Date: 20090210

Docket: T-891-07

Citation: 2009 FC 137

Toronto, Ontario, February 10, 2009

PRESENT: The Honourable Mr. Justice Hughes

BETWEEN:

BRISTOL-MYERS SQUIBB CANADA CO. and BRISTOL-MYERS SQUIBB COMPANY

Applicants

and

APOTEX INC. and THE MINISTER OF HEALTH

Respondents

REASONS FOR JUDGMENT AND JUDGMENT

[1] This is an application brought under the provisions of the *Patented Medicines (Notice of Compliance) Regulations* SOR/93-133, as amended (*NOC Regulations*) in which the Applicants Bristol-Myers Squibb Canada Co. et al. seek to restrain the Respondent Apotex Inc. from obtaining a Notice of Compliance from the Respondent Minister of Health to sell a generic version of a drug containing cefepime dihydrochloride monohydrate (which the parties refer to as CDM) until the expiry of Canadian Patent No. 1,298,288 ('288 patent). For the reasons that follow, I find that the application is dismissed with costs to Apotex Inc.

THE PARTIES

[2] The Applicants are Bristol-Myers Squibb Canada Co. (BMS Canada) which company is, as agreed by counsel for the parties at the hearing, the holder of a Notice of Compliance from the Minister for the drug in question. BMS Canada is known as a "first person" in the scheme of the *NOC Regulations*. The second Applicant Bristol-Myers Squibb Company (BMS US) is the owner of the '288 patent at issue and presumably is corporately related to BMS Canada. Collectively the Applicants will be referred to as BMS or the Applicants.

[3] The Respondent Apotex Inc. is a generic drug company, known as a "second person" in the scheme of the *NOC Regulations*. It will be referred to as Apotex. The Respondent, Minister of Health, herein referred to as the Minister, is charged with issuing Notices of Compliance to permit the sale and distribution of certain drugs in Canada and is charged with certain duties under the *NOC Regulations*. The Minister was not represented in these proceedings although served with the appropriate documents.

THE DRUG

[4] The drug in question is generally known as cefepime dihydrochloride monohydrate (CDM). It is a crystalline dihydrochloride monohydrate acid addition salt of 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-pyrrolidinio)methyl]-3-cephem-4-carboxylate. It is an antibiotic.

[5] CDM is a member of a class of beta-lactam antibiotics known as cephalosporins. It is a complex molecule. Such molecules are known to possess an electrical charge + or – at certain locations. Those molecules which exist in a form in which the totality of such electrical charges around the molecule is zero are considered to be neutral or in the language of the patent are a zwitterion or are said to be zwitteric. BMS acknowledges that the zwitterion form of the cefepime molecule is prior art to the patent at issue having been disclosed for instance in a previous patent, Canadian Patent No 1,213,882 (the '882 patent).

[6] BMS Canada has received a Notice of Compliance from the Minister to market this drug in Canada which it does under the brand name MAXIPIME.

THE PROCEEDINGS

[7] Apotex wishes to receive a Notice of Compliance from the Minister to market a generic version of this drug in Canada. Apotex has availed itself of procedures to abbreviate its submissions to the Minister by referencing BMS Canada's Notice of Compliance. Thus Apotex must comply with the provisions of the *NOC Regulations*. In that regard, Apotex served BMS Canada with a Notice of Allegation dated April 2, 2007 alleging that each of the claims of the '288 patent is invalid. In response, the Applicants commenced this application to prohibit the Minister from issuing a Notice of Compliance to Apotex until the expiry of the '288 patent.

THE ’288 PATENT

[8] Canadian Patent 1,298,288 (the ’288 Patent) was issued and granted to BMS US on March 31, 1992. The application for the patent was filed in the Canadian Patent Office on January 18, 1989. Since this date of application precedes the date of the substantial revisions of the *Patent Act*, R.S.C. 1985, c. P-4 on October 1, 1989, consideration of the ’288 patent and the validity of its claims is to be decided having regard to the pre-October 1, 1989 or “old” version of the *Patent Act*.

[9] The application for the ’288 Patent claims priority from an application filed on January 19, 1988 in the United States Patent Office as number 144,899. The ’288 Patent endures for the term of 17 years from the date of its grant that is, until March 31, 2009. This application was launched by the Applicants by filing a Notice of Application on May 23, 2007, thus under the provisions of the *NOC Regulations*, this application must be determined by May 23, 2009. I inquired of the parties as to whether they were content simply to await the expiry of the ’288 Patent since the expiry date predates by about two months the date set by the *NOC Regulations* for determination of this application. Apotex was not content to wait citing a number of reasons in its correspondence with the Court such as a right to claim damages and possible early entry into the market. This application has proceeded to a hearing and this determination.

[10] On May 22, 2008, the day before the Applicants filed the Notice of Application in these proceedings, BMS US as patentee filed with the Canadian Patent Office a document known as a disclaimer. That disclaimer was directed to claims 1 and 2 of the ’288 Patent and stated, in part:

> *4. The patentee disclaims the entirety of claim 1 with the exception of the following:*

> *1. Substantially pure temperature stable crystalline dihydrochloride hydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 7.0% by weight of water.*

5. The patentee disclaims the entirety of claim 2 with the exception of the following:

> *2. Substantially pure temperature stable crystalline dihydrochloride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

[11] Prior to May 22, 2008, the date of filing of the disclaimer, claims 1 and 2 had read:

> *1. Temperature stable crystalline dihydrochloride hydrate acid addition salt of 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio)methyl]-3-cephem-4-carboxylate containing from 2.5% to 7.0% by weight of water.*
>
> *2. Temperature stable crystalline dihydrochloride monohydrate acid addition salt of* 7-[α-*(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio)methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

[12] In effect, the disclaimer adds the words "Substantially pure" before the rest of the wording of each claims 1 and 2. No change in wording was made to any other claim.

[13] Claim 3 of the '288 Patent which was not the subject of the disclaimer reads and has always read as follows:

3. Temperature stable crystalline dihydrochlioride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate having the following X— ray powder diffraction pattern

X-RAY POWDER DIFFRACTION

Dihydrochloride Monohydrate

d	*I/I_o (%)*
10.21	*100*
8.62	*13*
6.78	*23*
6.28	*9*
5.84	*9*
5.12	*4*
5.01	*9*
4.95	*5*
4.74	*38*
4.62	*4*
4.50	*4*
4.44	*4*
4.26	*32*
4.10	*4*
3.95	*33*
3.90	*28*
3.78	*39*
3.64	*5*
3.59	*13*
3.48	*10*
3.39	*15*
3.32	*10*
3.21	*10*
3.11	*10*
3.04	*5*
2.99	*13*
2.93	*15*
2.76	*5*
2.63	*10*
2.51	*10*
2.43	*5*
2.38	*7*

[14] Claim 4 claims a physical mixture of what is set out in claim 3 together with L (+) lysine. Claim 5, the last claim, claims a physical mixture of what is set out in claim 3 together with L(+) arginine.

[15] In proceedings such as this the Applicants do not need to take issue with every challenge to validity made by a second person such as Apotex in respect of every claim. In the present proceedings, the Applicants have, in argument, restricted themselves to challenges raised in respect of claims 2 and 3 only. Therefore, the Court need not be concerned with challenges to the validity of any of claims 1, 4 or 5. No issue of infringement of any claim has been raised by Apotex in its Notice of Allegation.

WITNESSES

[16] Evidence in these proceedings has taken the usual form of affidavits, exhibits to affidavits, transcripts of cross-examination and exhibits identified in cross-examination.

[17] The Applicants put forward in evidence the affidavits of the following witnesses in chief:

- Dr. Stephen R. Byrn, professor of chemistry, Purdue University, West Lafayette, Indiana. He gave evidence as to the chemistry involved in this proceeding.
- Dr. Paul A. Bartlett, professor of chemistry, emeritus, University of California, Berkley, California. He gave evidence as to the chemistry involved in this proceeding.

- Mr. Kevin Murphy, Canadian and United States registered patent agent, partner of Ogilvy Renault LLP, Montreal, Quebec. He gave evidence respecting the file history of the ’288 patent and Patent Office practices.

[18] In reply, pursuant to an Order of Prothonotary Tabib, the Applicants filed the following affidavits:

- Reply affidavit of Dr. Stephen R. Byrn
- Reply affidavit of Dr. Paul A. Bartlett
- Mr. Scott Brown, patent litigation counsel for the Applicant BMS US. He gave evidence as to the disclaimer involved in the ’288 patent.

[19] Each of Byrn, Bartlett and Murphy were put forward as an expert witness. No challenge has been made to their claim to be experts. Brown was put forward as a fact witness. Each one of Byrn, Bartlett, Murphy and Brown were cross-examined by counsel for Apotex.

[20] Apotex put forward in evidence the affidavits of the following witnesses:

- Antigone Dialinou, a Certified Translator of the Greek and English languages. She translated into English a Greek Patent 862055 (the ‘055 patent) and the application for that patent. She was not cross-examined. The accuracy of these translations was not challenged.
- Jenny L. Gerster, a chemist employed by an Apotex related company who carried out experiments said to replicate certain examples in the prior art.

- Nadia K. Corelli-Rennie a chemist employed by an Apotex related company who carried out certain experiments intended to replicate certain examples given in the prior art.
- Dr. Robert A. McClelland, professor of chemistry emeritus, University of Toronto. He gave evidence as to the chemistry involved in this proceeding.
- Dr. Robert S. Langer, professor of chemistry, Massachusetts Institute of Technology, Boston Massachusetts. He gave evidence as to the chemistry involved in this proceeding.
- Mr. Douglas N. Deeth, Canadian lawyer and Patent Agent. He gave evidence as to patent application procedures and the application for the ’288 patent and disclaimer.
- Dr. Michael J. Cima, Professor Massachusetts Institute of Technology, material science relating to pharmaceuticals. He gave evidence respecting the testing conducted by Gerster and Corelli-Rennie.
- Ms. Kimberly Kreider, employee in the firm of Apotex’s co-counsel. She attached to her affidavit copies of a number of documents identified in Apotex’s Notice of Allegation. No challenge was raised as to the authenticity of these documents.

[21] Each of McClelland, Langer, Deeth and Cima were offered as expert witnesses. No challenge was made to their claim to be experts. Each of them was cross-examined by counsel for the Applicants. The other Apotex witnesses were offered as fact witnesses and were not cross-examined.

ISSUES

[22] There is only one main issue in this proceeding. That issue is whether the allegation made by Apotex that the claims of the ’288 patent are not valid are justified having regard to the provisions of the *NOC Regulations* particularly sections 5(1)(b)(iii) and 6(2). If such allegation is not justified, then the Court shall make an order prohibiting the Minister from issuing an NOC to Apotex until the expiry of that patent.

[23] The particular arguments raised as to invalidity are simplified by the Applicants’ reliance only on claims 2 and 3 of the ’288 patent but are complicated by the filing of a disclaimer by one of the Applicants with the Patent Office the day before they instituted these proceedings. That disclaimer directly affects claim 2 but not claim 3.

[24] Apotex raised a number of grounds for arguing invalidity of claims 2 and 3 and, in argument at the hearing dropped two grounds. First it dropped any assertion that section 53 of the *Patent Act* which deals false and misleading statements, was violated by the patentee BMS US. Second it dropped any argument as to inutility. Further one of the arguments as to ambiguity dealing with crystals was abandoned by Apotex but it maintained arguments as to ambiguity of the words substantially pure.

[25] Having regard to the written and oral submissions the arguments as to invalidity of claims 2 and 3 of the ’288 patent are:

1. Effect of the disclaimer;

2. Anticipation
3. Obviousness
4. Double Patenting
5. Selection Patents
6. Ambiguity-substantially pure

[26] Before consideration of these matters, the Court is required to place a construction upon claims 2 and 3. Further, the Court must determine where the burden of proof lies in respect of these matters. Lastly, the Court must consider who is the person skilled in the art to whom the patent is addressed.

[27] A preliminary matter was raised by the Court which is the issue of mootness. It will be considered first.

MOOTNESS

[28] The Court is asked by the Applicants to grant an Order prohibiting the Minister from issuing a Notice of Compliance to Apotex until the expiry of the ’288 patent. That patent will expire March 31, 2009 which is just over two months after the hearing of this matter has been held. The *NOC Regulations* provide in section 7(1)(e) that this proceeding should be determined within 24 months from the date it was instituted, that is, by May 23, 2009. Thus the ’288 patent will expire before the last date upon which this Court should determine this matter in which case there could be no Order for prohibition since the patent would have expired.

[29] The question of mootness was considered by the Supreme Court of Canada in *Borowski v. Canada (Attorney General)*, [1989] 1 S.C.R. 342 where it was held that, as an aspect of general policy or practice, a court may decline to decide a case which raises merely a hypothetical or abstract question and where the decision of the court will not have the effect of resolving some controversy which affects or may affect the rights of the parties. Sopinka J. of the Court wrote at paragraph 15:

> ***15*** *The doctrine of mootness is an aspect of a general policy or practice that a court may decline to decide a case which raises merely a hypothetical or abstract question. The general principle applies when the decision of the court will not have the effect of resolving some controversy which affects or may affect the rights of the parties. If the decision of the court will have no practical effect on such rights, the court will decline to decide the case. This essential ingredient must be present not only when the action or proceeding is commenced but at the time when the court is called upon to reach a decision. Accordingly if, subsequent to the initiation of the action or proceeding, events occur which affect the relationship of the parties so that no present live controversy exists which affects the rights of the parties, the case is said to be moot. The general policy or practice is enforced in moot cases unless the court exercises its discretion to depart from its policy or practice. The relevant factors relating to the exercise of the court's discretion are discussed hereinafter.*

[30] In the present case, Apotex argues that, even if the patent expires, a holding that its allegation as to invalidity was justified would entitle it to make a claim for relief under section 8 of the *NOC Regulations*. Further, it argues, a decision could be made before the patent expires which, if favourable, could permit its early entry into the market even if for only a few days. There is, however, no evidence in the record to indicate whether or not Apotex is in fact ready, before the patent expires, to enter the market or whether it is in a position to make a viable claim under section 8 of the *Regulations*.

[31] I am guided by the decision of the Federal Court of Appeal in *Apotex Inc. v. Bayer AG* (2004), 32 C.P.R. (4th) 449 where a motion was brought to dismiss an appeal in NOC proceedings for mootness on the basis that the patent at issue had expired and the generic had been issued its Notice of Compliance. The Court, at paragraph 5, was satisfied that the appeal was moot in that the live controversy between the parties had ceased to exist. However, the Court found that there remained what it described as "collateral consequences" such as the possibility of proceedings brought by the generic for relief under section 8 of the *NOC Regulations*. Rothstein JA. (as he then was) for the Court wrote at paragraph 14:

> ***14*** *There is no indication in section 8 that the reversal on appeal must occur prior to expiry of the patent at issue or the issuance of a Notice of Compliance to the generic. Nor is there any rationale for such a requirement. If a generic manufacturer has been wrongly excluded from the market during the lifetime of a patent, the fact that an appeal is decided after the patent expires should have no bearing on the generic's entitlement to damages. In my respectful opinion, it would be inconsistent with the object of the current Regulations to deprive a generic manufacturer of the opportunity to avail itself of section 8 of the Regulations merely because a patent has expired or a Notice of Compliance has issued. The liability referred to in section 8 arises from the period prior to the expiry of the patent or issuance of the Notice of Compliance to the generic and the mere fact that the appeal is decided after that date has no bearing on the application of section 8.*

[32] I will, in the circumstances, make a determination of the issues, notwithstanding a concern as to mootness. I do so because it was the Court, not a party, who raised the issue of mootness, thus the parties were deprived of an opportunity to lead evidence one way or the other, as to whether there exists a live controversy. It may be in future cases where a patent has or is about to expire

during the course of proceedings such as this, that there would be a proper record upon which the issue of mootness could be addressed.

BURDEN OF PROOF

[33] The issue is one of validity of two claims of the '288 patent. No issue as to infringement has been raised.

[34] Counsel for the Applicants agreed during the oral hearing that the burden of proof as to validity in NOC proceedings is as I expressed at paragraphs 57 and 58 of *Abbott Laboratories v. Canada (Minister of Health)*, 2008 FC 1359:

> ***57*** *This is a proceeding brought under the provisions of section 6 of the PMNOC Regulations for a determination of several issues including whether Sandoz's allegations that claim 5 of the '527 patent is "not valid" is "justified". The use of the term "not valid" comes from section 5(b)(iii) of the PMNOC Regulations and, as the Supreme Court of Canada (Rothstein J. for the Court) wrote in Apotex Inc. v. Sanofi-Synthelabo Canada Inc., [2008] S.C.J. No. 63, 2008 SCC 61 (Sanofi) at paragraph 17, the inquiry parallels what would otherwise be a defence to an infringement action as referred to in section 59 of the Patent Act.*
>
> ***58*** *The Patent Act, section 43(2), in the case of a post October 1, 1996 patent such as the '527 patent here, provides that a patent shall, in the absence of evidence to the contrary, be valid. In Pfizer Canada Inc. v. Canada (Minister of Health), [2008] F.C.J. No. 3, 2008 FC 11, I reviewed the recent authorities, including two from the Federal Court of Appeal, on the question as to who had the burden of proof as to validity particularly in NOC proceedings such as this, and concluded that a patentee such as Abbott may rely on the presumption of validity however, if the attacking party, Sandoz, has lead reliable evidence, then the Court must weight all the evidence on the usual civil burden of proof, if the matter was then seen to be evenly balanced, the attack on validity fails. At paragraph 33 of that decision, I wrote:*

> ***33*** *If the matter were an ordinary action for, say, infringement of a patent where validity is put in issue, the party challenging validity bears the burden such that, it must put in evidence to support the allegation of invalidity. The patentee may rely on the presumption but only to the extent that the attacking party must lead some reliable evidence to support its allegation. At the end of the day, the Court must weigh the evidence on the usual civil burden of proof (Tye-Sil Corp. Ltd. v. Diversified Products Corp. (1991), 35 C.P.R. (3d) 350 at 357-359 (F.C.A.)). Only if the Court finds the evidence to be "evenly balanced" (a rare event) would the question of burden arises in an ordinary case the party attacking validity, bearing the burden, would fail.*

Counsel for Apotex agreed that this was a proper statement of the law.

