provided with the opinions of a number of experts: for the Defendants, Drs. Thorsett and Ehlers, and Drs. Bartlett, Patchett and Nelson, for the Plaintiffs. These experts provided substantive views, supported by their reading of the research carried out by the Schering scientists and of the literature and other publicly available information. Not surprisingly, the Defendants' experts concluded that there was no factual basis and the Plaintiffs' experts reached the opposite conclusion.

[155] The opinions of the experts were of assistance, particularly in the understanding of the literature and knowledge in the field. However, in assessing the factual basis, the task facing me was to comprehend the nature and extent of the work of the Schering scientists. Fortunately, I had the benefit of hearing from Dr. Smith and Dr. Neustadt, two of the named inventors of the '206 Patent. These two witnesses spoke candidly and honestly about the research program of Schering and about their understanding of the knowledge in the field at the relevant time of October 20, 1981.

(1) Importance of Stereochemistry

[156] The stereochemistry of potential ACE inhibitors and, thus, of the compounds of Claim 12 is an important element in assessing the potential activity of any given compound. I begin by expanding on the stereochemistry of Claim 12. For the assistance of the reader, I have included a diagram of Claim 12, taken from the Report of Dr. Thorsett, showing the location of the five chiral centres of the compounds covered by that claim.



Molecular Depiction of Claim 12

[157] The skilled person would recognize that the compound described in Claim 12 would have five chiral centres. Two of the centres – at the 2 position or the carboxylic acid position of the bicyclic ring moiety (2(S)-carboxy group) and at the alanyl position on the backbone – have been specified as being in the S configuration. The stereochemistry of the bridgehead carbons – at the 3a

and 6a positions – and the chiral centre nearest the carboethoxy moiety have not been specified. Throughout the experts' reports, the chiral centre nearest the carboethoxy group is referred to by a variety of names. The experts (as have I in these Reasons) interchangeably described this position on the molecule as the carboethoxy or pro-drug position, centre or site.

[158] The skilled person would recognize that there are four different orientations for the bridgehead carbons. When these carbons are both oriented in the same direction, the structure is described as "*cis*"; the two parts of the ring will form a "V" shape. When both are in the S configuration together with the 2(S) carboxy group, the result is a structure described as "*cis-endo*" ((S,S,S) configuration). When both are in the R configuration, with the carboxylic group still fixed in the S configuration, the result is "*cis-exo*" (R,R,S). If the carbons at the bridgehead are differently oriented from each other, the compound is said to be in the "*trans*" configuration. When joined with the carboxylic acid fixed as S at the 2-position, the two possible structures have configuration of (3aR,6aS,S) and (3aS,6aR,S). The shape of these two structures can be described as being in a "W" shape.

[159] The final unspecified chiral centre in Claim 12 is at the carboethoxy position on the enalapril backbone. Depending on whether this position is R or S, the resulting compounds will have materially different shapes. Combining the two possible configurations of the carboethoxy position on the backbone with the possibilities for the bridgehead, we can recognize that there are eight possible configurations for the compounds of Claim 12.

[160] The importance of the stereochemistry of the Claim 12 compounds was discussed by a number of experts. It appears to be common ground that even small changes to a molecule can have profound effects on activity.

[161] Therefore, depending on differences in stereochemical configuration, the eight 5,5 bicyclic stereochemical configurations possible for Claim 12 would have conformational and spatial differences. As a result of the different conformations, it may be difficult to extrapolate the activity of one stereochemical configuration based on that of another. This was confirmed by Dr. Ehlers and Dr. Thorsett.

[162] Moreover, it would be understood that a change in conformation or orientation of one group of an ACE inhibitor could have an impact upon the ability of other groups of the ACE inhibitor to bind to the enzyme. Dr. Nelson agreed that "the effects of multiple chiral centres are not expected to be additive, since a change from R to S at one centre may alter other aspects of the ligand enzyme interactions". In his expert report, Dr. Ehlers described the situation as follows:

> Generally, most of the substituents (including the side chains) on an inhibitor will interact with the active site in a manner analogous to a key fitting into a lock. If a side chain or group is no longer present, or if its shape or orientation has changed, then the compound may no longer fit in the active site and therefore may no longer act as an inhibitor. Alternatively, an absent or altered group or side chain may force the inhibitor to reposition itself in the active site, thereby causing other binding groups to go out of alignment, again leading to ineffective binding of the inhibitor to the active site and reduced or no activity.

[163] With this background, I turn to the question of whether the Schering scientists had a factual basis for soundly predicting, as of October 20, 1981, that all of the stereochemical configurations represented by Claim 12 would have utility.

(2) The Schering Work

[164] In reviewing the possible factual basis for Schering's sound prediction, there are three distinct timeframes: pre-Troy conference; immediate post-Troy to the date of conception (June 20, 1980); and from the date of conception to the Canadian filing date of October 20, 1981. Dr. Smith and Dr. Neustadt described the events, in their oral testimony and through many Schering documents entered as exhibits.

(a) *Pre-Troy*

[165] The Schering scientists provided the company with semi-annual reports of their "Antihypertensive Program", which reports give some indication as to their work up leading up to the Troy conference. In the January 1980 report, Dr. Smith described the work of her team as the synthesis of a series of "N-[3-mercapto-2(R,S)-methylpropanoyl]-(S)-prolines…having substituents at the 4 position on proline".

[166] The bulk of Schering's work up to this date had been on proline rings that were substituted with one or two substituents at the 4-position. Some of these compounds were described as active

and some were described as inactive. The results can best be described as inconsistent. For example, SCH 30077 and 30078 were two closely-related compounds with one in the *cis* configuration and the other in the *trans* configuration. The *trans* configuration showed *in vitro* activity and the *cis* showed no activity at the dose tested. In other compounds, the *cis* showed activity and the *trans* showed no activity.

[167] The program included the synthesis of SCH 30178, a molecule with a spirocyclic moiety at the proline end of a captopril model. SCH 30178 was found to have activity *in vitro*. In test results for the period between December 18, 1979 and February 7, 1980, the activity was described as being "same or slightly greater than that of captopril".

[168] Prior to June 20, 1980, the only compound synthesized with the captopril backbone or side chain fused to a 6,5 bicyclic ring was SCH 30928. This was a mixture of diastereomers in which the configuration of the chiral centres was *cis-endo*. SCH 30928 was synthesized on May 2, 1980 and tested *in vitro* on May 8, 1980; its *in vitro* activity was described as "slightly less potent than captopril". SCH 30928 was tested *in vivo* on June 12, 1980 and showed activity described as "moderate". However, later testing, in July, August and September, 1980, showed inconsistent results.

[169] Schering had not made either a *trans* or *cis-exo* 6,5 bicyclic ring fused to the captopril side chain.

[170] The results of SCH 30178 and SCH 30928 demonstrated to the Schering scientists that there is considerable structural latitude with respect to alterations to the proline moiety of the captopril backbone. Their work seemed to show that both ACE inhibition *in vitro* and antihypertensive activity *in vivo* could be maintained while incorporating different ring structures in place of the proline right of a captopril-like compound. However, with the inconsistency in certain of the test results and the various choices made for synthesis, it is not clear to me that these pre-Troy compounds alone could provide the factual basis for the inventors of the Claim 12 compounds to formulate a sound prediction.

(b) *Troy and Dr. Smith's Disclosure*

[171] By June, 1980, the Merck scientists had succeeded in replacing the thiol moiety of captopril; the result was enalapril. Dr. Patchett, in his presentation at the Troy conference, on June 18, 1980, disclosed the results of the Merck work to an audience of several hundred scientists. Dr. Patchett did not provide any written materials. Our understanding of what was disclosed is based on the testimony of Dr. Patchett and that of Dr. Smith, who attended the conference. We also have some photocopies of poorly reproduced photographs which Dr. Smith confirmed were photographs of Dr. Patchett's slide presentation.

[172] Significantly, Merck had not disturbed the proline end of the captopril model. Thus, Dr. Smith immediately felt that the work of the Schering scientists could be combined with the enalapril backbone to produce some molecules of interest.

[173] In her Disclosure Notebook, Dr. Smith's entry of June 20, 1980 reflects what Schering describes as the "conception" of the '206 Patent. Dr. Smith began her disclosure entry on p. 8 with the words, "[T]his disclosure relates to N-α-(α-substituted)acetic acid (or acetate) dipeptides of type 1, 2, 3, 4 as inhibitors of angiotensin converting enzyme and antihypertensive agents". The molecule diagrams set out include 6,5 and 5,5 rings with "Z" being the enalapril backbone of Merck. On p. 9, Dr Smith wrote down a model synthesis.

[174] In her semi-annual report of July 3, 1980, Dr. Smith described the work her team intended to pursue. Included in that report was the following:

> From the structure activity relationships in the N-(3-mercapto-2-methylpropanoyl) substituted-(S)-prolines, two compounds SCH 30178 and SCH 30928 showed an interesting biological profile as compared to captopril. Therefore it is of great interest to incorporate the substituted proline moiety from SCH 30178 and SCH 30928 into the novel target compounds 130 and 131.
>
> [Target compound 130 incorporated a spirocyclic onto the enalapril backbone and 131, a 6,5-bicyclic onto the enalapril backbone.]
>
> . . . In 131 the stereochemistry of the ring junction is probably cis and either syn or anti to the (S) carboxylic acid group. . . .

[175] At this stage, neither 130 nor 131 had been synthesized. Dr. Smith had envisioned a model synthesis of at least these two compounds and had made an educated guess as to some of the stereochemistry of the chiral centres on the 6,5 bicyclic rings. Thus, even taking into account Dr. Smith's July 3, 1980 report, Schering's work up until July 1980 falls far short of a factual basis for a sound prediction.

(c) *Post-Troy*

[176] We now move onto the post-Troy phase of Schering's "Antihypertensive Program".

[177] The first compound to be synthesized using the Merck disclosure was SCH 31309, a spirocyclic at the proline position of enalapril. It was a mixture of R and S at the carboethoxy position. In vitro testing demonstrated activity described as "moderate". I agree with Dr. Ehlers that the spiro compounds have a very different shape than the bicyclic rings. With the rings of the spiro compound being attached only at one carbon, one could reasonably expect the spiro structure to be more flexible and not particularly helpful in predicting whether the 6,5 or 5,5 ring compounds would have utility.

[178] It is more likely that helpful insight could be obtained from the synthesis and testing of compounds incorporating a 6,5-ring at the proline end of the molecule. SCH 31335 and SCH 31336, both with a 6,5-bicyclic ring on an enalapril backbone, were synthesized in August 1980. The only difference between the two appears to have been the stereochemistry. On August 19, 1980, when the two compounds were tested *in vitro*, SCH 31336 showed some activity even though the compound included three stereocentres (out of five possible) in the R configuration. SCH 31335, however, was reported to be "10 fold more active than SCH 31336".

[179] SCH 31846 – one of the individual diastereomers of SCH 31335 – was synthesized December 10, 1980. SCH 31847 – the other diastereomer of SCH 31335 – was synthesized December 11, 1980. Because SCH 31846 showed activity *in vivo* and SCH 31847 did not show *in*

vivo activity, the Schering scientists concluded that SCH 31846 had the S configuration at the carboxyalkyl position; it was the S,S,S(S,S)-isomer. SCH 31847 was concluded to have the R configuration at the carboxyalkyl position – the R,S,S(S,S)-isomer. Dr. Bartlett agreed that SCH 31847 – a 6,5 enalapril backbone compound with the only R at the carboethoxy position – was described by the Schering scientists as inactive *in vivo* up to 300 μ/kg.

[180] Two other compounds synthesized were SCH 32494, a compound with a *trans* 6,5-bicyclic ring configuration and SCH 31846, a *cis-endo* 6,5 bicyclic configuration. SCH 32494 was inactive and SCH 31846 was active at the levels tested. In short, Schering was unable to show that any 6,5 bicyclic enalapril analogue with a *trans* configuration at the bridgehead exhibited ACE inhibition. The testing results of these two compounds demonstrate that Schering could not predict, based on the results from *cis-endo* compounds, that compounds with a *trans*- 6,5 bicyclic configuration would have activity.

[181] In February 1981, the Schering scientists made and tested their first (and only) 5,5-bicyclic analogues. SCH 31925 was a mixture of two compounds, one of which was – as we now know – ramipril. SCH 31924 differed from SCH 31925 only in its stereochemistry. As reported by Dr. Smith in her semi-annual report of July 1, 1981, "Stereochemistry has not been assigned to the ring junction in relationship with the hydrogen at the position 2, however the stereochemistry is assumed to be cis-syn". That is, Dr. Smith assumed the stereochemistry of SCH 31924 was R at the 2-position of the bicyclic ring and (R,R) on the bridgehead and that of SCH 31925 was S (S,S). Thus, SCH 31925 was a mixture of two diastereomers having an S,S,S(S,S) configuration and an R,S,S(S,S) configuration. SCH 31924 was a mixture of an S,S,R(R,R) configuration and an

R,S,R(R,R) configuration. Because of the R configuration at the 2-position carboxylic acid, the diastereomers of SCH 31924 are not included in Claim 12 but would be included in Claims 1, 2, 3 and 6 of the '206 Patent.

[182] In the semi-annual report of July 1, 1981, Dr. Smith reported that SCH 31925 was tested *in vivo* and identified as "active" and SCH 31924 was identified as "inactive". Schering did not synthesize any other of the possible stereochemical configurations of the 5,5 bicyclic moiety, namely *cis-exo* or *trans*. Moreover, Schering did not synthesize any 5,5 bicyclic compounds where there was only an R configuration at the carboethoxy position. All of these configurations are included in Claim 12.

[183] As acknowledged by Dr. Smith and Dr. Neustadt during their appearances, Schering attempted but was unable to synthesize and isolate other *trans* configurations beyond SCH 32494 and was unable to synthesize any *cis-exo* stereochemical configurations of the 6,5 bicyclic moieties.

(d) *Summary of Schering work*

[184] In summary, the Schering scientists' synthesis and testing program was limited. With respect to compounds that included a 5,5 bicyclic ring within Claim 12, only one compound – a mixture – has been made and tested by the Canadian filing date. Of particular interest, the scientists:

- Had not synthesized a single stereoisomer within Claims 6 and 12;

- Had not synthesized compounds with 5,5 bicyclic moieties in the *cis-exo* and *trans* configurations;

- Had synthesized two mixtures of compounds with 5,5 *cis-endo* bicyclic moieties and found one to be active and the other to be inactive *in vivo*.

