FEDERAL COURT OF AUSTRALIA

Apotex Pty Ltd v AstraZeneca AB (No 4) [2013] FCA 162

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| Citation: | Apotex Pty Ltd v AstraZeneca AB (No 4) [2013] FCA 162 |
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| Parties: | **APOTEX PTY LTD v ASTRAZENECA AB and ASTRAZENECA PTY LIMITED****WATSON PHARMA PTY LTD v ASTRAZENECA AB and ASTRAZENECA PTY LIMITED****ASTRAZENECA AB and ASTRAZENECA PTY LIMITED v ASCENT PHARMA PTY LTD ACN 118 734 795**  |
|  |  |
| File number(s): | NSD 673 of 2011NSD 2342 of 2011NSD 208 of 2012 |
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| Judge: |  |
|  |  |
| Date of judgment: | 5 March 2013 |
|  |  |
| Corrigendum:  | 8 March 2013 |
|  |  |
| Catchwords: | **PATENTS –** pharmaceutical patents –invalidity – priority date – novelty – inventive step – entitlement – fair basis – utility – secret use – manner of manufacture – false suggestion – infringement – authorisation  |
|  |  |
| Legislation: | *Patents Act 1990* (Cth)*Patents Amendment Act 2001* (Cth)*Patents Act 1952* (Cth)  |
|  |  |
| Cases cited: | *Advanced Building Systems Pty Ltd v Ramset Fastners (Aust) Pty Ltd* (1998) 194 CLR 171; [1998] HCA 19*Allsop Inc v Bintang Pty Ltd* (1989) 15 IPR 686*Anaesthetic Supplies Pty Ltd v Rescare Ltd* (1994) 50 FCR 1*Aktiebolaget Hassle v Alphapharm Pty Ltd* (2000) 51 IPR 375; [2000] FCA 1303*Aktiebolaget Hassle v Alphapharm Pty Ltd* (2002) 212 CLR 411; [2002] HCA 59*Apotex Pty Ltd v Sanofi-Aventis* (2009) 82 IPR 416; [2009] FCAFC 134*Apotex Pty Ltd v Sanofi-Aventis* (2008) 78 IPR 485 [2008] FCA 1194*Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd (No 2)* (2012) 204 FCR 494; [2012] FCAFC 102*Apotex Pty Ltd v AstraZeneca AB (No 3)* (2012) 95 IPR 581; [2012] FCA 265*Austal Ships Pty Ltd v Stena Rederi Aktiebolag* (2005) 66 IPR 420; [2005] FCA 805*Australian Mud Co Pty Ltd v Coretell Pty Ltd* (2011) 93 IPR 188; [2011] FCAFC 121*Bristol-Myers Squibb Co v FH Faulding & Co Ltd* (2000) 97 FCR 524; [2000] FCA 316*Britax Childcare Pty Ltd v Infa-Secure Pty Ltd* (2012) 290 ALR 47; [2012] FCA 467*British Acoustic Films Ltd v Nettlefold Productions* (1935) 53 RPC 221*British United Shoe Machinery Co Ltd v A Fussell & Sons Ltd* (1908) 25 RPC 631*Catnic Components Ltd v Hill & Smith Ltd* [1982] RPC 183*Clorox Australia Pty Ltd v International Consolidated Business Pty Ltd* (2006) 68 IPR 254; [2006] FCA 261*Danisco A/S v Novozymes A/S (No 2)* (2011) 91 IPR 209; [2011] FCA 282*Decor Corporation Pty Ltd v Dart Industries Inc* (1988) 13 IPR 385*Ethyl Corp's Patent* [1972] RPC 169*Flexible Steel Lacing Co v Beltreco Ltd* (2000) 49 IPR 331; [2000] FCA 890*General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd* [1972] RPC 457*H Lundbeck A/S v Alphapharm Pty Ltd* (2009) 177 FCR 151; [2009] FCAFC 70*Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20; [2008] FCAFC 139*ICI Chemicals & Polymers Ltd v Lubrizol Corp Inc* (2000) 106 FCR 214; [2000] FCA 1349*ICI Chemicals & Polymers Ltd v Lubrizol Corp Inc* (1999) 45 IPR 577; [1999] FCA 345*IGT (Australia) Pty Ltd v Aristocrat Technologies Australia Ltd* (2008) 77 IPR 482; [2008] FCAFC 131*Inverness Medical Switzerland GmbH v MDS Diagnostics Pty Ltd* (2010) 85 IPR 525; [2010] FCA 108*Jupiters Ltd v Neurizon Pty Ltd* (2005) 222 ALR 155; [2005] FCAFC 90]*JMVB Enterprises Pty Ltd v Camoflag Pty Ltd* (2005) 67 IPR 68; [2005] FCA 1474*Kimberly-Clark v Multigate Medical Products* (2011) 92 IPR 21; [2011] FCAFC 86*Kinabalu Investments Pty Ltd v Barron & Rawson Pty Ltd* [2008] FCAFC 178*Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* (2004) 64 IPR 444 ; [2004] UKHL 46*Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 1)* (2004) 217 CLR 274; [2004] HCA 58*Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* [(2007) 235 CLR 173; [2007] HCA 21*Longworth v Emerton* (1951) 83 CLR 539*Martin v Scribal Pty Ltd* (1954) 92 CLR 17*Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) [154 FCR 31; [2006] FCAFC 91*Minnesota Mining & Manufacturing Co & 3M Australia Pty Ltd v Beiersdorf (Aust) Ltd* (1980) 144 CLR 253; [1980] HCA 9*Northern Territory v Collins* (2008) 235 CLR 619 [2008] HCA 49*Norton & Gregory Ltd v Jacobs* (1937) 54 RPC 271*Novozymes A/S v Danisco A/S* [2013] FCAFC 6*NSI Dental Pty Ltd v University of Melbourne* (2006) 69 IPR 542; [2006] FCA 1216*NV Philips Gloeilampenfabrieken v Mirabella International Pty Lt*d (1995) 183 CLR 655; [1995] HCA 15*PAC Mining Pty Ltd v Esco Corporation* (2009) 80 IPR 1; [2009] FCAFC 18*Pfizer Inc v Commissioner of Patents* (2005) 141 FCR 413; [2005] FCA 137*Pfizer Overseas Pharmaceuticals v Eli Lilly & Co* (2005) 68 IPR 1; [2005] FCAFC 224*Polwood Pty Ltd v Foxworth* (2008) 165 FCR 527; [2008] FCAFC 9*Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC* (2008) 77 IPR 449; [2008] FCAFC 82*Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC (No 2)* (2006) 71 IPR 46; [2006] FCA 1787*RD Werner & Co Inc v Bailey Aluminium Products Pty Ltd* (1989) 25 FCR 565*Root Quality Pty Ltd v Root Control Technologies Pty Ltd* (2000) 49 IPR 225; [2000] FCA 980*Sachtler GmbH & Co KG v RE Miller Pty Ltd* (2005) 221 ALR 373; 65 IPR 605 ; [2005] FCA 788*Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No. 3)* (2011) 196 FCR 1; [2011] FCA 846*Sigma Pharmaceuticals (Australia) Pty Ltd v Wyeth* [2011] FCAFC 132*SNF (Australia) Pty Ltd v Ciba Specialty Chemicals Water Treatments Ltd* (2011) 92 IPR 46; [2011] FCA 452 *Stanway Oyster Cylinders Pty Ltd v Marks* (1996) 66 FCR 577*Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346*Wake Forest University Health Sciences v Smith & Nephew Pty Ltd (No 2)* (2011) 92 IPR 496; [2011] FCA 1002*Welch Perrin and Co Pty Ltd v Worrel* (1961) 106 CLR 588*Welcome Real-Time SA v Catuity Inc* (2001) 113 FCR 210; 51 IPR 327 ; [2001] FCA 445Wellcome Foundation Ltd v VR Laboratories (Aust) Pty Ltd (1981) 148 CLR 262; [1981] HCA 12 Fletcher Moulton, *The Present Law and Practice Relating to Letters Patent for Inventions*, (1913) |
|  |  |
| Date of hearing: | 22-26, 28-31 October 2012; 1-2, 5-9 November 2012 |
|  |  |
| Place: |  |
|  |  |
| Division: |  |
|  |  |
| Category: | Catchwords |
|  |  |
| Number of paragraphs: | 523 |
|  |  |
| **In NSD 673 of 2011:** |  |
|  |  |
| Counsel for the Applicant: | Mr D K Catterns QC with Ms K Howard SC, Mr A J Maryniak and Mr C Smith |
|  |  |
| Solicitor for the Applicant: | Herbert Smith Freehills |
|  |  |
| Counsel for the Respondents: | Mr A Bannon SC with Mr D Kell, Mr C Dimitriadis and Mr C J Burgess |
|  |  |
| Solicitor for the Respondents: | Ashurst Australia |
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| **In NSD 2342 of 2011:** |  |
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| Counsel for the Applicant: | Mr A J Ryan SC and Mr I P Horak |
|  |  |
| Solicitor for the Applicant: | King & Wood Mallesons |
|  |  |
| Counsel for the Respondents: | Mr A Bannon SC with Mr D Kell, Mr C Dimitriadis and Mr C J Burgess |
|  |  |
| Solicitor for the Respondents: | Ashurst Australia |
|  |  |
| **In NSD 208 of 2012:** |  |
|  |  |
| Counsel for the Applicants: | Mr A Bannon SC with Mr D Kell, Mr C Dimitriadis and Mr C J Burgess |
|  |  |
| Solicitor for the Applicants: | Ashurst Australia |
|  |  |
| Counsel for the Respondent: | Mr A J Ryan SC and Mr I P Horak |
|  |  |
| Solicitor for the Respondent: | King & Wood Mallesons |

FEDERAL COURT OF AUSTRALIA

Apotex Pty Ltd v AstraZeneca AB (No 4) [2013] FCA 162

**CORRIGENDUM**

1. In paragraph 361 of the reasons for judgment delete the words “and no manner of manufacture”.
2. In paragraph 483 of the reasons for judgment delete the words “and no manner of manufacture.”

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| I certify that the preceding two (2) numbered paragraph is a true copy of the Corrigendum to the Reasons for Judgment herein of the Honourable Justice Jagot. |

Associate:

Dated: 8 March 2013

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| IN THE FEDERAL COURT OF AUSTRALIA |  |
| NEW SOUTH WALES DISTRICT REGISTRY |  |
| GENERAL DIVISION | NSD 673 of 2011 |

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| --- | --- |
| BETWEEN: | APOTEX PTY LTDApplicant/Cross Respondent |
| AND: | ASTRAZENECA ABFirst Respondent/Cross ClaimantsASTRAZENECA PTY LIMITEDSecond Respondent/Cross-Claimants |

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| --- | --- |
| JUDGE: | JAGOT J |
| DATE OF ORDER: | 5 MARCH 2013 |
| WHERE MADE: | SYDNEY |

THE COURT ORDERS THAT:

1. Order 2 of the orders of 14 December 2011 be dissolved.
2. The parties file agreed or competing proposed orders reflecting the reasons for judgment published today within 7 days.
3. The proceedings be listed on a date within a further 7 days thereafter, the date to be allocated in consultation with the parties.

Note: Entry of orders is dealt with in Rule 39.32 of the Federal Court Rules 2011.