PERSON SKILLED IN THE ART

[35] A patent, as well as prior art, is to be considered from the viewpoint of a person skilled in the art. There is no controversy as to who is such a person in this case as Applicants' counsel has agreed that Apotex has correctly characterized such a person through the evidence of one of its expert witnesses, Dr. McClelland, at paragraph 9 of his affidavit:

> *9. The '288 Patent is thus addressed to chemists, medicinal chemists, chemical engineers, formulators and pharmaceutical chemists. Such an individual (or group of individuals) has a university degree in one of these areas. This individual (or group of individuals) will also have several years experience in the pharmaceutical industry or in a pharmaceutically related area. In respect of such an individual (or group of individuals), if such an individual (or group of individuals) had only an undergraduate degree, then such an individual (or group of individuals) would have more experience in the pharmaceutical industry or in a pharmaceutically related area. That experience would take the form of chemical synthesis, the preparation of crystalline solids such as salts by*

> *crystallization/recrystallization, the preparation of solvates including hydrates, the characterization of such crystalline solids, salts and hydrates by techniques such as infrared spectroscopy and X-ray powder diffraction, and the study of the stability of compounds intended for use of pharmaceuticals.*

[36] No particular controversy arises in these proceedings in respect of this characterization of such a person skilled in the art.

CONSTRUCTION OF CLAIMS 2 AND 3

[37] The Supreme Court of Canada has instructed that the Court must first construe the claims at issue before moving to consideration of issues such as validity and infringement of those claims, the purpose in doing so is to identify what it is in the claims that the inventor considered to be essential. This construction is to be conducted in a purposive manner so as to endeavour to be fair to both the patentee and the public per Binnie J. for the Court in *Whirlpool Inc. v. Camco Inc.*, [2000] 2 S.C.R. 1067 at paragraphs 42 to 50. I repeat part of paragraphs 43 and 45:

> ***43*** *The first step in a patent suit is therefore to construe the claims. Claims construction is antecedent to consideration of both validity and infringement issues. The appellants' argument is that these two inquiries -- validity and infringement -- are distinct, and that if the principles of "purposive construction" derived from Catnic are to be adopted at all, they should properly be confined to infringement issues only. The principle of "purposive construction", they say, has no role to play in the determination of validity, and its misapplication is fatal to the judgment under appeal.*
>
> ...
>
> ***45*** *The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what*

> *the inventor considered to be the "essential" elements of his invention.*

[38] The ’288 patent is governed by the provisions of the old *Patent Act*, thus is to be construed by the Court as of the date of its grant, March 31, 1992, through the eyes of a person skilled in the art, assisted if needed by expert evidence as to the meaning of certain terms and the knowledge that a person skilled in the art would have had as of trial date. As Sharlow JA. for the Federal Court of Appeal wrote at paragraph 4 of *Novopharm Limited v. Janssen-Ortho Inc.*, (2007), 59 C.P.R. (4th) 116, 2007 FCA 217 respecting an old *Patent Act* patent:

> ***4*** *In any case in which the validity or infringement of a patent claim is in issue, it is necessary to construe the claim: Whirlpool Corp. v. Camco Inc., [2000] 2 S.C.R. 1067 at paragraph 43. The relevant date for the construction of the 080 patent is the date of its issuance, June 23, 1992. The patent must be understood as being addressed to a person skilled in the art, taking into consideration the knowledge that such a person is expected to possess on that date. The construction of a patent claim is a task for the Court and must be based on the whole of the disclosure and the claim, assisted by expert evidence as to the meaning of certain terms and the knowledge that a person skilled in the art is expected to possess on the relevant date.*

[39] Claims 2 and 3 are to be construed. Since claim 2 was the subject of a disclaimer, its form both before and after the disclaimer should be considered. I repeat claim 2:

> Before disclaimer:
>
> > *2. Temperature stable crystalline dihydrochloride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

After disclaimer:

> *2. Substantially pure temperature stable crystalline dihydrochloride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

[40] Claim 3 is unaffected by the disclaimer and I repeat it:

> *3. Temperature stable crystalline dihydrochlioride monohydrate acid addition salt of 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate having the following X— ray powder diffraction pattern*

X-RAY POWDER DIFFRACTION
Dihydrochloride Monohydrate

d	*I/I_o (%)*
10.21	*100*
8.62	*13*
6.78	*23*
6.28	*9*
5.84	*9*
5.12	*4*
5.01	*9*
4.95	*5*
4.74	*38*
4.62	*4*
4.50	*4*
4.44	*4*
4.26	*32*
4.10	*4*
3.95	*33*
3.90	*28*
3.78	*39*
3.64	*5*
3.59	*13*
3.48	*10*
3.39	*15*
3.32	*10*

3.21	*10*
3.11	*10*
3.04	*5*
2.99	*13*
2.93	*15*
2.76	*5*
2.63	*10*
2.51	*10*
2.43	*5*
2.38	*7*

EFFECT OF THE DISCLAIMER

[41] I pause in the consideration of construction for consideration of the effect of the disclaimer filed by the Applicants the day before they instituted this proceeding. Section 48 of the old *Patent Act* (a provision continued in the later versions of the *Act*) provides in subsection 48(1)(a) that whenever a patentee determines that by any mistake, accident or inadvertence, and without any wilful intent to defraud or mislead the public, the patentee has made his specification too broad, claiming more than that of which he invented, he may disclaim the parts which he does not claim to hold. Subsection 48(4) says that a disclaimer does not affect a pending action unless there has been unreasonable delay or neglect. Subsection 48(6) says that, after the disclaimer has been filed, the patent as it is then intended to be read is deemed to be valid.

[42] A patent which claims more than what was invented or disclosed can be found to be invalid for being overly broad. As Nadon JA. for the Federal Court of Appeal wrote at paragraph 115 of *Pfizer Canada Inc. v. Canada (Minister of Health)*, (2007), 60 C.P.R. (4th) 81, 2007 FCA 209:

> ***115*** *It is now settled law that a patent which claims more than what was invented or disclosed can be found invalid for being overly broad. As explained in Lovell Manufacturing Co. and*

> *Maxwell Ltd. v. Beatty Brothers Ltd. (1962), 41 C.P.R. 18 (Ex. Ct.) at p. 66:*
>
> > ***The other attack was that the claims were too wide and that they claimed more than had been invented****. This repeats the central them to which I have referred, namely, the contention that all that had been invented were the specific wringer constructions described in the specification and that unless the claims were limited in their application to inventions of the said specific constructions they were too wide and, therefore, invalid.* ***There is a simple answer to the contention, If the claims read fairly on what has been disclosed and illustrated in the specification and drawings, as they do, they are not wider than the invention.*** *The specific wringer constructions described in the specification are simply embodiments or illustrations of the invention. The claims embrace them and might well embrace similar other embodiments or illustrations. There is nothing in any of the specifications that would limit the claims to one of the specific wringer constructions or to all of them.*

[43] Thus a claim which is overly broad in a patent that has not yet been adjudged to be invalid may be saved from a finding of invalidity by a Court if a disclaimer is filed but only if filed in a timely way.

[44] In the present case, a disclaimer was filed by one of the Applicants BMS US as it is the patentee. The document as submitted to the Patent Office on May 22, 2007 says:

> *1. The patentee at Patent No. 1,298,288, granted on March 31, 1992 for an invention entitled "Cephalosporin Salts and Injectable Compositions", has, by mistake, accident or inadvertence, and without any wilful intent to defraud or mislead to public made the specification too broad, claiming more than that of which the patentee or the person through whom the patentee claims was the first inventor.*

> *2. The name and complete address of the patentee is Bristol-Myers Squibb Company, 345 Park Avenue New York, NY 10154, United States of America.*
>
> *3. Due to inadvertence, accident or mistake, some claims in the application issued in a broader scope than the applicant was entitled. Accordingly, Claims 1 and 2 will be partially disclaimed to limit the scope of the claims.*
>
> *4. The patentee disclaims the entirety of claim 1 with the exception of the following:*
>
> > *1. Substantially pure temperature stable crystalline dihydrochloride hydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 7.0% by weight of water.*
>
> *5. The patentee disclaims the entirety of claim 2 with the exception of the following:*
>
> > *2. Substantially pure temperature stable crystalline dihydrochloride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

[45] This is a public document, filed with the Patent Office, affecting claims 1 and 2 of the ’288 patent which states in unequivocal terms that the patentee “*made the specification too broad*, *claiming more than that…of which it was the first inventor*” and the claims were “*broader in scope*” than what was intended. The document is a clear admission by the patentee that the original claims were too broad. Thus, if a Court were to have considered only the original claims prior to the filing of the disclaimer, they could have been declared to be invalid for overbreadth.

[46] The Applicants submitted in these proceedings, but not with the Patent Office, the affidavit of Brown, who is not one of the inventors and not the attorney who drafted or prosecuted the original application, but who is a current in-house lawyer with BMS US. On cross-examination, he stated that the disclaimer was, in effect, only precautionary. He testified that once the Applicants received Apotex's Notice of Allegation, it was thought prudent to clear up any doubt as to the scope of claims 1 and 2. Even though he thought the original claims to be limited to substantially pure product, it was believed prudent by the Applicants to clear up any doubt by filing a disclaimer.

[47] I cannot accept this argument. The Applicants filed a document with the Patent Office, intending it to be acted upon by that Office and knowing that it would be seen and relied upon by the public. That document clearly and unequivocally says that the patentee made the original claims too broad. Private reservations of in-house counsel or litigation tactics cannot allow the Applicants to resile from those public statements.

[48] Given those statements, what is the effect of the disclaimer? These proceedings are not an "action" as spoken of in subsection 48(4) of the *Patent Act*, *supra*. These proceedings are not the kind in which the Court may expunge a patent or claims for invalidity. In these proceedings under the *NOC Regulations* all that a Court may do is determine whether the allegations made, in this case by Apotex in its Notice of Allegation, are justified.

[49] The Commissioner of Patents has no discretion to exercise upon a disclaimer as filed, it must be accepted as is. However the patentee must accept the possibilities afforded by litigation as

to the effect of such disclaimer. This is what the Federal Court of Appeal held in *Distrimedic Inc. v. Richards Packaging Inc.* (2008), 66 C.P.R. (4th) 1 (FCA) per Letourneau JA. at paragraphs 9 and 12:

> ***9*** *Indeed, not only is there no mention of such power in the provision, the Act, and more specifically section 48, as well as the Rules, provide no administrative and procedural framework to properly and effectively allow a substantive consideration of the contents of a disclaimer. This is in contrast with numerous other situations where an administrative structure is provided and authority is given to the Commissioner or delegate to act: see for example section 35 (request for examination), Rule 30 (procedural guarantees), section 65 and ff. (abuse of rights under patents).*
>
> ...
>
> ***12*** *Finally, if the Commissioner does not possess the power to refuse to record a disclaimer, as is presently the case, the appellant recognizes that it suffers no loss of rights and no prejudice other than having the trouble and bearing the cost of litigating the effect of the disclaimer. Once the possibility of recording a disclaimer is given to a patentee, possible litigation as to the effect of the disclaimer is something inherent to the very fact that a disclaimer is made and sought to be recorded.*

[50] The Privy Council on appeal from the Supreme Court of Canada in *Canadian Celanese Ltd. v. B.V.D. Co. Ltd.*, [1939] 2 D.L.R. 289 dealt with a situation where the Supreme Court held in its Reasons delivered before formal Judgment was entered, that the claims of a patent were too broad and hence the claims were invalid. Before judgment was entered the patentee filed a disclaimer limiting the scope of the claims, then sought a rehearing by the Supreme Court on the basis that the reformulated claims overcame the objections raised by the Court, hence validity was preserved. The Supreme Court refused to rehear the matter. The patentee appealed to the Privy Council which dismissed the appeal. The Privy Council in its advice to His Majesty said that, in making the

amendments by way of disclaimer, the patentee had accepted that the findings of the Supreme Court were valid and it was not open to appeal against those findings. At page 294 of its advice, the Privy Council wrote:

> *The disclaimer is an unconditional disclaimer; it must necessarily be unconditional. The statute does not contemplate or authorize a contingent disclaimer. As soon as the disclaimer was filed and recorded in the office of the Commissioner, it as made part of the Patent; the only existing Claims are the Claims as amended by virtue of the disclaimer, and the only invention protected by the Letters Patent is the invention a description whereof is contained in the Specification as so amended. In these circumstances the present Appellants, having filed a disclaimer for the purpose of changing the construction which the Supreme Court had declared to be the true construction of the original Claims, must be taken to have finally accepted that construction as being the true construction of those claims; and it is not open to them to appeal successfully against the Court's declaration of that construction.*

[51] In the present case, Apotex served its Notice of Allegation on April 2, 2007; the Applicants filed their disclaimer on May 22, 2007 and instituted these proceedings the next day, May 23, 2007. Section 6(2) of the *NOC Regulations* requires that this Court make a determination as to whether Apotex's allegations as to invalidity are justified.

[52] Justice Stone in the Federal Court of Appeal has held that a Notice of Allegation is a document beyond the reach of a Court's jurisdiction. The Court cannot strike such a document as it is not a document filed with the Court. In *Pharmacia Inc. v. Canada (Minister of National Health and Welfare)* (1994), 58 C.P.R. (3d) 207 (FCA) he wrote at paragraph 6:

> ***6*** *It seems to us that while a notice of allegation does play an important role in the ultimate outcome of litigation of this nature, is not a document by which the judicial review application may be launched under section 6 of the Regulations. That document was*

> *put in as a piece of evidence by the appellants; it originated with the application filed before the Minister. Because it is not a document that was filed with the Court but with the Minister, in our view the notice of allegation is beyond the reach of the Court's jurisdiction in a judicial review proceeding. That being so, the Court, in our opinion, lacks jurisdiction to strike out the notice of allegation.*

[53] In *AB Hassle v. Canada (Minister of National Health and Welfare)* (2000), 7 C.P.R. (4th) 272 (FCA) Stone JA. held that the Notice of Allegation "casts a long shadow" and NOC proceeding as it serves to frame the issues. At paragraph 20 he wrote:

> ***20*** *While it is true that the detailed statement is not filed in a section 6 proceeding, it nevertheless casts a long shadow over that proceeding. Indeed, it is upon the content of that statement that the patentee must decide whether or not to commence a section 6 proceeding and to assess its chances of success or failure. In this sense the allegation and detailed statement assist in an important way in framing the issues and facts to be determined in the section 6 proceedings for in seeking prohibition the patentee is obliged to show that, contrary to what is stated in the detailed statement, the patentee's patent right will be infringed if an NOC for the drug is issued prior to the expiration of the listed patent.*

[54] Therefore the Court must consider the various possibilities since the Court cannot amend a Notice of Allegation. If the patentee disclaimed certain claims but did not commence proceedings in the court, the generic would get its Notice of Compliance as soon as the 45 day period provide by subsection 7(1)(d) of the *NOC Regulations*. If the patentee commenced proceedings and the generic did not defend, the patentee would get judgment prohibiting the generic from receiving a Notice of Compliance until the patent expired. If a generic wishes to attack the validity of the claims as reformulated by the disclaimer, it cannot revise its Notice of Application since proceedings, as in this case, have already been commenced. Apotex cannot raise new grounds for invalidity nor allege

non-infringement since the proceedings in this Court were initiated immediately after the filing of the Disclaimer thus, in effect, locking in the Notice of Allegation.

[55] The only proper way to approach the matter is to do so in the way that the Privy Council did in *BVD* namely fix a date prior to the disclaimer for the purpose of construing the claims. The Privy Council fixed that date as the date of the Supreme Court decision even though formal judgment had not yet been entered. Here that date must be April 2, 2007, the date that the Notice of Allegation was served. I must add however, that this date for construction relates only to claim 2 and only for purposes of this particular NOC proceeding.

[56] Should the Applicants assert the patent subsequent to the date of the disclaimer in an action or other proceeding, then claim 2 may well be considered in the form as disclaimed.

[57] If this were not a proceeding under the *NOC Regulations* but an ordinary patent infringement action, then a disclaimer even if filed during the course of the action, would serve to amend the patent and, therefore, possibly change the issues as to validity and infringement. In an action parties may amend their pleadings and conduct further discovery. This was, for instance, the circumstance in *Cooper & Beatty v. Alpha Graphics Ltd.* (1980), 49 C.P.R. (2d) 145 (FC) per Mahoney J. at pages 162-164. None of this is possible in a proceeding under the *NOC Regulations*.