[185] Given that Schering tried unsuccessfully to synthesize the *cis-exo* form of the 6,5 bicyclic ring compound and had never even attempted such syntheses for the 5,5 *cis-exo* configuration, it is difficult to accept that, based on their experimental work, the Schering scientists had a factual basis to predict that these configurations, which are included in Claim 12, would be active either *in vitro* or *in vivo*. For the stereoisomers in the *cis-exo* and *trans* configurations, this conclusion would apply even if the promise of the patent is for ACE inhibition only.

[186] I digress for a moment to discuss an argument made by the Plaintiffs in respect of the "inactive" testing results reported by Schering. The Plaintiffs submit that the "inactive" results should be read in the context of the limits of the testing. Schering had evidently set an internal testing threshold to provide them with guidance on which compound warranted further testing. At a higher dosage, they assert, it is entirely conceivable that the compounds would show activity. Thus, the Plaintiffs argue, I should not conclude that a compound is devoid of ACE inhibition or antihypertensive effect on the basis of an "inactive" finding by the Schering scientists.

[187] The critical flaw in this argument is that, in respect of some of the compounds covered by Claim 12, the Schering scientists have no results that could lead to a prediction of activity at any

level. Inactive test results do not provide any insight as to how the Schering scientists could predict activity at a higher dose. A prediction of activity at a higher does would be pure speculation.

[188] Having concluded that no factual basis for a sound prediction can be founded on the Schering work alone, it is necessary to turn to the knowledge that was available to Schering as of the relevant date. Upon consideration of all of the testimony and arguments by the parties, I believe that there are two determinative areas. The first of these relates to the stereochemistry at the carboethoxy position. The second area is the overall "space" theory, which relates to the notion of the three-dimensional shape of the active site of ACE

(3) The stereochemistry at the carboethoxy position

[189] I begin with a review of what was understood about the chirality of ACE inhibitors. In 1977, a hypothetical model of the ACE active site was proposed by the Squibb group (Cushman et al., "Design of Potent Competitive Inhibitors of Angiotensin-Converting Enzyme. Carboxyalkanoyl and Mercaptoalkan Amino Acids", *Biochemistry,* 1977, 16, No. 25, 5485-5491 [*Biochemistry, 1977*]). The model disclosed is commonly referred to as the "Cushman-Ondetti model". The *Biochemistry, 1977* publication provided the following teachings on stereochemical considerations:

- First, that the choice of carboxy terminal amino acid from among the natural L-amino acids can vary considerably. The data established that a D-amino acid at the carboxy terminus markedly attenuated inhibitory activity; in one instance, the D-proline analogue was about 9000-fold less active than the L-proline analogue.

- Second, the data in Table III establish that the stereochemistry of the second chiral position must also correspond to the L-configuration of a natural amino acid.

[190] In a later paper ("Design of New Antihypertensive Drugs: Potent and Specific Inhibitors of Angiotensin-Converting Enzyme", *Progress in Cardiovascular Diseases* (1978) 21, No. 3, 176-82), the same authors, in comparing two of the compounds tested, noted that "[T]he requirement for a substituent of the proper optical configuration is again strikingly apparent".

[191] As we know, Merck first disclosed enalapril at the Troy conference on June 18, 1980. The enalapril molecule has three stereocentres. At the Troy conference, according to the evidence before me, Dr. Patchett commented that the potency of the ACE inhibition was dependent on each of the three chiral centers being in the S configuration. Merck's first published reference to enalapril was in European Patent Application No. EP 12,401 (published June 25, 1980) [EP 401]. This publication reinforced that the preferred stereochemistry at the three chiral centers of the enalaprilat class of molecules is S.

[192] This point was later confirmed by the inventors in November 1980 (Patchett et al., "A New Class of Angiotensin-Converting Enzyme Inhibitors", *Nature* (1980) 288, No. 5788, 280-3 [*Nature, 1980*]), when the Merck enalapril group presented a comparison of *in vitro* ACE inhibition data for compound 6a (enalaprilat in the (S,S,S) configuration) to compound 6b (an enalaprilat analogue in the (R,S,S) configuration). A change in chirality of the single chiral center resulted in a 683-fold loss of activity from separated isomers.

[193] In the result, it was common knowledge, well before the Canadian filing date of October 20, 1981, that an S configuration at the carboethoxy position, together with S at the 2-position carboxylic acid on the proline end of the molecule and at the alanyl position would be preferable.

[194] As noted above, SCH 31925 was synthesized at the same time as SCH 31924. The Schering scientists did not immediately know the stereochemistry of each. However, when tested, SCH 31925 was found to have an ID_{50} value of 126 micrograms per kilogram of body weight (μg/kg) in the test animals. SCH 31924 did not show activity at 300 μ/kg. Thus, in the view of Dr. Bartlett, "it was apparent that SCH 31925 was the diastereomeric mixture with the favoured S configuration at the C-terminal carboxy position and that the S configuration at the bridgehead carbons as well". No further separation was carried out. However, from Schering's test results coupled with the Merck disclosure that an all-S configuration for enalapril was preferred, one could reasonably predict that an all-S configuration would be an active compound. In other words, a factual basis and line of reasoning exists for a prediction that ramipril would meet the promise of the '206 Patent. But, what about the other seven compounds?

[195] It does not necessarily follow that the results from the mixture of SCH 31925 would enable Schering to make a sound prediction that both diastereomers would be active if separated. In the first place, as acknowledged by Dr. Nelson during his cross-examination, it might not be possible to ascertain which of the diastereomers was the active one: "you would not know whether one was active or two were active". In addition to Dr. Nelson, each of Drs. Thorsett and Ehlers accepted that the SCH 31925 would not enable one to conclude that the other member of the mixture – that is, the *cis-endo* (R,S,S,S,S) compound would be active. I agree.

[196] In the '206 Patent, Schering did not claim only an (S,S,S) configuration; it also claimed the (R,S,S) configuration. Thus, the question remaining is: was there a factual basis upon which to predict that an (R,S,S) configuration would be active, leaving aside, for the moment, the bridgehead chirality? It appears that very little work can be found in the publicly-available literature to directly respond directly to the question of possible activity for those four compounds of Claim 12 with an R configuration at the carboethoxy position.

[197] In his written report, Dr. Nelson provided his opinion on what was known about the stereochemistry at the carboethoxy position. In his view, the work done by the Merck group supports a prediction that either an S or an R configuration at this position would be active. The Merck group, he stated, reported activity for this group in both the R and S configurations (see *Nature, 1980*, above). Dr. Nelson observed that, in A. Maycock, et al., "Inhibition of Thermolysin by N-Carboxymethyl Dipeptides", *Biochemical and Biophysical Research Communications* (1981) 102, No. 3, 963-969, the Merck group tested two diastereomers of the pro-drug phenyipropyl-Leu-Trp analogues, having opposite configurations at the pro-drug end of the molecule. Both diastereomers were potent ACE inhibitors, with one diastereomer having greater ACE inhibition. In Dr. Nelson's opinion, this demonstrates that a change in configuration at the carboethoxy position does not eliminate ACE inhibition activity.

[198] In my view, there are a number of problems with Dr. Nelson's opinion:

- As brought out during cross-examination, both articles cited and their underlying studies were really directed at the inhibition of thermolysin.

- Dr. Nelson also acknowledged that both papers provided data on molecules with an acid – and not an ester as was the case with all of the compounds of Claim 12 – at the carboethoxy position. Indeed, as accepted by Dr. Nelson, Schering had synthesized monoesters with an R configuration at the carboethoxy position that were found to be inactive when tested in vivo (SCH 31924 and 31847).

- Finally, Dr. Nelson agreed that he could not cite a single compound, in which all of the carboethoxy, alanyl and 2-position of the proline ring were in the R configuration, that was active as an ACE inhibitor.

[199] Referring to the *Biochemistry, 1977* paper, which reported activity for compounds with both the S and R at the terminal proline carboxyl group (which is fixed by Claim 12 as S), Dr. Nelson also opined that, "while stereochemistry clearly impacts on the ACE inhibitory activity, changes to stereochemistry would not be expected to abolish such activity". However, such a statement is not born out by the work of the Schering scientists. For example, the only difference between the 6,5-bicyclic compounds SCH 31846 and 31847, was the stereochemistry at the carboethoxy position. When tested, one compound was found to be active *in vivo* and the other to be inactive. Based on these results, the Schering scientists assigned the S configuration at the carboethoxy position to

SCH 31846 and the R configuration to the inactive SCH 31847. These results diminish the reliance that I would place on Dr. Nelson's opinion. While he may be correct in general terms, the very work being done by Schering – for whatever reason – did not provide consistent support for Dr. Nelson's opinion. Ultimately, the Cushman paper and other literature cited by Dr. Nelson could not reasonably have been used by Schering to predict activity of some of the Claim 12 compounds.

[200] In brief, I find, on a balance of probabilities, that the literature referred to by Dr. Nelson would not have provided the Schering scientists with a prediction that an R configuration at the carboethoxy position would lead to ACE inhibition activity.

[201] Given the uncertainty of available information, one would expect the Schering scientists to carry out confirmatory testing on at least a critical few configurations to allow them to predict that all configurations would show activity. This would be particularly true for any change from an S configuration at the carboethoxy position on the enalapril backbone. However, as described above, the Schering scientists' "Antihypertensive Program" contained only one testing of a 5,5-bicyclic ring compound in the R configuration at that position. And, that compound was only made as a mixture of two diastereomers, one of which was the active (S,S,S,S,S) configuration.

[202] In sum, the combination of Schering's work and the available literature or knowledge does not, in my view, form a factual basis upon which one could form a sound prediction that the four compounds of Claim 12 with an R configuration at the carboethoxy position would be active as ACE inhibitors and antihypertensive agents. This finding means that the Defendants have satisfied their burden of demonstrating, on a balance of probabilities, that Schering could not soundly predict,

as of October 20, 1981, that at least four of the eight compounds of Claim 12 (i.e. those with an R configuration at the carboethoxy position) would meet the promise of the patent. On this basis alone, the Defendants have, in my view, succeeded in their counterclaim of invalidity. Nevertheless, I will continue these reasons to consider the other arguments made on these questions.

(4) The "space" theory

[203] In the Plaintiffs' submissions, the strongest argument in support of a factual basis lies in a theory relating to the three-dimensional shape of the active site of ACE. A number of the experts commented on the work done by the scientists at Squibb in developing the Cushman-Ondetti model, which appeared in various scientific papers at the time (see, for example, ***Biochemistry, 1977***, above; Cushman et al., "Development of Specific Inhibitors of Angiotensin I Converting Enzymes (kininase II)" *Federal Proceedings* (1979) 38, No. 13, 2778-2782). In simple terms, the Squibb team developed a hypothetical model of the active site that included three "pockets" or "subsites" – referred to as S1, S1′ and S2′ – that could each accommodate and bind to a distinct substrate or side chain of a molecule, resulting in ACE inhibition.

[204] By the late 1970s, researchers at a number of companies were attempting to discern the exact nature of the optimal types of side chains; there was little certainty as to what would work (as to size, polarity, charge, and chirality) at each of the sites. Schering argues that the knowledge available to its scientists was that the S2′ site could accommodate large moieties at the proline end of the captopril (and, subsequently, the enalapril and lisinopril) molecules.

[205] The Plaintiffs point to other evidence that was publicly available to support their submissions on the "space" theory. Between June 20, 1980 and October 30, 1981, additional teachings regarding C-terminus groups that could be accommodated by ACE were published. In Cheung et. al "Binding of Peptide Substrates and Inhibitors of Angiotensin-Converting Enzyme", *J. Biological Chemistry* (1980) 255, No. 2, 401-407, Squibb scientists, assuming the correctness of the Cushman-Ondetti model, demonstrated considerable tolerance for large side chains at the C-terminus position.

[206] The Cushman-Ondetti model was, at this time, hypothetical; it is difficult to see how the fact that there was significant space at the S2′ subsite of ACE could have been of much assistance without further information on such matters as size, polarity, charge, and chirality of molecules that could be accommodated. As far as I can see, Schering did not have or develop significant advancements to the hypothetical framework.

[207] Dr. Bartlett, in his reports and testimony, explored how Schering could have used the Cushman spatial theory to predict the utility of the claimed compounds. As I understand Dr. Bartlett's opinion, he begins with Schering's syntheses of SCH 30178 and SCH 30928. The spiro ring of SCH 30178 would occupy a different region of space than the fused 6,5 ring of SCH 30928. Since both of these compounds were shown to have ACE inhibition, Schering had evidence that the ACE active site is very tolerant of different structures at the proline site of captopril analogues. Using computer-modeling techniques, Dr. Bartlett mapped the spatial requirements of a number of moieties to show that compounds with useful levels of ACE inhibition could fit within the dimensional regions carved out by SCH 30178 and SCH 30928. Such models included compounds

with *cis* and *trans* substituted moieties and compounds with spirocyclic and fused bicyclic ring structures. As such, it is alleged, Schering could have predicted utility for a large number of compounds with moieties that fit within the spatial limitations of SCH 30178 and SCH 30928.

[208] The main problem with Dr. Bartlett's theory is that I have no evidence that the Schering scientists had incorporated this theory or concept into their conceptualization. Dr. Bartlett, with the help of today's sophisticated software provides a fine explanation of why many of the compounds included in the '206 Patent could be effective ACE inhibitors. However, this does not assist with the question of whether the Schering scientists had, as of October 20, 1981, considered this as part of the factual basis for their prediction.

[209] For example, Dr. Smith makes no mention whatsoever of this concept in her Disclosure Notebook. In the semi-annual report of January 2, 1980, there is reference to the Squibb hypothesis. However, as confirmed by Dr. Smith, there is no description in that document of the volume, space or dimension that might explain how the Cushman-Ondetti model assisted the Schering scientists with their prediction. Similarly, the July 3, 1980 report contains only a passing remark of a "binding hypothesis". Dr. Smith, in her oral testimony, expanded substantially on this small reference:

> A. I have a hypothesis of where these groups would fit and, remember, it's a hypothesis, and in this day and age, when I look at projects like this and you would crystallize something out into an active site and you would be able to view it and see where things fit. At this time, there was an hypothesis.
>
> Q. Right, you … couldn't do then what you can do now in terms of--
>
> A. But you knew from the structure activity that Dr. Patchett's group had presented that you needed something like the phenethyl group out there, those compounds were better. You had the

> carboxylic the carboxylate group in the left hand portion which was believed to bind to zinc. The NH to the enzyme, you knew that there was a space for the methyl of the alanyl or the lysine of compound 129. The carbonyl attached to the proline, also, you know, was needed for binding as well as the carboxylic acid.
>
> And when you go through their SAR and where parts are missing or substituted or whatnot, you know, they are not as active. So looking at their results, you can depict that you need these groups there, or they are allowed there for the best . . . activity.