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| IN THE FEDERAL COURT OF AUSTRALIA |  |
| NEW SOUTH WALES DISTRICT REGISTRY |  |
| GENERAL DIVISION | NSD 2342 of 2011 |

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| --- | --- |
| BETWEEN: | **WATSON PHARMA PTY LTD**Applicant/Cross Respondent |
| AND: | ASTRAZENECA ABFirst Respondent/Cross ClaimantASTRAZENECA PTY LIMITEDSecond Respondent/Cross Claimant |

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| --- | --- |
| JUDGE: | JAGOT J |
| DATE OF ORDER: | 5 March 2013 |
| WHERE MADE: | SYDNEY |

THE COURT ORDERS THAT:

1. Order 1 of the orders of 15 March 2012 be dissolved.
2. The parties file agreed or competing proposed orders reflecting the reasons for judgment published today within 7 days.
3. The proceedings be listed on a date within a further 7 days thereafter, the date to be allocated in consultation with the parties.

Note: Entry of orders is dealt with in Rule 39.32 of the Federal Court Rules 2011.

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| IN THE FEDERAL COURT OF AUSTRALIA |  |
| NEW SOUTH WALES DISTRICT REGISTRY |  |
| GENERAL DIVISION | NSD 208 of 2012 |

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| --- | --- |
| BETWEEN: | ASTRAZENECA ABFirst Applicant/Cross RespondentASTRAZENECA PTY LIMITEDSecond Applicant/Cross Respondent |
| AND: | ASCENT PHARMA PTY LTD ACN 118 734 795Respondent/Cross Claimant |

|  |  |
| --- | --- |
| JUDGE: | JAGOT J |
| DATE OF ORDER: | 5 March 2013 |
| WHERE MADE: | SYDNEY |

THE COURT ORDERS THAT:

1. Order 1 of the orders of 15 March 2012 be dissolved.
2. The parties file agreed or competing proposed orders reflecting the reasons for judgment published today within 7 days.
3. The proceedings be listed on a date within a further 7 days thereafter, the date to be allocated in consultation with the parties.

Note: Entry of orders is dealt with in Rule 39.32 of the Federal Court Rules 2011.

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| IN THE FEDERAL COURT OF AUSTRALIA |  |
|  DISTRICT REGISTRY |  |
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| --- | --- |
| BETWEEN: | APOTEX PTY LTDApplicant/Cross Respondent |
| AND: | ASTRAZENECA ABFirst Respondent/Cross ClaimantASTRAZENECA PTY LIMITEDSecond Respondent/Cross-Claimant |

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| --- | --- |
| IN THE FEDERAL COURT OF AUSTRALIA |  |
|  DISTRICT REGISTRY |  |
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|  |  |
| --- | --- |
| BETWEEN: | WATSON PHARMA PTY LTDApplicant/Cross Respondent |
| AND: | ASTRAZENECA ABFirst Respondent/Cross ClaimantASTRAZENECA PTY LIMITEDSecond Respondent/Cross Claimant |

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| IN THE FEDERAL COURT OF AUSTRALIA |  |
|  DISTRICT REGISTRY |  |
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| --- | --- |
| BETWEEN: | ASTRAZENECA ABFirst Applicant/Cross RespondentASTRAZENECA PTY LIMITEDSecond Applicant/Cross Respondent |
| AND: | ASCENT PHARMA PTY LTD ACN 118 734 795Respondent/Cross Claimant |
| : |  |
| DATE: | 5 March 2013 |
| PLACE: |  |

**REASONS FOR JUDGMENT**

##### THE THREE PATENTS

These proceedings involve the construction, validity and, if valid, alleged infringement of three patents. AstraZeneca AB and AstraZeneca Pty Ltd (together referred to as **AZ**) are the registered proprietor and exclusive licensee of three Australian patents:

1. Australian Patent No. 200023051 entitled “Use of cholesterol-lowering agent”. This patent is known as the **051 patent** or **low dose patent** by the parties.
2. Australian Patent No. 2002214165 entitled “Use of rosuvastatin (ZD-4522) in the treatment of heterozygous familial hypercholesterolemia”. This patent is known as the **165 patent** or the **HeFH patent** by the parties (the shorthand for heterozygous familial hypercholesterolemia being **HeFH**).
3. Australian Patent No. 200051842 entitled “Pharmaceutical compositions”. This patent is known as the **842 patent** or **cation patent** by the parties.

Watson Pharma Pty Ltd and Ascent Pty Ltd (which had common representation in the proceedings and are referred to as **Watson** and **Ascent**) and Apotex Pty Ltd (**Apotex**) each wish to supply generic versions of rosuvastatin products. Watson, Ascent and Apotex are referred to as the generic parties where convenient to deal with them as a group. The generic parties each wish to supply pharmaceutical products in the form of tablets of 5 mg, 10 mg, 20 mg and 40 mg in which the active ingredient is rosuvastatin. The proposed supply of those products caused AZ to allege infringement of each of the three patents and the generic parties each to allege that the patents (or at least the claims on which AZ relied to assert infringement) were invalid and should be revoked.

Rosuvastatin is a compound which is used to treat hypercholesterolemia (high cholesterol). The three patents in issue relate to rosuvastatin but are not patents for the invention of the compound rosuvastatin. There is not and never has been a patent in Australia for the invention of the compound rosuvastatin.

Each of the generic parties is subject to interlocutory orders restraining them from infringing the patents. One feature of AZ’s submissions is detailed reference to the reasoning used to found the grant of the interlocutory relief. Given the different nature of an interim and final hearing I do not consider it necessary or appropriate to revisit the reasons for the grant of interlocutory relief in these reasons which concern the final resolution of all of the issues in dispute on the basis of the evidence admitted in the final hearing.

##### ABBREVIATED REFERENCES

In these reasons for judgment the following abbreviations are used:

**051 or low dose patent** means Australian Patent No 200023051 (769897) entitled “Use of cholesterol-lowering agent”.

**165 or HeFH patent** means Australian Patent No 2002214165 entitled “Use of rosuvastatin (ZD-4522) in the treatment of heterozygous familial hypercholesterolemia”.

**841 application** means the application for Australian Patent No. 200051841

**842 or cation patent** means Australian Patent No 200051842 (781269) entitled “Pharmaceutical compositions”.

**471 patent** means European Patent Application No 0521471.

**the Act** means the *Patents Act 1990* (Cth).

**FDA guidelines** means the FDA Guidelines for the clinical evaluation of lipid-altering agents in adults and children dated September 1990.

**FH** means familial hypercholesterolemia, a genetic disorder characterised by high cholesterol levels.

**HDL-C** means high density lipid cholesterol.

**HeFH** means heterozygous familial hypercholesterolemia, a form of FH.

**HMG-CoA reductase inhibitor** means a drug which inhibits the HMG-CoA reductase, thus lowering cholesterol.

**IUPAC** means International Union of Pure and Applied Chemistry.

**Japanese guidelines** means the Japanese Guidelines on Clinical Evaluation Methods for Antihyperlipidemia Drugs dated January 1988.

**Joshi article** means European Patent Application no. 89105625.1 entitled “Pharmaceutical compositions having good stability”.

**Kabadi article** means UK Patent Application no. 9225659.3 entitled “Stabilized Pharmaceutical Compositions Comprising an HMG-CoA Reductase Inhibitor Compound”.

**LDL-C** means means low density lipoprotein cholesterol.

**Mills article** means European Patent Specification EP 0680320 B1.

**Olsson article** means the article published by Olsson et al in the *European Heart Journal* 2000 (21) titled “ZD4552- a new HMG-CoA reductase inhibitor – causes rapid and profound reductions in plasma LDL-C levels in patients with primary hypercholesterolaemia”.

**Pears article** means the article published by Pears et al in the *Canadian Journal of Cardiology* 2000 (17) titled “Dose-ranging study of the HMG-CoA reductase inhibitor ZD4522 in patients with primary hypercholesterolemia”.

**SCRIP article** means the article published in SCRIP No 2573 on 8 September 2000 titled “Statin reverses FH athersclerosis”.

**Statin** means a drug used to lower cholesterol by inhibiting the enzyme HMG-CoA reductase.

**Stein article** means the article published by Stein et all in the *Journal of the American Medical Association* 1999 (281)2 titled “Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia”.

**TC** means total cholesterol.

**Watanabe article** means the article published by Watanabe et al in *Bioorganic & Medicinal Chemistry* 1997 (5)2 titled “Synthesis and biological activity of methansulfonamide pyrimidine- and N-methanesufonyl pyrrole-substituted 3,5-dihtyroxy-6-heptenoates, a novel series of HMG-CoA reductase inhibitors”.

##### OVERVIEW of the patents

###### The 051 or low dose patent

The 051 or low dose patent nominates Ali Raza as the inventor. The patent claims a priority date of 6 February 1999 based on the filing of UK Patent Application GB 9902590. There is a dispute about the inventor and AZ’s entitlement to the invention. The priority date is also in dispute.

The specification of the 051 or low dose patent describes the invention as follows:

USE OF CHOLESTEROL-LOWERING AGENT

The present invention relates to the use of a cholesterol-lowering agent, and more particularly to the administration of a particular dose or dosage range of the HMG CoA reductase inhibitor, [the formula for the compound rosuvastatin]… and pharmaceutically acceptable salts thereof, hereinafter referred to as “the Agent” and illustrated (as the calcium salt) in formula I hereinafter. The invention further relates to the dosage range, start dose and dosage forms of the Agent.

The Agent is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase) which is a major rate-limiting enzyme in cholesterol biosynthesis. The Agent is taught as useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. HMG-CoA reductase inhibitors are the most widely used prescription medication for the treatment of hypercholesterolaemia. A number of HMG-CoA reductase inhibitors are marketed, namely lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and cerivastatin, and are collectively referred to as ‘statins’. Despite the benefits of statin therapy, less than optimal results may be achieved in patients, due to the level of efficacy and safety achieved at the recommended dosages of the currently marketed statins. Accordingly it is important to find dosages of alternative statins which beneficially alter lipid levels to a significantly greater extent than similar dosages of currently used statins and which have a similar or improved safety profile.

Surprisingly it has now been found that when dosed orally to patients with hypercholesterolemia at particular dosages or in a particular dosage range the Agent lowers total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) by an unexpected degree, and without any significant adverse side effects. When dosed at the same dosages or in the same dosage range, the Agent also modifies other lipoprotein levels (such as raising high density lipid cholesterol (HDL-C) levels, lowering triglyceride (TG) levels and lowering apolipoprotein B-100 (Apo-B) levels) to an unexpected and beneficial extent, without any significant adverse side effects. Elevations of alanine aminotransferase (ALT) liver enzyme levels are reported for other HMG-CoA reductase inhibitors. Surprisingly it has now been found that when the Agent is dosed at the dosages or in the dosage ranges discussed herein, clinically significant rises in these levels are less frequently observed.

Accordingly, one aspect of the present invention comprises a method of lowering LDL-C levels by 40% or more, and/or lowering total cholesterol levels by 30% or more, and/or lowering triglyceride levels by 10% or more, and/or lowering apolipoprotein B-100 levels by 30% or more, and/or raising HDL-C levels by 5% or more, in a patient in need thereof, by administration of 5 to 80 mg per day of the Agent.

A further aspect of the present invention comprises a method of …

…

A particularly suitable starting dose of the Agent in the methods referred herein is 5 to 10 mg per day, especially 10 mg per day. After initiation and/or upon titration of the Agent, lipid levels may be analysed and the dosage adjusted accordingly. A further aspect of the invention is therefore a method as defined above when the Agent is administered at a starting dose of 5 or 10 mg per day, for example a method of lowering LDL-C levels in a patient in need thereof by 40% or more by administration of 5 or 10 mg per day …A starting dose of 5 or 10 mg per day of the Agent unexpectedly has a superior efficacy and a comparable or better safety profile compared to the starting doses of other statins, and is therefore particularly advantageous.