[58] Apotex argues that the disclaimer is invalid and, since it is invalid and since the original claims 1 and 2 were disclaimed, nothing is left of claims 1 and 2, they have disappeared. The basis

upon which Apotex argues that the disclaimer is invalid is that the evidence of Brown, BMS US's in-house attorney is clear that the only motivation is filing the disclaimer was an attempt to avoid a construction of those claims that would, because of their breadth, read on the prior art. Brown was neither an inventor nor a draughtsman of the original patent specification. Relying on the reasons of Mosley J. in *Pfizer Canada Inc. v. Apotex Inc.* (2007), 61 C.P.R. (4th) 305 (FC) at paragraphs 37 and 38, Apotex argues that the validity of a disclaimer depends solely on the state of mind of the patentee at the time he drafted his specification. Mosley J. wrote:

> ***37*** *As was recently noted by the Court in* Richards Packaging Inc. v. Canada (Attorney General), *2007 FC 11, [2007] F.C.J. No. 21 at para. 28, the Commissioner and the examiners have no authority under the Act and the Rules to make a decision on the validity of a disclaimer filed by a patentee; this power belongs to the courts. The fact that the Patent Office has accepted a disclaimer is therefore not determinative of whether the requirements of subsection 48(1) have been met:* ICN Pharm.*, above at para. 70.*
>
> ***38*** *I agree with the findings of the Ontario High Court of Justice in* Trubenizing Process Corp. v. John Forsyth, Ltd.*, [1942] O.R. 271-300, 2 C.P.R. 89, rev'd on other grounds [1943] S.C.R. 422, [1943] S.C.J. No. 35, wherein Chevrier J. held that the validity of the disclaimer depends solely upon the state of mind of the patentee at the time he made his specification. Chevrier J. further made it clear that the onus rests on the party who files a disclaimer to justify the need for the disclaimer at the time it was filed by reason of mistake, accident or inadvertence and that there was an absence of intent to defraud or mislead the public. Where the filing party does not discharge this burden, the disclaimer will be held to be invalid and the patent will remain in its original form.*

[59] I disagree with these arguments by Apotex for two reasons. The first is that Apotex's argument ignores the last two lines of Mosley J.'s reason at paragraph 38. A disclaimed claim does not disappear if the disclaimer is invalid. One returns to the original claim. In the present

proceeding we are dealing with the original claim as it stood as of the date the Notice of Allegation was served.

[60] Secondly, the sentence quoted with approval by Mosley J. in paragraph 30 from Chevrier J.'s reasons speaks of the state of mind of the patentee.

The patentee is defined in section 2 of the *Patent Act* as the person who is entitled to the benefit of the patent. This includes the inventor, his heirs and assignees. Here the patent and application for that patent in Canada was owned by BMS US, it is the patentee. Brown can speak to the state of mind of BMS US as patentee. The motivation of BMS US in disclaiming appears to be no different than that of the patentee in *Cooper & Beatty*, *supra*, namely to narrow the claims in an attempt to preserve their validity. From the evidence before me I cannot find the disclaimer to be invalid.

A BRIEF REVIEW OF THE PATENT AND THE TECHNOLOGY

[61] Returning to construction of the claims, the Court must put itself in the position of a person skilled in the art as of the date of grant of the patent, March 31, 1992, read the patent and interpret the claims in the context of the disclosure of the patent. Expert evidence can be received by the Court to explain the meaning of certain terms and to provide the background, if necessary, as to what such a person would understand.

[62] Turning to the patent, the technical field is succinctly set out at page 3:

> *Technical Field*
> *This invention is directed to temperature stable semi-synthetic cephalosporin salts whose preparation has not been described in the literature, to the preparation of such salts, and to admixtures containing these parts.*

[63] At the same page, the patent sets out the background, acknowledging that another patent called Aburaki et al. constitutes relevant prior art. Aburaki, U.S. Patent No. 4,406,899 (the '899 patent) is acknowledged by counsel for the parties to be for all material purposes here, the same as Canadian Patent No. 1,213,882 (the '882 patent). Apotex relies on these patents interchangeably as prior art in its arguments as to anticipation and obviousness.

[64] At page 3 the patent at issue acknowledges that Aburaki discloses the following:

> *Background Of The Invention*
>
> *Aburaki et al. U.S. Patent No. 4,406,899 discloses 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoxyiminaocetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate in the zwitterion form and mentions corresponding acid addition salts (which are present in the zwitterion form in injectable compositions) and show that the zwitterion form has broader spectrum activity than ceftazidime and cefotaxime.*
>
> *However, the aforementioned Aburaki et al. cephalosporins are stable only for a few hours as injectable compositions and the zwitterion form even as a dry powder is unstable at room temperature and loses 30% or more of its activity on storage at elevated temperatures (e.g. 45 deg. C. and above) for even one week and therefore requires special insulated packaging and/or refrigeration and is at a packaging and storage disadvantage compared to ceftazidime and cefotaxime.*
>
> *While Aburaki et al. mentions acid addition salts, the patent does not state how to make these or state which if any of these salts have good stability in dry powder form. Kessler et al., "Comparison of a New Cephalosporin, BMY 28142, with Other Broad-Sprectrum β-Lactam Antibiotics", Antimicrobial Agents and Chemotherapy, Vol. 27, No.*

> *2, pp. 207-216, February 1985 mentions the sulphate salt, but does not disclose how to prepare such or that this salt has room temperature stability and good elevated temperature stability in dry powder form.*

[65] What is being said, in the parlance of this proceeding, is that the known cefepime molecule which can simply be referred to as the zwiterrion form is disclosed in the prior art and is used in an injectable composition. It has a problem with stability. The patent acknowledges that Abukari and another piece of prior art, a Kessler article, do mention acid addition salt forms of the zwitterion form but not how to make them or which if any of the salts have good stability.

[66] A "Summary of the Invention" is given at page 4 and following. At page 4 the patent says:

> *Summary Of The Invention*
>
> *It has been discovered herein that certain crystalline acid addition salts* of *7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoxyiminaocetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate in dry powder form have excellent room temperature stability and have superior elevated temperature stability compared to the zwitterion form. The term "dry powder form" as used herein means a moisture content of less than 5% by weight when measured by loss in weight on drying at atmospheric pressure and a temperature of less than 70°C.*
>
> *These acid addition salts are the crystalline salts of of 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoxyiminaocetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate selected from the group consisting of the sulphuric, di-nitric, monohydrochloric, and di-hydrochloric acid addition salts and orthophosphoric acid addition salts (1.5-2 moles of authophosphoric acid per mole of salt, e.g. a range of from the sesqui-to the di-orthophosphoric acid salts), or solvates thereof. The term "crystalline" is used herein to mean at least some characterizing arrangement of molecules. While the sulphuric, di-nitric, di-hydrochloric and orthophosphoric acid addition salts herein are prepared in clearly crystalline form (as evidenced by birefringence under a polarizing microscope) with*

> *precise arrangement of molecules, the mono-hydrochloric acid addition salt has been prepared only with some regularity in the arrangement of its molecules (as evidenced by poor birefringence under polarization microscope) and not a precise predictable arrangement and thus is "poorly" crystalline. The term "crystalline" is used herein to embrace not only the clearly crystalline salts but also the "poorly" appearing crystalline mono-hydrochloric acid addition salt.*

[67] What is being said is that certain crystalline acid addition salts of the zwitterion form have superior elevated stability when compared to the zwitterion form alone. These salts are listed as the sulphuric, di-nitric, monohydrochloric, and di-hydrochloric and ortho-phosphoric addition salts. "Crystalline" is defined to embrace not only clearly crystalline salts but "poorly" appearing crystalline mono-hydrochloric addition salts.

[68] At page 5 reference is made to the prior art Aburaki to demonstrate the utility of the salts against various organisms:

> *The broad spectrum utility against various organisms of the zwitterion form, and thus of aqueous compositions made up from the salts herein, is shown by the data in Aburaki et al. US. 4,406,899.*

[69] Thus it is acknowledged that the salt forms have the same utility as the prior art zwitterion form.

[70] The preferred salt is identified at page 5 of the patent as the sulphuric acid addition salt.

> *The preferred salt for use as a manufacturing intermediate is the crystalline sulphuric acid addition salt. It is preferred because its low solubility in water (25 mg/ml) allows high recovery from aqueous medium on crystallization, and good purity.*

[71] Thus the preferred salt is not the dihydrochloride salt of the claims at issue, or any of the claims, but a different one, the sulphuric acid salt. No explanation is given in the '288 patent as to why dihydrochloride and not sulphuric acid salt was the subject of the claims.

[72] The sulphuric acid salt form is said to be "*readily prepared*" by a process set out at page 6 of the '288 patent.

> *The crystalline sulphuric acid addition salt is readily prepared by a process comprising the steps of (a) forming an admixture of (i) at least 1 molar equivalent of sulphuric acid and (ii) zwitterion in an amount so as to be present in the admixture at a concentration greater than 25mg/ml, (b) causing crystallization of the sulphuric acid addition salt to occur, and (c) isolating crystalline sulphuric acid addition salt.*

[73] The Detailed Description at page 6 of the '288 patent defines its use of the word "salts" in the patent to mean all the named salts, that all have excellent stability, and that the sulphuric acid salt is preferred. It is said that if hydrochloric salts are to be used they should preferably be crystallized from organic solvents:

> <u>*Detailed Description*</u>
>
> *The crystalline salts herein (herein after referred to simply as the salts herein) have excellent stability at room temperature and have a potency loss (as determined by HPLC), of less than 1% on storage for a month at room temperature. These salts also have excellent stability at elevated temperatures and have a potency loss (as determined by HPLC) of less than 15% on storage for a month at 45-56 deg. C.*
>
> *The sulphuric acid addition salt is a preferred salt herein. It has a potency loss of less than 10% on storage for a month a 45-56 deg. C. Very importantly, it has a low solubility in water, i.e. about 25 mg/ml, and therefore is crystallized from water with minimized residual loss.*

> *The di-nitric acid addition salt herein also has a low solubility in water, i.e. about 60 mg/ml, and therefore also provides low residual loss on crystallization from water.*
>
> *The mono-hydrochloric, di-hydrochloric and sesqui- or di-orthochloric acid addition salts have water solubilities greater than 200 mg/ml., and therefore are preferably crystallized from organic solvents, rather than from water, in order to obtain good yields.*

[74] From page 7 of the ’288 patent to line 5 of page 10 there is a description of various processes to make the various compositions. This discussion is not relevant to the issues here. The patent at issue contains no claim directed to a process.

[75] Remembering that at page 6 of the patent at the beginning of the Detailed Description a definition is given for salts so as to comprise all the salts discussed in the patent one can look at page 10 where it is stated at lines 6 and following that:

> *“The salts herein are formed into injectable compositions by diluting with sterile water…”*

[76] At lines 30 to 32 at page 10 the patent describes such salts as having “purity” which varies from lot to lot:

> *The exact proportions of ingredients in the physical admixture vary from lot to lot of the salt since the purity of the salt varies from lot to lot.*

[77] At pages 12 and following to the end of the descriptive part of the ’288 patent at page 29, thirteen Examples are provided.

[78] Example VII at pages 16 and 17 is directed to data as to stability. It is to be noted that while the right side of the table (reproduced as per original) is captioned as "Percent Loss" the description preceding the table tells the reader that a + sign indicates gain in potency, not loss.

Example VII

Stabilities at Elevated Temperatures

Elevated temperature stabilities were determined by storing the preparations in dry containers at temperatures and for time periods as denoted below and potency losses or gains were determined by HPLC. A % potency gain is indicated by a plus sign in front of a figure. A less than 10% potency loss over a 2 to 4 week period at 45-56 deg. C is usually indicative of less than lot potency loss over a 2-3 year period at room temperature.

	PERCENT LOSS							
	45 Deg. C (Weeks)				56 Deg. C (Weeks)			100 Deg. C (Days)
Form	1	2	4	6	1	2	4	1
Zwitterion	37	51	71	-	57	-	-	100
H_2SO_4 Salt	2.4 to +5	3	+5	1.4	5 to +6	+3	0 to +6	0-10
$(HNO_3)_2$ Salt	8.8	3.4	0.68	10.3	3.7	2.4	-	-
HCl Salt	4.8	2.3	6.0	6.4	6.4	-	-	-
$(HCl)_2$ Salt	0	-	7.4	-	0	-	7.2	12.4
$(H_3PO_4)_2$ Salt	0	3.0	1.0	-	2.7	5.0	-	-

[79] It is to be noted that the sulphuric acid salt (H_2SO_4 salt) shows at times a gain (e.g. +6) not a loss whereas a hydrochloride salt ($(HCl)_2$ salt) which is said to be an anhydrate and not the claimed monohydrate salt shows no loss (0) and thereafter a loss of 7.2 and 12.4 percent. In other words, as the patent previously said, sulphuric acid salt is best whereas dihydrochloride salt (presumably anhydrous) is, with the exception of the unsalted zwitterion, the worst. No data is given for the dihydrochloride monohydrate salt which is the subject of claims 2 and 3.

[80] Example XI is directed to what it describes as preparation of the dihydrochloride monohydrate salt of the zwitterion. This is the first specific mention of the monohydrate version of the dihydrochloride salt. At page 25 an analytical calculation as to the contents as well as a "found" (that is as determined by actual inspection of the sample) is provided. It is important to note that the theoretical water (H_2O) content is 3.15 percent and the found H_2O content is 3.34 percent.

Anal. Calcd for $C_{19}H_{26}N_6O_5S_2Cl_2 H_2O$:		C, 39.93; H, 4.94; N, 14.70; S, 11.22 Cl, 12.41; H_2O, 3.15
Found	:	C, 39.70; H, 4.80; N, 14.64; S, 11.12; Cl, 12.44; H_2O, 3.34

[81] At pages 25 and 26 an x-ray diffraction pattern of the sample is presented. I will not repeat the data, it is the same as presented in claim 3 of the '288 patent previously set out in these reasons.

[82] As to Powder X-Ray Diffraction (PXRD), I accept what Dr. McClelland says at paragraph 18 of his affidavit (reproduced later in these reasons), that PXRD is an analytical technique which serves to distinguish one particular crystalline form from another. I also accept Dr. Bartlett's

evidence to the same effect as stated in paragraph 7 of his Reply affidavit where the describes PXRD (or XRPD) as a "signature":

> *7. Powder X-ray diffraction (PXRD, also abbreviated XRPD) analysis characterizes the sate of crystallinity of a sample and, for a crystalline sample, provides a "signature" that reflects the manner in which the molecules are arranged in the crystal framework.*

It is to be noted that claim 3 and the specification of the patent give the two PXRD columns of data At the left is (d) which identifies certain spacings. On the right is relative intensities (I/I_o) – see pages 25 and 26 of the '288 patent. I accept what Dr. Byrn said during his cross-examination in answer to Questions 368 to 372 that the (d) values or spacings should be in quite good agreement between a reference and a sample so that the sample can be said to be the same crystal hydrate form as the reference, wherein the intensity can vary up to twenty percent from sample to sample.

[83] Thus any particular crystal form will have its own PXRD profile or signature. This data serves to identify what is in the product being tested. It does not define a different product. The relative intensity of the peaks may vary from sample to sample but the position of the peaks themselves should be in very good agreement. Thus to say a product has a certain PXRD profile is simply another way of identifying that product. To provide a profile as in claim 3 serves simply to identify a product as the dihydrochloride monohydrate form, it does not create or identify a different form.

[84] Example XII of the '288 patent describes the preparation of the dihydrochloride monohydrate version of the salt and includes a statement as to what the Applicants argue is the utility of the dihydrochloride monohydrate salt. That version of the salt however is compared only to the anhydrate version of the dihydrochloride and not to any other form of that or any other salt.

The water content of the monohydrate said to have been produced is said to vary from between 2.46% and 3.70% averaging 3.31%. At lines 22 of page 27 to line 1 of page 28 it says:

> *The foregoing procedures of Examples XI and XII routinely produce monohydrate having a water content in the range of 2.46% to 3.70% with an average value of 3.31%. The value calculated from the stoichiometric formula is 3.15%. Drying at 57^0C in a desiccator at reduced pressure (0.001 mm Hg) over P_20_5 for 5 days or at reduced pressure (10 mm Hg) at 45^0C for 2 days results in no loss in weight. Storage stability at 56^0C for 3 weeks produced a potency loss of 0.6%, and was substantially improved, therefore, as compared to the anhydrate (1.25% H_20) described in Example V hereof (7.2% loss in 4 weeks at 56°C).*

[85] Example XIII at page 29 describes the stability of the monohydrate form with a reported water content from between 2.5% to 4.1%:

> *The storage stability at elevated temperatures as measured by chemical and biological potency of the sample was similar for the monohydrate and dihydrate, but the formation of trace amounts of insoluble particle was observed with the dihydrate. Accordingly, the monohydrate caring up to about 1% by weight of adventitious water is the preferred form (total water content ca. 2.5-4.1%). Such material when stored at 56°C for 3 weeks exhibits at least a 96% retention of potency.*

[86] This salt and its stability, which can be recharacterized as a 4% loss over 3 weeks, is not reflected in the Table of Example VII nor presented anywhere else in the patent so that a proper comparison can be made.