[210] The difficulty that I have with this explanation is that it is not contained anywhere in the semi-annual reports. If this hypothesis was so central to the thinking of the Schering scientists, one would reasonably expect it to be included in the semi-annual reports. Dr. Smith's notes, in general, were very detailed. Omission of this important explanation from any of the relevant reporting documents leads me to an inference that, at the time period in question, it was not in the thinking of the Schering scientists. I find that the spatial notion of Cushman-Ondetti model was not relied on in any material way to predict the activity of the compounds being explored by Schering in 1980 to 1981. Quite simply, it is not part of any articulable line of reasoning that could support a prediction that all of the compounds of Claim 12 would have utility as ACE inhibitors.

[211] Moreover, I also observe that Dr. Bartlett's hypothesis is not consistent with the data obtained by Schering. Schering's own work indicated that some of the compounds that fall within the relevant volume or space mapped by Dr. Bartlett were, in fact, likely to be inactive. One example would be the R,S,S(S,S) component of the SCH 31925 mixture, which was a stereoisomer with an R configuration at the carboethoxy position that falls within Claim 12. Although this compound would have come within the volume carved out by Dr. Bartlett's hypothesis, the combined inactivity of other compounds with an R configuration at the carboethoxy position (i.e. SCH 31847, 32457 and 31924) taught that the R,S,S,(S,S) stereoisomer would have been inactive *in*

vivo. In other words, even if the Schering scientists were aware of the theory, their own experimental work taught away from such a theory. While Dr. Bartlett has provided a theoretical framework that may or may not have been known as of October 1981, there is no evidence that this line of reasoning was or could have been used to predict the utility of the compounds of the '206 Patent.

[212] To be sound, there must be a factual basis for Schering's prediction, and the inventors must have had an articulable line of reasoning from which the desired result could have been inferred from the factual basis. I appreciate that the jurisprudence teaches that I should approach these issues "with a judicial anxiety to support a really useful invention" (*Wellcome AZT (SCC)*, above, at para. 92). However, for the reasons given, I am satisfied, on a balance of probabilities, that as of October 20, 1981, the prediction made by Schering that the eight compounds within Claim 12 (with the exception of ramipril) would be useful as ACE inhibitors and as antihypertensive agents was not sound.

C. *Sound Prediction: Disclosure*

[213] In the event that I am in error and there was, as of October 20, 1981, a factual basis and an articulable line of reasoning upon which inventors could soundly predict the utility of the compounds of Claim 12, I turn to the final criterion of sound prediction. Specifically, the test for sound prediction obliges the patentee to disclose the facts and reasoning for soundly predicting the utility of his invention.

[214] The Federal Court of Appeal recently provided the following guidance on the disclosure requirement in *Eli Lilly Canada Inc. v. Apotex Inc*., 2009 FCA 97 at paras. 13-15 [*Raloxifene (FCA)*]:

> 13. The importance of the disclosure obligation in applying for a patent has been emphasized by the Supreme Court of Canada on a number of occasions in recent years (*Pioneer Hi Bred Ltd. v. Canada (Commissioner of Patents)*, [1989] 1 S.C.R. 1623 at paragraph 23; *Cadbury Schweppes Inc. v. FBI Foods Ltd.*, [1999] 1 S.C.R. 142 at paragraph 46; *Free World Trust v. Électro Santé Inc.* 2000 SCC 66, [2000] 2 S.C.R. 1024 at paragraph 13; *Apotex Inc. v. Wellcome Foundation Ltd.*, 2002 SCC 77, [2002] 4 S.C.R. 153 at paragraph 37 (commonly referred to as *AZT* and hereinafter referred to as such)).
>
> 14. The decision of the Supreme Court in *AZT* is particularly significant to the disposition of this appeal. According to *AZT*, the requirements of sound prediction are three-fold: there must be a factual basis for the prediction; the inventor must have at the date of the patent application an articulable and sound line of reasoning from which the derived result can be inferred from the factual basis; and third, there must be proper disclosure (*AZT*, supra, at paragraph 70). As was said in that case (para. 70): "the sound prediction is to some extent the *quid pro quo* the applicant offers in exchange for the patent monopoly". In sound prediction cases there is a heightened obligation to disclose the underlying facts and the line of reasoning for inventions that comprise the prediction. [Emphasis added]
>
> 15. In my respectful view, the Federal Court Judge proceeded on proper principle when he held, relying on *AZT*, that when a patent is based on a sound prediction, the disclosure must include the prediction.

[215] In *Raloxifene (FCA)*, a particular study (the Hong Kong study) was necessary to turn the prediction on which the patent was predicated into a sound one. The result of failure to disclose the Hong Study in the patent was that “the underlying factual basis for the prediction and the sound line of reasoning that grounded the inventors’ prediction were not disclosed” (*Raloxifene (FCA)*, above, at para. 12).

[216] *Raloxifene (FCA)* arose from an application under the *NOC Regulations*. The underlying patent was for the use of certain chemical compounds for the treatment of osteoporosis. Nevertheless, I can see no reason why the legal principles applied by the Court of Appeal in that NOC proceeding on the question of sound prediction should not apply in the case before me. Nor can I accept the Plaintiffs' apparent argument that this "heightened obligation" for disclosure only applies when we are dealing with a use patent, as was the case in *Wellcome AZT (SCC)* and *Raloxifene (FCA).* Indeed, the Federal Court of Appeal has stated unequivocally that the doctrine of sound prediction applies to a claim for a new compound (*Pfizer Canada Inc. v. Apotex Inc.*, 2007 FCA 195, 60 C.P.R. (4th) 177 at para. 3).

[217] The case before me stands in contrast to *Wellcome AZT (SCC)* where the court held that the disclosure requirements had been met given that both the underlying facts (the test data) and the sound line of reasoning (the chain terminator effect) were in fact disclosed. The facts of the case before me are closer to those in *Raloxifene (FCA)* than to those in *Wellcome AZT (SCC)*.

[218] The disclosure provided by Schering in its '206 Patent is insufficient for several reasons. First, there is no test data included in the specification of the patent. Test data may provide the public with enough information from which to make significant inferences. The '206 Patent provides no *in vitro* or *in vivo* data for any of the compounds disclosed in the claims. It does not describe how the allegedly useful properties of ACE inhibition and antihypertensive activity were established. It also does not give any indication as to how potent or selective any of the compounds are.

[219] Second, nowhere in the patent is there any discussion that the active site of the ACE inhibitor has sufficient volume to fit all stereoisomers of the bicyclic rings disclosed in the '206 Patent. Further, there is no explanation that this belief is based on certain spiro and 6,5 bicyclic rings fused to the enalapril or captopril backbone or how activity for all the clamed compounds can be inferred from the limited information the inventors had with respect to these compounds.

[220] Third, the '206 Patent also makes no reference to the Troy conference or any publications. There is also no evidence that the inventors relied on those disclosures to predict that all of the various permutations of the side chain claimed in the '206 Patent would have utility. Likewise, the '206 Patent makes no reference to any Squibb disclosures about captopril.

[221] Fourth, no reference to any of the work Schering did on captopril analogues, including the analogues where the proline ring was substituted with one or more substituents, is set out.

[222] Finally, I turn to the argument of the Plaintiffs that the promise of the '206 Patent is a differentiated promise that all of the compounds will have ACE inhibition with a potential or possibility of reducing hypertension in mammals. As discussed in the section of these reasons dealing with the construction of the patent, certain of the Plaintiffs' experts argue for a stepwise or quasi-bifurcated promise of utility in which all of the claimed compounds are promised to be ACE inhibitors while only certain compounds are promised to exhibit antihypertensive effect. If this is a correct interpretation of the promise of the '206 Patent (which I do not accept), then I have further difficulty with the lack of disclosure in the Patent.

[223] The failure to provide information as to which claimed compounds have the promised utility of a patent was specifically addressed by the English Court of Appeal in *American Home Products Corp, v. Novartis Pharmaceuticals*, [2001] R.P.C. 8 (Eng. C.A.). In *American Home Products*, Lord Justice Aldous held that a sufficient specification requires that there be an enabling disclosure across the breadth of the claimed invention.

> The invention as described was the discovery that rapamycin had those advantages. Some derivative would be expected to have similar advantages, but the skilled person would not be able to predict which ones would have that actuality and, even if the right one was selected, it would take prolonged tests to find out whether it had the appropriate qualities. It follows that, as Lord Hoffmann pointed out in *Biogen*, the patent, to be sufficient, must provide an enabling disclosure across the breadth of the claim. [Emphasis added]
>
> . . .
>
> There is a difference between on the one hand a specification which requires the skilled person to use his skill and application to perform the invention and, on the other, a specification which requires the skilled person to go to the expense and labour of trying to ascertain whether some product has the required properties. When carrying out the former the skilled person is trying to perform the invention, whereas the latter requires him to go further and to carry out research to ascertain how the invention is to be performed. If the latter is required the specification would appear to be insufficient. [Emphasis added]
>
> (*American Home Products*, at paras. 37, 40)

[224] Although Lord Aldous wrote these comments under the heading "Insufficiency", they are, on any plain reading, directed to more than the simple question of whether the specification discloses a method of preparation. As I read these reasonable and comprehensive remarks of Lord Aldous, the principles contained therein are directly applicable to the situation before me. This interpretation of the disclosure obligation is also fully consistent with the broader principles of disclosure set out by the Supreme Court of Canada in cases such as *Free World Trust v. Électro*

Santé Inc., 2000 SCC 66, [2000] 2 S.C.R. 1024 [*Free World Trust*], *Consolboard*, *Wellcome AZT (SCC)* and others.

[225] Assuming that the patent promises that some but not all of the claimed compounds are potential antihypertensive agents, the '206 Patent does not specify which of the compounds within the scope of the patent would have a potential for *in vivo* antihypertensive activity. As acknowledged by Dr. Horovitz, the '206 Patent provides no criteria by which the skilled reader would be able to ascertain which compounds would be antihypertensive agents. Furthermore, as mentioned above, there is no *in vitro* or *in vivo* activity data contained within the '206 Patent. Thus, a skilled reader of the patent could not determine which compounds are promised to have antihypertensive activity without going to "the expense and labour of trying to ascertain whether some product has the required properties" (*American Home Products,* above, at para. 40).

[226] The Plaintiffs rely quite heavily on a concept called ADME to support their argument that the '206 Patent contains a bifurcated promise of utility. ADME refers to the following pharmacological considerations: oral absorption of the compound (A); distribution of the compound (D); metabolism (M); and excretion of the compound and/or its metabolites (E). According to the Plaintiffs, the promise of the patent is that the compounds disclosed are useful as ACE inhibitors and, subject to ADME, as antihypertensive agents. Thus, the concept of ADME assists in determining whether any given ACE inhibitor would have the potential to lower blood pressure in mammals. Yet, this principle is not disclosed anywhere in the specification of the '206 Patent. The absence of information on ADME in the specification could possibly have been overcome by the inclusion of test results. Had the inventors provided test results in the specification, it is possible that

the skilled person reading the patent could draw reasonable inferences from that information. Yet, no test results are included.

[227] In light of the foregoing, the lack of information in the '206 Patent makes it very hard, if not impossible, for a person skilled in the art to make a decision about exactly which of the compounds disclosed are active, and which are not active. As a result, if the invention of the '206 includes a promise that some of the compounds will be active as antihypertensives, the patent fails to teach what is the invention and how it works; there is no enabling disclosure across the breadth of the claimed invention.

[228] In conclusion, on the question of disclosure, I find that there is inadequate disclosure in the '206 Patent. The '206 Patent discloses neither the underlying facts (their test data) nor a sound line of reasoning (for example, ADME considerations and space theory). The underlying factual basis and line of reasoning that grounded the inventors' alleged prediction were not disclosed.

D. *Conclusion on Sound Prediction*

[229] I return to the words of Justice Binnie in *Wellcome AZT (SCC)*, above, at paragraph. 56, where he stated:

> If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, per Pigeon J. in Monsanto Co. v. Commissioner of Patents, [1979] 2 S.C.R. 1108, at p. 1117, the prediction at the date of 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".

[230] In this case, the Defendants' challenge of the Plaintiffs' claim of sound prediction succeeds; they have persuaded me that, on a balance of probabilities, Schering's prediction at the date of application (October 20, 1981) was not sound. The Plaintiffs have failed on all three requirements making up the test for sound prediction – factual basis, articulable line of reasoning and disclosure. On this basis, Claims 1, 2, 3, 6 and 12 are found to be invalid for lack of sound prediction.

[231] Given this conclusion, there is no need to consider the other grounds of invalidity advanced by the Defendants. Nevertheless, I will express my views of the balance of the arguments advanced by the Defendants, in the hope that they will be of assistance.

X. Sound Prediction of Making

[232] In addition to arguing that the claims in issue should be held to be invalid on the grounds of no sound prediction of the subject matter, Apotex also submits that Schering had no sound basis to predict that it would be able to make and isolate each of the stereoisomers of Claim 12. However, if I were required to reach a conclusion on this issue, I would begin by noting that there are two serious problems with this argument. The first is that the doctrine of sound prediction does not extend as far as proposed by Apotex; rather, the sufficiency requirement set out in the *Patent Act* protects a third party from patents that provide inadequate disclosure of how the patent is to be practised. The second problem is that the evidence demonstrates that the Claim 12 compounds could be made and separated either by the methods set out in Example 20 or by methods known as of the Canadian filing date.

A. *The requirement to soundly predict how to make*

[233] There is no question that a patentee must disclose a methodology for making its invented compounds. Section 34(1)(b) of the *Patent Act* requires that a patentee set out, in the specification, the method of making or using the composition "in such full, clear and concise and exact terms as to enable any person skilled in the art ... to make ... or use it". Considerable jurisprudence has developed that reinforces the sufficiency requirement (see, for example, *Consolboard*, above, at 517). The material date for determining the sufficiency of a specification is the publication date of the patent. The "bargain" that is struck between the inventor and the public exists only from the date of the grant. Until then, the inventor has limited rights to protect his invention and the public cannot expect to acquire any rights in the bargain. Given the nature of the bargain, it is logical to measure sufficiency as of the date of the grant.

[234] In the particular facts of this case, much happened between the Canadian filing date of October 1981 and the issuance of the '206 Patent in 2001. Because of the conflict proceedings, the '206 Patent did not issue until 20 years after the application. During that period of time, the advances in chemistry – both as to known methodology and sophistication of equipment – made the synthesis and separation of the compounds of the compounds of Claim 12 viable on a large commercial scale. An argument by the Defendants on the sufficiency of the specification as of 2001 would be certain to fail. In response to this difficulty, it appears, Apotex has developed the novel argument that the doctrine of sound prediction requires that, at the time of the Canadian filing, Schering was required to soundly predict and disclose in its specification methods of making and isolating each of the stereoisomers of Claim 12.