In carrying out the methods of the invention, the Agent will be administered to a patient in the form of a pharmaceutical composition. A further aspect of the invention is therefore a pharmaceutical composition which comprises 5 to 80 mg of the Agent together with a pharmaceutically acceptable excipient or diluent. Particular pharmaceutical compositions which themselves are further independent aspects of the invention comprise, for example, 5 mg, 10 mg, 20 mg, 40 mg and 80mg of the Agent together with a pharmaceutically acceptable excipient or diluent. The pharmaceutical compositions will be in the form of a conventional dosage unit form, for example, tablets or capsules. Accordingly, a further aspect of the invention comprises, a tablet or capsule containing the Agent in the amounts given above. The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Preferably the Agent is administered as a single dose once daily.

…

Pages 11A and 11B of the specification, amongst other things, found the argument in respect of the priority date. Extracts from those pages include the following:

In a further aspect of the invention there is provided a pharmaceutical composition adapted for oral administration as a single, once daily dose which comprises 5 mg to 10 mg of [the Agent]… in the form of the free acid or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

…

**Pharmaceutical compositions**

The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms which are suitable for use in the invention as defined herein:

…

The specification includes reference to trial including in these terms:

To illustrate the invention, a randomised, dose response parallel-group study with [the Agent] calcium salt (hereinafter referred to as ZD4522) and atorvastatin (ATORV) in subjects with primary hypercholesterolaemia was carried out.

**Primary objectives**

The primary objective of this trial was to estimate the dose-response relationship between the dose of ZD4522 and the percentage reduction of LDL-C from the baseline value with respect to placebo.

**Secondary objectives**

Secondary objectives of this trial included:

to estimate the effect of 10 and 80 mg doses of atorvastatin on LDL-C levels; to estimate the effects of ZD4522 and atorvastatin on HDL-C, TG, TC, apolipoprotein A-1, apolipoprotein Lp(a), apolipoprotein B-100 levels and LDL-C (by indirect method); to assess the pharmacokinetics of oral doses of 1, 2.5, 5, 10, 20, and 40 mg ZD4522 (capsule formulations) over a 6 week treatment period; and to assess the tolerability and safety of ZD4522 in comparison with placebo.

**Trial Design**

After a 6-week dietary run-in, subjects were randomised to either atorvastatin doses (10 or 80 mg), supplied open labelled, or to placebo or 1 of 6 ZD4522 doses (supplied blinded). Analysis of the blinded portion of the trial addressed the primary objective. The open atorvastatin groups were included to obtain additional data on the starting and high doses, of a proven cholesterol-lowering agent in this patient population.

**Trial Plan**

…

**Number of Subjects**

The primary endpoint on which the sample size is based is on percentage reduction from baseline in LDL-C (LDL cholesterol) values. A sample size of 9 in each group will have 90% power to detect a difference in means of 25% between 2 groups, assuming that the common standard deviation is 15%, using a 2 group t-test with a 0.05 two-sided significance level. This has been increased to 12 subjects per group to adjust for multiple comparisons of groups against placebo while preserving a power of at least 90% (based on simulations). This sample size also leads to an estimate of the dose-response curve for percentage decline in LDL-C with a width of the confidence band less than 10% for most of the dose range.

**Inclusion Criteria**

For inclusion in the dietary run-in period, subjects had to fulfil all of the following criteria:

(1) fasting LDL cholesterol (>4.14 but <6.21 mmol/L);

…

**Exclusion Criteria**

Any of the following was regarded as a criterion for exclusion from the trial:

(1) Subjects using cholesterol lowering drugs (this therapy must have been discontinued at least 4 weeks before the start of the dietary run-in period. Subjects taking probucol should have discontinued 12 months before inclusion in this study).

(2) History of serious or hypersensitivity reactions to other HMG-CoA reductase 30 inhibitors.

…

(7) Known homozygous familial hypercholesterolaemia or known type III hyperlipoproteinemia (familial dysbetalipoproteinaemia).

Page 21 of the specification contains the following paragraphs:

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

There are three claims, claim 1 of which is as follows:

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating a patient suffering from hypercholesterolemia which comprises administration as a starting dose of a single, once daily, oral dose of 5 to 10 mg of the compound … or a pharmaceutically acceptable salt thereof, in the form of a pharmaceutical composition.

Claim 2 is in these terms:

A method of treating a patient suffering from hypercholesterolemia which comprises administration of a single, once daily, oral dose of 5.2 to 10.4 mg of the calcium salt of the compound [rosuvastatin], in the form of a pharmaceutical composition.

Claim 3 is dependent on claims 1 and 2 and adds limitations relating to the LDL-C (low density lipoprotein cholesterol) levels and other conditions of the patient receiving the treatment. AZ alleges infringement of all of the claims of the 051 or low dose patent.

The issue of construction between the parties about the 051 or low dose patent is the reference to “starting dose” in claim 1.

In addition to the issues concerning the priority date and the inventor and thus entitlement of AZ to the patent, the validity of the 051 or low dose patent is challenged on numerous grounds under s 138(3) of the *Patents Act 1990* (Cth) (**the Act**) including that: - (i) the claimed invention is not novel, (ii) the claimed invention lacked any inventive step, (iii) the claimed invention does not involve a manner of manufacture, (iv) the claims are not fairly based on the matter described in the specification, (v) the claimed invention lacks utility, and (vi) the 051 or low dose patent was obtained on a false suggestion.

###### The 165 or HeFH patent

The 165 or HeFH patent nominates Ali Raza and Howard Hutchinson as the inventors. The 165 or HeFH patent claims a priority date of 22 November 2000. There is a dispute about the inventors and AZ’s entitlement to the invention but the priority date is not in dispute.

The specification of the 165 or HeFH patent describes the invention as follows:

**USE OF ROSUVASTATIN (ZD-4522) IN THE TREATMENT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA**

The present invention relates to a new use of a statin drug in the treatment of severe heterozygous familial hypercholesterolemia (HeFH) and in particular patients with baseline LDL-C>220mg/dL.

There is now a large body of evidence obtained from clinical trials demonstrating that pharmacological agents (particularly the statins) that reduce low density lipoprotein-cholesterol LDL-C levels also decrease Chronic Heart Disease (CHD) risk (Lipid Research Clinics Program 1984, Gould et al 1998). Taken together, the trials published to date support the concept that lowering LDL-C levels should be the principal goal of lipid altering therapy (Ansell et al 1999), and that the reduction in coronary risk that occurs during treatment with statins is directly related to these agents’ LDL-C lowering effects (Gould et al 1998, Pedersen et al 1998).

Primary hyperlipidemia is a term used to describe a defect in lipoprotein metabolism. The lipoproteins commonly affected are LDL-C, which transports mainly cholesterol, and VLDL-C, which transports mainly TG. Most subjects with hyperlipidemia have a defect in LDL metabolism, characterised by raised cholesterol, LDL-C, levels, with or without raised triglyceride levels; such subjects are termed hypercholesterolemic (Fredrickson Type II). Familial hypercholesterolemia (FH) is caused by any one of a number of genetically-determined defects in the LDL receptor, which is important for the entry of cholesterol into cells. The condition is characterised by a reduced number of functional LDL receptors, and is therefore associated with raised serum LDL-C levels due to an increase in LDL. In its heterozygous form (HeFH) it is one of the commonest genetic diseases, with a frequency of about 1 in 500 in the United Kingdom (US), the United States (US), and Japan (Myant 1981, Mabuchi et al 1979).

LDL and VLDL are known to be atherogenic, and thus subjects with hypercholesterolemia are at increased risk of developing atherosclerosis, a disease process that results in widespread clinical manifestations, including coronary heart disease (CHD), cerebrovascular disease (CVD) and peripheral vascular disease (PVD). In subjects with HeFH, the clinical manifestations of heart disease can occur as early as the mid-twenties. Many subjects with hypercholesterolemia die each year as a result, and many have a reduced quality of life; inevitably, this places very heavy demands on health service resources.

One important goal of therapy in these subjects is to reduce blood cholesterol levels, since this may reduce the progression of the disease and may even induce regression (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 1993).

Quoting the % of subjects brought within relevant guidelines (NCEP, EAS) targets for LDL-C levels is a useful way of expressing the efficacy of lipid-regulating agents, and is becoming more commonplace in the literature. The guidelines of the National Cholesterol Education Program (NCEP) and European Atherosclerosis Society (EAS) are well recognised and have been accepted internationally.

Therapies available to treat HeFH include resins, such as cholestyramine and colestipol. Resins reduce LDL-C levels by sequestering bile acids (essential for the absorption of dietary lipid) from the gut and preventing their reabsorption; however, their use is limited by unpalatability and poor subject compliance. Fibrates, such as fenobibrate and gemfibrozil, have a complex mechanism of action on LDL-C, and appear to be of more use in reducing blood TG levels than cholesterol levels; these drugs are therefore less useful in subjects with HeFH (who typically do not have significantly elevated triglyceride levels). Fibrate drugs are thought to act through peroxisomal proliferating activator receptor-ɑ (PPAR-ɑ) and affect gene activation at a number of genes involved in atheroma. Patients on fibrate drugs show improved LDL subfraction distribution (reduced VLDL and raised HDL), reduced LDL and reduced triglyceride levels and possible advantages through improving insulin sensitivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol. Nicotinic acid and its derivates have some benefit, but are limited by prostaglandin-mediated side effects, such as flushing and dizziness.

A breakthrough in treating hypercholesterolemia has come from agents known as statins. These drugs, which include atorvastatin, pravastatin and simvastatin, lower LDL-C levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate-limiting step in cholesterol biosynthesis in the liver. Partial inhibition of hepatic cholesterol metabolism is thought to result in an increase in the number of cellular receptors for LDL-C, leading to an increased removal of LDL-C from the circulation.

Despite the benefits of statin therapy less than optimal therapeutic results are achieved by the use of statins in patients suffering from HeFH. Typically the majority of patients suffering from HeFH are treated with at least a statin and a fibrate or a statin and a bile acid sequestrant or possibly all these in an aggressive attempt to reduce the patients LDL-C levels within acceptable guideline limits. Myopathy and rhabdomyolysis have been associated with taking a statin in combination with gemfibrozil and niacin (HMG CoA reductase inhibitors, Hunninghake, Current Opinion in Lipidology (19921) 3, 22-28) as they are all substrates for P450 3A4 and may lead to clinically significant drug interactions.

Therefore, currently there is no single drug treatment which may be used on its own which consistently brings a significant number of patients suffering from HeFH within NCEP or EAS guidelines.

…

We have discovered that [the formula for the compound rosuvastatin]… or a pharmaceutically acceptable salt thereof (hereinafter called ZD4522), the calcium salt of which is shown in Fig.1 below, is particularly good at treating heterozygous familial hypercholesterolemia, in particular severe heterozygous familial hypercholesterolemia (HeFH).

We have conducted a Phase III trial designed to assess the efficacy of ZD4522 in subjects with HeFH. The dose-response of ZD4522 was compared with atorvastatin using the percentage change from baseline in LDL-C levels as the primary end-point. Doses of ZD4522 up to 80 mg per day were used. Atorvastatin was chosen as the comparator statin in this trial because it has the best LDL-C lowering activity of the currently marketed statins.

A larger percentage of patients with heterozygous familial hypercholesterolemia are brought within NCEP or EAS guidelines with treatment of ZD4522 alone than with any other therapy, in particular in high risk patients.

ZD4522 is a statin that demonstrates potent *in vitro* and *in vivo* inhibition of HMG-CoA reductase. Early clinical trials have shown that ZD4522 has a beneficial effect on the lipid profile, by reducing LDL-C, total cholesterol (TC) and TG levels. In addition, ZD4522 has been shown to raise high-density lipoprotein cholesterol (HDL-C) levels.