[87] I accept the evidence of Dr. Byrn as to water content in a crystal structure, which is that a crystal structure which has one proportionate measure of water incorporated into the crystal-a monohydrate- has a certain calculated water content. Other forms such as dihydrate (two measures)

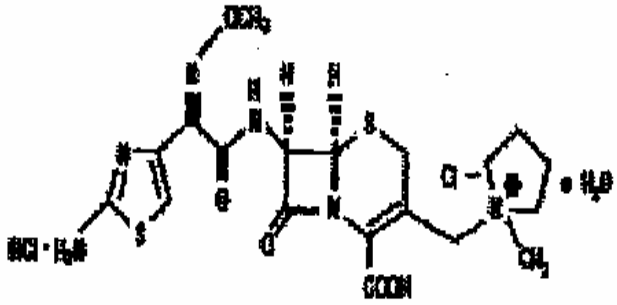
or hemi-hydrate (half a measure) have twice as much or half as much respectively. Water that is found in a sample but not incorporated into the crystal is called unbound or adventitious water. The theoretical water content for cefepime dihydrochloride monohydrate is 3.15%. He says at paragraph 25 to 30 of his first affidavit:

> *25 Furthermore, many therapeutically useful compounds can exist in alternative forms. Each of the forms may have different physical and chemical properties.*
>
> *26. Many pharmaceutically important materials exist as solids. When in the solid form, a number of different forms may be available. Some of the terms that may be used to describe these different forms of these compounds include amorphous, hydrates, anhydrate, polymorphs, and solvates. As a particular chemical compound may exist in any number of these different forms, it is necessary to identify the particular form to understand the reference to the compound. It is therefore useful to define these terms:*
>
> > *(a) "Amorphous" forms are non-crystalline solids.*
> >
> > *(b) 'Polymorphs" exist when two forms have the same chemical composition but different crystal structures.*
> >
> > *(c) "Hydrates" exist when a form, in addition to containing molecules of a given substance also contain molecules of water regularly incorporated into the crystal structure.*
> >
> > *(d) "Anhydrates" exist when there is no solvent incorporated into the structure. Different anhydrous forms are termed polymorphs. These compositions however may still have variable amounts of water present, in an unbound form. An anhydrate can contain a certain amount of unbound water.*
> >
> > *(e) "Solvates" exist, when solvents, such as alcohols like ethanol or isopropanol, or compounds such as acetonitrile, or acetone are incorporated into the crystal structure.*

27. A hydrate with approximately one stoichometic equivalent of water regularly incorporated into the crystal structure is called a monohydrate. Likewise, approximately two stoichiometric equivalents incorporated, is called a dihydrate and approximately half an equivalent, a hemihydrate. For each solid form, the theoretical stoichiometric equivalent can be calculated based on the molecular weight of the solid.

28. Additionally, a solid may have water present which is not incorporated into the crystal structure. This is sometimes called unbound or adventitious water. A common way to measure the total amount of water in a solid is the Karl Fischer (KF) method which involves utilizing titration to determine the moles of water present. This test does not determine conclusively whether all of the water is within the crystal lattice but when used together with other tests such as Xray powder diffraction, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) one can determine the level of hydration of a product.

29. Cefepime dihydrochloride monohydrate has the following structural formula:



30. Cefepime dihydrochloride monohydrate has the following molecular formula $C_{17}H_{24}ClN_6O_5S_2HCl\ H_2O$ and therefore has a molecular weight of 571.5. The theoretical water content for the monohydrate is therefore 3.15%.

[88] What can be concluded, in summary, from the descriptive portion of the patent as it would be read against the background of a person skilled in the art, is that the original zwitterion form was useful as an antibiotic but had stability problems. Converting the zwitterion form to a salt form using a selected group of five salts including sulphuric acid and dihydrochloride, improves that stability. Among the selected group of salts the sulphuric acid salt is the best. In Example XII the dihydrochloride monohydrate form is mentioned only to say that it is better than the anhydrate form of the dihydrochloride. The dihydrochloride monohydrate form has a water (H_2O) content theoretically of 3.15 percent and a found water content in the Examples of between 2.46% and 4.1%. The purity of the salt is said to vary from lot to lot.

[89] I turn to the evidence as to what a person skilled in the art would know as of March 1992 respecting matters of interest here. I accept in this regard the evidence of Dr. McClelland as to the basic understanding of a person skilled in the art as set out in paragraphs 16 to 19 of his affidavit:

> *16. It has been known for some time that basic drug substances are advantageously converted to acid addition salts. Because of the ionic nature of the salt, this can impart a better solubility in water. Converting to the salt can also provide a more stable solid, indeed a more crystalline solid, providing advantages in handling, storage and incorporation into dosage units.*
>
> *17. With respect to solids (and solid salts), these are normally distinguished as being <u>crystalline</u> or <u>amorphous</u>. Crystalline solids have an ordered arrangement of the atoms and molecules into what is termed a well-defined crystalline lattice, with the lattice pattern repeating over large distances in 3 dimensions. Amorphous solids lack long range order.*
>
> *18. A particular molecule or salt may crystallize in two or more crystal forms termed polymorphs, i.e. where the packing and orientation of the molecules and atoms in the crystal lattice is different. A molecule or salt may also crystallize as a <u>solvate</u>, a*

> *crystal form where solvent molecules are incorporated in the crystal lattice. When the solvent molecule is water, the term hydrate is employed. Polymorphs and solvates, i.e. the different crystalline forms of a solid, can be identified and distinguished by several solid state analytical techniques – X-ray powder diffraction, infrared spectroscopy, differential scanning calorimetry, and themogravimetric analysis being four such techniques.*
>
> *19. "Cefepime hydrochloride" is the monohydrate of the dihydrochloric acid addition salt of cefepime, i.e it is a solvate or hydrate where the formal ratio of water and cefepime is 1:1. The molecular formula therefore is* $C_{19}H_{26}Cl_2N_6O_5S_2.H_2O$.

[90] I also accept what Dr. Bartlett says at paragraphs 25 to 28 of his first affidavit:

> *25. The precise regular, three-dimensional arrangement of the molecules in a crystal, referred to as the crystal lattice, determines the physical properties of the crystalline solid, such as its melting point, its stability, the shape of the individual crystals, etc. The relationship that the individual cations and anions adopt when crystals form, and thus the structure of the lattice and the physical properties of the crystals, depends on many factors. The most important factor is the identity of the individual components that make up the crystal, because different cation and anion combinations usually adopt different relationships when they come together to form the crystal lattice. Even very subtle differences in the structure of one of the components can result in the formation of crystals with different arrangements of the cation and anions and thus different physical properties. As a consequence, it is not possible to predict the physical properties of the crystals that a salt will form.*
>
> *26. When a salt crystallizes, the crystals themselves remain electrically neutral; that is, the positive charges of the cations must be balanced by the presence of an equal number of negative charges from the anions. As a result, the need to accommodate both of these species is one of the factors that affects the crystal lattice of a salt and hence its physical properties.*
>
> *27. The crystal lattice may also include other molecules in addition to those of the compound itself or its salt. If they are present, these additional molecules typically come from the solvent from which the compound is crystallized. A solid or crystalline form that includes such molecules is referred to as a solvate; when the included solvent*

> *molecules are water, the material is called a hydrate. In a regular crystalline lattice, there is a fixed ratio of solvate or hydrate molecules to those of the compound itself, as expressed by terms such as monohydrate or dihydrate a crystal of the same compound that does not include water molecules in the lattice would be referred to as an anhydrate.*
>
> *28. The manner in which a molecule crystallizes is critically dependent on all the species that are present in the crystal lattice. Thus, the crystalline form of a hydrate or of a salt will be different from that of the anhydrate or of the neutral form of a molecule.*

[91] I further accept the Glossary of Terms provided by Dr. Langer at paragraph 10 of his affidavit:

> ***Glossary of Terms***
>
> *10. I was first asked by co-counsel for Apotex to provide some basic definitions with respect to several chemical terms associated with the matter at hand, these being (the following definitions were paraphrased from standard textbooks in the field of pharmaceutical science that include (i) Remington: The Science and Practice of Pharmacy, 20th Edition, (ii) Martin's Physical Pharmacy and Pharmaceutical Sciences, Fifth Edition) and (iii) Byrn et al: Solid-State Chemistry of Drugs:*
>
> > ***Solvate****—A crystal form that contains either stoichiometric or nonstoichiometric amounts of solvent. Solvates can be comprised of multiple molecules of the compound with a single solvent molecule (i.e., such as a hemi-solvate for the case of 2 compound molecules with one solvent molecule), a 1:1 ratio (a "monosolvate") or two or more solvent molecules per compound molecule. Typical solvent molecules found in solvates are solvents of crystallization, such as water (referred to as hydrates as discussed below), ethanol, acetone or other organic solvents.*
> >
> > ***Hydrate*** *— A hydrate is generally defined as a crystal form of a material comprised of a given compound in combination with a specific ratio of water molecules. Hydrates can include hemihydrates (one water molecule per two compound molecules), monohydrates (a 1:1 ratio of water to compound*

> *molecules), dihydrates (two water molecules per compound molecule) and the like. The water present in such a stochiometric hydrate is typically referred to as bound water; as opposed to unbound or adventitious water that also may be - present in the solid as a function of the hygroscopicity of the solid and the relative humidity the solid is exposed to.*
>
> ***Zwitterion*** *— A zwitterion is a compound that is overall neutral but possesses distinct regions of positive and negative charge. A simple example of a zwitterionic compound is the amino acid glycine in a solution at neutral pH, with glycine possessing a negatively charged carboxyl group and a positively charged amine group at these conditions.*
>
> ***Polymorph*** *—A polymorph is generally defined as a solid crystal form of a compound or compounds that possesses a distinct lattice arrangement of the compounds. Polymorphs are often identified by their specific x-ray powder diffraction (XRPD) pattern.*

THE CLAIMS THEMSELVES CLAIM 2 AND 3

[92] Claim 2, in its pre-disclaimer form which I have held to be the relevant form for consideration here, says:

> *2. Temperature stable crystalline dihydrochloride monohydrate acid addition salt of 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate containing from 2.5% to 4.1% by weight of water.*

[93] Given the description of the patent and the general knowledge as provided by the experts, I find that in construing claim 2:

- It is directed to a product – a crystalline dihydrochloride monohydrate of a previously known zwitterion form of cefepime- the salt must be dihydrochloride and must be the monohydrate form of the dihydrochloride

- That salt is "temperature stable"
- That salt can contain from 2.5% to 4.1% water – given that the theoretical water content is said in the expert evidence and in the patent to be 3.15 or 3.16 percent and given that the patent states that the "purity" of the salt can "vary". I find that a proper construction of this claim is such as would include not only "substantially pure" crystalline dihydrochloride monohydrate acid addition salt of the zwitterion but includes a range of other hydrated and anhydrous dihydrochloride salts.

[94] The essential features of each of claims 2 and 3 are that there is a composition provided that is said to be temperature stable comprising the crystalline dihydrochloride monohydrate acid addition salt of cefepime. The purity of the composition is not an essential feature. The range of water content specified in claim 2 is not essential but serves to demonstrate that the purity is variable. The PXRD data of claim 3 is not essential and simply provides additional confirmation that the material in the composition is the dihydrochloric monohydrate.

[95] If I were to construe the disclaimed version of claim 2, I would recognize that an attempt was made to restrict the salt to a "substantially pure" salt version but the fact that the range of water content from 2.5% to 4.1% remains would be confusing and ambiguous since on the one hand the composition is said to be pure, on the other hand a range of impurities arising from other hydrated and unhydrated forms is provided for in the range of water content from 2.5% to 4.1%.

[96] Claim 3 is unaffected by the disclaimer. I repeat it without listing the X-Ray data:

> *3. Temperature stable crystalline dihydrochloride monohydrate acid addition salt 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-pyrrolidinio) methyl]-3-cephem-4-carboxylate having the following X- ray powder diffraction pattern*

[97] Thus claim 3 is the same as claim 2 except there is no definition of water content in claim 3, but there is in claim 3 a definition provided by a Powder X-Ray Diffraction (PXRD) fingerprint. That fingerprint does not make the dihydrocloride monohydrate any different, it simply identifies it by one of its inherent characteristics. There is no limitation in claim 3 as to any level of purity.

VALIDITY-GENERALLY

[98] The *Patent Act*, section 2, defines an invention as something that is new and useful. Inherent in that definition is that there must have been an exercise of inventive ingenuity to arrive at what has been claimed. In *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 Rothstein J. for the Supreme Court of Canada at paragraph 51 wrote:

> ***51*** *The definition of invention in s. 2 of the Act is relevant because at the time the pre-October 1, 1989 version of the Act was in force, there was no statutory provision expressly providing that obvious inventions were unpatentable. As explained by Professor D. Vaver in Intellectual Property Law: Copyright, Patents, Trade-marks (1997), at p. 136:*
>
> > *Until very recently, the Patent Act did not expressly say that obvious inventions were unpatentable. Courts implied this criterion from the notion of "invention". Inventions implied inventive ingenuity, without which an advance was obvious; and patents are not granted for the obvious.*
>
> *The definition of invention in s. 2 of the Act provided:*

> *"invention" means any new and useful ... composition of matter, or any new and useful improvement in any ... composition of matter*

PRIOR ART

[99] In the present case most of the arguments raised as to the validity of claims 2 (pre disclaimer) and 3 of the patent can be considered in the context of two pieces of prior art. The first is referred to in the ’288 patent itself as Aburaki – it may also be referred to as United States Patent No. 4,406,899 (the ’899 patent) or Canadian Patent No. 1,213,882 (the ’882 patent), they are all the same thing for this purpose. The second in a Greek patent 862 055 (the ’055 patent) which was published on December 31, 1986. The applicant for the Greek patent was a predecessor of BMS US and the three inventors named in the Greek patent are the same persons as three of the five inventors named in the ’288 patent at issue here. There is no issue that both pieces of prior art were published sufficiently in advance of any date relevant to the ’288 patent, thus, from a date point of view, they are relevant pieces of prior art.

[100] Aburaki has been described in the specification of the ’288 patent at issue. As previously discussed in these reasons, the ’288 patent at page 3 acknowledges that Aburaki discloses the zwitterion form of cefepime and mentions corresponding acid addition salts. At the same page, the ’288 patent states that Aburaki, while mentioning acid addition salts, does not state how to make them or which, if any, are stable in drug powder form. This much “prior art” is acknowledged in the ’288 patent itself.

[101] Turning to the Greek ’055 patent it is immediately apparent that the disclosure is almost word for word identical to that of the ’288 patent at issue here up to and including Example IX (that

is, up to the end of page 22 of the ’288 patent). Before the end of page 22 the differences are unimportant: in the ‘288 patent a reference to Figure 4 is added at page 2 lines 17 to 21; a definition of dry powder form is added at page 4 lines 9 and 10; the words “and good purity” are added to line 25 at page 5 in reference to the sulphuric acid addition salt. The claims of the Greek ’055 patent are broader than those of the ‘288 patent at issue here and can, for instance with respect to claim 1, be said to encompass generally but not specifically what is claimed in claims 2 and 3 at issue here.

[102] It is to be noted, with respect to the Greek ’055 patent, that there is a reference to a dihydrochloride salt of the zwitterion form of cefepime, as there is in the ’288 patent. Using the ’288 patent as a reference (since it has numbered lines and the wording is identical) such references occur at page 4 line 15 and lines 20 and 21; at page 6 line 24; at page 9 line 24 to 28 there is a description as to the preparation of the dihydrochloric salt. Throughout the specification of each of the ’288 and ’055 Greek patents there are general references to “salts” which just as in the ‘288 patent is defined to include all five salts. Example IV of the Greek ’055 patent which is the same as Example IV of the ’088 patent is entitled “Preparation of the Monohydrochloride Acid Addition Salt”. Example V of each of the Greek ’055 and ’288 patents is entitled “Preparation of the Dihydrochloride of the Monohydrochloride Acid Addition Salt From It”. An identical Table is presented at the end of Example VII of both the ’055 Greek and ’288 patent where there presented tabulated data as to potency loss (gain) for a number of salts including a dihydrochloride, $(HCl)_2$, Salt.

[103] Nowhere, however, in the Greek ’055 patent is reference made to the hydration of the dihydrochloride crystals or, if there is hydration, whether it is as a hemi-hydrate or monohydrate, or dihydrate or whatever. In Examples IV and V of both the ’055 Greek and ’288 patent there is presented data as to the percentage of constituent elements and the amount of water. In Examples IV and V, the calculated water content is not given but the found water content is. In Example IV it is 4.5 %, in Example V, it is 1.25%.

[104] The ’288 Canadian patent at issue picks up where the Greek ’055 patent left off by adding Examples X to XIII as found at pages 23 to 28 of the ’288 patent. Example X deals with preparation of a phosphate salt and is not of interest in this proceeding. Examples XI and XII are of interest as they deal with preparation of the dihydrochloride monohydrate salt. Example XIII is of some interest as it deals with the preparation of a dihychloride dihydrate (not monohydrate) salt. Examples XI and XII are the only places where the words dihydrochloride monohydrate are actually used in the ‘288 patent.

[105] The issues as they have evolved and been reduced in argument essentially are whether the Greek ’055 patent anticipates claims 2 and 3 of the ’288 patent and whether the Greek ‘055 patent contains a disclosure of the dihydrochloride monohydrate and enables how it is to be made. If there is no such disclosure and enablement, does the Greek ’055 patent nonetheless give a person skilled in the art sufficient information such that what is claimed in claims 2 and 3 of the ’288 patent, is obvious.

ANTICIPATION AND OBVIOUSNESS – LEGAL PRINCIPALS

[106] The legal principles as to the law in Canada respecting anticipation and obviousness were recently considered by the Supreme Court of Canada in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, *supra*. Subsequent to the release of that decision, I reviewed the law particularly as to anticipation in *Abbott Laboratories v. Canada (Minister of Health)*, 2008 FC 1359. The Federal Court of Appeal within the last few weeks has released its decision in *Apotex Inc. v. Pfizer Canada Inc.*, 2009 FCA 8 where it considered the decision of the Supreme Court of Canada in the context of obviousness.