[235] In my view, Apotex is merely attempting to circumvent the sufficiency assessment date.

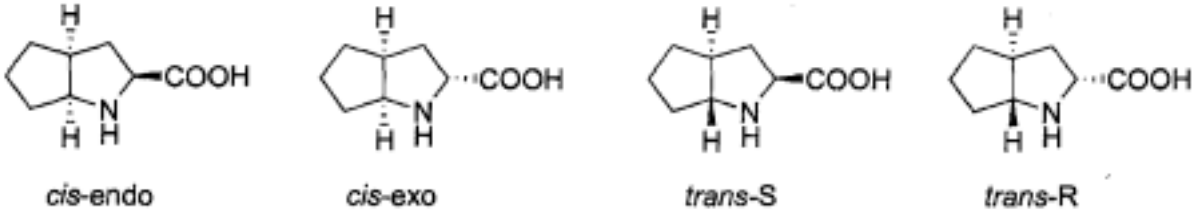
[236] Apotex weaves snippets of the jurisprudence on sound prediction together to support its arguments. However, when those extracts are analyzed, I cannot find a single case that stands for the proposition now advanced by Apotex.

[237] In any event, even if such a doctrine can be said to apply, the evidence does not support Apotex's contention. As discussed above (at paragraph [93]), the '206 Patent specification includes, but is not limited to, the methodology set out in Example 20. I begin by reviewing what methods, beyond Example 20, might have been known to a person skilled in the art as of October 20, 1981 that could have been used to synthesize the Claim 12 compounds. If I am satisfied, on a balance of probabilities, that even one of those methods could be made to work, Apotex's argument fails, regardless of whether Example 20 works or not.

B. *Alternative Synthesis Methodologies*

[238] The key experts on the question of methodologies known in the art as of October 20, 1981 were Dr. Charette, for Sanofi, and Dr. McClelland, for Apotex. Dr. Charette was asked to address whether a skilled person in the art could have prepared the compounds covered by Claim 12 of the '206 Patent by using methods known in the art other than that of Example 20 as of October 23, 1980, October 20, 1981 and March 20, 2001. He described 15 alternative synthetic models all of which he opined were "based upon well-established literature reactions that were known before

1980". Dr. Charette focused on and presented the alternative syntheses of the following compounds described in Example 20A of the '206 Patent:



Compounds Described in Example 20A

[239] It was generally accepted that, once these intermediate compounds were obtained, the steps remaining to produce the actual Claim 12 compounds were possible with known methods, including separation. Dr. McClelland confirmed that both conventional chromatographic and fractional crystallization methods were known as general methods for separating diastereomers. He also acknowledged that fractional crystallization techniques were known in 1980, even though some trial and error would be required. However, Dr. McClelland's opinion was that none of the 15 methods of preparing the necessary intermediate proposed by Dr. Charette would be available to the skilled person in 1981.

[240] All of the methodologies described by Dr. Charette could be described as "paper exercises". During cross-examination, Dr. Charette agreed that he did not actually carry out any of the syntheses that he designed. Nevertheless, just because there is no evidence that any one of these 15 methods was used in 1980 or 1981 to make the compounds of Claim 12, it does not inevitably follow that they would not have worked, had they been tried. If the proposed method contains a sound line of reasoning and includes steps that would be known to the skilled – but unimaginative – chemist, then I am not prepared to reject it simply because it is a "paper exercise". After all, the root

concept of sound prediction is that something has not been done but, on close inspection, can be predicted to work in the fashion expected by the patent. In general, I found Dr. Charette's methods to be well articulated and to have a reasonable factual basis. Dr. Charette's proposed methods were not the subject of cross-examination, other than with some general questions.

[241] Based on the evidence, I am prepared to accept, without deciding, that several of the examples proposed by Dr. Charette could not reliably be predicted to work. I have rejected those methods that involve steps that were the subject of patents, indicating that they were inventive and, thus, not methods that would be within the knowledge of the skilled worker. This was the opinion of Dr. McClelland and it was not vigorously objected to by the Plaintiffs. The methods that I have rejected are the following:

- Method 1, 2 and 3: Synthesis of the *cis* isomer from *cis*-octahydrocyclopenta[b]pyrrole proposed with three possible variations;

- Method 6, 7: Synthesis of the *cis* isomer from cyclopentanone;

- Method 9: Synthesis of the *cis* isomer from ring contraction;

- Method 10, 11: Synthesis of the *cis* isomer from pyrrole hydrogenation, in two variations;

- Method 14: Synthesis of the *trans* isomer from ring contraction; and

- Method 15: Synthesis of the *trans* isomer from trans-octahydrocyclopenta[b]pyrrole.

[242] This leaves Methods 4, 5, 8, 12 and 13. In respect of these proposed synthetic methods, I am persuaded that, on a balance of probabilities, they could be predicted to work.

[243] One of Dr. McClelland's general criticisms is that the remaining methods involve multiple steps. In my view, while this may make any given synthesis more difficult, it does not mean that a person of ordinary skill in a chemical laboratory could not have carried it out with due diligence and motivation. From first-year chemistry laboratory courses, university students are taught to carry out multi-step processes.

[244] An example within this remaining class of methods is Dr. Charette's proposed Method 8: synthesis of *cis* isomer from cyclopentadiene. Dr. Charette based this synthesis on known methods from the literature, most of which dates back to the 1960s. In his report, Dr. McClelland's only criticism of Method 8 was that it was a "complex multi-step sequence". He offered no explanation beyond this to justify his opinion.

[245] In addition to criticizing the number of steps involved in Methods 4, 5, 12 and 13, Dr. McClelland commented that these methods involved ring closure processes that were "analogous" to a claimed process in US Patent No. 4,727,160 (the US '160 Patent). I will accept Dr. McClelland's argument that the novel process disclosed in the US '160 Patent would make it less likely that Methods 6 and 7, both of which directly utilize the invention of the US '160 Patent,

would be known to the skilled person. However, absent some further explanation, which was not offered by Dr. McClelland, I do not accept that every process that might be termed "analogous" to a patented process is novel.

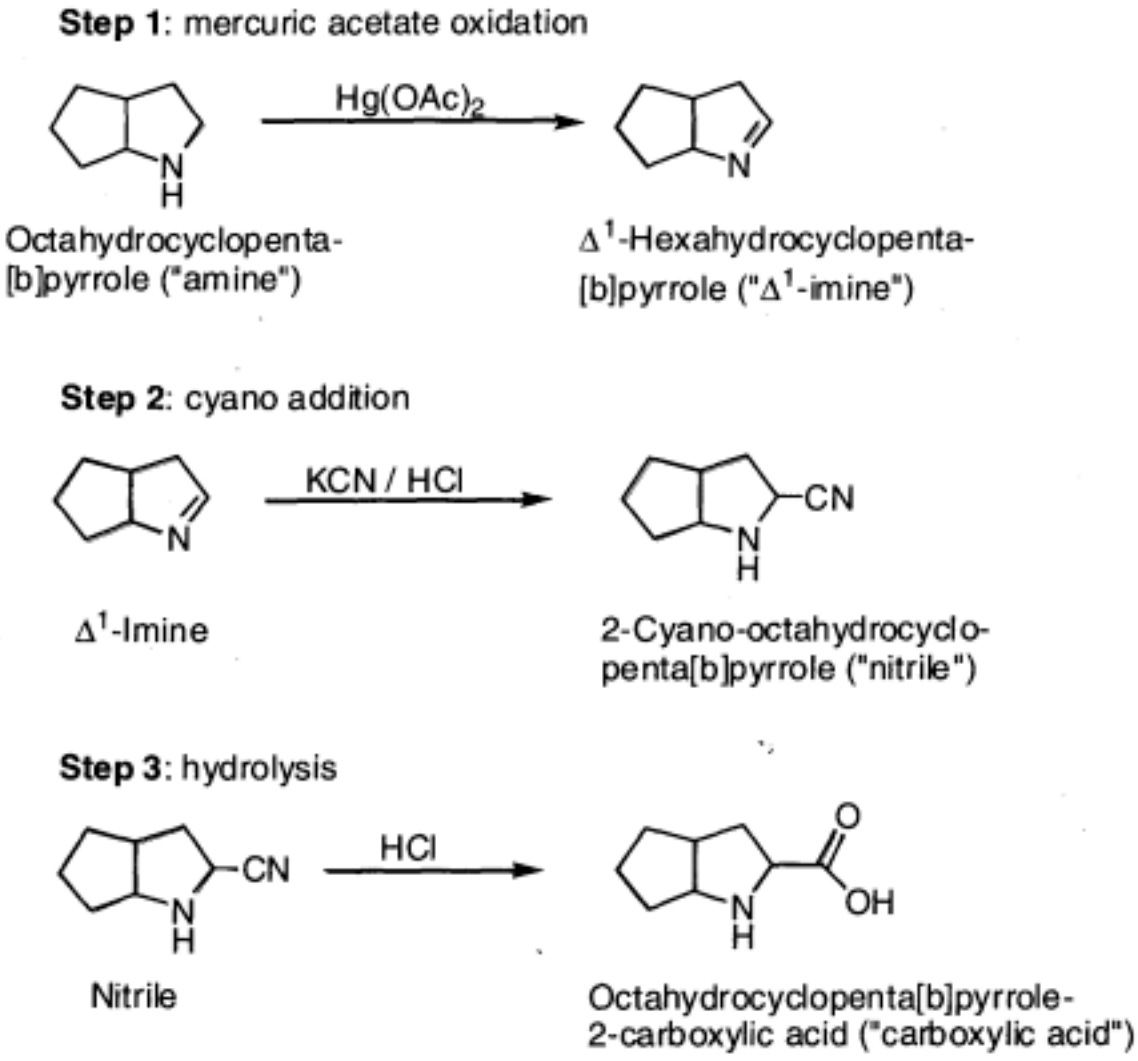
[246] In sum, if there is a requirement for sound prediction to make the compounds of Claim 12, at least five of the methods outlined by Dr. Charette would satisfy that requirement.

C. *Example 20*

[247] Much evidence was produced with respect to Example 20. I begin by observing that, in light of my conclusion on the other methods by which the Claim 12 compounds could be made, Example 20 is not determinative. Even if Example 20 would not produce the results indicated, it is more likely than not that the Claim 12 compounds could have been made by other known methods. Nevertheless, it may be helpful for me to briefly address the evidence on this very contentious point.

[248] I have set out the full text of Example 20 above at paragraph [95] and will not repeat it here.

[249] In short, Example 20 teaches preparation of eight stereoisomers, one of which is ramipril. I was assisted by the various experts who tried to explain Example 20 in more accessible terms. Dr. Lautens reduced the text of Example 20 to the following diagram:



Example 20A of the '206 Patent

[250] During his testimony, Dr. Fleming commented that Example 20 was "notably lacking in any experimental detail". He described the process in Example 20 as follows:

> 20A describes the starting material by merely calling it octahydrocyclopenta[b]pyrrole. It says it is prepared by reduction of a particular starting material and is then fed into 18A.
>
> So, you then have to go to 18A and replace the starting material in that, and then go through the sequence using this new starting material until you get to the end, I guess.

[251] Dr. Fleming continued on to express his understanding of the steps of Example 20. His steps 2, 3 and 4 equate to steps 1, 2 and 3 in Dr. Lautens depictions.

1. The first step is the one that is mentioned in parentheses in 20A, prepared by reduction of 2 keto, so the 2 keto octahydrocyclopenta[b]pyrrole is the compound on the left, in that stereochemistry. The product is the octahydrocyclopenta[b]pyrrole.

2. The next step is, of course, the problematic one, the mercuric acetate oxidation.

3. Next step, the next arrow? Is the addition of HCN effectively across that double bond, effected by KCN in a protic solvent of some kind. The target compound of the step 3? That's the, I guess, 2-cyano-octahydrocyclopenta[b]pyrrole.

4. And the fourth and final step depicted there? Is a reagent with the HCL. That must be aqueous HCL, to achieve the reaction that is shown, so that is probably the concentrated hydrochloric acid. Heated probably means reflux, and it gives the carboxylic acid, which is the octahydrocyclopenta[b]pyrrole 2-carboxylic acid.

[252] All of the experts agreed that the reaction described by Dr. Bihovsky as, “an $Hg(OAc)_2$-promoted oxidation of the amine (-NH) group in the starting material to form an imine” (i.e. the mercuric oxidation reaction described by Dr. Fleming as Step 2 of Example 20) is the most difficult of the steps.

[253] This is not the first litigation where Example 20 has been in issue. The problem of Example 20 was raised in the late 1980s, in the context of litigation involving a European patent opposition. In those proceedings an expert retained by Schering, Dr. Roach, working with Dr. Jerrold Meinwald, succeeded in following the direction of Example 20. In 2003, in the context of Canadian NOC proceedings, Dr. Gabriela Mladenova, working under the direction of Dr. Lee-Ruff, failed to do so. For this litigation, each party retained experts who were asked to replicate Example 20. The other side was permitted to have observers attend the experiments.

[254] There were issues raised by the parties with respect to the earlier experiments by Dr. Roach and Dr. Mladenova. Accordingly, I will focus on the experimental work of Dr. Lautens and Dr. Bihovsky as these two highly-qualified synthetic organic chemists were retained for the purposes of these two actions. Dr. Lautens was able to successfully follow Example 20; Dr. Bihovsky was not. They both prepared expert reports and were available for cross-examination. Dr. Lautens was retained on behalf of the Plaintiffs and Dr. Bihovsky on behalf of the Defendants.

[255] One serious area of disagreement was the decision taken by Dr. Bihovsky to filter the initial mixture to remove mercurous acetate precipitate before the addition of hydrogen sulfide. In his method, yellow solids that had precipitated during the reaction were removed by filtration. The question that was raised was whether Dr. Bihovsky lost the desired material in the filtration. In E. Farkas, E.R. Lavignino, and R. T. Rapala, "Preparation of 3- Dehydroeserpic Acid Lactone and Its Conversion to Reserpic Acid Lactone", *Journal of Organic Chemistry* (1957) 22, No. 10, 1261-1263 (Farkas), the authors report the mercuric oxidation of a tertiary amine. When the Farkas article was reviewed by Dr. Fleming, he stated that he "found it ambiguous as to whether it was filtered or

not". In light of this ambiguity, Dr. Fleming expressed the view that "I think the skilled chemist might well try both ways to see what would happen . . .". Dr. Bihovsky did not "try both ways".