By the use of the term heterozygous familial hypercholesterolemia we mean patients who have been diagnosed with this type of condition such as patients whose genotype has been determined to be indicative of HeFH. Particular HeFH patients who benefit from ZD4522 are those suffering from severe HeFH. By the use of the term “severe HeFH” we mean patients who are high risk category patients, as defined by the NCEP guidelines (as outlined in JAMA 1993; 269:3015-23 which guidelines and charts are incorporated herein by reference), such patients target LDL-C levels being lower, i.e. ≤100mg/dL.

For the purposes of clarity patients who suffer from homozygous familial hypercholesterolemia are excluded from the scope of this invention.

Therefore we present as a first feature of the invention a method for treating heterozygous familial hypercholesterolemia in a patient suffering heterozygous familial hypercholesterolemia, comprising administering to the patient ZD4522.

ZD4522 is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase). Preferably the calcium salt is used as illustrated in Figure 1. Preferably the ZD422 is used at a dose of 5 to 80 mg per day, in particular 40 to 80mg per day.

The pharmaceutical compositions of the present invention may be administered in a standard manner for example by oral or parenteral administration, using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred, for example as disclosed in International Patent Application, Publication No. WO 01/54668.

The dose of ZD4522 which can be administered in accordance with the present invention depends on several factors, for example the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen and the desired result. In the treatment of severe heterozygous familial hypercholesterolemia the maximum lipid lowering effect is desired and therefore a maximum dose of at least 40 mg a day is recommended, preferably 80 mg a day.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 100 mg of ZD4522. Preferably a unit dose formulation will contain 5 to 80 mg ZD4522.

The specification describes a trial in these terms:

A clinical protocol testing the effectiveness of ZD4522 in heterozygous familial hypercholesterolemia and results is set out below.

**A 24-week, Randomised, Double-blind, Multicentre, Multinational Trial**

**to Evaluate the Efficacy and Safety of**

**ZD4522 and Atorvastatin in the Treatment of**

**Subjects with Heterozygous Familial Hypercholesterolemia**

**OBJECTIVES**

The primary objective was to compare the efficacy of ZD4522 (titrated to 80 mg) with that of atorvastatin (titrated to 80 mg) in reducing low-density lipoprotein cholesterol (LDL-C) levels in subjects with heterozygous familial hypercholesterolemia (HeFH) after 18 weeks of treatment.

The secondary objectives were to compare the efficacy of ZD4522 with that of atorvastatin in relation to the following: reducing LDL-C levels after 2, 6 and 12 weeks of treatment; in modifying other lipids and lipoprotein fractions after 2, 6, 12, and 18 weeks of treatment; in reducing LDL-C levels to within relevant national and international guidelines after 6, 12, and 18 weeks of treatment; in modifying the inflammatory marker C-reactive protein (CRP) after 18 weeks of treatment. A further secondary objective was to determine the safety of ZD4522.

…

In the primary efficacy analysis (LOCF data from the ITT), ZD4522 20/40/80 mg resulted in a significantly (p<0.001) greater % reduction in LDL-C levels than did atorvastatin 20/40/80 mg at 18 weeks. The difference between treatments was >6%, the difference on which the trial was powered, and was therefore considered to be clinically relevant (mean % reduction in LDL-C was 57.88% in the ZD4522 20/40/80 mg group and 50.41% in the atorvastatin 20/40/80 mg group). ZD4522 resulted in significantly (p<0.001) and clinically greater % reduction in LDL-C at Week 2, 6 and 12. ZD4522 20/40/80 mg also resulted in significantly (p<0.001) greater % reductions in TC and significantly (p≤0.003) greater % increase in HDL-C than did atorvastatin 20/40/80 mg at all time points (observed data for Week 2, 6 and 12; observed and LOCF for Week 18). Both ZD4522 20/40/80 mg and atorvastatin 20/40/80 mg reduced TG levels at all time point, but the % reductions were similar in both treatment groups and the differences were not significantly different (p>0.050 at 2, 6 and 12 weeks for observed data and 18 weeks for LOCF). ZD4522 20/40/80 mg resulted in significantly (p<0.001) greater decreases in ApoB and increases in ApoA-I than did atorvastatin 20/40/80 mg at Week 18 (LOCF). In addition ZD4522 20/40/80 mg resulted in significantly (p<0.001) greater reductions in the LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C ratios at all time points.

…

**OVERALL CONCLUSIONS**

ZD4522 was significantly more effective than atorvastatin in improving the atherogenic lipid profile (LDL-C, HDL-C and TC); ZD4522 was also clinically superior to atorvastatin with respect to effect on LDL-C levels, the primary lipid of interest. ZD4522 resulted in more subjects achieving guideline targets for LDL-C than did atorvastatin, particularly with those at high-risk of cardiovascular disease. ZD4522 had a satisfactory safety profile, which was comparable to atorvastatin.

…

The claims of the 165 or HeFH patent include the following:

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for treating heterozygous familial hypercholesterolemia in a patient suffering heterozygous familial hypercholesterolemia, comprising administering to the patient [formula for rosuvastatin] or a pharmaceutically acceptable salt thereof.

2. A method as claimed in claim 1 wherein the patient is suffering from severe heterozygous familial hypercholesterolemia.

…

21. A method as claimed in any one of claims 1 to 5 wherein 20-40mg of …[the formula for rosuvastatin] is administered once a day to the patient in the form of the calcium salt.

Claims 3 to 10, which are not reproduced above, are dependent on claims 1 or 2. AZ alleges infringement of claims 1 to 10 and 21 of the 165 or HeFH patent.

There are no issues of construction about the 165 or HeFH patent. In addition to the issue concerning the inventors and thus the entitlement of AZ to the patent, the validity of the 165 or HeFH patent is challenged on the grounds of: - (i) lack of novelty, (ii) lack of inventive step, (iii) secret use, (iv) lack of a manner of manufacture, (v) the claims of the 165 or HeFH patent not being fairly based on the matter described in the specification, and (vi) the 165 or HeFH patent was obtained on a false suggestion.

###### The 842 or cation patent

The 842 or cation patent nominates Joseph Creekmore and Norman Wiggins as the inventors. The 842 or cation patent claims a priority date of 26 January 2000. The priority date is in dispute but there is no issue about the inventors and AZ’s entitlement to the invention (if it be an invention).

The specification of the 842 or cation patent describes the invention as follows:

**Pharmaceutical compositions**

…

The present invention relates to pharmaceutical compositions and more particularly to a pharmaceutical composition containing … or a pharmaceutically-acceptable salt thereof (and referred to hereinafter as “the Agent”). In particular the sodium and calcium salts, and especially the calcium salt … (shown as Formula I below).

The Agent is disclosed as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase) in European Patent Application, Publication No. 0521471 and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 and is useful in the treatment of hypercholesterolemia, hyperlipidproteinemia and atherosclerosis.

The problem associated with the Agent is that it is particularly sensitive to degradation under certain conditions. The major degradation products formed are the corresponding (3R, 5S) lactone (hereinafter referred to as “the lactone”) and an oxidation product (hereinafter referred to as “B2”) in which the hydroxy group adjacent to the carbon-carbon double bond is oxidised to a ketone functionality. The potential for significant degradation of the Agent makes it difficult to formulate and provide a pharmaceutical composition with acceptable storage life for a marketed product.

Pharmaceutical formulations of certain 7-substituted-3,5-dihydroxy-6-heptenoic acid salts, which are HMG CoA reductase inhibitors, are disclosed in UK Patent 2 262 229, and that they are sensitive to pH degradation. These formulations require the presence of an alkaline medium (such as a carbonate or bicarbonate) capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition.

However, we have found that for the Agent it is not sufficient to improve stability by solely controlling pH in the formulation. We have found that with the Agent stability is improved by selection of an inorganic salt to be added to the composition which contains one or more multivalent inorganic cations. Whilst not wishing to be bound by theory we believe that the multivalent inorganic cation stabilises the structure of the Agent and makes it less susceptible to oxidation and/or lactonization.

We present as aspects of the invention

(1) A pharmaceutical composition comprising the Agent or a pharmaceutically acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent, provided that: the inorganic salt is not hydrotalcite or synthetic hydrotalcite and the counter anion to the inorganic salt is not a phosphate.

(2) The use of an inorganic salt in which the cation is multivalent to stabilise the Agent or a pharmaceutically acceptable salt thereof, provided that: the inorganic salt is not hydrotalcite or synthetic hydrotalcite and the counter anion to the inorganic salt is not a phosphate.

Preferred features of the invention are:

(1) wherein the Agent is present in the composition is more than 5 mg, preferably more than 10mg. Excluded compositions are those wherein the Agent is present at 1mg, 2mg, 5mg and 10mg. Preferred compositions are those where the amount of Agent is 20mg, 40mg or 80mg.

(2) wherein the stabilising compound is not hydrotalcite or synthetic hydrotalcite.

(3) the pharmaceutical composition formed is a tablet or powder.

Preferably the pharmaceutical composition of the invention is a tablet.

The multivalent cation found in the inorganic salt may be selected from the following, calcium, magnesium, zinc, aluminium and iron or a mixture thereof. Preferred multivalent cations are calcium, aluminium and magnesium or a mixture thereof. Especially preferred multivalent cations are aluminium and magnesium or a mixture thereof.

The counter anion in the inorganic salt may be selected from a phosphate, a carbonate, a silicate, an oxide and a metasilicate. Preferred counter anions are selected from a carbonate, a silicate, an oxide or a metasilicate. Especially preferred counter anions are selected from a silicate, an oxide or a metasilicate.

Individual aspects of the invention include an inorganic salt comprising a multivalent cation selected from any of the above and a counter anion also selected from any of the above.

Preferred inorganic salts for use in the present invention are; aluminium magnesium metasilicate (NeusolinTM, Fuji Chemical Industry Limited), dibasic or tribasic calcium phosphate, tribasic magnesium phosphate and tribasic aluminium phosphate. Aluminium magnesium metasilicate and tribasic calcium phosphate are especially preferred.

It is also preferable that such a composition has a good flow rate to assist processing into unit dosage forms for oral administration, for example into tablets, and good disintegration and dissolution characteristics when processed into tablets for oral administration, which tablets can be in different dosage strengths.

The ratio of inorganic salt to Agent in the pharmaceutical composition is, for example, within the range of 1:80 to 50:1 by weight, for example 1:50 to 50:1 by weight, such as 1:10 to 10:1 by weight, and more particularly 1:5 to 10:1 by weight.

Preferably the pharmaceutical composition of the invention is formulated into an oral dosage form, such as a tablet. Accordingly a further aspect of the invention comprises a pharmaceutical composition comprising the Agent, an inorganic salt in which the cation is multivalent, and one or more fillers, binders, disintegrants or lubricants. A still further aspect of the invention relates to a pharmaceutical composition for oral administration comprising the Agent, one or more fillers, one or more binders, one or more disintegrants, one or more lubricants and an inorganic salt in which the cation is multivalent.

…

According to the specification:

The pharmaceutical composition of the invention may be prepared, using standard techniques and manufacturing processes generally known in the art, for example by dry blending the components. For example, the Agent and an inorganic salt in which the cation is multivalent, one or more fillers, one or more binders and one or more disintegrants, as well as other additional excipients if desired are blended together. The components of the blend prior to blending, or the blend itself, may be passed through a mesh screen, for example a 400-700 ųm mesh screen. A lubricant, which may also be screened, is then added to the blend and blending continued until a homogeneous mixture is obtained. The mixture is then compressed into tablets. Alternatively, a wet granulation technique can be employed. For example, the Agent and an inorganic salt in which the cation is multivalent, one or more fillers, one or more binders and a portion of a disintegrant, as well as other additional excipients if desired, are blended together, for example by using a granulator, and the powder blend is granulated with a small volume of purified water. The granulate is dried and passed though a mill. The remainder of the disintegrant and a lubricant are added to the milled granulation and after blending the resultant homogeneous mixture is compressed into tablets. It will be appreciated that modifications of the dry blending and wet granulation techniques, including the order of addition of the components and their screening and blending prior to compression into tablets, may be carried out according to principles well known in the art.