[107] In *Sanofi*, Rothstein J. for the Supreme Court wrote that, with respect to anticipation, there must be in the prior art under consideration both a disclosure of what is claimed in the claims at issue, and sufficient information given so as to enable what is disclosed to be put into practice. At paragraph 30, he wrote:

> ***30*** *Two questions now must be answered: (1) what constitutes disclosure at the first stage of the test for anticipation, and (2) how much trial and error or experimentation is permitted at the enablement stage?*

[108] In the particular circumstances of *Sanofi* the Supreme Court had to consider what is sometimes called a selection patent where there has been a disclosure of a genus of compositions but the patent at issue selected a member from the genus because it had special advantages. In that context, Rothstein J.'s commentary as to disclosure at paragraph 32 of *Sanofi* can be best understood:

> ***32*** *In the context of disclosure as explained in* Synthon*, "the absence of the discovery of the special advantages" to which Lord*

> *Wilberforce was referring in* Witsiepe's *means that* the genus patent does not disclose the special advantages of the invention covered by the selection patent. Where there is no such disclosure, there is no discovery of the special advantages of the selection patent as compared to the genus patent*, and the disclosure requirement to prove anticipation fails. At this stage, the person skilled in the art is reading the prior patent to understand whether it discloses the special advantages of the second invention. No trial and error is permitted. If in reading the genus patent the special advantages of the invention of the selection patent are not disclosed, the genus patent does not anticipate the selection patent.*

[109] Rothstein J. then turned enablement and drew up a non-exhaustive list of four factors that could be considered in determining whether what has been disclosed has also be enabled that is, has enough information been given to enable a skilled person to put that which has been disclosed into practice. He wrote at paragraph 37:

> ***37*** *Drawing from this jurisprudence, I am of the opinion that the following factors should normally be considered. The list is not exhaustive. The factors will apply in accordance with the evidence in each case.*
>
> > *1. Enablement is to be assessed having regard to the prior patent as a whole including the specification and the claims. There is no reason to limit what the skilled person may consider in the prior patent in order to discover how to perform or make the invention of the subsequent patent. The entire prior patent constitutes prior art.*
> >
> > *2. The skilled person may use his or her common general knowledge to supplement information contained in the prior patent. Common general knowledge means knowledge generally known by persons skilled in the relevant art at the relevant time.*
> >
> > *3. The prior patent must provide enough information to allow the subsequently claimed invention to be performed without undue burden.*

> *When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and would not be considered undue burden. But experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be laid down; however, prolonged or arduous trial and error would not be considered routine.*
>
> *4. Obvious errors or omissions in the prior patent will not prevent enablement if reasonable skill and knowledge in the art could readily correct the error or find what was omitted.*

[110] I reviewed this decision in *Sanofi* and other current cases in *Abbott*, *supra* and drew up a list of considerations respecting anticipation to which counsel for both the Applicants and Respondent Apotex have ascribed in the present case. I summarized at paragraph 75:

> ***75*** *To summarise the legal requirements for anticipation as they apply to the circumstances of this case:*
>
> > *1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.*
> >
> > *2. The disclosure does not have to be an "exact description" of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.*
> >
> > *3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out*

> *what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.*
>
> *4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.*
>
> *5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation.*
>
> *6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.*
>
> *7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.*

[111] Turning to the question of obviousness, the Supreme Court reviewed a number of authorities and found the restated *Windsurfing* questions to be a useful approach. At paragraph 67 of *Sanofi* Rothstein J. wrote:

> ***67*** *It will be useful in an obviousness inquiry to follow the four-step approach first outlined by Oliver L.J. in Windsurfing International Inc. v. Tabur Marine (Great Britain) Ltd., [1985] R.P.C. 59 (C.A.). This approach should bring better structure to the obviousness inquiry and more objectivity and clarity to the analysis. The Windsurfing approach was recently updated by Jacob L.J. in Pozzoli SPA v. BDMO SA, [2007] F.S.R. 37, [2007] EWCA Civ 588, at para. 23:*
>
> > *In the result I would restate the Windsurfing questions thus:*
> >
> > *(1) (a) Identify the notional "person skilled in the art";*

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

[112] As to the fourth issue which can be characterized as the "obvious to try" issue, Rothstein J. adopted the words of Jacob L.J. in *Saint-Gobain PAM SA. V. Fusion Provida Ltd.*, [2005] EWCA Civ 177 at paragraph 35, that is, was it "more-or-less self evident" that what is being tested ought to work. Rothstein J. wrote at paragraphs 65, 66, 69 and 70:

> ***65*** *In Saint-Gobain PAM SA v. Fusion Provida Ltd., [2005] EWCA Civ 177, Jacob L.J. stated, at para. 35:*
>
> > *Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is not enough. If it were otherwise there would be few inventions that were patentable. The only research which would be worthwhile (because of the prospect of protection) would be into areas totally devoid of prospect. The "obvious to try" test really only works where it is more-or-less self-evident that what is being tested ought to work.*
>
> *In General Tire, Sachs L.J. said, at p. 497:*
>
> > *"Obvious" is, after all, a much-used word and it does not seem to us that there is any need to go*

> *beyond the primary dictionary meaning of "very plain".*

In Intellectual Property Law, at p. 136, Professor Vaver also equates "obvious" to "very plain". 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 L.J., more or less self-evident that what is being tested ought to work.

66 *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.*

...

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

> *(1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?*
>
> *(2) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?*
>
> *(3) Is there a motive provided in the prior art to find the solution the patent addresses?*

70 *Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.*

[113] The Federal Court of Appeal in *Pfizer* reviewed a decision of this Court that had been given before the Supreme Court had released its decision in *Sanofi*. The issue was whether in this Court the Judge has applied the appropriate test. The Federal Court of Appeal held that the appropriate test had been applied. At paragraphs 36 and 37, Noel JA. for the Court wrote:

> *[36]It is apparent from the above review that the Federal Court Judge throughout his analysis looked for more than possibilities understanding that mere possibilities were not enough, and that the prior art had to show more than that. His appreciation of the matter is summed up and further demonstrated by his concluding remarks (Reasons, para. 125):*
>
> > *Although there was a significant amount of evidence indicating that cGMP PDE inhibitors should be further explored with regards to the treatment of ED in the months leading up to the Pfizer discovery, the evidence does not in my view establish that the solution taught by the patent was obvious at the time. At best there was speculation, which in hindsight proved to be correct, that PDE5 inhibitors might treat impotence. Experiments with zaprinast, a cGMP PDE inhibitor, had been performed but in an effort to understand how the erectile process works, not how to treat ED.*
>
> *[37]In so holding, the Federal Court Judge drew the line precisely where the Supreme Court drew it in Sanofi-Synthelabo when it held that (para. 66) "the mere possibility that something might turn up is not enough".*

[114] With these legal principles in mind, I will turn to the prior art and in particular, as emphasized by Counsel at the hearing, the Greek '055 patent.

ANTICIPATION-GREEK ’055 PATENT

[115] As previously stated the Greek ’055 patent discloses the dihydrochloride salt form of the zwitterion but does not, in so many words, disclose a dihydrochloride monohydrate form.

[116] Apotex argues that there is a sufficient disclosure of the dihydrochloride monohydrate form. It does so in two ways. First through the expert evidence of Drs. McClelland and Langer it says that a person skilled in the art would read Examples IV and V of the ’055 Greek patent and know that, notwithstanding the title of those Examples, a dihydrochloride monohydrate, or at least a mixture containing some of the monohydrate form, was disclosed. Secondly, through the evidence of Gerster and Corelli-Rennie who performed experiments intended to replicate Examples IV and V, which experiments were commented upon by the Apotex experts, Example IV does in fact result in the production of material containing at least some dihydrochloride monohydrate. In this regard, Apotex’s argument at the hearing focused on an experiment conducted by Corelli-Rennie identified as LSU-I-007 which was intended to replicate the first part of Example V of the Greek ‘055 patent.

[117] The Applicants refute this evidence saying that there is no disclosure and no enablement of dihydrochloride monohydrate in Examples IV and V of the Greek ’055 patent and that the experiments conducted by Apotex are flawed and inadmissible.

[118] The Applicants did not put in evidence any testing of their own.

[119] I turn first to the evidence of Drs. McClelland and Langer, Apotex's experts, as to what they say that the Greek '055 patent discloses and enables.

[120] Dr. McClelland says at paragraphs 37 to 46 of this affidavit with respect to Example IV (I have omitted the tables and some comments for brevity):

> ***Example IV of the '055 Patent and the '288 Patent***
>
> *37. Example IV of the '055 Patent and Example IV of the '288 Patent are identical. Both are titled "Preparation of the Monohydrochloride Acid Addition Salt". Each involves dissolving 1 gram of zwitterionic cefepime in 2.08 mLs of 1 N HCl, followed by 30 mLs of acetone over a 15 minute period, followed by stirring for 1 hour. Crystals are isolated by vacuum filtration, washing with 10 mLs of acetone, and vacuum drying at 50°C for 2 hours.*
>
> *38. Identical elemental analysis data are listed for Example IV in both the '055 Patent and the '288 Patent, for example at page 14, lines 9-13 of the '288 Patent. While Example IV identifies the product as a monohydrochloride, the elemental analysis data show that the product was in fact a dihydrochloride. Thus, while Example IV reads *Calculated* for $C_{19}H_{24}N_6O_5S_2$ HCl the percentages that follow "%C, 41.37; %H, 4.75; %N, 15.2, %S, 11.63; %Cl, 12.86" correspond to the values in Example V "calculated for $C_{19}H_{24}N_6O_5S_2$ HCl", i.e. the values for the dihydrochloride.*
>
> *39. I illustrate the difference between the "Calculated" values of the monohydrochloride $C_{19}H_{24}N_6O_5S_2$ HCl and the dihydrochloride $C_{19}H_{24}N_6O_5S_2$ 2HCl in the table below. As can be seen, not only are the Calculated values of Example IV and Example V the same, they are very different from values Calculated for a monohydrochloride. The difference between mono and di-hydrochloride is seen in the values for all the elements, but is particularly apparent in the values of chlorine.*
>
> *Chart Omitted*
>
> *40. The "Found" (experimentally determined) values for Example IV of the '055 and '288 Patents also point to the material as being the dihydrochloride. The table below compares the Found values with*

> *those Calculated for the di- and mono-hydrochloride salts, the latter calculated on the basis that the compound contains 4.5% water. There is acceptable agreement* between the Found values and those Calculated for the dihydrochloride and very poor agreement (especially for chlorine) between the Found values and those calculated for the monohydrochloride. (*Acceptable agreement in elemental analysis means ±0.4% for each element).*
>
> *41. Example IV of the '055 Patent refers to the product as crystalline. Thus, the material produced in this example is crystalline cefepime dihydrochloride. Moreover, the crystalline material contains 4.5% water, despite been dried at 50°C under vacuum for 2 hours. This indicates to me that the water is relatively tightly bound, i.e. that this material is a hydrate. I note that, according to Example XIII of the '288 Patent, cefepime dihydrochloride dehydrate "can be easily dried" to the monohydrate, and that this can be accomplished by drying in vacuo, as has been done on the material in Example IV. Thus, the product of Example IV is not the dihydrate.*
>
> *42. It is my conclusion that the crystalline product of Example IV of the '055 Patent is cefepime dihydrochloride monohydrate. This contains excess or adventitious water (since pure monohydrate contains 3.16% water).*

[121] Dr. Langer's opinion as expressed in his affidavit at paragraphs 15, 16 and 55 is that Example IV discloses the dihydrochloride monohydrate notwithstanding its title:

> *15. I first note that, although Example IV from the '288 Patent is entitled "Preparation of the Monohydrochloride Acid Addition Salt", it appears that this example instead provides analytical results for the dihydrochloride hydrate salt from cefepime. This conclusion is bases on the calculated and measured elemental analysis results shown in Example IV, which shows a calculated percentage of 12.86 for chlorine. Based on the molecular weight of cefepime, this percentage corresponds to a dihydrochloride acid addition salt instead of a monohydrochloric acid salt addition. The measured result for chlorine of 13.03% also indicates that the product described in Example IV is indeed a dihydrochloric acid addition salt (this result can also be confirmed by noting the similarities in the calculated percentages of the various elements for both Examples IV*

and V, with Example V of the '288 Patent describing a dihydrochloride acid addition salt of cerepime).

16. Further, the measured water content of the dihydrochloride acid addition salt of cefepime from Example IV is described to be 4.5%. The molecular weight of anhydrous cefepime dihydrochloride is 553.5, meaning that the monohydrate would theoretically possess approximately 3.15% water and the dehydrate approximately 6.11% water. Additionally, as I discussed in paragraph 10 above, stochiometric crystalline hydrates of salts (i.e., hydrates for which water molecules are regularly incorporated into the crystal lattice), as well as anhydrates, can also contain unbound or "adventitious" water, with such water being present in varying amounts bases on such things as the hygroscopicity of the material, the degree of drying of the material and its subsequent storage conditions, etc. as a result, in my opinion, Example IV of the '288 Patent discloses cefepime dihydrochloride monohydrate (i.e., with approximately 3.15% bound water) that also contains approximately 1.35% of unbound or adventitious water.

…

55. The remainder of the specification of the '055 Patent is very similar to that of the '288 Patent, including several of the examples such as Examples IV (preparation of cefepime monohydrochloride hydrate) and V (preparation of cefepime dihydrochloride hydrate). Analogous to the case that I described above for the '288 Patent, although Example IV from the '055 Patent is entitled "Preparation of the Monohydrochloric Acid Addition Salt", the product discussed in this example is a hydrated (4.5% water) dihydrochloric acid addition salt of cefepime based on the elemental analysis calculated and measured results. As a result, for similar reasons to those that I described in paragraphs 15 and 16 above, it is my opinion that a person skilled in the art would consider Example IV of the '055 Patent to disclose cefepime dihydrochloride monohydrate. Additionally, although the water content of the cefepime monohydrochloride hydrate salt disclosed in Example IV of the '055 Patent (4.5%) is 0.4% higher than the upper limit of the range of water content (2.5 to 4.1%) purportedly disclose in the '288 Patent for the monohydrate (e.g. as purportedly disclosed in claim 2 of the '288 Patent), it is my opinion that this 0.4% difference is insignificant, particularly given admissions of the inventors of the '729 Patent discussed in paragraphs 33 and 34 above.

[122] These conclusions are contested by the Applicant's experts Drs. Bartlett and Byrn. Dr. Bartlett makes general comments in this regard at paragraphs 61 to 69 of his first affidavit, I repeat just paragraphs 61 and 69:

> *The '055 Patent*
>
> *61. Apotex alleges that all of the claims of the '288 Patent are anticipated by Greek '055 Patent. In constructing its anticipation argument Apotex has searched though the disclosure of the Greek '055 Patent to find components of the claims of the '288 Patent Apotex asserts that "knowledge of the teachings of the '055 Patent including repeating Examples IV and V produce [sic] temperature stable crystalline dihydrochloride hydrate (including the monohydrate) acid addition salts of cefepime including all limitations of the claims of the '288 Patent" [page 25 of Apotex NOA] However, nowhere in the Greek '055 Patent is there a specific disclosure of a substantially pure temperature stable crystalline monohydrate form of cefepime dihydrochloride, let alone any procedure that would teach "in every case and without any possibility of error" a method for its preparation.*
>
> ...
>
> *69. However, the single disclosure in the '055 Patent of a dihydrochloride addition salt of cefepime (Example V) is for material with a water content of only 1.25%. Moreover, <u>no</u> analysis presented in this Patent discloses <u>any</u> salt form of cefepime with a water content in the range of 2.5% to 4.1% by weight. Finally, there is no x-ray powder diffraction pattern disclosed in the Greek '055 Patent for any hydrochloride or dihydrochioride salt.*

[123] In his Reply affidavit, Dr. Bartlett specifically responds to the comments of Drs. McClelland and Langer at paragraph 29:

> *29. Drs. McClelland and Langer conclude from the Greek '055 Patent itself that the material produced in Example IV is cefepime **di**hydrochloride monohydrate. They reach this conclusion based on the elemental analysis that is reported in the patent, putatively for this material. As they point out, based on the chloride content reported, this elemental analysis is consistent with the*

> *dihydrochloride, not with the monohydrochloride that is the stated product of the procedure. However, what Drs. McClelland and Langer have overlooked is that the reported product of this procedure cannot be cefepime dihydrochloride. The procedure of Example IV is reported to produce 900 mg of a cefepime salt starting with 1 g of the zwitterion and one equivalent of hydrochloric acid. As described, the procedure involves the combination of 1.0 g (2.08 mmoles) of cefepime with 2.08 mL (1 equivalent or 2.08 mmoles) of 1.0 N HCl to give a typical yield of 900 mg of product. If this product is the monohydrochloride (mw = 517), it represents 1.74 mmoles of material and would contain 1.74 mmoles of chloride ion. However, if it were the dihydrochloride (mw 553.5), it would contain 3.25 mmoles of chloride ion, which is more than 1.5 times as much chloride as was introduced into the reaction mixture. In short, the addition of 2.08 mmoles of hydrochloric acid to the reaction mixture is not enough chloride to give a product that contains 3.25 mmoles of chloride ion. The inescapable conclusion is that the elemental analysis reported in Example IV in the Greek '055 and Canadian '288 Patents cannot have come from the material produced from that procedure. Thus, nothing can be inferred from these data as to the composition of material produced according to Example IV.*

[124] Dr. Byrn took a somewhat different approach than Dr. Bartlett. Dr. Byrn opined that Examples IV and V of the Greek '055 patent may theoretically possibly produce some monohydrate material; they would not produce substantially pure monohydrate and that the patent and claims at issue were directed to a substantially pure product, thus the Greek '055 patent did not disclose what Dr. Byrn believed was what the patent was directed to. In his first affidavit, Dr. Byrn opined at paragraphs 76 to 81:

> *76. Further, the '055 Patent neither discloses how to make cefepime dihydrochloride monohydrate, nor provides any instructions, let alone clear and unmistakable directions, which inevitably result in the formation of the monohydrate.*
>
> *77. The '055 Patent only provides generally that various salts, of which dihydrochloride is one, can be made, including solvates thereof. There is no teaching that one should focus on the*

> *dihydrochloride salt and that a specific hydrated form of that salt would have unique preferred qualities.*
>
> *78. Examples IV and V of the '055 Patent, which Apotex' NOA focuses on, do not relate to a hydrated form of the dihydrochloride salt at all. Example IV relates to a different salt, the monohydrochloride.*
>
> *79. Example V of the '055 Patent describes a preparation of a non-hydrated dihydrochloride salt: anhydrate or hemihydrate form. In particular, the preparation describes a solid which is said to contain 1.25% by weight of water. This is less than one half of the theoretical water content (3.15%) required for a monohydrate of cefepime dihydrochloride. Accordingly, this crystalline form would not be considered to be a monohydrate but would be considered an anhydrate from which adventitious (unbound) water had not been completely removed on drying or a hemihydrate form.*
>
> *80. While it is theoretically possible that some of the material made may be monohydrate and some of the material may be completely anhydrous so as to end up with a showing of 1.25% by weight of water, in no case could one ever get substantially pure temperature stable crystalline cefepime dihydrochloride monohydrate of claim 2. This would be impossible.*
>
> *81. Further, considering the water content, there is no way that one would get the Xray powder diffraction as claimed in claim 3. Consequently, someone following Example V would not be led directly in every case and without the possibility of error to substantially pure temperature stable crystalline cefepime dihydrochloride monohydrate.*

[125] In his reply affidavit, Dr. Byrn directed his remarks on Drs. McClelland and Langer's opinion in the context of the disclaimer and the concept of "substantially pure". Dr. Byrn says at paragraphs 59 to 61 of his reply affidavit:

> ***DISCLAIMER***
>
> *59. Apotex' experts assert that they do not understand what the words substantially pure mean in claims 1 and 2. For example, Dr. McClelland states that he does not understand them to refer to the*

> *purity of the crystalline form but instead as defining potency. Further, he seems to not understand what level of purity is required. However, I note that he has no difficulty using this term throughout his affidavit in other contexts. A person skilled in the art would understand that what is being described and claimed is the monohydrate form of cepfepime dihydrochloride where it has been shown that it has greater stability over the anhydrate form. Accordingly, it would be important that the material be substantially pure monohydrate to achieve this result.*
>
> *60. The person skilled in the art would understand that it relates to substantially pure monohydrate and that this is what Examples XI and XII teach. The description makes it clear that the monohydrate is conveying the benefit of high temperature stability over the previously disclosed anhydrate. This advantage cannot be achieved if just one crystal of monohydrate is necessary to fall within the claims.*
>
> *61. Thus, while the person skilled in the art would understand the claimed invention to be substantially pure monohydrate, to the extent that the court would otherwise except an argument that the claims cover mixtures, the disclaimer disclaims all but substantially pure monohydrate.*

[126] I have not found, nor have I been directed by Counsel to any portion of the transcript of the cross-examinations of any of Drs. Langer, Bartlett or Byrn that would make any meaningful addition, retraction or further explanation as to what they have said in their affidavits as aforesaid except that Dr. McClelland did give an opinion as to Example V of the Greek ’055 patent (identical to Example V of the ’288 patent at issue here) in response to questions 77 and 78 of his cross-examination where he said:

> *77. Q. Does example V of the 055 patent not describe -- take out the negatives. Example 5 of the 055 patent describes a preparation of nonhydated dihydrochloride salt in the anhydrate and hemi-hydrate form. Would you agree with that?*
>
> *A. It provides preparation of the dihydrochloric acid addition salt that contains 1.25 percent water. It could be a mixture of --it*

> *could be a hemi-hydrate, it could be mixture of monohydrate and anhydrate form. It has water in it. It has little more than a third of the amount from the monohydrate. Monohydrate requires 3.1 percent water. This is 1.25 percent water.*
>
> *78. Q. So this crystalline form would have been considered a monohydrate but would have been considered an anhydrate formed with adventitious water?*
>
> *A. That is one interpretation. The other interpretation is that it is a mixture of anhydrate and the monohydrate. That is the product based on the data that are given with the example.*

TESTING BY APOTEX

[127] In Apotex's Counsel's submissions at the hearing, reliance on testing performed by employees of an Apotex related company, was limited to tests conducted by Corelli-Rennie identified as number LSU-I-007 said to be a reproduction of the first part of Example V of the Greek '055 patent conducted on a 21 times larger scale (Corelli-Rennie affidavit, paragraph 9 and Tab 2G). According to paragraph 60 of Dr. McClelland's affidavit two samples were obtained from this experiment. LSU-I-007-1 contained 5.48% water after filtration and acetone washing but before drying. LSU-I-007-3 was a solid containing 3.64% water obtained after drying LSU-I-007-1 under vacuum for 24 hours at 40-45^{o}C.

[128] I have given this testing and any expert commentary upon this testing little weight. I have not removed the testing evidence and related commentary from the record simply because a higher Court, if any party appeals this decision, may wish to have it before them. I give this evidence little weight for two reasons, the first is procedural, the second is substantive.

[129] First, as to the procedural reason. The evidence of Corelli-Rennie as found at Tab 2G of her affidavit shows that this testing was conducted from in about September to November 2006. The Apotex Notice of Allegation was not served until about April 2, 2007. That Notice does not give any detail as to this testing except to say that Apotex reserves its right to submit results. At pages 27 and 29, the Notice says:

> *We further allege that a person skilled in the art in reproducing either or both of Examples IV and V and by following the teachings of the '055 Patent, arrives at the invention as claimed in Claims 1-5 of the '288 Patent. The reproduction of either or both of Examples IV and V results in the product of Claims 1-3 of the '288 Patent.*
>
> ...
>
> *Should you deny this allegation, we reserve the right to submit results of the reproductions of the '055 Patent including Examples IV and V.*

[130] A Notice of Allegation is intended to be fulsome, putting the first party on notice as to the allegations made and the factual and legal basis for those allegations. The intent is that the entire factual basis upon which a second person relies is set out with particularity. The second person assumes the risk if the notice is incomplete. I quote from the reasons of the Federal Court of Appeal given by Stone JA. in *AB Hassle v. Canada (Minister of Health and Welfare)*, previously referred to in these reasons when I was dealing with the disclaimer issue. He wrote at paragraph 21and 23:

> ***21*** *In my view, all of these considerations suggest that a second person must do what, in fact, paragraph 5(3)(a) requires, i.e. set forth in the detailed statement "the legal and factual basis" for the paragraph 5(1)(b) allegation and to do so in a sufficiently complete manner as to enable the patentee to assess its course of action in response to the allegation. See Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1994), 58 C.P.R. (3d) 209 (F.C.A.), per Strayer J.A. at 216. An examination of the detailed statement in issue is thus required in order to determine*

whether it measures up to this requirement with respect to the allegation that the '693 and '891 Patents are not valid for obviousness.

...

23 *The respondent suggests that the list of prior art in the detailed statement was not intended to be exhaustive, hence the presence of the word "including", so that the way was left open to add to that list in the section 6 proceeding. I am of the view, however, that paragraph 5(3)(a) does not contemplate such possibility. The intent appears to be that the entire factual basis be set forth in the statement rather than be revealed piecemeal when some need happens to arise in a section 6 proceeding. This Court has cautioned persons in the position of the respondent that they assume a risk that a particular allegation may not be in compliance with the Regulations and that the deficiency cannot be cured by the Court in a section 6 proceeding. In Bayer AG v. Canada (Minister of National Health and Welfare) (1995), 60 C.P.R. (3d) 129 (F.C.A.), Strayer J.A. stated, at 133-134, in reference to the decision of this Court in Pharmacia Inc. v. Canada (Minister of National Health and Welfare) (1994), 58 C.P.R. (3d) 207:*

> *The order appealed from here was made before this court had had occasion to clarify certain issues arising out of the Regulations. In particular, this court in Pharmacia Inc. v. Canada (Minister of National Health and Welfare)...[since reported at 58 C.P.R. (3d) 207]...stated the following [at p. 209]:*
>
> > *It seems to us that while a notice of allegation does play an important role in the ultimate outcome of litigation of this nature, it is not a document by which the judicial review application may be launched under s. 6 of the regulations. That document was put in as a piece of evidence by the appellants; it originated with the application filed before the Minister. Because it is not a document that was filed with the court but with the Minister, in our view the notice of allegation is beyond the reach of the court's jurisdiction in a judicial review proceeding. That being so, the court, in our opinion,*

> *lacks jurisdiction to strike out the notice of allegation.*
>
> *This clearly means that the court has no jurisdiction to make orders concerning the filing of notices of allegation or requiring them to be perfected in some way. The principle is that, by the scheme of the Regulations, the notice of allegation precedes the institution of prohibition proceedings in this court. It forms part of the background to that proceeding, perhaps what one might loosely refer to as part of the "cause of action". A court cannot order that a cause of action be created, or that it be created at a certain time, or in a certain way. It can only deal with it after it is created or allegedly created. Those who fail to file notices of allegation, or adequate notices of allegation, must assume their own risk when it comes to attacks on the adequacy of such allegations once prohibition proceedings are commenced before the court.*

[131] A first party has 45 days to respond to a Notice of Allegation and, if an application for prohibition is launched it must be determined by a judgment within two years. A generic (second party) has all the time that it wishes before serving a Notice of Allegation in which time it can, for instance, conduct testing. The first party upon receiving the notice has little time to do testing and, if it is unaware as to what testing has been done by the second party, it cannot anticipate what testing that it might want to do to support its case or rebut the testing done by the other party. I am aware that in *Pfizer Canada Inc. v. Apotex Inc.* (2004), 31 C.P.R. (4th) 214 (FC) affirmed (2004), 38 C.P.R. (4th) 400 (FCA) my colleague Snider J. permitted Apotex to submit test results into evidence, reference to which is made at paragraphs 61 and following of her reasons. However that testing was conducted in response to testing done by experts retained by a first person and disclosed in evidence by that first person who had initiated the application. That circumstance is quite different than the circumstance here where Apotex conducted tests months before serving a Notice of Allegation and only hinted at the results in is Notice.

[132] The second reason why I gave little weight to the test results is that, having regard to the evidence of all the experts, I find the results to be controversial and inconclusive. Therefore, on a balance of probabilities, they should be given little weight.

[133] I turn first to Apotex's experts opinions as to these experiments as given by Drs. McClelland, Langer and Cima.

[134] The affidavit of Dr. McClelland discusses these test results, including LSU-I-007-1 and -3. I reproduce paragraphs 60, 61, 67 and 69 of his affidavit:

> *60. Procedure LSU-I-007 was a reproduction of Example V of the '055 Patent, with the difference being that LSU-I-007 was performed on a 20-fold greater scale, i.e. all of the quantities were increased 20-fold. The larger scale also required that the periods of time over which the acetone was added was increased. Two samples were obtained from the experiment, LSU-I-007-1 containing 5.48% water obtained after filtration and acetone washing but before drying, and LSU-I-007-3, solid containing 3.64% water obtained after drying LSU-I-007-1 under vacuum for 24 hours at 40-45^{o}C as specified in Example V of the '055 Patent.*
>
> *61. The XRPDs of both LSU-I-007-1 and LSU-I-007-3 contained sharp peaks, indicating that these solids were highly crystalline. I will not compare these XRPDs with that of the cefepime dihydrochloride monohydrate claimed in claims 1-3 of the '288 Patent. The latter is provided in the '288 Patent as a list of 'd' spacings and intensity in claims 3 at page 31. An identical list appears in the disclosure at page 26 of the '288 Patent.*
>
> ...
>
> *67. My conclusion is that LSU-I-007-3 is cefepime dihydrochloride monohydrate. Moreover, the XRPD patterns shows that this is substantially a single crystal form and the elemental analysis shows*

> *that it is substantially chemically pure. Thus, LSU-I-007-3 is substantially pure crystalline cefepime dihydrochloride hydrate containing from 2.5% to 7.0% by weight of water, as claimed in claim 1 and from 2.5 to 4.1% water as claimed in claim 2 of the '288 Patent. Moreover, LSU-I-007-3 is cefepime dihydrochloride monohydrate as claimed in Claim 3 of the '288 Patent by its XRPD pattern.*
>
> ...
>
> *69. Example V of the '055 Patent, when scaled-up, results in substantially pure cefepime dihydrochloride monohydrate. This is the subject matter that appears in Examples XI and XII of the '288 Patent. This is the subject matter that is claimed in Claims 1 and 2 the '288 Patent in terms of substance, in Claim 3 of the '288 Patent in terms of XRPD peaks, and in Claims 4 and 5 in terms of admixtures with L(+)lysine and L(+)arginine. In my opinion, the subject matter of the claims of the '288 Patent is not new subject matter over what is set out in the '055 Patent. A chemist to whom the '288 Patent is directed would arrive at substantially pure cefepime dihydrochloride monohydrate as claimed in Claims 1 and 2, and as claimed by XRPD pattern in Claim 3 by following the teachings of the '055 Patent, in particular by reproducing Example V on a greater scale in the course of routine development. Indeed, as I have shown in the table in paragraph 49, and discussed in paragraphs 49-54, Examples XI and XII of the '288 Patent constitute no more than a simple scaling up of Example V of the '055 Patent.*

[135] The affidavit of Dr. Langer also discusses those test results. I repeat paragraphs 64 and 69 of his affidavit:

> *64. Finally, it appears that an increase in the scale of the runs resulted in generally similar results to those described above with the possible exception of a lower amount of unbound or adventitious water retained by the dried product. For example, a 10X increase in scale over that utilized in LSU-I-001 resulted in little change in water content after drying, as evidenced by a water content (Karl Fisher) of 4.96% (page 10) and a similar observed XRPD pattern (page 15) obtained for run LSU-I-002 as compared to the results for run LSU-I-001 described above. However, as described for run LSU-I-007, A 20X increase in scale resulted in a measured water content (Karl Fisher) for the dried product of 3.64% (page 75, with*

this result also supported by the Thermogravimetric Analysis (TGA) results shown on page 94 that display a step weight loss of a similar magnitude). The XRPD results for sample LSU-I-007-3 (pages 100 through 102) also appear to be much sharper (less diffuse) than those described above, which may indicate a reduction in the level of disordered regions present in this sample. The sharpness of the peaks also allows for a better comparison of the main peaks seen for LSU-I-007-3 as compared with those described in Example XI and claim 3 of the '288 Patent. Upon inspection, it appears that the positions and relative intensities of the peaks match up very well between these data sets (I note that several additional peaks are listed in the XRPD data corresponding to LSU-I-007-3 as compared to those listed in the '288 Patent; however, most of these additional peaks are of a low intensity and may have simply not been reported by the inventors of the '288 Patent). For example, the seven highest intensity (>20%) peaks listed in the table from claim 3 of the '288 Patent (d=10.21, 6.78, 4.74, 4.26, 3.95, 3.90 and 3.78 appear to match well with corresponding high intensity peaks seen for LSU-I-007-3 (d=10.28, 6.80, 4.75, 4.25, 3.95, 3.89 and 3.79).

...

69. Thus, the data described in the API Results in my opinion indicates that the reproduction of Example V resulted in the production of crystalline cefepime dihydrochloride monohydrate with an XRPD pattern represented by that described for LSU-I-007-3 discussed above. As described above, the XRPD pattern appears to match closely with that purportedly disclosed in Example XI and Claim 3 of the '288 Patent. Additionally, as I described above, the Karl Fisher and TGA data related to LSU-I-007-3 indicates that this material is a monohydrate. Further, the elemental analysis results for LSU-I-007-3 shown on page 89 of the API Results (i.e., %N-14.65, %C=40.00, %H= 5.17) appear further to confirm that the material is indeed cefepime dihydrochloride monohydrate. I also note that these elemental analysis results indicate that the LSU-I-007-3 material is also relatively pure. Based on this, in my opinion, one would consider said material to be substantially pure as defined in the '288 Patent as I described in paragraphs 47 through 52 above. As a result, it is my opinion that the '055 Patent also discloses claim 3 of the '288 Patent.

[136] Dr. Cima, another one of Apotex's experts, also addressed the test results. I repeat paragraphs 21 and 22 of his affidavit:

> *21. 1 was provided by Marcelo Sarkis of Ivor M. Hughes, co-counsel to Apotex Inc. with the Affidavit of Nadia Corelli-Rennie which included laboratory notebooks of reproductions of Example V in the '055 Patent. The scientist performed minor variations in scale and equipment among these various reproductions that in my opinion are within the scope of the '055 Patent's teaching. As indicated above, minor variations in precipitation reactions to obtain crystalline product is common and routine. Several of the attempts resulted in poorly crystalline produce which I will describe below but she quickly arrived at conditions (which are well known and routine in crystallization) that produced superbly crystalline product that I will discuss first.*
>
> *22. Experiment LSU-1-007 is a slightly larger scale than Example V, but follows Example V in every other way. Importantly, no attempt was made to cool the zwitterion hydrogen chloride solution prior to or during addition of acetone. Thus, experiment LSU-I-007 provides a direct test of whether cooling the solution is important to produce the desired product as described in Example XI of the '288 Patent. PXRD of the vacuum dried sample LSU-I-007-3 shows it to be crystalline. I compared these PXRD results with the reported product of the '288 Patent's Example XI (and the PXRD of claim 3 of the '288 Patent) and found them to be identical. This comparison is shown below. I first calculated the positions of the PXRD reflections for the dihydrochloride monohydrate as described in Example XI and claim 3 of the '288 Patent. These are plotted below along with the peak position and intensities determined for sample LSU-I-007-3. The two results are unquestionably identical. The water content of LSU-I-007-3 as determined by KF titration is 3.64% which is within the range described and claimed in claims 1 and 2 in the '288 Patent (2.46% to 3.70%). The solution NMR results of LSU-1-007-3 show no change in the cefepime structure. Thus, I conclude that LSU-I-007-3 is the same cefepime dihydrochioride monohydrate described an Example XI and claimed in claims 1-3 of the '288 Patent.*

[137] By an Order dated April 21, 2008, Prothonotary Tabib permitted the Applicants to file reply evidence in respect of this testing all without prejudice to their ability to argue on this hearing, the impropriety of this evidence (paragraph 1 of her Order).