[256] In addition to the possibility that the desired imine was discarded, I am also concerned that Dr. Bihovsky only attempted the synthesis once. If any one of his steps was even a little "off", his results become questionable. The most obvious example is the filtration step. What would have happened if Dr. Bihovsky had understood the ambiguity of the Farkas article and had carried out a second experiment with a different process? Or, would Dr. Bihovsky still have been unable to replicate the experiment if he had attempted the oxidation at higher concentrations? We will never know.

[257] Most of the experts, I believe, would accept, without question, that a skilled person would be expected to use some trial and error in any experimental process. For example, in the context of discussing the concept of separation, Dr. Ward opined that:

> In any separation, . . . in attempting it, and this has happened many, many times in my career, sometimes we are very fortuitous, but first conditions I will pick will result in a successful separation, sometimes it may take extensive trial and error, and then sometimes I may never be successful. [Emphasis added]

I find it surprising that an expert of Dr. Bihovsky's calibre did not carry out further experimentation.

[258] Dr. Lautens' work was also the subject of criticism. The most serious – and troubling – concern expressed by the Defendants is that Dr. Lautens was unduly influenced by the earlier work of Dr. Roach. Dr. Roach supervised laboratory work conducted in 1988, in which Example 20 was successfully followed. In effect, the Defendants are asserting that Dr. Lautens was biased in his

approach to the experiment. Impugning the objectivity of a scientist is a serious allegation. Having reviewed the expert report of Dr. Lautens and his oral testimony, I am satisfied that this allegation is unjustified. Dr. Lautens, throughout his testimony, exhibited all the hallmarks of an objective and competent scientist. I am not persuaded in the least that his access to the earlier work of Dr. Roach caused Dr. Lautens to come to any particular result. I believe Dr. Lautens when he stated:

> . . . we were neither trying to repeat anybody's results per se. We were trying to say: Can we run a reaction using information that would have been available.

[259] The evidence before me demonstrates unequivocally that running Example 20 involves complex chemical processes. However, the difficulty of the exercise does not, in and of itself, render Example 20 undoable as of the relevant date. In terms of how the experiments were run, I prefer the evidence of Dr. Lautens. Accordingly, I find that the Defendants have not persuaded me that Example 20 would not have worked, if carried out by a skilled person in October 1981.

XI. Obviousness

A. *General Principles*

[260] The term "invention" is defined in s. 2 of the *Patent Act* to include "any new and useful . . . composition of matter". In the alternative to their submissions that the claims of the '206 Patent do not demonstrate utility, Apotex and Novopharm assert that the claims of the '206 Patent were obvious, as of the relevant date, in that they were not "new". Briefly stated, they submit that, if the Court finds that a sound prediction could be made on the basis of the prior art, that same prior art would have made the claims obvious to a person skilled in the art.

[261] The test for obviousness was recently clarified by the Supreme Court of Canada in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61, [2008] 3 S.C.R. 265 [*Sanofi-Synthelabo*]. Justice Rothstein, writing for a unanimous Court, adopted a four-step approach (at paragraph 67):

> 1. Identify: (a) the notional "person skilled in the art"; and, (b) 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?

[262] As part of his analysis, Justice Rothstein stated that the so-called "obvious to try" test, derived from UK jurisprudence, should be approached cautiously and with the understanding that "obvious to try" means "very plain" or "more or less self evident".

> ... I am of the opinion that the “obvious to try" test will work only where it is very plain or, to use the words of Jacob LJ., more or less self evident that what is being tested ought to work.
>
> For a finding that an invention was "obvious to try”, there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough.
>
> (*Sanofi-Synthelabo*, above, at paras. 65-66)

[263] If an "obvious to try" analysis is warranted, Justice Rothstein proposed a non-exhaustive list of factors that may apply (*Sanofi-Synthelabo*, above, at paras. 69-71):

> 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?
>
> 4. What was the actual course of conduct that culminated in the making of the invention, including whether time, money and effort were expended?

[264] In the recent case *Apotex Inc v. Pfizer Canada Inc*., 2009 FCA 8, 385 N.R. 148 at para 29 [*Sildenafil*], the Federal Court of Appeal provided further guidance on the "obvious to try" notion.

> The test recognized is "obvious to try" where the word "obvious" means "very plain". According to this test, an invention is not made obvious because the prior art would have alerted the person skilled in the art to the possibility that something might be worth trying. The invention must be more or less self-evident. [Emphasis added]

[265] As noted by all parties, there are significant differences between the tests for obviousness and utility. Obviousness is not merely the reverse of sound prediction. A finding that an invention is based on a sound prediction does not necessarily mean that the invention was obvious. In its final

written submissions, Schering provided a very helpful summary of the differences; that chart is reproduced below:

	Sound Prediction	**Obviousness**
Who is the relevant person	Inventor	Person of ordinary skill in the art
Abilities of the relevant person	Someone who is by definition "inventive"	Average person, no imagination; not "inventive"
What information can be considered	Common general knowledge, previous private work	Common general knowledge published before the date of the invention;
Level of certainty required	Must be more than a lucky guess, but certainty is not required. a reasonable prediction	Must be very plain that it would work

[266] With these principles in mind, I turn to the issues before me.

B. *The Invention*

[267] As expressed by Justice Rothstein in *Sanofi-Synthelabo*, obviousness of the "invention" is to be measured. However, it appears to me that the assessment must be focused on the "inventive concept of the claim in question" and not to some larger "invention" that might be described in the specification of the patent. Otherwise, we would have the illogical result that a finding of obviousness could invalidate all of the claims in a patent and not just those in issue. Thus, I will proceed with my analysis on the basis that the "invention" or "inventive concept" being examined is limited to those "inventions" as identified by Claims 1, 2, 3, 6 and 12.

[268] Because Claims 1, 2, 3 and 6 include the eight compounds of Claim 12, it follows that a finding that Claim 12 was obvious will necessarily mean that Claims 1, 2, 3 and 6 are also obvious.

A conclusion that even one of the compounds of Claim 12 was obvious will invalidate all of the compounds of Claim 12.

C. *Date of Invention*

[269] Before turning to the application of the approach taught by Justice Rothstein in *Sanofi-Synthelabo*, a preliminary issue arises on the arguments before me. As of what date should I examine the question of obviousness?

[270] Obviousness must be assessed as of the date of the invention. In the absence of proof of an earlier invention date, the date of invention is presumed to be the first priority date (see, for example, *Pfizer Quinipril (FC)*, above, at paragraph 89). Should a party wish to assert an earlier date, that party bears the burden of establishing that the date of invention was different than the first priority date (*Westaim Corp. v. Royal Canadian Mint* (2001), 23 C.P.R. (4th) 9 at para. 87). In this case, the parties disagree on the date of invention. Apotex and Novopharm assert that the date should be October 23, 1980 – the first priority date – when the US application was filed. Schering argues that the date of invention should be the much earlier date of June 20, 1980, that being the date on which Dr. Smith had reduced her invention to writing. Sanofi makes no submissions on this point. Alternatively, Schering argues, the date of invention should be mid-August 1980, when Schering made and tested the first compounds of the invention.

[271] Much turns on this date. Between June 20, 1980 and October 23, 1980, a number of patent applications and publications related to ACE inhibitors were published. The question of whether

this art preceded or followed Dr. Smith's invention is directly relevant to the question of obviousness. If that art followed the invention, it cannot be said that it is "prior art" for purposes of assessing obviousness. If, however, the invention was preceded by the art, the question is whether that prior art would have led a person skilled in the art to the invention claimed by Schering in its '206 Patent.

[272] There is considerable jurisprudence considering the issue of the date of an invention. An early statement of the test was set out in the Supreme Court of Canada decision in *Christiani v. Rice* [1930] S.C.R. 443, where Justice Rinfret adopted the statement of the Lord Chancellor (Viscount Cave) in *Permutit Company v. Borrowman* (1926) 43 R.P.C. 356 at 359, who stated that:

> It is not enough for a man to say that an idea floated through his brain; he must at least have reduced it to a definite and practical shape before he can be said to have invented a process.

[273] More recently, Justice Binnie in *Wellcome AZT (SCC)*, above, at paragraph 53, stated as follows:

> Glaxo/Wellcome says the invention was complete when the draft patent application was circulated internally on February 6, 1985. Its argument here, as in the United States, was that the written description identified the drug and its new use sufficiently to give the invention "definite and practical shape". It taught persons skilled in the art how the invention could be practised. This, however, misses the point. The question on February 6, 1985, was not whether or how the invention could be practised. The question was whether AZT did the job against HIV that was claimed; in other words, whether on February 6, 1985, there was *any* invention at all within the meaning of s. 2 of the *Patent Act*.

[274] Summarizing my understanding of the date of invention, the date of invention will be the date on which the inventor can demonstrate three things:

1. the invention is identified;

2. the invention has been reduced to writing: and

3. the invention is "practical" in that it will do the job that is claimed; in other words, it will have utility.

[275] The question before me is a factual one. On or about June 20, 1980, had the Schering scientists identified and written down an invention that would be expected to have some practical use as an ACE inhibitor and, arguably, as an antihypertensive agent? In my view, they had not. There are a number of reasons why I have come to this conclusion.

[276] The main problem that I have with the position of Schering is that there is little evidence to support that there was an invention as of June 20, 1980. The most direct evidence linking June 20, 1980 to a date of invention is Dr. Smith's Disclosure Notebook. As noted earlier, Dr. Smith first recorded a "concept" for bicyclics on the enalapril backbone in her Disclosure Notebook on June 20, 1980. In my view, this evidence disclosed very little beyond bare sketches of a proposed chemical structure.

[277] The evidence is clear that, as of June 20, not a single compound within the scope of the genus of compounds included in Dr. Smith's Disclosure Notebook or subsequently claimed in the claims in issue had been made or tested.

[278] Further, Dr. Smith described the contents of her Disclosure Notebook in the following terms:

> Q. And on these two pages, what was it that you were trying to disclose, or what did you disclose in these two pages, in your understanding?
>
> A. What we disclosed was our -- our plans, our hypothesis to make 4,4 disubstituted prolines, the spiro compounds related to them, to make I'll call them proline bridge compounds shown by 3 and 4, and attached them to what I'll refer to as the Merck side chain . . .

[279] Dr. Smith had some idea as to what would support her hypothesis. During her oral testimony, she described her "invention" in the following terms:

> Q. So, what led you to contemplate those various what I'll call fused ring structures?
>
> A. [We] contemplated those fused ring structures after the captopril analogue that we had made, where we had the perhydroindole in place of the proline. The results we obtained from that for ACE inhibition *in vitro* looked very promising, that compounds of this type should be as active or more active than the captopril analogue that we had prepared. And if we used the Merck side chain, they should also display activity as good or better than the Merck compound, which I'll refer to as enalapril.

[280] Such a statement provides some reasoning behind Dr. Smith's concept. However, it does not, in my view, rise to the level of an "invention".

[281] When the Plaintiffs' expert, Dr. Bartlett, was asked about the contents of Dr. Smith's Disclosure Notebook, he expressed the view that, as of June 20, 1980, Dr. Smith "imagined that these compounds would be active ACE inhibitors". Later in the same exchange with counsel for Apotex, Dr. Bartlett stated as follows:

> Q. So, would you describe what she wrote on these pages as a sort of thought experiment?
>
> A. In the context of what I answered, I think I said yes, there has been no experimental application of the reactions that she's written down that had not been carried out before.

[282] In my view, there is a great difference between an invention and some writings that are characterized as a "thought experiment". I believe that the better view is that, as of June 20, 1980, there was insufficient information to call the contents of Dr. Smith's notebook an "invention". Dr. Smith had a hypothesis that a huge genus of compounds could have useful properties. She had a concept that – arguably – was inventive. That is all.

[283] With respect to the mid-August 1980 date, there is the additional evidence that some of the compounds had been made and tested. By this date, it is true that Schering had made and tested two compounds with bicyclic rings coupled with an enalapril side chain or backbone (SCH 31309 and SCH 31335). Further, I also observe that, for purposes of the conflict proceedings, the Commissioner of Patents determined that August 8, 1980 was the date of the invention for at least one of the claims of the '206 Patent. This is of some importance since the Commissioner was tasked with the problem of determining the first inventor of a number of compounds. His very job was to identify the date of invention and he did not identify June 20, 1980 for the Schering invention. Nevertheless, before me in this trial, there is little evidence that would allow me to determine

whether the Commissioner's finding of an August 8, 1980 invention date was reasonable. Thus, I conclude that the Commissioner's decision in this regard is of little assistance.

[284] Apotex also submits that Schering is precluded from asserting a date of invention that is earlier than the first priority date, having failed to make an affirmative plea of this material fact and allegation. Apotex pleaded in its Statement of Defence and Counterclaim, at paragraphs 45 and 46, that the subject matter of the claims in issue was obvious in light of the common general knowledge as of either October 23, 1980 or October 20, 1981. This was not a general pleading that the claims were obvious; rather, two specific dates are referred to. In response, each of Sanofi and Schering responded with a bare denial, with no reference to any different date. At paragraph 37 of its Reply and Defence to Counterclaim, Schering states:

> Schering denies the allegations in paragraphs 45 to 51, namely that the claims of the '206 are invalid since the alleged invention claimed and disclosed was obvious . . .

[285] Schering, in response to this argument of inadequate pleadings, argues that Apotex was well aware that Schering was relying on an invention date of June 20, 1980. Further, Schering notes, Novopharm, in its Statement of Defence and Counterclaim, at paragraph 65, merely refers to any of "the invention date, October 23, 1980, and October 20, 1981".

[286] I agree with Apotex. The question of the invention date is not a minor detail. The invention date sets up the test for obviousness which, in turn, can invalidate a patent. The failure to expressly plead in reply that Schering was relying on an earlier invention date than was asserted by Apotex in its pleadings is, in my view, misleading. The fact that questions were asked and responded to during discovery that made reference to the June 20, 1980 date does not provide Apotex with knowledge of

the facts upon which Schering is now relying to respond to the allegation that the subject matter of the patent was obvious. Accordingly, I conclude that Schering is precluded from asserting anything other than October 23, 1980 as the date of invention, at least as against Apotex.

[287] In conclusion on this question, while the issue is not free from doubt, the better view is that the date of invention was neither June 20, 1980 nor August 8, 1980. Accordingly, I will address the question of obviousness as of the first priority date – that being October 23, 1980.

D. *Application of the Sanofi-Synthelabo Test for Obviousness*

[288] I turn now to the four-stage analysis described by Justice Rothstein in *Sanofi-Synthelabo*, above.

(1) Identify the "person skilled in the art"

[289] The qualifications of the person skilled in the art are as set out above at paragraph [85]; there is no disagreement amongst the parties. That person would hold a Master's or Ph.D. degree in synthetic organic chemistry, medicinal chemistry, pharmacology or another area of biochemistry biology and would have at least a few years of experience in either industry or academia.