A tablet coating may then be applied, for example by spray-coating with a water-based film coating formulation. The coating may comprise, for example, lactose, hydroxypropyl methylcellulose, triacetin, titanium dioxide and ferric oxides. Coating ingredient combinations are commercially available, such as those described in the Examples hereinafter. The coating may comprise, for example, 0.5 to 10% by weight of the tablet composition, particularly 1 to 6%, and preferably 2 to 3%. Coatings containing ferric oxides are especially preferred as they reduce the rate of formation of photodegradation products of the Agent.

Accordingly we present as a feature of the invention a pharmaceutical composition comprising the Agent, the composition having a ferric oxide light protective coating.

A further aspect of the present invention comprises a method of preparing a stabilised pharmaceutical composition which comprises admixing the Agent with an inorganic salt in which the cation is multivalent. A further aspect of the present invention comprises a method of producing a stabilised pharmaceutical composition which comprises incorporating a inorganic salt in which the cation is multivalent in a pharmaceutical composition containing the Agent.

Four examples are then given in these terms:

**Example 1**

|  |  |
| --- | --- |
| The Agent | 2.50 mg |
| Tribasic calcium phosphate | 20.0 mg |
| Microcrystalline cellulose | 47.0 mg |
| Lactose monohydrate | 47.0 mg |
| Sodium starch glycollate | 3.00 mg |
| Butylated hydroxytoluene | 0.05 mg |
| Magnesium stearate | 1.00 mg |

The Agent, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, tribasic calcium phosphate, and butylated hydroxytoluene were blended together for 10 minutes. Magnesium sterate was screened through a #40 mesh (425 µm) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

The tablets were stored at 70ºC/80% relative humidity for one week. After one week there was found to be only 0.11%w/w of the oxidation product B2 formed and only 0.50%w/w of the lactone.

**Example 2**

|  |  |
| --- | --- |
| The Agent | 2.50 mg |
| Povidone | 2.50 mg |
| Tribasic calcium phosphate | 20.0 mg |
| Microcrystalline cellulose | 47.0 mg |
| Mannitol | 47.0 mg |
| Sodium starch glycollate | 3.00 mg |
| Butylated hydroxytoluene | 0.05 mg |
| Magnesium stearate | 1.00 mg |

The Agent, povidone, mannitol, microcrystalline cellulose, butylated hydroxytoluene, tribasic calcium phosphate and sodium starch glycollate (in the amounts given below) were blended for 5 to 60 minutes. Magnesium stearate was screened through a #40 mesh (425 µm) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of hydroxpropyl methylcellulose, polyethylene glycol 400, titanium dioxide and ferric oxide (sold as Spectrablend™ by Warner-Jenkinson)) and water in a coating pan. The weight gain provided by the coating was 1 to 6%w/w, and preferably 2 to 3%w/w.

The tablets were stored at 70ºC/80% relative humidity for one week. After one week there was found to be only 0.06%w/w of the oxidation product B2 formed and only 2.22%w/w of the lactone.

**Example 3**

|  |  |
| --- | --- |
| The Agent | 2.60 mg |
| Crospovidone | 3.75 mg |
| Tribasic calcium phosphate | 5.66 mg |
| Microcrystalline cellulose | 15.5 mg |
| Lactose monohydrate | 46.5 mg |
| Magnesium stearate | 0.94 mg |

The Agent and crospovidone were blended together for 5 minutes and the blend then passed through a 400-700µm screen. A small portion of the microcrystalline cellulose was passed through the screen afterwards. The screened material was blended with the other ingredients, excluding the lubricant, for 10 minutes. Magnesium stearate was passed through a #40mesh (425 µm) screen and added to the blend and the mixture was blended for a further 3 minutes. The resulting homogeneous mixture was compressed into tablets. The compressed tablets were coated by spraying with a mixture of lactose monohydrate, hydroxypropyl methylcellulose, triacetin and ferric oxide (sold as Opadry II™ by Colorcon) and water in a coating pan. The weight gain provided by the coating is 1 to 6%w/w, and preferably 2 to 3%w/w.

The tablets were stored at 70º/80% relative humidity for one week. After this time only 0.19%w/w of the oxidation product B2 had formed and only 2.71%w/w of the lactone.

**Example 4**

|  |  |
| --- | --- |
| The Agent | 2.50 mg |
| Povidone | 2.50 mg |
| Tribasic calcium phosphate | 20.0 mg |
| Microcrystalline cellulose | 34.5 mg |
| Lactose monohydrate | 34.0 mg |
| Sodium starch glycollate | 6.00 mg |
| Magnesium stearate | 1.00 mg |
| Butylated hydroxytoluene | 0.05 mg |

A portion of the tribasic calcium phosphate and butylated hydroxytoluene were blended for 30 seconds in a bag. The Agent, povidone, remainder of the tribasic calcium phosphate, microcrystalline cellulose, lactose monohydrate, tribasic calcium phosphate, microcrystalline cellulose, lactose monohydrate, tribasic calcium phosphate/butylated hydroxytoluene mixture and a portion of the sodium starch glycolate were blended in a granulator for 30 seconds. The powder blend was granulated with purified water for 1 minute at the addition rate of 70 mg/tablet/minute. The granulation is dried in a fluidized bed drier at 50ºC until the loss on drying is less than 2% w/w. The dried granulation is passed through a mill (e.g. Comil™). The milled granulation and the remainder of the sodium starch glycolate was blended for approximately 5 minutes. Magnesium stearate was screened through a #40 mesh (425 µm) screen and added to the blend and blending continued for a further three minutes. The resulting homogeneous mixture was compressed into tablets.

The tablets were stored at 70ºC/80% relative humidity for one week. After this time only 0.23% w/w of the oxidation product B2 had formed and only 0.28%w/w of the lactone.

…

Page 10 of the specification contains the following statement:

Throughout this specification and the claims which follow, unless the context required otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

The claims include the following:

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical composition comprising … or a pharmaceutically acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent, provided that:

(i) the inorganic salt is not hydrotalcite or synthetic hydrotalcite; and

(ii) the counter anion to the inorganic salt is not a phosphate.

2. A pharmaceutical tablet comprising … or a pharmaceutically acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent, provided that the counter anion to the inorganic salt is not a phosphate.

3. A pharmaceutical composition according to claim 1 or claim 2 wherein the cation of the inorganic salt is selected from calcium, magnesium, zinc, aluminium and iron.

4. A pharmaceutical composition according to any one of claims 1 to 3 wherein the counter anion of the inorganic salt is selected from a carbonate, a silicate, an oxide and a metasilicate.

5. A pharmaceutical composition according to any one of claims 1 to 3 wherein the counter anion of the inorganic salt is selected from a silicate, an oxide or a metasilicate.

6. A pharmaceutical composition according to claim 1 or claim 2 wherein the inorganic salt is aluminium magnesium metasilicate.

7. A pharmaceutical composition according to claim 1 which is a tablet or powder.

Claim 8 is dependent on claims 1 or 2. Claim 9 is dependent on any of claims 1 to 8. Claims 10 to 18 inclusive are also dependent claims.

There are two main issues of construction about the 842 or cation patent, being the meaning of “pharmaceutical composition” and of “inorganic salt” as each appears in the claims. In addition to the issues concerning the priority date, the validity of the 842 or cation patent is challenged on the grounds of: - (i) lack of novelty, (ii) lack of inventive step, (iii) lack of a manner of manufacture, (iv) lack of utility, (v) secret use, (vi) the claims of the 842 or cation patent not being fairly based on the matter described in the specification, (vii) the 842 or cation patent was obtained on a false suggestion, (viii) lack of clarity, and (ix) failure of the specification to include the best method known to the applicant of performing the invention.

###### Relevant version of s 7 of Patents Act

Because the complete application for each patent was made before the day on which the amendments to s 7 of the Act by the *Patents Amendment Act 2001* (Cth) commenced (being 1 April 2002) the version of s 7 which applies is that which existed before these amendments. Section 7, as it applies to the three patents in issue, provides as follows:

(1) For the purposes of this Act, an invention is to be taken to be novel when compared with the prior art base unless it is not novel in the light of any one of the following kinds of information, each of which must be considered separately:

(a) prior art information (other than that mentioned in paragraph (c)) made publicly available in a single document or through doing a single act;

(b) prior art information (other than that mentioned in paragraph (c)) made publicly available in 2 or more related documents, or through doing 2 or more related acts, if the relationship between the documents or acts is such that a person skilled in the relevant art in the patent area would treat them as a single source of that information;

(c) prior art information contained in a single specification of the kind mentioned in subparagraph (b)(ii) of the definition of prior art base in Schedule 1.

(2) For the purposes of this Act, an invention is to be taken to involve an inventive step when compared with the prior art base unless the invention would have been obvious to a person skilled in the relevant art in the light of the common general knowledge as it existed in the patent area before the priority date of the relevant claim, whether that knowledge is considered separately or together with either of the kinds of information mentioned in subsection (3), each of which must be considered separately.

(3) For the purposes of subsection (2), the kinds of information are:

(a) prior art information made publicly available in a single document or through doing a single act; and

(b) prior art information made publicly available in 2 or more related documents, or through doing 2 or more related acts, if the relationship between the documents or acts is such that a person skilled in the relevant art in the patent area would treat them as a single source of that information;

being information that the skilled person mentioned in subsection (2) could, before the priority date of the relevant claim, be reasonably expected to have ascertained, understood and regarded as relevant to work in the relevant art in the patent area.

##### OVERVIEW OF WITNESS EVIDENCE

###### AstraZeneca executives

Mike Bull

Mike Bull is the Director of Primary Care at AZ in Australia. Mr Bull gave evidence on a range of topics, including the importation and sale in Australia of Crestor by AZ, the use of private prescriptions in Australia and the marketing of Crestor in Australia.

Charles Waterfield

Charles Waterfield is the Director of Market Access and External Affairs at AZ. He gave evidence on the regulatory, pricing and reimbursement regimes that apply to the supply of pharmaceutical products in Australia, including the operation of the Australian Register of Therapeutic Goods and the Australian Pharmaceutical Benefits Scheme and prescriptions of Crestor in Australia including for patients with HeFH.

###### Data providers

John Frost

John Frost is the Chief Executive Officer of Health Communication Network Ltd (HCN). HCN compiles electronic health record data. Mr Frost explained HCN’s procedures and data supplied by HCN to AZ relating to the incidence of general practitioners allowing generic substitution of prescribed medicines.

Atul Muchhala

Atul Muchhala is the Director, Strategic Partners Australia and New Zealand at IMS Health. IMS Health provides information in relation to the pharmaceutical industry in Australia and overseas. Mr Muchhala provides an overview of the processes utilised by IMS to create and maintain datasets, some of which are purchased by AZ.

Ben Ramsey

Ben Ramsey is the Director of Finance, Australia and New Zealand at IMS Health. In his evidence Mr Ramsey elaborates on certain aspects of Mr Muchhala’s evidence with respect to IMS’s data processing procedures.

###### Patent attorneys

Rodney Cruise

Rodney Cruise holds a Bachelor of Science degree in Applied Chemistry and qualified as an Australian and New Zealand Patent and Trade Mark Attorney in 1995. Mr Cruise’s evidence concerned patent and non-patent literature searches of databases available prior to 2000.