[138] Dr.Byrn in his reply affidavit criticized these experiments on a number of grounds and concluded that Ms. Corelli-Rennie did not make the claimed cefepime dihydrchloride monohydrate. He gave his general opinion at paragraphs 7 to 10:

> *7. Ms. Corelli-Rennie states that she as [sic] asked to carry out Example IV, V and the zwitterion formation from the Greek '055 Patent. Yet, a number of her experiments do not follow the protocols in those examples. Nowhere does she explain why she elected to change the protocol.*
>
> *8. Generally, most of Ms. Corelli-Rennie's experiments yielded material which is not identifiable, based on the analysis conducted. In many cases, Apotex' chemist did not perform the necessary tests to confirm the product of her experiments. I agree with Apotex' witness, Dr. Cima, that the best confirmation of product is from single crystal x-ray diffraction data. This analysis was not performed by Apotex. However, based on the limited analysis it is possible to determine that Ms. Corelli-Rennie did not make the claimed cefepime dihydrochloride monohydrate. In particular, none of the XRPD matches that described and claimed in the '288 patent. Further, most of the experiments conducted by Ms. Corelli-Rennie yield material which might be considered non-crystalline or possibly a mixture of one or more non-crystalline materials such as a mixture of cefepime mono and dihydrochloride. In particular broad peaks were shown on the XRPD that were run that are not what would be expected for a crystalline material. Further analysis would be needed to determine the identity of the material made.*
>
> *9. Furthemore, no reference standard was used to confirm the presence of mono- or dihydrate. No analytical method was developed to look at mixtures, if they are present as suggested in some instances by Apotex' witnesses. In the article provided by Dr. Cima, authored by Dr. Bugay, it shows how to conduct a proper*

> *analysis of a mixture. Without such a method, it is not possible to reliably determine what is present in a mixture.*
>
> *10. In addition, the testing appears to have been done at random times upon completion of experiments. No standard protocol was applied between the experiments. Thus, the analysis performed should be treated with caution.*

[139] Specifically as to LSU-I-007, Dr. Byrn said at paragraphs 24 to 28 of this reply affidavit:

> ***LSU-I-007***
>
> *24. This experiment is admittedly different from the first part of Example V. The scale has been increased: approximately 21 fold. Further, unlike what would be understood by a person skilled in the art reading Example V, the drying step as not done directly after filtration but instead was done almost 4 days later. The material in the meantime was left in a vial, damp. Further, unlike Example V, the acetone was added over a much longer period, namely 50 minutes and 60 minutes vs. 5 minutes.*
>
> *25. PXRD was performed on both the damp material and the material after drying. The PXRD from the damp material clearly does not match claim 3 of the Patent. The PXRD from the dry material is closer, but is missing two peaks at d spacing 4.95 and 3.65. Further, the material made by Ms. Corelli-Rennie contains additional peaks from example peaks with d spacings of 16.35 and 8.16. In addition, the intensity of many of the peaks is quite different from those found in the patent. Without additional experiments it is unclear what this data means.*
>
> *26. Furthermore, the KF value obtained was 3.64. Although the KF value falls within that for claims 1 and 2, anticipation cannot be established of KF alone. The product must also be shown to be substantially pure cefepime dihydrochloride monohydrate. This has not been shown. Thus, it cannot anticipate claims 1 and 2.*
>
> *27. Finally, the DSC does not appear to correlate. The exotherms are shown, where the patent only talks about one.*
>
> *28. This experiment is not a reproduction of what is taught in the '055 patent. Further, the PXRD while closer to that of the claimed cepfepime dihydrochloride monohydrate is not the same.*

> *Considering the differences in the other characterizing data, it is not clear to me that what as produced. As noted above, Dr. Cima previously has indicated that single crystal data is determinative of crystal form, but this analysis was not done here. In any event, it is my opinion that this material is not anticipatory as it is not a reproduction of what was taught in the prior art.*

[140] Dr. Bartlett as well criticized Ms. Corelli-Rennie's LSU-I-007 experiment in his reply affidavit. He cited a number of procedural differences from Example V of the Greek '055 patent leading him to conclude that, including the modifications, it cannot be said that in every case without the possibility of error that she obtained cefepime dihydrochloride monohydrate. He said at paragraphs 23 to 27 of his reply affidavit:

> *23. In Experiment LSU-I-007, the procedure Ms. Corelli-Rennie followed differed from that of Example V of the Greek '055 Patent in several respects. First, Ms. Corelli-Rennie's experiment was carried out at about 20 times the scale of Example V. Second, the first and second portions of acetone were added to the hydrochloric acid solution of cefepime over 50-minute and 60-minute periods, instead of the 5-minute periods specified in Example V. And third, after filtration and washing, the wet filter cake was allowed to sit for 4 days, in a closed sample vial, before the material was placed in the vacuum oven and freed from residual solvent. No such interval is described or implied in the Greek '055 Patent. The final material was again analyzed by NMR, PXRD, KF and elemental analysis. The sharp peaks in the PXRD analysis show that crystalline material was obtained.*
>
> *24. The PXRD analysis of the product of Experiment LSU-I-007 is similar to that of the PXRD disclosed and claimed in the '288 patent, but it is not identical. While the KF and elemental analyses of this material are consistent with monohydrate, no single crystal X-ray analysis was performed. I note that Apotex's expert, Dr. Cima, would consider this analysis to be the definitive way to characterize the crystalline form of this material and to determine whether it was the claimed monohydrate or not.*
>
> *25. In my opinion, Ms. Corelli-Rennie did not obtain a different result in this experiment because she performed it on larger scale*

than Example V of the Greek '055 Patent. In her Experiments LSU-I -002 and LSU-I-005, she had increased the scale 10-fold and 5.4-fold and obtained the same results as the on-scale experiments. In my opinion, she obtained a different result in this experiment because of the other procedural differences. By slow addition of the acetone portions, she brought the cefepime dihydrochloride out of solution much more slowly than occurred in the experiments that more closely followed Example V. Decreasing the solubility of a compound slowly has long been understood to be more conducive to formation of a crystalline, as opposed to an amorphous or poorly crystalline, material. Moreover, even if an amorphous or poorly crystalline form of cefepime dihydrochloride of ill-defined water content had been formed, by standing for 4 days as a wet product alter filtration and washing with acetone, without evaporation, or other means by which the excess solvent could be removed, it could have been transformed into the crystalline material. A significant amount of excess solvent was present in the wet material, as its weight was reduced from 5.21 g to 5.05 g when it was eventually dried.

26. Whichever one of these procedural modifications was responsible for the different result Ms. Corelli-Rennie obtained in Experiment LSU-I-007, they were not part of Example V of the '055 Patent. The time period over which the acetone portions are added was clearly stated as 5 minutes, not 50 and 60 minutes. No time period is stated for the interval between filtering and washing the product with acetone and placing it in a vacuum oven for drying, but one of skill in the art would understand the phrase "The crystals are removed by vacuum filtration, washed with two 5 ml portions of acetone and vacuum dried at 40-45 deg. C for 24 hours" to mean that there is no intervening time period. Indeed, it was Ms. Corelli-Rennie's usual procedure to dry her products immediately after filtration and washing.

<u>Summary of Experiments Relating to Example V</u>

27. Based on the various experiments done by Ms. Corelli-Rennie with respect to Example V, including those involving modifications, it cannot be said that in every case and without the possibility of error that she obtained cefepime dihydrochloride monohydrate.

[141] There is nothing in the cross-examination transcripts of any of these experts that materially detracts from or adds to what has been said in these quoted passages from their affidavits.

[142] In considering all of this evidence as to testing and weighing it on a balance of probabilities, I have concluded, as I previously stated, that the evidence is controversial and inconclusive. Therefore, the evidence as to testing should be given little weight.

CONCLUSION AS TO ANTICIPATION

[143] In conclusion as to anticipation I find that the evidence of the experts, excluding the evidence as to testing, is contradictory and leads to an inconclusive result. Apotex has the burden in this matter, evidence has been led by both parties, and, on a balance of probabilities, I find that the evidence cannot lead me to conclude that claims 2 and 3 of the ’288 patent were anticipated.

[144] Even if I were to consider the testing evidence, I find it too is inconclusive and would not serve to change the balance of probabilities. I do not find claim 2 or 3 to be anticipated.

OBVIOUSNESS – CLAIM 2 AND CLAIM 3

[145] An examination of obviousness can be approached using the restated *Windsurfing* questions approved by the Supreme Court of Canada in *Sanofi* at paragraph 67 previously set out in these reasons. Those questions are:

> *(1) (a) Identify the notional "person skilled in the art";*
> *(b) Identify the relevant common general knowledge of that person;*

> *(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*
> *(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;*
> *(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

[146] As to question 1(a) the parties are agreed as to who is the notional person skilled in the art as previously set out in these reasons. In brief it is an experienced pharmaceutical chemist with a university degree.

[147] As to question 1(b), the parties in their argument and evidence have essentially focused on Aburaki (the ’899 patent) which is a patent which is discussed in the ’288 patent at issue here and in the Greek ’055 patent. I will do likewise.

[148] Question 2 is directed at the “inventive concept” of the claim in question. I have already construed claims 2 (pre-disclaimer) and 3 to mean essentially that they are directed to crystalline dihydrochloride monohydrate (CDM) of cefepime of varying purity that is temperature stable. Non essential parts of the claims, with respect to claim 2, are that it has a range of water content indicating the presence of other forms and with respect to claim 3 there is provided a particular PXRD profile which profile simply identifies the inherent identity of CDM. It must be remembered that it is the “inventive concept” as defined by the claims that is the subject of the inquiry.

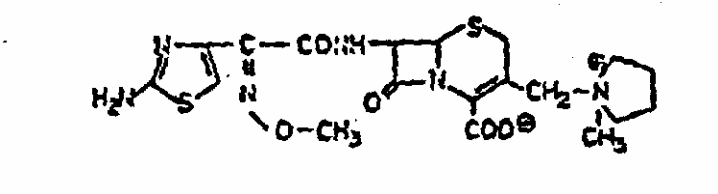
[149] Question 3 requires that the Court discern what differences, if any, exist between the "inventive concept" of the claims and the matter cited as "state of the art", here Aburaki and the Greek '055 patent.

[150] Question 4 requires an examination of the differences, if any, between the "inventive concept" of the claims and the "state of the art" and a determination as to whether such differences, if any, would have been obvious to the person skilled in the art. At this point I would add that by "obvious" it is understood that the Court must ask whether, as instructed by *Sanofi* and the Federal Court of Appeal in *Pfizer,supra*, the differences, if any, were "more-or-less self evident".

[151] Returning to Question 3, which requires a determination of the "state of the art", one should start with what the '288 patent at issue itself says is the state of the art. In that regard it acknowledges with respect of Aburaki (the '899 patent) at pages 3 and 5:

> *Aburaki et al. U.S. Patent No. 4,406,899 discloses 7-[α-(2-aminothiazol-4-yl)-α-(Z)- methoximinoacetamido]-3-[(1-methyl-1-pyrrolidinio)methyl]-3-cephem-4-carboxylate in the zwitterion form and mentions corresponding acid addition salts (which are present in the zwttterion form in injectable compositions) and shows that the zwitterion form has broader spectrum activity than ceftazidime and cefotaxime.*
>
> *However, the aformentioned Aburaki et al. cephalosporins are stable only for a few hours as injectable compositions and the zwitterion form even as a dry powder is unstable at room temperature and losses 30% or more of its activity on storage at elevated temperatures (e.g. 45 deg. C and above) for even one week and therefore requires special insulated packaging and/or refrigeration and is at a packaging and storage disadvantage compared to ceftazidime and cefotaxime.*

> *While Aburaki et al. mentions acid addition salts, the patent does not state how to make these or state which if any of these salts have good stability in dry powder form. Kessler et al., "Comparison of a New Cephalosporin, BMY 28142, with Other Broad-Spectrum β-Lactam Antibiotics", Antimicrobial Agents and Chemotherapy, Vol. 27 No. 2, pp. 207-216, February 1985 mentions the sulfate salt, but does not disclose how to prepare such or that this salt has room temperature stability and good elevated temperature stability in dry powder form.*
>
> ...
>
> *The acid addition salts herein when formed into aqueous injectable composition and adjusted to pH 6.0 provide the zwitterion in solution. The zwitterion has the structure*



> *The broad spectrum utility against various organisms of the zwitterion form, and thus of aqueous compositions made up from the salt herein, is shown by the data in Aburaki et al. U.S. 4,406,899.*

[152] Thus the '288 patent at issue here itself acknowledges that the "state of the art" discloses the zwitterion form of cefepime which has utility as an injectable broad spectrum (antibiotic). The '288 patent says that the "state of the art" includes a disclosure as to acid additions salts but not how to make them and not which have good stability.

[153] Given this acknowledgement in the '288 patent at issue the Greek '055 patent must be considered. As previously stated that patent is for all practical purposes here, identical to the '288 patent at issue except that the '288 patent adds Examples X to XIII. What, then, does the Greek

'055 patent add to the "state of the art". It adds what the '288 patent says is lacking in the Aburaki reference namely, the Greek '055 patent identifies certain salts that provide temperature stability and how to make them. Among the salts identified are the dihydrochloride. All identified salts are said to have superior temperature stability. I repeat from page 3 of the translation of the Greek patent which is essentially the same as the wording on page 4 of the '288 patent at issue:

> *Summary Of The Invention*
>
> *It has been discovered herein that certain crystalline acid addition salts* of *7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoxyiminaocetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate in dry powder form have excellent room temperature stability and have superior elevated temperature stability compared to the zwitterion form. The term "dry powder form" as used herein means a moisture content of less than 5% w/w.*
>
> *These acid addition salts are the crystalline salts of of 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoxyiminoacetamido]-3-[(1-methyl-1-pyrrolidinio) methyl]-3-cephem-4-carboxylate which are selected from the group comprised of the sulphuric, dinitric, monohydrochloric, and dihydrochloric addition salts and the orthophosphoric addition salts (1.5-2 molecules of orthophosphoric acid per molecule of salt, e.g. a range of from the sesqui-to the diorthophosphoric acid salts), or its solvates.*

[154] At page 5 of the translation of the Greek '055 patent (page 6 of the '288 patent) all the salts are said to have excellent stability with the sulphuric acid addition salt being preferred. Dihydrochloric acid addition salts are mentioned and a method for their crystallization is provided:

> *Detailed Description*
> *The crystalline salts of the present [document], hereinafter referred to simply as the salts of the present [document], have excellent stability at room temperature and have a loss of activity (as determined by HPLC) of less than 1% after storage for one month at room temperature. These salts have excellent stability at elevated temperatures and have a loss of activity (as determined by HPLC) of less than 15% after storage for one month at 45-56°C.*

> *The sulphuric acid addition salt is the preferred salt here. It has a loss of activity of less than 10% after storage for one month a 45-56°C. It is noteworthy that it has low solubility in water, i.e. approximately 25 mg/cc, and it is therefore crystallized from water with very little loss.*
>
> *The dinitric acid addition salt of the present [document] also has low solubility in water, i.e. approximately 60 mg/cc, and therefore also gives low residual loss during crystallization from water.*
> *The monohydrochloric, dihydrochloric and sesqui- or diorthophosphoric acid addition salts have water solubilities greater than 200 mg/cc, and therefore are crystallized preferably from organic solvants, rather than water, in order to obtain good yields.*

[155] Detailed descriptions as to methods of preparations follow. Among the Examples is Example V previously discussed which in the title says it produces the dihydrochloric acid addition salt.

[156] In summary, the "state of the art" as described in the Greek '055 patent is:

- There is a group of five acid addition salts that provide excellent temperature stability to the cefepime zwitterion disclosed in Aburaki
- Among those salts is crystalline dihydrochloride – a method for its preparation is provided.

[157] Thus the "state of the art" provides everything that is essential in claims 2 and 3 of the '288 patent except to further identify the hydration of the crystalline dihydrate as being a monohydrate. That is the answer to question 3 of the *Windsurfing* line of inquiry.