(2) Identify the relevant common general knowledge

[290] The next task before me is to consider what "common general knowledge" would be held by the skilled person as of the relevant date. There is no doubt that I am restricted to considering information in the public domain.

[291] There are five bodies of work which, in my view, should be considered. Of interest, Sanofi, in its final argument, provides a helpful list of "prior art" which includes all of the following.

[292] First, the work done by Squibb, as disclosed in a series of scientific papers that are important for the reasons detailed below, would be part of the common general knowledge:

(a) Ondetti et. al., "Design of Specific Inhibitors of Angiotensin-Converting Enzyme: New Class of Orally Active Antihypertensive Agents", *Science* (1977) 196, No. 4288, 441-444; Cushman et al., "Design of Potent Competitive Inhibitors of Angiotensin-Converting Enzyme. Carboxyalkanoyl and Mercaptoalkanoyl Amino Acids", *Biochemistry* (1977) 16, No. 25, 5485-5491. Together, these papers taught:

— The Cushman-Ondetti model discussed earlier in these reasons, which allowed for the design of potential ACE inhibitors.

— The preferred stereochemistry of the captopril series of compounds. The papers showed that the S configuration is better than the R configuration with respect to the stereochemistry of the proline carboxy group. They also showed that the stereochemistry of the methyl group in the side chain was also important (it needed to be in the S configuration); and

(b) Cushman et al., "Development of Specific Inhibitors of Angiotensin I Converting Enzymes (kininase II)", *Federal Proceedings*, (1979), 38, No. 13, 2778-2782 at 2780, which further expounded theory that had been provided by the Cushman-Ondetti model of how peptide inhibitors bind to the active site of ACE.

[293] Secondly, the skilled worker would also look to work done by Merck in respect of enalapril. Specifically, Merck's EP 401 (published June 25, 1980), and the Merck disclosure at the Troy conference on June 18, 1980 were significant because they:

- Disclosed the compound enalapril;

- Corroborated the Squibb work and further preferred an all-S stereochemistry at the three chiral centers of the enalaprilat class of the molecule; and

- Disclosed that a pipecolic acid (a 6-membered ring analog of enalapril) could be used in place of proline on the enalapril backbone.

[294] Thirdly, a person of ordinary skill in the art would have been aware of a publication by Fisher and Ryan, entitled "Superactive Inhibitors of Angiotensin Converting Enzyme: Analogs of BPP_{9a} containing dehydroproline", *FEBS Letters* (1979) 107, No. 2, 273-276, [referred to as "Fisher and Ryan"] which suggested that there may be an advantage, in terms of potency, to making the proline ring at the C-terminus more conformationally rigid rather than more flexible.

[295] Fourthly, the skilled person can be presumed to be aware of patent applications filed in the same area of research. Referring specifically to the late 1970s and early 1980s, Dr. Patchett stated that "the groups tried to be on top of everything that was published, including in the patent literature". Further, Dr. Nelson agreed that researchers would most likely be looking for a drug product that is not already claimed and patented. The Defendants highlight a number of patent applications related to ACE inhibitors, which applications disclosed that, despite the fact that proline was the most common head group, moieties other than proline could be used to produce ACE inhibitory compounds. The more significant of these applications, all but one of which were published before August 8, 1980, are:

- U.S. Patent No. 4,046,889 (published September 6, 1977), U.S. Patent No. 4,052,511 (published October 4, 1977), U.S. Patent no. 4,105,776 (published August 8, 1978) and EP 401, which taught that the C-terminal proline group (a 5-membered ring structure) could be substituted with a 2-S pipecolic acid group (a 6-membered ring structure);

- U.S. Patent No. 4,129,566 (published December 12, 1978), U.S. Patent No. 4,154,942 (published May 15, 1979), U.S. Patent No. 4,156,084 (published May 22, 1979) and EP 401 (June 25, 1980), which disclosed that proline was substitutable with a dehydroproline, a 5-membered unsaturated ring or, a dehydropipecolic acid, a 6-membered unsaturated ring;

- UK Patent No. 2,000,508 (published January 10, 1979), which disclosed that proline could be substituted with thiazolidine derivatives;

- UK Patent Application No. 2,018,248 (published October 17, 1979), which disclosed a series of thiazolidinecarboxylic acid analogues of captopril that used bulky substituents attached to the thiazolidine ring;

- European Patent Application No. 0.012,845 (published July 9, 1980) [referred to as Tanabe], which disclosed ACE inhibitors with a tetrahydrosiquinoline (THIQ) head group; and

- UK Patent Application No. 2,039,478 (published August 13, 1980), which disclosed a series of captopril analogues, wherein the proline moiety had been substituted with a spiro-type bicyclic moiety.

[296] Fifthly, the literature of the day included a series of work, which taught that there was sufficient volume for groups larger than the proline ring at the ACE active site, including bicyclic rings. The most significant of those publications and their teachings are as follows:

- Funae Y, et al, "Effects of N-mercaptoacylamino acids on inhibition of angiotensin I converting enzyme", *Japanese Journal of Pharmacology* (1978) 28, No. 6, 925-7; Mita I, et al., "New sulfhydryl compounds with potent antihypertensive activities", *Chemical & Pharmaceutical Bulletin* (1978) 26, No. 4, 1333-5; and Iso T, et al, "Pharmacological studies on SA 446, a new angiotensin I-converting enzyme inhibitor", *Japanese Journal of Pharmacology* (1979) 30, Supp: 136P, which disclosed ACE inhibition activity for thiazolidine analogues with terminal residues larger than proline;

- Holmquist B and Vallee BL, "Metal-coordinating substrate analogs as inhibitors of metalloenzymes", *Proceedings of the National Academy of Sciences of the United States of America* (1979) 76, No. 1, 6216-20, which examined the interaction of metal-ion coordinating peptides having an N-terminal sulfhydryl group with ACE;

- Iso T, et al, "Potentiating mechanism of bradykinin action on smooth muscle by sulfhydryl compounds", *European Journal of Pharmacology* (1979) 54, No. 3, 303-5, which disclosed that compounds with terminal residues larger than proline or thiazolidine (such as N-Thioacetyl tryptophan, tyrosine and dihydroxyphenylalanine (DOPA) derivatives) exhibited ACE inhibition activity; and

- Cheung et. al., "Binding of Peptide Substrates and Inhibitors of Angiotensin-Converting Enzyme", *J. Biological Chemistry* (1980) 255, No. 2, 401-407, published January 25, 1980, which disclosed activity for amino acids tryptophan, phenylalanine and tyrosine—molecules that are larger than proline.

[297] In very non-specific terms, it was relevant general knowledge of the skilled person, by August 8, 1980 – and even more so by October 23, 1980 – that the proline of captopril and enalapril could be replaced by larger structures and even fused-ring structures. Further, on the basis of Fisher and Ryan, the skilled person would know that there may be an advantage to making any variants to the proline ring at the C-terminus more rigid as opposed to more flexible.

(3) Identify the inventive concept

[298] The next step, as taught by *Sanofi-Synthelabo*, is to identify the inventive concept of the claim in question. In my view, the allegedly inventive concept of Claim 12 is the combination of the enalapril backbone with a 5,5 bicyclic ring moiety, at the C-terminus, in place of the proline ring of enalapril.

(4) Identify the Differences Between the "State of the Art" and the inventive concept

[299] The next step in the approach for considering obviousness is to identify any differences between the relevant general knowledge of the skilled person – the "state of the art" – and the inventive concept.

[300] As acknowledged by Apotex, in their final written argument, "[T]he difference between the state of the art as of October 1980 and the inventive concept was that the relevant prior art had not disclosed all of the bicyclic moieties of the Claims in Issue and had disclosed no bicyclic moieties on the enalapril backbone". Whether one uses the date of October 1980 or August 1980, I agree.

(5) Would the differences constitute steps that would have been obvious?

[301] The critical step in the analysis is whether this difference – the 5,5, bicyclic ring as opposed to other moieties on the enalapril backbone – would have been obvious.

[302] In order to provide context for the assertions of obviousness (and sound prediction), some appreciation for the state of the prior art as of various dates is required. Sanofi, in its written argument, provides a long list of what it describes as "prior art". In Sanofi's view, "[t]aken as a whole, the art demonstrates inventiveness and provides data that supports a sound prediction by Schering (including when combined with Schering's work)". However, with respect to the issue of obviousness, Sanofi submits that the prior art discloses a "diverse number of options" and that "[o]nly after the fact can one trace a direct patent through the forest of art to the invention".

[303] As we know, interest in developing new, patentable ACE inhibitors was high. Thus, our person skilled in the art, by October 1980, would have been highly motivated to come up with new ACE inhibitors. The skilled person would no doubt be reviewing any and all publications on ACE inhibitions. In their arguments on sound prediction, the Plaintiffs refer to much of this prior art as supporting a sound prediction. Just as this information would have been reviewed by the Schering

scientists, it would also have been available to and likely reviewed by persons skilled in the art. The question is whether the notional skilled person, having reviewed this same art, would consider that a 5,5-bicyclic ring on an enalapril backbone would have been "obvious to try".

[304] I agree with the Plaintiffs that there is a long list of prior art. As I see it, the term "general knowledge" is not so much the "forest of art" or list of documents, publications and patent applications. Rather, it is the knowledge that emerges from this prior art and whether such knowledge would have been generally known. When the art referred to by the parties is examined, it is clear that there are some general themes that emerge that would come to the attention of our person skilled in the art. All of the art referred to by the Defendants and their experts is in the field of ACE inhibition, unlike *Perindopril*, above, where some of the art was in relation to non-ACE research and development. The skilled person, in this case, in assessing the information described by the parties, would not be asked to extend his research beyond the ACE inhibition field.

[305] The first obvious concept or theme is the enalapril backbone. I think that it is undisputed that the skilled person would have been aware of and able to understand the implications of the disclosure by the Merck scientists at the Troy conference, as reinforced by subsequent publications. The Troy conference disclosures and subsequent art established that enalapril was the new standard in ACE inhibition research. Given the excitement generated by the enalapril disclosure, I agree with Dr. Thorsett when he states, in his report:

> In my opinion, the unimaginative notional person skilled in the art seeking to design a novel compound possessing some level of ACE inhibition activity would have derivitized enalapril in a manner that was analogous to, or a simple variant of previously described derivatives of captopril or would have prepared a simple variant of the previously described class of compounds disclosed within

> Merck's "enalapril" patent – European Patent Application No. 12,401.

[306] In other words, there would have been much motivation in the industry to develop "novel" analogues of enalapril.

[307] In addition to the molecular structure itself disclosed at Troy, the concept of all-S configuration on the backbone was reinforced. Thus, whatever else emerged, it would have been obvious to the skilled person to focus his experimentation on compounds with an all-S configuration on the enalapril backbone.

[308] The second concept or theme is the possibility of replacing the proline ring of enalapril. The Schering scientists were not the only ones to investigate this possibility. Several publications disclosed that the proline ring of captopril could be replaced by other structures and still maintain activity. It logically would follow that our notional skilled person would look to draw analogies with the work done on the captopril model. The majority of the experts appear to accept that the teachings with respect to the C-terminus of the captopril analogues were transferable to the C-terminus of the enalapril analogues. For example, during cross-examination of Dr. Bartlett, the following exchange took place:

> Q. . . . You are aware of the Tanabe patent application which was published on July 25th, 1980?
>
> A. Yes.
>
> Q. And you are aware that are it discloses in my lingo, my lay lingo a 6,6 THIQ on a captopril backbone?

> A. A 6,6 tetrahydroisoquinoline, but captopril backbone, yes.
>
> Q. So, we understand each other. And would you say that with the benefit of the Merck disclosure, that a person skilled in the art, having Tanabe, would arrive at the conclusion that he or she could transpose the THIQ 6,6 to enalapril and get an ACE inhibitor?
>
> A. So, the tetrahydroisoquinoline head group with the Merck enalapril backbone, I think one would have an expectation that that would be an active ACE inhibitor. [Emphasis added]

[309] Dr. Nelson in his report noted that, as of October 23, 1980, it was known that:

> The C-terminus end of the ACE inhibitors could incorporate a large number of structures varied in size, shape and conformation, based on activity obtained for ACE inhibitors having various different amino acid groups, substituted proline analogs, fused bicyclic rings with an aromatic second ring or other large substituents on captopril, enalapril or related backbone structures.

[310] The next step is the size and shape of any proline replacements. The clearest signpost to a fused ring structure would have been the Cushman-Ondetti model together with the Tanabe patent. The Cushman-Ondetti model, together with Tanabe and other literature, taught that the S2′ site of ACE was relatively promiscuous and could, thus, accommodate bulkier substitutions for proline at the C-terminus. In discussing his views of sound prediction, Dr. Bartlett presented the hypothesis that 5,5 bicyclic ring structures would fall within the space available. If that theory was available to Schering to assist in founding a sound prediction (which, of course, I have found was not the case), it was also available to others in the field.

[311] From this point, it is more likely than not that the skilled person would be motivated to try various fused-ring structures. I acknowledge that having to try every size and shape of fused rings would be extremely difficult for the skilled person. The syntheses involved are, as I have learned in

this trial, not simple. However, in my view, some of the prior art would have led the skilled person quickly to try a 5,5 bicyclic ring structure.

[312] Fisher and Ryan suggested that there may be an advantage, in terms of potency, to making the proline ring at the C-terminus more conformationally rigid rather than more flexible. In light of this, a skilled person would understand that the fusion of a second ring to proline would accomplish this goal. Sanofi argues that the Fisher and Ryan article is of limited assistance, primarily because it disclosed two different hypotheses to explain the increased potency. I agree that the art of Fisher and Ryan, on its own, would not make trying a 5,5 bicyclic ring obvious. Nevertheless, in combination with the other art, I accept the view of Dr. Thorsett that Fisher and Ryan would teach toward increasing the rigidity of the any substituents at the C-terminus.

[313] Further, as discussed by Dr. Heathcock, in his report:

> A medicinal chemist would understand that there are a finite number of ways of rigidifying the proline ring. The most obvious way would be to fuse a further ring to proline at two different carbon atoms.

Dr. Heathcock also opined that a person skilled in the art would likely consider 3, 4, and 5 membered rings (cyclopropane, cyclobutane and cyclopentane) for the added ring.

[314] The Plaintiffs' experts suggested that there were other more obvious options. One possibility was that, instead of adding a fused ring to the proline, the skilled person might have added a double bond or two double bonds to the proline ring. The first problem with this suggestion is that Merck had already done this in EP 401. Common sense dictates that our skilled person would not waste his time pursuing research paths that were already crowded with existing patent applications. The

second problem with this notion is that, as described by Dr. Heathcock, the compounds would not be very stable. I have similar difficulties in accepting that fusing a benzene ring onto the proline ring would be of interest to the skilled person.