Nicole Watling

Nicole Watling obtained a Doctorate of Philosophy in Organic Chemistry from the University of Western Australia in 2001 and was registered as a patent attorney in Australia and New Zealand in 2005. She has worked at Freehills Patent Attorneys as a registered patent attorney and senior associate for 11 years. Dr Watling’s evidence primarily dealt with the history of the 842 patent and its amendments and the 051 patent.

###### Tablet splitting

AZ adduced evidence of the purchase of tablet splitting devices from several pharmacies in the following locations:

* Mt Hawthorn ChemMart, Mt Hawthorn, Western Australia [Leon Firios 18/7/12]
* PharmaSave Maylands Compounding Pharmacy, Maylands, Western Australia [Leon Firios 18/7/12]
* TerryWhite Chemist, Westfield Bondi Junction, New South Wales [Siobhan Murphy 17/7/12]
* PharmaSave Bob’s Chemist, Newtown, New South Wales [Siobhan Murphy 17/7/12]
* PharmaSave Melbourne City Pharmacy, Melbourne, Victoria [Claire Roberts 17/7/12]
* TerryWhite Chemist, Clarendon Centre, South Melbourne, Victoria [Claire Roberts 17/7/12]
* PharmaSave Patrick’s Road Pharmacy, Ferny Hills, Queensland [Katherine Skene 18/7/2012]
* Ashgrove West ChemMart, Ashrove, Queensland [Katherine Skene 18/7/2012]

The tablet splitting devices were in evidence. One, purchased from PharmaSave Melbourne City Pharmacy, states on its packaging that it is “ideal for when half or quarter doses are required”.

###### Pharmacist

Divesh Sanghvi

Divesh Sanghvi is a registered pharmacist. His evidence primarily covered the regulatory scheme governing pharmacy practice in Australia, including dispensing prescription medicines, tablet splitting, and product information leaflets.

###### Medical practitioners

Peter Hay

Peter Hay is a general medical practitioner at Castle Hill Medical Centre. He completed a Bachelor of Medicine and Bachelor of Surgery degree in 1980 and became a fellow of the Royal Australian College of General Practitioners in 1989. Dr Hay has worked as a general practitioner since 1984. His research interests include cardiovascular disease, diabetes and influenza. He has been involved in carrying out influenza research and was also involved with a study concerning atorvastatin and the management of cholesterol at the Royal North Shore Hospital.

Dr Hay gave evidence mainly relating to his practice as a GP and his prescription practices, including tablet splitting and the prescription of statins.

Andrew Wilson

Professor Wilson is a cardiologist and Associate Professor at St Vincent’s Hospital in Fitzroy, Victoria. He obtained a Bachelor of Medicine and a Bachelor of Surgery degree with first class honours in 1993. Professor Wilson has worked at St Vincent’s Hospital since the completion of his internship there in 1994, eventually working in the position of cardiology registrar from 1999 to 2000. He obtained specialist qualifications in cardiology in 2002 when he became a Fellow of the Royal Australasian College of Physicians. From 2002 to 2005 he was employed as a cardiologist and physician at St Vincent’s Hospital and also acted as consultant to the University of Melbourne Lipid and Cardiovascular Risk Reduction Clinic at St Vincent’s Hospital. Professor Wilson completed a PhD at the University of Melbourne in 2005 on the relationship between obesity, inflammation and insulin resistance. Professor Wilson completed a fellowship as an Interventional Cardiology Fellow in the Cardiovascular Medicine Division at Stanford University Medical Center in the United States in 2006 and a fellowship as a Post Doctoral Research Fellow at the Falk Cardiovascular Institute at Stanford University in 2007. Since returning to Australia in 2007 Professor Wilson has held the positions of cardiologist as St Vincent’s Hospital and Director of the LCR Clinic at the University of Melbourne.

Professor Wilson has a special interest in the vascular and endothelial biology of atherosclerosis and the prevention of atherosclerosis. He was involved in establishing the Translational Cardiovascular Biology Laboratory at the University of Melbourne, Department of Medicine in 2007. Professor Wilson conducts cell-based research in relation to the role of fat cells in diabetes and heart disease. He has also been involved in a number of clinical trials, generally at a pre-clinical stage or at Phase III or IV. Professor Wilson has authored or co-authored over 50 peer-reviewed manuscripts in leading journals in the areas of cardiology and atherosclerosis and has presented at many international scientific meetings and symposiums.

Professor Wilson’s evidence dealt primarily with his prescription practices and tablet splitting (both generally and in the context of statins), his experience in treating and prescribing medications for patients suffering from HeFH and clinical trials.

Richard O’Brien

Professor O’Brien obtained a Bachelor of Medicine/Bachelor of Surgery in 1981. He became a member of the Fellowship of the Royal Australasian College of Physicians in 1988 and completed a PhD in 1992 in the area of diabetic nephropathy. In 2009 he obtained a Graduate Certificate in Health Professional Education. Professor O’Brien was employed at Austin Hospital from 1982 to 1992, eventually becoming Honorary Endocrinologist. From 1992 to 2001 he was Head of Diabetes section at Monash Medical Centre. He was also Director, Special Medicine, Renal and Vascular Program, Southern Health from 1998 to 2000. From 2001 to 2004 Professor O’Brien was Director of Diabetes at Monash Medical Centre and went on to be Director of Lipid Services and Deputy Director of Diabetes at Southern Health from 2005 to 2007.

Professor O’Brien is currently Clinical Dean at the Austin Clinical School of the University of Melbourne and Associate Professor, Faculty of Medicine at the University of Melbourne, both positions he has held since 2007. He is also Senior Endocrinologist (since 2007) and Director of Lipid Services (since 2009) at the Austin Hospital, where he specialises in the management of cardiovascular risk, lipid disorders, general endocrinology and diabetes. Since 2004 Professor O’Brien has held the position of Visiting Scientist at the Baker Heart Research Institute. Professor O’Brien is also currently Chair of the Lipid Management in Diabetes Guidelines Committee of the National Health and Medical Research Council (since early 2010) and a Council Member of the Asia Pacific Society of Atherosclerosis and Vascular Diseases (since 2008). Professor O’Brien has written approximately 60 peer-reviewed articles in scholarly journals. A number of these articles have concerned statins, in particular simvastatin and atorvastatin. Professor O’Brien has also been involved in a number of clinical trials involving statins, including trials prior to 2000 involving a number of studies on simvastatin and atorvastatin.

Professor O’Brien gave evidence on a range of topics including the clinical trial process, hypercholesterolaemia and HeFH, statins (including their use in the treatment of hypercholesterolaemia), and the low dose and HeFH patents.

David Colquhoun

Dr Colquhoun obtained a Bachelor of Medicine/Bachelor of Surgery degree in 1976. In 1977 he completed an internship at St Vincent’s Hospital in Sydney and went on to become a resident at the Fairfield District Hospital and Lidcombe Hospital in Sydney, holding the position of Medical Registrar at Lidcombe Hospital from 1979 to 1980. He then worked at the Royal Prince Alfred Hospital, first as a Cardiology Registrar (1981-1982) and then as a Research Fellow (1983-1984). In 1984 Dr Colquhoun became a Fellow of the Royal Australian College of Physicians. In that year he also became a clinical tutor at the University of Queensland before becoming a clinical senior lecturer in medicine in 1993 and an Associate Professor in 1994, a position he still holds.

In 1986 Dr Colquhoun set up private rooms at the Wesley Medical Centre as a Consultant Cardiologist and continues to hold this position. He has also held the position of Consultant Cardiologist at the Repatriation Hospital in Brisbane (renamed the Greenslopes Private Hospital in 1995) since 1981. Since 1985 he has been actively involved in clinical trials, with particular interest in lipids and dietary management and the role of psychological factors in coronary heart disease. In 2004 he became a Fellow of the Cardiac Society of Australia and New Zealand.

Dr Colquhoun is currently Chairman of the National Heart Foundation stress working group. Dr Colquhoun has also been a reviewer and assessor for medical publications since 1987 and is currently an assessor for several medical journals. He has been a member of many advisory committees since 1998, including the lipid advisory committees of pharmaceutical companies including AZ, Pfizer, Merck Sharp & Dohme and Bristol-Myers Squibb. He was also a member of the Queensland Government committee on the prevention of heart disease in 2009.

Dr Colquhoun’s evidence primarily dealt with his involvement as an investigator in a clinical trial of the use of rosuvastatin to treat HeFH conducted between July 1999 and June 2000.

Andrew Tonkin

Professor Tonkin completed a Bachelor of Medicine/Bachelor of Surgery in 1967 and a Doctor of Medicine in 1975. Following his graduation in 1967 he worked at the Royal Melbourne Hospital, moving to Sydney in 1972 to take up the position of Cardiology Registrar at the Royal Prince Alfred Hospital. In late 1973 he moved to the United States where he worked as a Cardiology Fellow at the Duke University Medical Centre in Durham, North Carolina and then as Research Associate between 1974 and 1975, while also working as visiting physician at Watts Hospital in Durham. In 1975 Professor Tonkin became a Fellow of the Royal Australasian College of Physicians.

Between 1975 and 1976 Professor Tonkin was employed as a Research Associate of the German Heart Centre in Munich, returning to Australia in 1976 to work at Flinders Medical Centre in South Australia as a Senior Specialist in Cardiovascular Medicine. In 1977 he became the Director of Coronary Care at Flinders Medical Centre, a position he held until 1981 when he was appointed the permanent Head and Senior Director of Cardiology. Professor Tonkin was also Senior Visiting Cardiologist at the Repatriation General Hospital in South Australia between 1976 and 1988 and Senior Consultant Specialist at the Royal Adelaide Hospital between 1980 and 1988. Between 1976 and 1988 Professor Tonkin held honorary appointments with Flinders University, including Senior Lecturer and Associate Professor of Medicine.

In 1988 Professor Tonkin took up the position of Director of Cardiology at the Austin Hospital in Melbourne and Visiting Specialist Cardiologist at the Repatriation General Hospital, Heidelberg. Professor Tonkin subsequently became Director of Cardiology of the Austin and Repatriation Medical Centre in January 1996 when the two hospitals were amalgamated. During this time Professor Tonkin was appointed a Professorial Fellow of the University of Melbourne responsible for coordinating cardiology components of both undergraduate and postgraduate teaching.

In May 1997 Professor Tonkin became Director of Health, Medical and Scientific Affairs of the National Heart Foundation of Australia, a position he held until 2006. In July 2012, having been a Sessional Consultant Cardiologist since May 1997, Professor Tonkin was made Honourary Consultant Cardiologist with Austin Health in Victoria. Since 2004 Professor Tonkin has been the Head of the Cardiovascular Research Unit within the Department of Epidemiology and Preventive Medicine at Monash University. He is also currently Adjunct Professor in the Department of Medicine at Flinders University.

Professor Tonkin has been involved in clinical research since 1973 and his major research interests include cardiac electrophysiology, randomised controlled clinical trials, epidemiology, health inequalities and translational research. As part of his research activities Professor Tonkin has been a member of the Steering Committees of major multicentre trials of lipid-modifying therapy and has also been Chairman of a number of Australian Expert Committees on cardiovascular disease and health. Professor Tonkin has also published over 348 articles, editorials and book chapters concerned primarily with various aspects of cardiovascular disease.

Professor Tonkin’s evidence dealt with a range of topics, including the treatment of hypercholesterolaemia prior to November 2000, the clinical trials process, tablet splitting and the HeFH.

###### Pharmaceutical formulators and pharmacologists

William Charman

Professor Charman obtained a Bachelor of Pharmacy in 1981 and a PhD in pharmaceutical chemistry in 1985. He also received a Doctor of Science degree in 2011. He is currently the Dean, Faculty of Pharmacy and Pharmaceutical Sciences, and Director, Monash Institute of Pharmaceutical Science at Monash University in Melbourne. He has been a Sir John Monash Distinguished Professor since 2011.