[158] Turning to question 4 - is the difference, namely the identification of the monohydrate form of the crystalline dihydrochloride acid addition salt as having "temperature stability", obvious? In this regard we must start with recognizing that the Greek '055 patent does not distinguish between the various hydrated forms of the selected salts, it says that all the selected salts have excellent stability. What does the '288 patent at issue say about the particular monohydrate? That must be found, if at all, somewhere in Examples X through XIII since the rest of the disclosure is essentially the same as the Greek '055 patent. The only place that one can find any description of any "advantage" is in Example XII at page 27 of the '288 patent:

> *The foregoing procedures of Examples XI and XII routinely produce monohydrate having a water content in the range of 2.46% to 3.70% with an average value of 3.31%. The value calculated from the stoichiometric formula is 3.15%. Drying at 37°C in a desiccator at reduced pressure (0.001 mm Hg) over P_2O_5 for 5 days or at reduced pressure (10 mm Hg) at 45°C for 2 days results in no loss in weight. Storage stability for 56°C for 3 weeks produced a potency loss of 0.6%, and was substantially improved, therefore, as compared to the anhydrate (1.25% H_2O) described in Example V hereof (7.2% loss in 4 weeks at 56 °C).*

[159] What is being said is that the monohydrate as compared to the anhydrate of the same salt has substantially improved stability. No comparison is made to other hydrated forms of the same salt or of different salts. Only one data point is given. It must be remembered that the Greek '055 patent has already told us that the class of all five salts all have excellent stability.

[160] Is it unexpected that given a class of materials all having excellent stability, that one member of the class, when tested once, would exhibit superiority over another? All members of a professional basketball team are accomplished players, it is not unexpected that on a particular day

one player will perform better than one of the other players. That does not mean that such a player is surprisingly or unexpectedly better than all or most of the rest of the team

[161] The Applicants' experts Drs. Byrn and Bartlett discuss the matter. Dr. Byrn at paragraph 120 of his first affidavit says:

> *120. Similarly, although the '055 Patent generally mentions "temperature stable crystalline salts of [cefepime] ... or their solvates", it does not say or suggest that cefepime dihydrochloride monohydrate would have improved temperature stability properties over other forms of cefepime, nor does it disclose how to make substantially pure temperature stable crystalline cefepime dihydrochloride monohydrate. Rather, the '055 Patent discloses the preparation of cefepime dihydrochloride anhydrate.*

[162] Dr. Bartlett at paragraph 76 of his first affidavit says:

> *76. The Greek '055 Patent is the only prior art reference cited by Apotex that addresses temperature stability of cefepime or describes the synthesis or testing of any acid addition salt of this compound. Hydrated forms of cefepime addition salts are included in the invention only in the generic description of "Temperature stable crystalline salts of [cefepime]…, or their solvates." As discussed above, this reference discloses a preparation of the dihydrochloride salt of cefepime, but only as the anhydrate. There is no description in this reference of the preparation of the monohydrate form of the dihydrochloride of cefepime, nor any direction that would lead one to attempt to do so. Moreover, there is no suggestion that the monohydrate form would have beneficial properties in comparison to the anhydrate or any other form of cefepime.*

[163] It is interesting to note what Drs. Byrn and Bartlett say. They say that the '288 discloses that the dihydrocloride monohydrate has improved stability "over other forms of cefepime". This is not so. There is no comparison in the '288 patent with other forms of cefepime other than, in one Example, a single mention of a single measurement in respect of only one other form.

[164] Apotex's experts Drs. McClelland and Langer address this issue. Dr. McClelland says at paragraph 136 of his affidavit:

> *136. In fact, it is very difficult to assess the advantage, if any, of the dihydrochloride monohydrate over those listed in the prior art. There is only the one actual data point for the dihydrochloride monohyrdate compound of Examples XI and XII, namely, storage stability at 56°C for three weeks producing a potency loss of 0.6%. A later, general statement provides a different figure, at least 96% retention after three weeks at 56°C. In the table provided in the '055 Patent provides stability data at 56°C after storage for 1, 2 and 4weeks, for example for the H_2SO_4 salt at all three times, and for the $(HCl)_2$ salt for 1 week and 4 weeks. There is no data in the '055 Patent for 3 weeks at 56°C and there is no data in Example XI and XII for 1, 2, or 4 weeks at 56°C. Thus, it is impossible to direct comparison of the compounds of Example XI and XII with the prior art compounds in order to assess any substantial advantage of the former over the salts of the prior art.*

[165] Dr. Langer says at paragraph 153 of his affidavit:

> *153. However, in my opinion, Drs. Bartlett and Byrn both fail to note with respect to these arguments that the case at hand is different from the case of a new pharmaceutical compound for which salt and/or hydrate forms thereof have not been previously identified or produced. As I described above, the '055 Patent discloses pharmaceutically acceptable, crystalline and temperature stable monohydrochloride and dihydrochloride acid addition salts of cefepime and hydrates thereof, including the dihydrochloride monohydrate salt itself. Additionally, the '882 and '899 patents disclose hydrochloric, hydrobromic, formic, nitric, sulfuric, methane-sulfonic, phosphoric, acetic and trifluoracetic acid pharmaceutically acceptable acid-addition salts of cefepime. Thus, one would not be confronted with the case of having to select produce and characterize a pharmaceutically acceptable salt of cefepime from scratch from a wide range of possible types of salts. Instead, the results purportedly disclosed in the '288 Patent related to cefepime dihydrochloride monohydrate, in particular Examples XI and XII, are simply the outcome of standard and routine work towards the confirmation of the properties of a known and previously disclosed salt of cefepime.*

[166] Returning to claims 2 and 3, they simply claim that the dihydrochloride monohydrate form is temperature stable. From the Greek ’055 patent use are told that the dihydrochloride form is not only temperature stable but is excellent in that regard. There is nothing in the Greek ’055 patent to suggest that differently hydrated forms would perform differently. The ’288 patent at issue simply tells us that the monohydrate, tested once after three weeks was better than the anhydrate form. This does not indicate any unexpected result; it is more-or-less evident that within a group having “excellent” properties one member, tested once, would be better than another.

[167] I was invited by Applicants’ Counsel to consider this case as being similar to that determined by the Supreme Court in *Sanofi, supra*. Justice Rothstein considered, in the context of anticipation and the disclosure made in the prior art, the ’875 patent, and wrote at paragraphs 40 and 41 of the decision:

> ***40*** *There was no evidence that the person skilled in the art would know from reading the '875 patent that the more active dextro-rotatory isomer would be less toxic than the racemate or levo-rotatory isomer or any of the other compounds made and tested. Indeed, Dr. McClelland's evidence was that while you "often" get more activity by separating isomers, the answer to the question whether this increased activity was to be found in the levo-rotatory isomer or the dextro-rotatory isomer was unknown. (Affidavit, at para. 42, and cross-examination, at pp. 928-30 and question 322).*
>
> ***41*** *Since the '875 patent did not disclose the special advantages of the dextro-rotatory isomer and of its bisulfate salt, as compared to the levo-rotatory isomer or the racemate and their salts, or the other compounds made and tested or otherwise referred to in the '875 patent, the invention of the '777 patent cannot be said to have been disclosed and therefore it cannot be said to have been anticipated.*

[168] In respect of obviousness, he wrote in terms of what would be more-or-less evident at paragraphs 84 and 85:

> ***84*** *As I have observed earlier, Shore J. found that the skilled person would not know, before separating this particular racemate into its isomers and then testing the separated isomers, that the properties of the dextro-rotatory isomer would be different from the properties of the racemate or the levo-rotatory isomer (para. 81). Similarly, he found that the person skilled in the art would not know before trying the different salts in combination with the dextro-rotatory isomer what the bisulfate salt's beneficial properties would be (para. 82).*
>
> ***85*** *Just because there are known methods of separating a racemate into its isomers does not mean that a person skilled in the art would necessarily apply them. The fact that there are such known methods of separation will be of no account if the evidence does not prove that it was more or less self-evident to try them. It is true that at the relevant time there was evidence that a skilled person would know that the properties of a racemate and its isomers might be different. However, a possibility of finding the invention is not enough. The invention must be self-evident from the prior art and common general knowledge in order to satisfy the "obvious to try" test. That is not the evidence in this case.*

[169] The patent at issue in *Sanofi* Canadian Patent 1,336,777 (’777 patent) was provided to me at the hearing by Applicants’ Counsel with the agreement of Apotex’s Counsel. The difference between the ’077 patent and the ’288 patent at issue here illustrates how, in *Sanofi,* the Court determined that the patent was valid. The ’777 patent dealt with a previously disclosed pharmaceutical composition that was racemic, that is it was composed of equal portions of two molecular structures which were identical to each other except that they were twisted into one configuration or another when viewed in three dimensions (enantiomers). One was called the “dextro-rotatory enantiomer” the other the “levo-rotary enantiomer”. The ’777 patent at page 1 describes the invention:

> *In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers.*

[170] There follows in the '777 patent many pages as to how to separate the enantiomers from each other in the racemic mixture. At pages 11 through 20 detailed tabulated data is given comparing the racemic mixture with each of the dextro and levo enantiomer showing the superiority of the dextro.

[171] We have none of this in the '288 patent at issue. All salts of the prior art are said to have excellent temperature stability. One piece of data reflecting a measurement at one time of the monohydrate is given and compared only with one other form, the anhydrate. Nothing is said about this being unexpected. No expert for any party in this case gave evidence that this result was surprising or unexpected.

[172] I therefore conclude that the essential elements of the "invention" as claimed in claims 2 and 3 of the '288 patent (I have directed by findings to the pre-disclaimer version of claim 2 but my findings would be the same with respect to post disclaimer since there is no essential difference between the two versions for this purpose) are obvious in that the essential element, namely that the monohydrate is temperature stable, is more-or-less self-evident having regard to the "state of the art", in particular the Greek '055 patent. Apotex's allegation as to invalidity for obviousness is justified.

DOUBLE PATENTING

[173] Double patenting, put simply, involves the concept that a person cannot get a second patent for the same thing for which they already have received a patent. A patent is a monopoly for a limited period of time and that period should not be extended by the expedient of getting a subsequent patent for the same thing.

[174] 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.

[175] Even when the same person has received two patents the test for distinguishing one from the other is like anticipation or obviousness. One asks whether the second patent is claiming the same thing as the first (literal or co-terminus) or is the second patent claiming something that is obviously within the scope of the first. The Supreme Court of Canada has accepted both approaches as sound: see *Whirlpool Inc. v. Camco Inc.*, [2000] 2 S.C.R. 1067 at paragraphs 63 to 75.

[176] Here a Canadian Patent No. 1,284,994 (the ’994 patent) was issued and granted to BMS US on June 18, 1991. It is alleged by Apotex that the ’288 patent issued and granted to BMS US on March 31, 1992 constitutes a “double patent” over the ’994 patent.

[177] The disclosure of the ’994 patent is the same as the Greek ’055 patent and claims 1 and 2 of the ’994 patent emcompass within their scope the temperature stable crystalline dihydrochloride monohydrate and addition salt of claims 2 and 3 at issue here. There is no unobvious difference.

[178] Fortunately Counsel for the parties have agreed that if I find that claims 2 and 3 are obvious over the Greek ’055 patent I may simply consider that there is also double patenting. I so find, therefore Apotex’s allegation as to double patenting is justified.

SELECTION PATENTS

[179] Apotex alleges that the claims at issue of the ’288 patent are invalid in that they do not meet the criteria of what it calls a selection patent and at best verify inherent properties of previously disclosed substances without disclosing a substantial advantage.

[180] There is a danger in giving names to certain patents and then, having given such names, arguing whether the patent meets criteria for such names as may have been discussed in one or another piece of jurisprudence. The Applicants do not call the ’288 patent a “selection” patent, they say it is an “improvement” patent.

[181] In *Sanofi,* the Supreme Court of Canada adopted, in paragraph 9 of their reasons, what Maugham J. of the English Chancery Division said in *Re I. G. Farbeneindustrie A.G.’s Patents* (1930), 47 R.P.C. 289 at page 321, namely that a selection patent “does not in its nature differ from any other patent”. At paragraph 9, Rothstein J. wrote:

> ***9*** *The locus classicus describing selection patents is the decision of Maugham J. in In re I. G. Farbenindustrie A. G.'s Patents (1930), 47 R.P.C. 289 (Ch. D.). At p. 321, he explained that in the field of chemical patents (which would of course include pharmaceutical compounds), there are often two "sharply divided classes". The first class of patents, which he called originating patents, are based on an originating invention, namely, the discovery of a new reaction or a new compound. The second class comprises patents based on a selection of compounds from those described in general terms and claimed in the originating patent. Maugham J. cautioned that the selected compounds cannot have been made before, or the selection patent "would fail for want of novelty". But if the selected compound is "novel" and "possess[es] a special property of an unexpected character", the required "inventive" step would be satisfied (p. 321). At p. 322, Maugham J. stated that a selection patent "does not in its nature differ from any other patent".*

[182] Rothstein J. at paragraph 10 listed criteria established by Maugham J. for a selection patent to be valid:

> ***10*** *While not exhaustively defining a selection patent, he set out (at pp. 322-23) three conditions that must be satisfied for a selection patent to be valid.*
>
> > *1. There must be a substantial advantage to be secured or disadvantage to be avoided by the use of the selected members.*
> >
> > *2. The whole of the selected members (subject to "a few exceptions here and there") possess the advantage in question.*
> >
> > *3. The selection must be in respect of a quality of a special character peculiar to the selected group. If further research revealed a small number of unselected compounds possessing the same advantage, that would not invalidate the selection patent. However, if research showed that a larger number of unselected compounds possessed the same advantage, the quality of the compound claimed in the selection patent would not be of a special character.*

[183] This was a useful starting point for Rothstein J. as he wrote in paragraph 11. What is really being said is, if a patent claims to have "selected" a particular member from a previously disclosed larger group, then to be an unobvious selection, the selected member or group should have previously undisclosed (i.e. not anticipated) and unexpected (i.e. not obvious) advantages over what was previously disclosed.

[184] Given my findings as to anticipation and obviousness here there is no need to somehow further the discussion through any lens created by labelling the patent a selection patent.

AMBIGUITY – SUBSTANTIALLY PURE

[185] I have previously construed claim 2, pre-disclaimer and claim 3. In so doing, I have not found them to be ambiguous.

[186] I have also construed the post-disclaimer version of claim 2 which I have found to be ambiguous. If required, which I am not, I would find the post-disclaimer version of claim 2 to be invalid for ambiguity.

CONCLUSION AND COSTS

[187] In conclusion, I have found that:

1. The disclaimer is valid but does not affect the construction of claim 2 as it stood before the disclaimer was filed. It is the pre-disclaimer version of claim 2 that is to be considered in this proceeding.
2. Claims 2 (pre-disclaimer) and 3 of the ’288 patent are not anticipated.
3. Claims 2 (pre-disclaimer) and 3 are obvious hence invalid having regard to the relevant state of the art. If required I would also find the post-disclaimer version of claim 2 obvious hence invalid.
4. The double patenting allegations are by agreement of Counsel to be determined in the same manner as obviousness.
5. There is no need to give special consideration to a so-called “selection patent”.
6. Claims 2 (pre-disclaimer) and 3 of the ’288 patent are not ambiguous. If required, I would decide that claim 2 (post-disclaimer) is ambiguous, hence invalid.

[188] As to costs, I will award them to the successful party, the Respondent, Apotex Inc. The Respondent Minister of Health did not actively participate in these proceedings and no costs for or against the Minister are awarded.

[189] The costs awarded to Aptoex shall be assessed as is usual in these proceedings, at the middle of Column IV. Because Apotex alleged and ultimately at the hearing did not pursue allegations concerning section 53 of the *Patent Act,* which allegations I have discussed in *Shire Biochem Inc. v.*

Canada (Minister of Health), 2008 FC 538 at paragraph 110 raise an implication of fraud. As a result, costs and disbursements taxed and allowed to Apotex shall be reduced by twenty-five percent.

[190] Costs for two counsel at the hearing, one senior and one junior for the first two days, and one senior for the third, may be taxed. Two counsel, if present, one senior and one junior, in conducting cross-examination, may be taxed. Only one counsel, a senior, is allowed in defending a cross-examination. No costs are allowed for other lawyers, in house or out house, students, paralegal or clerical persons.

[191] I remain concerned that the fees allowed for experts may be excessive. I have tried to limit those fees with regard to having rates and capping these at the rate charged by senior counsel. Fees, of course, may be calculated by multiplying the rate times number of hours, thus one can avoid the hourly fee cap by increasing the hours. This is not what I intend. What I propose here is that the fees be allowed to one particular expert shall not be disproportionately large when compared to the fees charged by any other expert for any other party. In this case, I have not found any particular expert to be significantly more helpful, or put another way, more valuable than another. Apotex is free to pay its experts whatever has been agreed upon but that does not entitle those fees to be taxed at such a rate. I have therefore left the matter to be considered by counsel on the basis that no fee shall be allowed that is disproportionately large.

[192] Further, fees for experts shall be limited to fees for the services only of the experts who attested to affidavits filed by Apotex in this proceeding namely Drs. McClelland, Langer and Cima. No fees are allowed for experts or others who may have been retained by Apotex or by these named experts to assist them.

[193] Apotex is not entitled to any recovery in respect of the testing done by Corelli-Rennie or Gerster.

[194] Counsel have advised that they will attempt to resolve the question of costs between themselves and, if needed, seek further directions from the Court in that regard. I will leave the matter there.

JUDGMENT

For the Reasons provided:

THIS COURT ORDERS that:

1. The application is dismissed;

2. The Respondent Apotex Inc. is entitled to costs in accordance with these Reasons.

"Roger T. Hughes"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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STYLE OF CAUSE:	BRISTOL-MYERS SQUIBB CANADA CO. and BRISTOL-MYERS SQUIBB COMPANY v. APOTEX INC. and THE MINISTER OF HEALTH
PLACE OF HEARING:	Ottawa, Ontario
DATE OF HEARING:	January 27-29, 2009
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