[315] Having reviewed all of the evidence presented on the question of obviousness, I am persuaded that the 5,5 bicyclic ring substituted for the proline ring on the enalapril backbone would have been obvious to try. This is not a case where "the prior art would have alerted the person skilled in the art to the possibility that something might be worth trying" (*Sildenafil*, above, at para. 29). On these particular facts, I am satisfied that the invention of ramipril, as embodied in Claim 12, was "more or less self evident".

[316] This is not to say that the skilled person would not also have tried synthesizing and testing a 6,5 bicyclic ring moiety or other configurations on an enalapril backbone. I do not know. But, even if that is the case, the existence of more than one possibility does not automatically exclude the possible obviousness of any given option.

[317] The final question that would be asked of our notional skilled person is whether it was obvious that the 5,5 bicyclic ring on an enalapril backbone "ought to work". I think that the answer to that question is a qualified "yes". If Dr. Bartlett is correct that, on the basis of his "space" theory, one could soundly predict that a 5,5 bicyclic ring on an enalapril backbone would work, then a skilled person would expect that compound to have activity. If the theory is applicable and available to the Schering scientists, I see no reason why it was not available to the person skilled in the art.

[318] Referring to those factors identified by Justice Rothstein in *Sanofi-Synthelabo* as are directly relevant to this case, I can summarize as follows:

- Based on the general knowledge available to the skilled person, it would have been more or less self-evident that a 5,5-bicyclic ring substituted for the proline moiety of the enalapril molecule ought to work, particularly where the molecule is in an all-S configuration.

- The 5,5 ring would be one of a relatively small class of choices that would be predictable to a person skilled in the art.

- The effort, nature and amount of effort required to achieve the invention would not be insignificant. However, as noted above (see paragraph [242]), there were known methods of synthesis available to the skilled person to make, separate and test the targeted compounds.

E. *Conclusion on Obviousness*

[319] In conclusion, the answer to the question - Would the differences constitute steps that would have been obvious? – is "yes". Accordingly, in the alternative to my conclusion that the claims in issue are invalid on the basis that there was no sound prediction of utility, I would conclude that the same claims are invalid as being uninventive or obvious.

[320] I am well aware that, in *Perindopril*, above, I came to an opposite conclusion on the question of obviousness. There are a number of reasons why I have reached a different outcome in these proceedings. In very general terms, a reader of the two decisions would note two important distinctions. The first is that the patents and their claims are different. Secondly, in each case, I was presented with a unique and fundamentally different record.

XII. Best Mode

[321] Apotex submits that the Schering scientists failed to disclose the best (and only) method known to them to actually make the 5,5 bicyclic compounds when they filed the '336 Application. They argue that Schering's failure to disclose the "best mode" of putting the invention into practice is a breach of its obligations under s. 34(1) of the *Patent Act*. In Apotex's view, "the inventor's duty is to describe the best method known to him, not just a method known to him" (*TRW Inc. v. Walbar of Canada Inc.* (1991), 39 C.P.R. (3d) 176 at 195-197 (FCA) [*TRW*]).

[322] As acknowledged by Dr. Neustadt, Schering never made a compound with a 5,5-fused ring structure using the methods described in the '206 Patent, specifically Examples 18 and 20:

> Q. Am I correct that the only process Schering used to synthesize the 5,5 was the method that you devised, the catalytic hydrogenation?
>
> A. The only method that was used to produce a complete ACE inhibitor target with the 5,5 system is this.
>
> Q. Thank you. That is not in the '206 patent?
>
> A. I believe it is not.

[323] The catalytic hydrogenation method was conceived by the Schering scientists and was described as “a novel synthetic route”. Schering scientists employed this method of synthesis for two of the compounds tested – SCH 31924 and SCH 31925. These compounds were the first to contain a 5,5 bicyclic fused ring on an enalapril backbone. Both of these compounds were synthesized after the October 1980 priority date (the date of the US application), but before the Canadian filing date. It was conceded by Dr. Neustadt that his process would provide more ready access than the examples given in the patent; it would be easier to run than the mercuric acetate procedure described in Example 20 and 18 of the '206 Patent. In spite of this further work and acquired knowledge, the '336 Application – and, hence, the '206 Patent – made no reference to this superior method of synthesis.

[324] In *Minerals Separation North America Corp. v. Noranda Mines Ltd*., [1947] Ex. C.R. 306 at 316, President Thorson spoke of the standard to be applied in assessing the sufficiency of a disclosure required by section 36, when he stated:

> It must not contain erroneous or misleading statements calculated to deceive or mislead the persons to whom the specification is addressed and render it difficult for them without trial and experiment to comprehend in what manner the invention is to be performed. It must not, for example, direct the use of alternative methods of putting it into effect if only one is practicable, even if persons skilled in the art would be likely to choose the practicable method.... Moreover, the inventor must act *uberrima fide* and give all information known to him that will enable the invention to be carried out to its best effect as contemplated by him. [Emphasis added]

[325] In *Consolboard*, above, at page 520, Justice Dickson adopted the words of President Thorson:

> Section 36(1) [s. 34(1) of the *Patent Act*] seeks an answer to the questions: "What is your invention? How does it work?" With respect to each question the description must be correct and full in order that, as Thorson P. said in *Minerals Separation North American Corporation v. Noranda Mines, Limited* [[1947] Ex. C.R. 306]:
>
> ... when the period of monopoly has expired the public will be able, having only the specification, to make the same successful use of the invention as the inventor could at the time of his application. [Emphasis added]

[326] Apotex argues that these words of President Thorson, as endorsed in *Consolboard*, above. make it clear that the inventor's duty is to describe the best method known to him, not just a method known to him. Further, Apotex submits the date to assess the “best mode” is the time of the application – in this case, October 1981.

[327] I have considerable sympathy for the argument of Apotex. It appears that the Schering scientists were well aware of a better method of making some of the compounds of Claim 12. Schering made a conscious decision not to include this better method into the specification for the Canadian application. As I understand it, this could have caused legal difficulties for Schering with respect to the priority date of its invention. So, all that one can glean from the patent specification is that the Claim 12 compounds can be made using either Example 20 or by known methodology. As we have seen, the synthesis of compounds of Claim 12 using Example 20 is complex. Further, there is a clear difference of opinion between at least two of the experts on whether a person skilled in the art could, as of the relevant date, use known methods to synthesize the Claim 12 compounds (Dr. McClelland and Dr. Charette). Common sense and fair play would tell me that Schering ought

to have disclosed the catalytic hydrogenation method that its scientists had actually used to synthesize SCH 31924 and SCH 31925. Nevertheless, I must conclude that the position of Apotex is beyond the scope of the *Patent Act* and current jurisprudence.

[328] The first problem with Apotex's argument is with the use of the "best mode" requirement in respect of a patent to a medicinal compound. Section 34 of the *Patent Act* sets out the requirements for the specification in a patent. In part, that section reads as follows:

34. (1) An applicant shall in the specification of his invention	34. (1) Dans le mémoire descriptif, le demandeur :
. . .	. . .
(*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 appertains, or with which it is most closely connected, to make, construct, compound or use it;	*b*) expose 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'objet de l'invention;
(*c*) in the case of a machine, explain the principle thereof and the best mode in which he has contemplated the application of that principle;	*c*) s'il s'agit d'une machine, en explique le principe et la meilleure manière dont il a conçu l'application de ce principe;

[329] As can be seen from the words of the statute, the "best mode" obligation only arises in the case of a patent to a machine. Neither the words nor the underlying concept that a patentee must set out the best available manner of putting the invention into practice are used elsewhere in s. 34(1) or in the *Patent Act*. In *Sanofi-Synthelabo*, above, the Supreme Court reiterated the importance of the statutory scheme when interpreting patents. At paragraph. 12, Justice Rothstein stated as follows:

> At the outset, it is appropriate to refer to the words of Judson J. for this Court in *Commissioner of Patents v. Farbwerke Hoechst Aktiengesellschaft Vormals Meister Lucius & Bruning*, [1964] S.C.R. 49, at p. 57:
>
> > There is no inherent common law right to a patent. An inventor gets his patent according to the terms of the *Patent Act*, no more and no less.
>
> The most recent reference to the law of patents being wholly statutory are the words of Lord Walker in *Synthon B.V. v. SmithKline Beecham plc*,[2006] 1 All E.R. 685, [2005] UKHL 59, at paras. 57-58:
>
> > The law of patents is wholly statutory, and has a surprisingly long history... . In the interpretation and application of patent statutes judge-made doctrine has over the years done much to clarify the abstract generalities of the statutes and to secure uniformity in their application.
> >
> > Nevertheless it is salutary to be reminded, from time to time, that the general concepts which are the common currency of patent lawyers are founded on a statutory text, and cannot have any other firm foundation.

[330] Where Parliament has chosen to include a "best mode" obligation in respect of machine patents only, the courts must respect that choice. Accordingly, reading such a requirement into non-machine patents would be contrary to the principles of statutory interpretation.

[331] Even if the notion of "best mode" is applicable, the jurisprudence raises another difficulty. As noted, the Schering scientists developed the new method of synthesis in the time period between the US filing and the Canadian filing. Such a situation was addressed by the Federal Court of Appeal in the case of *Lido Industrial Products Ltd. v. Teledyne Industries Inc.* (1981), 57 C.P.R. (2d) 29. In that case, involving a patent for a showerhead, the inventors failed to refer to certain improvements to the device that were known to them after the US filing date of September 4, 1973 but before the Canadian filing date of February 27, 1974. In explaining the applicable date for application of the best mode test, Chief Justice Thurlow, speaking for the entire court on this point, concluded that the relevant date was that of the US filing. On that basis, he found (at paragraph 50) that:

> While the device with these modifications was contemplated by the applicant Teledyne Industries, Inc. at the material time it has not been established that it was known or contemplated by the applicant as the best mode for the application of the principle of its device.

Thus, on the facts before me, the best mode obligation, even if it applies, would not have required Schering to disclose the better synthesis method in its specification.

[332] I also note that the words of President Thorson in *Mineral Separation*, above, must be placed in context. President Thorson's words were *obiter* only; nowhere in the decision, did President Thorson apply the concept of best mode or good faith to his decision. Further, Justice Dickson's words referred to above, in the *Consolboard* decision, were addressed to the issue of sufficiency. In brief, I do not read either of these cases as importing a “best mode” requirement into a patent for a compound.

[333] Apotex also relies on the words of Justice Stone in *TRW*, above. There are two difficulties with relying on this Court of Appeal decision. The first is that the Court's analysis of the validity of the patent at issue was not "strictly necessary"; the Court had already concluded that the defence of non-infringement had been made out (*TRW*, above, at p. 191). Accordingly, the Court's comments on invalidity, including those on the best method requirement must be considered as *obiter*. Secondly, it appears that the patent in issue disclosed a practice that was in direct contradiction to how one would actually implement the invention. The patent, in that case, dealt with the method for producing compressor blades. The patent specification explicitly disclosed that the invention eliminated the need to clamp on the root portion of the compressor blade. However, the expert evidence was that a person skilled in the art would be expected to clamp onto the root "despite the teaching in the Patent away from any need to do so…and, accordingly, the disclosure fails to comply with s. 36(1) of the *Patent Act*" (*TRW*, above, at p. 197). Thus, even if the words of Justice Stone are accepted as authoritative (and not just as *obiter*), the case stands for the proposition that an inventor cannot provide directions in the specification that are misleading or in direct conflict with actual practice. The *TRW* case does not assist Apotex.

XIII. Double Patenting

[334] The Defendants argue that the claims in issue in the '206 Patent are invalid on the basis of double patenting over the invention described and claimed in claims 2 and 4 of the '087 Patent issued to Hoechst, a predecessor to Sanofi Deutschland.

[335] The '087 Patent issued May 14, 1985 to Hoechst, based on an application filed November 4, 1982 and claiming a first priority date of November 11, 1981. It is entitled "*Derivatives of Cis, Endo-2-Azabicyclo- (3.3.0) - Octane - 3 - Carboxylic Acid, a Process For Their Preparation, Agents Containing These Compounds and Their Use*". Of particular interest, Claim 2 and Claim 4 of '087 Patent are claims to compounds "whenever obtained according to a process as claimed in claim 1 or by an obvious chemical equivalent thereof"; these are product-by-process claims. Ramipril would be a compound to which Claims 2 and 4 of the '087 Patent applies, provided that it is made in accordance with the processes set out in that patent. The '087 Patent expired on November 4, 2002.

[336] The jurisprudence is clear that the same invention cannot be patented twice. As stated by Justice Binnie in *Whirlpool*, above, at paragraph. 63:

> The inventor is only entitled to "a" patent for each invention: *Patent Act*, s. 36(1). If a subsequent patent issues with identical claims, there is an improper extension of the monopoly. It is clear that the prohibition against double patenting involves a comparison of the claims rather than the disclosure, because it is the claims that define the monopoly.

Thus, a monopoly should not be granted, nor should previous inventions be "evergreened", by the expedient of obvious or uninventive additions (*Whirlpool*, above, at para. 37).

[337] The jurisprudence identifies two categories of double patenting. In the first category, "same invention double patenting", two patents are the same or have an identical or conterminous claim. The second category, "obviousness double patenting", is somewhat broader. In obviousness double patenting, the claims of the patents are not identical or conterminous, but the later patent has claims

that are not patentably distinct from the other patent, or involve no novelty or ingenuity (see *Whirlpool*, above, at paras. 65-67). Since the claims of the '206 Patent are not identical or conterminous with the claims of the '087 Patent, the invalidity allegation in this case must be understood as an allegation of obviousness double patenting.

[338] In my view, this argument of the Defendants must fail.

[339] The specific question of double patenting with respect to the '206 Patent and the '087 Patent was considered and rejected in a number of cases. In each of *Ramipril I (FC)*, *Ramipril I (FCA)*, *Ramipril II (FC)*, and *Ramipril II (FCA)*, the courts determined the very issue that the Defendants are putting forward in this case. Although these decisions were all made in the context of NOC proceedings, the Defendants have failed to persuade me that the evidence before me would lead to a different result.

[340] It is undisputed that the priority filing date of the '206 Patent is earlier than that of the '087 Patent. Even though the '206 Patent issued later than the '087 Patent, the date of the invention (as discussed above) is considered to be no later than October 23, 1980. Thus, the allegation of obviousness double patenting is inapplicable on these facts since the '206 Patent cannot be considered a "later patent" that has been made obvious by the '087 Patent.