Professor Charman describes his research as characterised by a multidisciplinary and collaborative approach to address major issues in drug discovery, drug delivery and the pharmaceutical sciences. Professor Charman has published over 350 scientific papers dealing with drug discovery, drug delivery, pharmaceutical formulation design and drug development, and he has also given over 170 invited national and international presentations. He is a member of four international editorial boards and was previously an Associate Editor of the Journal of Pharmaceutical Sciences.

Professor Charman has received several academic awards and was elected a Fellow of the American Association of Pharmaceutical Scientists in 2002. Professor Charman was Chairman of the Wellcome Trust Seeding Drug Discovery Funding Committee from 2006 to 2010. Other key external appointments include being a member of the Expert Scientific Advisory Committee of the Medicines for Malaria Venture (2005-2011), an advisor to the World Health Organisation, a co-founder of Acrux Limited and a member of various scientific advisory boards.

Professor Charman gave evidence about pharmaceutical formulations and chemistry relevant to the issues in dispute.

Angelo Morella

Dr Morella obtained a Bachelor of Science degree with Honours in organic chemistry in 1979. In 1985 he completed a PhD focusing on the synthesis of molecules. In 1985 Dr Morella commenced work as a chemist at Faulding Pharmaceuticals Pty Ltd (Faulding), becoming an analytical scientist later that year. In 1986 he became a Development Scientist in Faulding’s Pellet Production Development Group. Dr Morella remained at Faulding until 2000 in various roles, eventually becoming Product Development Manager in 1999. In these roles Dr Morella was responsible for managing and actively participating as a formulator in Faulding’s research efforts into the development of pharmaceutical products, from initial concepts through to commercial products. Dr Morella assisted in developing a number of tablet and capsule dosage forms and worked on several major formulation projects. Dr Morella was appointed Formulation Development Manager at Faulding in 2001 and Innovation Manager in 2003, eventually becoming General Manager – Research and Development in 2011. Dr Morella retired from Faulding in March 2012 and since then has worked as a self-employed consultant to the pharmaceutical industry.

Dr Morella’s evidence included an overview of the drug development process, formulating new or improved therapies with reference to dosage form and design, identifying formulation issues and other questions of chemistry relevant to the issues in dispute.

Allan Evans

Professor Evans obtained a Bachelor of Pharmacy in 1982. From 1983 to 1984 he worked as a pharmacist in Adelaide. Between 1985 and 1989 he completed a PhD. His research investigated the pharmacokinetics of enantiomers of ibuprofen. From 1989 to 1991 Professor Evans lived in the United Kingdom where he worked as a post-doctoral research associate at the University of Manchester in the School of Pharmacy and Pharmaceutical Sciences. He returned to Australia in 1991 and briefly worked as a research associate at the Department of Clinical & Experimental Pharmacology at the University of Adelaide before joining the School of Pharmacy and Medical Sciences at the University of South Australia as a lecturer in August 1992. He became Senior Lecturer in January 1995 and Associate Professor in January 2000, before being promoted to Professor of Pharmaceutics in January 2003 and then Head of School in September 2004. In August 2009 Professor Evans was appointed Pro Vice Chancellor and Vice-President of the Division of Health Sciences of the University of South Australia, a position he still holds. Professor Evans has responsibility for the teaching, research, human resources, financial and engagement activity of all health science activity at the University, and has lectured in pharmokinetics, biopharmaceutics, clinical pharmacology and pharmacy practice.

Professor Evans was also a faculty member of the Adelaide Pharmacology Group Drug Disposition Workshop faculty from 1992 to 2001, which ran seminars for Australian members of the pharmaceutical industry focusing on drug development. Between 1993 and 1995 he worked as a consultant for Faulding in relation to new drug delivery systems and formulations and worked extensively with Gebro Pharma GmBH from 1994 until 2009. Between 2001 and 2004 Professor Evans was Director of the Centre for Pharmaceutical Research at the University of South Australia, which performed research services for the University including preclinical and Phase I research.

Professor Evans’ evidence concerned the drug discovery and development process, clinical trials, the process followed by a pharmaceutical company developing a new product, the development of a new therapy for the treatment of hypercholesterolaemia and the process he would use to find dosages of a new statin.

Richard Oppenheim

Dr Oppenheim completed a Bachelor of Science degree in 1964. He obtained a PhD in 1970 on the topic of the surface chemistry of oxide minerals. In 1974 he completed a Diploma of Education (Tertiary). From 1971 to 1988 he was a Lecturer in Pharmaceutics at the Victorian College of Pharmacy, being appointed Senior Lecturer in 1975. He was employed by RP Scherer Australia (which became Cardinal Health Australia in 1998) from 1988 to 2003, starting as Scientific Affairs Manager and holding a range of positions before becoming Pacific Region Technical Director and Representative Director of RP Scherer Japan KK in 1998. During his time at RP Scherer Australia Dr Oppenheim was responsible for a number of aspects of product development and quality control and he developed wide experience in preparing oral formulations.

Dr Oppenheim is currently the Principal of Dr Richard C Oppenheim, a consulting company, and has held this position since 2003. In this role he provides consultancy services to therapeutic and food industry clients, both within Australia and abroad. He has been a Fellow of the Royal Australian Chemical Institute since 1981 and has participated in the Complementary Healthcare Council of Australia since 1994.

Dr Oppenheim has held several appointments overseas as a visiting academic. He has also consulted for a range of organisations including the Australian Government Office of Complementary Medicine Industry Consultation Group (2001-2009). Dr Oppenheim has held several key external appointments, including Member (1986-2003) and Governor (1987-1990) of the International Controlled Release Society, Member of the Australian Society of Cosmetic Chemists (2000-2003) and Member of the Australian Pharmaceutical Science Association (1971-2009). Dr Oppenheim has also been on the editorial board of the Journal of Controlled Release Society from 1987 to 1995. Between 1979 and May 1993 he was a referee for several national and international journals. Dr Oppenheim has written over 55 peer-reviewed articles and has contributed to 5 books. These include publications in the areas of drug delivery, local anaesthetics, particulate contamination, surface adsorption and general principles of pharmaceutical formulation chemistry. Dr Oppenheim has also given over 160 presentations at symposiums, research institutes and universities, both in Australia and abroad, in the areas of pharmaceutical formulation, dosage forms and drug delivery systems.

Dr Oppenheim’s evidence covered the drug and product development process, pharmaceutical formulations (including oral dosage forms), the preparation of a rosuvastatin formulation, and other questions of chemistry relevant to the issues in dispute.

Ian Pitman

Dr Pitman completed a Diploma of Pharmacy in 1957 and a Bachelor of Science degree (with first class honours) in 1962. In 1965 he obtained a PhD in medicinal chemistry. In 1981 Dr Pitman was awarded a Doctor of Science degree by the Australian National University to recognise the substantial contribution he made towards understanding the kinetic and the thermodynamic stability of drug molecules in solution and of how these properties can be used to control drug delivery.

From 1965 to 1975 Dr Pitman taught and carried out research in many aspects of drug delivery at the University of Wisconsin and the University of Kansas. In 1971 he was appointed Professor of Pharmaceutical Chemistry at the University of Kansas. In 1976 Dr Pitman moved back to Australia to take up the role of Dean of the School of Pharmaceutics at the Victoria College of Pharmacy, a position he held until 1986. Throughout this period Dr Pitman taught graduate and undergraduate courses in the areas of drug formulation, including preparation of oral formulations, and carried out pharmaceutical research. He also supervised or co-supervised the research training of at least 10 PhD and 10 Masters students. Dr Pitman has also authored or co-authored 74 publications on various aspects of drug formulation.

In 1986 Dr Pitman joined Faulding as Research and Development Director. In that role his primary responsibility was managing research into novel oral drug delivery systems. From 1995 to 2001 Dr Pitman was Innovation and Scientific Director of Faulding. While at Faulding Dr Pitman was a Fellow of the American Pharmaceutical Association, the American Academy of Pharmaceutical Scientists and the Royal Australian Chemical Institute. After leaving Faulding in 2001, Dr Pitman commenced working as a consultant in the life sciences with emphasis on the pharmaceutical industry.

Dr Pitman’s evidence also concerned the drug and product development process, pharmaceutical formulations (including oral dosage forms), the preparation of a rosuvastatin formulation, and other questions of chemistry relevant to the issues in dispute.

Arthur Kibbe

Professor Kibbe obtained a Bachelor of Science degree in Pharmacy in 1966, a Master of Science degree in Pharmacy in 1968 and a PhD in Pharmaceutics in 1973. His PhD was on the topic of the stability of solid dosage forms of pharmaceuticals. Professor Kibbe’s work has largely been concentrated in the fields of pharmaceutical formulation development, pharmacokinetics and the pharmaceutical testing, regulatory and approval processes. From 1972 to 1984 Professor Kibbe was Assistant/Associate Professor of Pharmaceutics at the School of Pharmacy of the University of Mississippi. He then served as Chief of Pharmaceutical Development Services for the National Institutes of Health from 1984 to 1985 before becoming Director of Client Services for BioResearch Laboratories Ltd from 1985 to 1987. Professor Kibbe was then employed as Senior Director of Professional and Scientific Affairs for the American Pharmaceutical Association from 1987 to 1992. Professor Kibbe has been Chair of the Faculty of the Department of Pharmaceutical Sciences at Wilkes University since 1994. In this role he continues to direct the faculty and teach undergraduate and professional courses in pharmaceutics (dosage form design and manufacture) and pharmacokinetics.

Professor Kibbe is a Fellow of the Academy of Pharmaceutical Research and Science and has served on various editorial boards. He presently serves on the Editorial Review Panel of the Journal of Drug Development and Industrial Pharmacy and as a reviewer for the Journal of Pharmaceutical Science and the Journal of the American Pharmacists Association. Professor Kibbe was also Chair of the Food and Drug Administration’s Pharmaceutical Sciences Advisory Committee from 2002 to 2004. He continues to be a member of this Advisory Committee and as a special employee of the Food and Drug Administration consulting on formulation issues.

Professor Kibbe has authored or co-authored numerous papers in refereed journals, has written essays and articles published in the professional press and has presented before national and international professional societies. Professor Kibbe has also served as Editor-in-Chief of the third edition of the Handbook of Pharmaceutical Excipients, and has served on the Steering Committee for subsequent editions.

Professor Kibbe’s evidence also concerned the drug and product development process, pharmaceutical formulations (including oral dosage forms), the preparation of a rosuvastatin formulation, and other questions of chemistry relevant to the issues in dispute.

James Rowe

Dr Rowe obtained a Bachelor of Pharmacy in 1966. He has been registered as a pharmacist in Australia since 1967 and in the United Kingdom since 1971. From 1967 to 1969 he was employed by Riker Laboratories, as a product development chemist based in Sydney. He then worked for Eli Lilly & Co as a quality assurance associate from March 1969 to July 1971, before working as a pharmacist in the United Kingdom in the dispensaries of St John’s Hospital and St Mary’s Hospital from July 1971 to December 1972. Dr Rowe was then employed by ER Squibb & Sons Limited as a Product Planning Manager between December 1972 and December 1976. In 1974 he commenced a Master of Science focusing on biopharmaceutics graduating in 1976. In 1976 Dr Rowe was appointed Research Fellow in the School of Pharmacy of the University of London. His research focused on the formulation and testing of non-steroidal anti-inflammatory agents. He completed his PhD in 1980 and was then appointed to a lectureship in pharmaceutics. He held this position until April 1983.