[341] I also observe that the inventors and owners of the '087 Patent are different from the inventors and owner of the '206 Patent. There is no corporate relationship between the owners of the respective patents. The fact that Sanofi Deutschland, the successor of the original owner of the '087

Patent, is a licensee under the '206 Patent, appears to be irrelevant to any question of double patenting. Although I considered and rejected the notion that double patenting could only exist where patents are owned by the same parties (see *Ramipril I (FC)*, at para. 59), subsequent jurisprudence has consistently assumed that double patenting can only arise where the two patents are held by the same parties (see *Merck v. Apotex*, 2006 FC 524, 53 C.P.R. (4th) 1, at para. 207; *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2006 FCA 421, 59 C.P.R (4th) 46 at para. 45, aff'd 2008 SCC 61). In *Bristol Myers v. Apotex*, 2009 FC 137 at paragraph 174, Justice Hughes described the applicability of double patenting as follows:

> Double patenting only applies when dealing with the same person getting two or more patents. If some other person has received an earlier patent, then the second patent is to be considered in the context of anticipation and obviousness or, in the case of pre-October 1989 patent applications, the first to invent.

[342] Further, in *Sanofi-Synthelabo*, above, at paragraph 102, the Supreme Court found that, for double patenting purposes, there was no identity between claims of one patent and those of another where the claims of one patent are process or product-by-process claims and the claims of the other are product claims.

[343] For these reasons, I am of the view that the Defendants would not succeed in their claims that the '206 Patent should be held to be invalid on the basis of double patenting.

XIV. ***Gillette*** **Defence**

[344] The decision of the UK House of Lords, in *Gillette Safety Razor Co. v. Anglo-American Trading Co.* (1913), 30 R.P.C. 465 (H.L.), gives rise with an argument raised by Apotex (supported

by Novopharm) referred to as the "*Gillette* defence". The *Gillette* decision dealt with a patent issued to the plaintiffs for safety razors. The plaintiffs sued the defendants for infringement. In the House of Lords, Lord Moulton commenced by examining the state of the art and, in particular, an earlier patent that had been issued to Mr. Butler, also for a safety razor. He then turned to an analysis of the defendant's razor, in light of the Butler patent, and then said (at p. 480, line 28 *et seq.*):

> I am of the opinion, therefore, that there is no patentable difference between the Defendants' safety razor and that shown and described by Butler. If the blade used by the Defendants be put into Butler's handle (and this, as I have said, involves no invention) you have a safety razor which is indistinguishable from the Defendants' razor in anything which bears on the question of invention. It follows, therefore, that no Patent of date subsequent to the publication of Butler's specification could possibly interfere with the right of the public to make the Defendants' razor. [Emphasis added]

[345] Apotex points out that the uncontradicted evidence is that the ramipril used in Apo-Ramipril is made in accordance with the process for making ramipril set out in the '087 Patent. As noted, the '087 Patent was issued in May, 1985 and expired in November, 2002, whereas the '206 Patent did not issue until 2001. Thus, Apotex submits, the reasoning and result in *Gillette* are directly applicable. In other words, Apotex argues, since Apo-Ramipril is made using ramipril that is made in accordance with teachings of the '087 Patent – which is the equivalent of the Butler patent – the existence of the '206 Patent cannot possibly interfere with Apotex's right to manufacture, use and sell Apo-Ramipri1 and there is no infringement of the '206 Patent.

[346] The *Gillette* defence has been referred to in at least three Canadian cases – *AB Hassle*, above, at paragraph 15 (FCA); *Eli Lilly Canada Inc. v. Apotex Inc.*, 2009 FC 320 [*Raloxifene (FC)*]; and *Pfizer Canada Inc. v. Apotex Inc.*, 2005 FC 1421, 282 F.T.R. 8. I accept that, in the proper

factual context, the *Gillette* defence could have applicability. However, this case does not present such a factual context.

[347] In dismissing this argument, I note that the application for the '087 Patent was filed after that for the '206 Patent. Given the unusual timing that arose because of the conflict proceedings under the old *Patent Act*, we should not look at the issue date of the respective patents, as was done in *Gillette*. Rather, we must consider the subject matter itself. Even though the '206 Patent – because of the conflict proceedings – issued later, its subject matter was in the public domain prior to the filing of the '087 Patent. Thus, if any patent is "old" or the equivalent of the Butler patent, it is the '206 Patent. On the facts before me, the *Gillette* defence is not available to the Defendants.

[348] In the recent case of *Raloxifene (FC)*, above, Justice Hughes considered the *Gillette* defence. Justice Hughes found, on the facts of that NOC proceeding, that Apotex's allegations as to the *Gillette* Defence were justified. However, his finding should be placed in context, at paragraph 64, where he concluded as follows:.

> . . I find, on the civil burden of proof, that the Apotex product to be produced in accordance with the process would not be different from that produced by the'068 patent process and would fall within the scope of the claims of the '399 patent. To that extent, it would infringe. However since I have found that the product of the '068 patent anticipates the product as claimed in the '399 patent, the claims are not valid. Therefore, as to the Gillette Defence would have it, no valid claim has been infringed. Apotex's allegations as to Gillette Defence are justified. The simple allegation as to non-infringement is not justified.

[349] As I read this part of the decision, Justice Hughes' conclusion on the *Gillette* Defence was entirely reliant on his conclusion of anticipation. Absent a conclusion of anticipation, the *Gillette*

defence would not have been available to Apotex. In the case before me, Apotex has not made a claim of invalidity due to anticipation by the '087 Patent. It follows that the *Gillette* defence cannot be sustained – in isolation – as a defence to the Plaintiffs' claims of infringement.

XV. First Inventorship

[350] Under the *Patent Act* – but not under the current *Patent Act* – the concept of first inventorship is fundamental. Section 27(a) of the *Patent Act* limits the grant of a patent to an inventor of an invention where it was not known or used by any other person before he invented it. Thus, where the invention was first known or used by another, an inventor may not receive a patent for that invention. There are limits to attacks that may be brought against a patent issued under the *Patent Act*. Specifically, pursuant to s. 61(1)(b) of the *Patent Act*, a patent cannot be declared invalid or void on the ground that the named inventors were not the first to have known or used the invention unless "that other person had, before the issue of the patent, made an application for patent in Canada on which conflict proceedings should have been directed".

[351] Apotex claims that the claims in issue should be held invalid on the basis that Schering was not the first to invent ramipril. Apotex argues that, because Schering did not isolate and test ramipril before Hoechst isolated and tested ramipril, scientists at Hoechst, not Schering were the first inventors of ramipril. Apotex points to this Court's findings in *Perindopril*, above, at paras. 440-455, where it was found that, for the purposes of a first inventorship inquiry, Dr. Smith had not first "invented" the invention of the '196 Patent (6,5 bicyclic substitutions on an enalapril backbone possessing a linear alkyl group) despite the fact that she had first synthesized and tested a 6,5

bicyclic substitution on an enalapril backbone and her "invention disclosure book" included substitutions with a linear alkyl group. In Apotex's view, my finding in *Perindopril* should be read to mean that a party has not first invented a compound or material for the purposes of a first inventorship inquiry until that compound or material has, in fact, made and tested the material claimed.

[352] I do not accept Apotex's arguments on this question. The first problem with this argument is that, in my view, it requires an interpretation of the conclusions in *Perindopril* that is not sustainable. In my view, *Perindopril* does not stand for the proposition that a compound cannot be invented unless it is actually made. The entire concept of sound prediction is predicated on the fact that an inventor may have a valuable invention that has not yet been made, provided that the requirements for sound prediction are met.

[353] This leads to the second difficulty that I have with the argument. Assuming, for purposes of this issue, that the requirements of sound prediction had been met by Schering, the date of invention would be either August 8, 1980 or October 23, 1980. These dates are discussed earlier in these reasons. The only evidence that I have of an invention date for the subject matter of the '087 Patent is that the Canadian filing date of the application was November 4, 1982, a date well after the invention disclosed in the '206 Patent. On these facts, I would find that the invention of the compounds of the invention included in Claims 1, 2, 3, 6 and 12 of the '206 Patent – including ramipril - was invented prior to the date of invention of the subject matter of the '087 Patent.

[354] Since I am not persuaded that Hoechst was an earlier inventor of the subject matter of the claims of the ‘206 Patent in issue, there is no need to consider s. 61(1)(b) of the *Patent Act* and Apotex’s argument that there was a missed conflict.

XVI. Conclusions

[355] In conclusion, the Plaintiffs’ actions, in each of Court File No. T-161-07 and T-1161-07, will be dismissed. The Defendants will be entitled to a declaration that Claims 1, 2, 3, 6 and 12 of the '206 Patent are invalid. A separate Judgment will issue in respect of each Court File.

[356] In summary form, my determinative finding is that the compounds of Claim 12 lack utility, in that the inventors were, as of October 20, 1981 (the Canadian application date), unable to soundly predict that all of the compounds of Claim 12 would have utility as ACE inhibitors and as antihypertensive agents. Further, I have found that, even if the promised utility is only that the compounds would be useful to inhibit ACE, the utility of the compounds – or at least some of them – could not be soundly predicted. Since the compounds of Claim 12 are also included in Claims 1, 2, 3 and 6, it follows that those claims fail as well.

[357] In closing, I would like to make one additional observation in relation to the '206 Patent. Reviewing the evidence as a whole, I am struck by the apparent rush in 1980 and 1981 by the Schering scientists to bring forward something – anything – that could give Schering’s patent

department enough information to file a patent application. The following exchange between Dr. Smith and counsel for Apotex is particularly telling:

> Q. . . . Let's go to the bottom of the page. You write: "This disclosure contemplates all possible stereoisomers" And obviously by this point, you hadn't tested very many different stereoisomers, certainly none of the enalapril backbone; is that correct?
>
> A. Right, because June—
>
> Q. Right.
> A. It was June 20th?
>
> Q. Right. And would I be correct that you had not even tested all of the stereoisomers of the bicyclics on the captopril backbone by this point? All the various possibilities?
>
> A. Right.
>
> Q. And I take it the reason you wrote that was to cover off the possibility that at some point down the road, a particular stereoisomer might surprisingly turn out to have a very good activity, because you didn't want to miss one and then have the patent department come back to you and say, "Dr. Smith, you missed a good one"?
>
> A. Right.
>
> Q. So you were just protecting yourself, and you wrote this down to just make sure in case there was an unexpected one down the road, you had it covered off?
>
> A. Yes, that would have it covered, and it's also what is done in patents.
>
> [Emphasis added]

[358] Patent protection rests on the concept of a bargain between the inventor and the public (*Free World Trust*, above, at para. 13). In the case before me, the Schering scientists chose to include compounds in their patent for which they had no data or sound line of reasoning. It seems that, as Dr. Smith states, Claim 12 was drafted just to cover off future possibilities. While it may be "what is

done in patents", this practice is not in keeping with the fundamental principles of patent protection. Schering failed to live up to its side of the bargain.

[359] In the alternative, in the event that the inventors could have soundly predicted the effectiveness of the compounds of Claim 12, I have found that, on the record before me and on a balance of probabilities, at least one of those compounds lacked inventiveness. That is, the inventive concept of placing a 5,5 bicyclic ring moiety onto an enalapril backbone was obvious in light of the general common knowledge of persons skilled in the art, as of either the first priority date or as of August 8, 1980.

[360] Further findings, none of which is determinative, are as follows:

- On a purposive construction, Claim 12 of the '206 Patent claims eight individual stereoisomers, one of which is ramipril; it does not claim only a mixture of the eight compounds;

- Both Apotex, with Apo-Ramipril, and Novopharm, with Novo-Ramipril, infringe Claims 1, 2, 3, 6 and 12 of the '206 Patent;

- Claims 1, 2, 3, 6 and 12 are not invalid on the basis of double patenting over the invention described and claimed in certain claims of the '087 Patent;

- The *Gillette* defence is inapplicable on the facts of this case;

- The Defendants' argument that Schering could not soundly predict, as of October 20, 1981, that it could make the compounds of Claim 12 fails, on the bases that:

    (a) there is no such requirement at law;

    (b) Example 20 described in the '206 Patent has not been shown to be unable to work; and

    (c) other methods of synthesis were available to the skilled person as of October 20, 1981; and

- Apotex has not persuaded me that Schering was not the first to invent the compounds of Claim 12.

[361] The question of costs was not addressed by the parties in their final submissions. As is normal in trials of this nature, the parties will be given a period of time to attempt to resolve the issue of costs among themselves. There have been a number of decisions recently where, in my view, principles have been sufficiently defined in cases such as these that the parties in these two actions should be able to settle the matter of costs without my intervention (see, for example, *Adir v. Apotex Inc.*, 2008 FC 1070, 70 C.P.R. (4th) 347). I hope that they do so. Prothonotary Milczynski has advised me that she would be available to assist the parties in settling this matter.

[362] In respect of any award of costs, I would point to the following factors specific to this litigation. The first is that, I feel that there was some duplication of expert evidence on both sides. Secondly, the parties should carefully consider the question of costs related to the damages/remedies phase of the trial. Had these proceedings been bifurcated, 16 days of evidence, two days of final argument, many days of discovery and countless pages of testimony and expert evidence could have been avoided.

[363] Should the parties be unable to agree on costs, they may serve and file written submissions as to costs on or before August 15, 2009, such submissions not to exceed ten pages. Reply submissions, not to exceed five pages may be served and filed by August 31, 2009.

[364] Once again, I thank the counsel involved in this litigation for their professionalism, competence, enthusiasm and courtesy towards the bench and each other. Justice is well served by such members of the bar.

POSTSCRIPT

[1] These Reasons for Judgment are un-redacted from confidential Reasons for Judgment which were issued on June 29, 2009 pursuant to the Direction dated June 29, 2009.

[2] The Court canvassed counsel for the parties whether they had concerns if the reasons were issued to the public without redactions. On June 30, 2009, July 2, 2009 and July 3, 2009, in separate emails, the parties advised that there are no portions of the confidential Reasons for Judgment that should be redacted. Counsel for Apotex requested that two dates described in paragraph 64 of the confidential Reasons for Judgment be amended to December 12, 2000 and March 20, 2001. Counsel for Sanofi agreed with the requested corrections. The corrected dates are included in paragraph 64 of these Reasons for Judgment.

"Judith A. Snider"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-161-07 and T-1161-07
STYLE OF CAUSE:	**SANOFI-AVENTIS CANADA INC. & SCHERING CORP. v. APOTEX INC. (T-161-07)** **SANOFI-AVENTIS CANADA INC. & SCHERING CORP. v. NOVOPHARM LIMITED (T-1161-07)**
PLACE OF HEARING:	TORONTO, ONTARIO
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DATED:	JUNE 29, 2009

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