In 1983 Dr Rowe founded HR Health Care Limited with a colleague, a company which provided pharmaceutical development, formulation and formulation stability testing services to pharmaceutical companies. He held the position of director until 1986. From September 1986 to August 1990 Dr Rowe returned to Sydney to work for Abbot Laboratories as Technical Manager, being responsible for product development and analytical chemistry. In 1990 he founded Technical Consultancy Services Pty Limited with a colleague. He held the position of Scientific Director from 1990 to September 2008. Dr Rowe was a visiting lecturer in pharmaceutics in the Faculty of Pharmacy, University of Sydney from 2002 to 2009 and a director of NxGen Pharmaceuticals from July 2007 until his retirement in December 2011. In this role he provided pharmaceutical product development services.

Dr Rowe’s evidence also concerned the drug and product development process, pharmaceutical formulations (including oral dosage forms), the preparation of a rosuvastatin formulation, and other questions of chemistry relevant to the issues in dispute.

Phillip Reece

Dr Reece obtained a Bachelor of Science in 1971. He was awarded a PhD in medical chemistry in 1976. Dr Reece was then employed as a Hospital Scientist, and subsequently as Principal Hospital Scientist, in the Department of Clinical Pharmacology at the Queen Elizabeth Hospital in Adelaide. In 1983 he was promoted to Chief Hospital Scientist and in 1985 to the ‘Excellence’ category of Chief Hospital Scientist, remaining in that position until September 1987. Between January 1986 and September 1987 Dr Reece was also an evaluator for the Australian Department of Health, which involved evaluating the pharmacokinetic component of applications for the regulatory approval of drugs.

In September 1987 Dr Reece became Clinical Trials Manager at Astra Pharmaceuticals in Sydney and in September 1988 he became Associate Regional Director of Clinical Research at Parke Davis Ltd, where he was responsible for its clinical trial research activities. In August 1990 he transferred to the United States offices of Parke Davis as Director of Clinical Pharmacology. In October 1993 Dr Reece returned to Australia to take up the position of Director of Research and Development at Biota Holdings. He held a range of positions at Biota Holdings, including CEO (July 1994 – May 1995) and non-executive director of Biota’s United States subsidiary (May 2001 – March 2002). In December 2001 Dr Reece was appointed General Manager of the Australian Operations of Biota. In these roles Dr Reece was responsible for the company’s research and development activities. In March 2002 Dr Reece left Biota Holdings to become CEO and Managing Director of Boron Molecular Ltd. In May 2003 Dr Reece became an independent consultant to the biotechnology and pharmaceutical industries, both in Australia and overseas.

Dr Reece has also been a member of the Royal Australian Chemical Institute since 1973, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (1976-1987 and 2009-present) and the American Society of Clinical Pharmaoclogy and Therapeutics (1989-1997).

Dr Reece’s evidence concerned drug discovery and drug development, clinical trials (particularly the design of Phase I and II clinical trials for a new statin), conducting literature searches to obtain information on statins, and clinical evaluation regulatory guidelines.

##### Expert evidence

###### Preliminary comment

Despite the limits on the proper role of expert evidence the evidence of the experts in this case traversed numerous issues which had little to do with the body of common general knowledge to those skilled in the relevant art or the meaning of technical or scientific terms and phrases. Although this evidence was admitted I would not wish that fact to be perceived as an indication that I consider such evidence proper or helpful. The evidence was admitted because attempting to disentangle the proper and helpful evidence about the body of common general knowledge to those skilled in the relevant art and the meaning of technical or scientific terms from the balance would have consumed more time in court than was worthwhile and was impractical in any event given the structure of the evidence. These observations are not a criticism of the evidence of any of the experts. It is the role of the legal representatives to ensure that the issues which an expert is asked to address are framed so as to elicit evidence which is relevant and admissible.

This said, I do not accept any of the attacks on the credit of the various experts who gave evidence. The attacks were not reasonably warranted. Many aspects of the attacks, particularly but not exclusively against the credit of Professor Charman, involved serious allegations none of which were put to him during the giving of evidence. Nothing in the evidence, written or oral, founded the submission that Professor Charman was an advocate for AZ. Nor were any of the other experts capable of being reasonably characterised as advocates for their client or partisans for a cause. The only issue of concern with much of the experts’ evidence was the time and effort they spent performing tasks of construction which are a matter for the court rather than expert evidence. That they did so inappropriately is the responsibility of the legal representatives who formulated the issues they should consider and not the fault of the experts.

The submissions against the credit of Professor Charman involve an extended, and wholly unjustifiable, personal attack, not supported by a rational or reasonable view of any aspect of the evidence he in fact gave. The best that can be said about the submissions is that they, rather than Professor Charman’s evidence, appear to be the result of an excess of partisan zeal on behalf of Apotex. None of the examples of evidence discussed at great length by Apotex show Professor Charman to have believed his role as assisting AZ. He was not “defensive, evasive and non-responsive” if he suspected a question might harm AZ’s interests. To the contrary, he did see his role as “being to listen to questions and answer them to the best of his ability to assist the Court”, as did all of the other experts. The ready communication of their expert opinions was hampered only by the issues with which they had been presented by the legal representatives as the proper subject of their written reports, which invited opinions about construction and apparently failed to instruct them about the proper limits of their roles as experts.

Contrary to Apotex’s submissions the fact that Professor Charman described his evidence in response to cross-examination as “our conversation” is to his credit. What is cross-examination of an expert other than a dialogue to expose the issues? Professor Charman, on any objective view of his evidence, was not concerned about the result of the case when he said “I’m worried you’re trying to trick me with something” and “I don’t get where you’re trying to go”. He was concerned, and rightly so, that if he gave a simple yes/no answer to the questions as posed his evidence would be misleading. He did not refuse to make even basic concessions. Where he could be firm about his views he was, but where he was giving evidence which involved hypothesis or speculation (albeit well-informed speculation), he made that clear as well. Answers Apotex saw as “guarded” or “evasive” were nothing more than careful about the substance of the opinion being communicated. The criticism of Professor Charman’s so-called “vigorous defence” of his hypothesis or speculation about how rosuvastatin might be stabilised by an inorganic salt in the coating misses the point that Professor Charman could not have been more open about the fact that he was operating in the realm of hypothesis or speculation. But as he fairly said, even speculation by someone with his expertise is informed speculation about rational possibilities which he had experienced in his professional work and not mere “dreamt up ideas”. The point he was making was that whether these possibilities were in fact occurring in this case or not was unknown because of lack of data. Professor Charman’s demeanour was not inappropriate for an expert witness. He was not “unreasonably pedantic”. The fact that he had read Dr William’s affidavit before he prepared his own evidence was a result of the procedural history of the case and provides no basis for criticism of Professor Charman or the opinions he proffered as his own. The cross-examination of Professor Charman involving a comparison of his affidavits with that of Dr Williams was tendentious and unhelpful. It failed to distinguish between the more formal parts of an affidavit and the substance of the opinions. Where it dealt with the substance of the opinions it gave an incomplete picture of the terms used by each witness. It was unnecessarily time consuming. It was vague and indirect when, to be fair, it needed to be clear and to the point.

The submission that Professor Charman is “pro-patentee” either because he “starts with the assumption that a granted patent involves an inventive step” or otherwise should be repeated only for the purpose of being rejected. It was not put to Professor Charman that he was “pro patentee” either generally or specifically. Nothing provides a proper foundation for that submission. If Professor Charman starts with the assumption that a granted patent involves an invention of some kind that does not make him “pro-patentee” in any event. Nor does it render his evidence worthless. His acknowledgment that he was “out of his depth” when referring to his assumption that a patent involves an “inventive step” was neither extraordinary nor an admission. It is hardly surprising that a person who is not a lawyer would assume that a patent involves an invention. Validity or invalidity is not a question an expert may decide.

The attacks against the credit of other experts were less vociferous than that against Professor Charman but similarly without merit.

###### Common general knowledge

As AZ submitted:

the common general knowledge “involves the use of that which is known or used by those in the relevant trade. It forms the background knowledge and experience which is available to all in the trade in considering the making of new products, or the making of improvements in old, and it must be treated as being used by an individual as a general body of knowledge” [*Minnesota Mining & Manufacturing Co & 3M Australia Pty Ltd v Beiersdorf (Aust) Ltd* (1980) 144 CLR 253 at 292]…common general knowledge is knowledge actually known or used by skilled persons generally, or accepted by “the bulk of those who are engaged in the particular art” [*British Acoustic Films Ltd v Nettlefold Productions* (1935) 53 RPC 221 at 250]. As the High Court emphasised in *Aktiebolaget Hassle*, information cannot be treated as part of the common general knowledge unless there is “evidence of its general acceptance and assimilation” by persons skilled in the art [*Aktiebolaget Hassle v Alphapharm Pty Ltd* (2002) 212 CLR 411; [2002] HCA 59 at [31]].

The hypothetical skilled addressees of the 051 or low dose patent and the 165 or HeFH patent are medical practitioners with specialised expertise in treating hypercholesterolemia. The hypothetical skilled addressees of the 842 or cation salt patent are likely to have been a pharmaceutical formulator. As Watson and Ascent submitted it is important to understand that the skilled addressee is not a reference to a specific person but is a legal construct (*Root Quality Pty Ltd v Root Control Technologies Pty Ltd* (2000) 177 ALR 231; [2000] FCA 980 at [71]). The legal construct may not be a single person but may be a team of persons “whose combined skills would normally be employed in that art in interpreting and carrying into effect instructions such as those which are contained in the document to be construed” (*General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd* [1972] RPC 457 at 485) (*General Tire*). And as Watson and Ascent also said:

A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and they read it knowing that its purpose is to describe and demarcate an invention. The person skilled in the art is unimaginative without inventive capacity.

Many aspects of what would have been common general knowledge to the hypothetical skilled addressees of the patents were not in dispute. My findings relating to and, where necessary discussion about, the common general knowledge immediately before the asserted priority dates are set out below.

Hypercholesterolemia, statins, and HeFH

Using the words of Professor O’Brien:

Cholesterol is a chemical that is made by the liver and is an important component of cell walls. It is also an important precursor to steroid hormones and brain tissue. Cholesterol is insoluble in blood and therefore exists as a complex of phospholipid, cholesterol and a type of protein called apoprotein. This complex, known as a lipoprotein, is the transport vehicle for lipids in the bloodstream. Lipoproteins are characterised by density and are divided into four main classes; chylomicrons, very low density lipoproteins (“**VLDL**”), low density lipoproteins (“**LDL**”) and high density lipoproteins (“**HDL**”). Low density lipoproteins are the main carrier of cholesterol in the bloodstream.

In Australia, cholesterol is measured in millimoles per litre which is denoted as “mmol/L”. In other parts of the world (such as the USA), milligrams per decilitre (“mg/dL”) is the measurement used. These are both measurements of the total amount of cholesterol in the blood. Lipoprotein metabolism is briefly detailed below:

(a) VLDL cholesterol (“**VLDL-C**”) refers to cholesterol packaged in VLDL particles which also contain triglyceride. VLDL-C is the form in which cholesterol is secreted from the liver, where most cholesterol is made.

(b) Once it enters the bloodstream, VLDL-C is converted to LDL cholesterol (“**LDL-C**”) by the removal of triglyceride. LDL-C refers to cholesterol which is packaged in LDL. These particles use the bloodstream to transport cholesterol from the liver to all the tissues of the body. This form of cholesterol is often termed “bad cholesterol” and is indicative of an increased risk of heart disease.

(c) HDL cholesterol (“**HDL-C**”) refers to the cholesterol which is packaged in HDL particles. The HDL-C complex returns cholesterol from the tissues or organs to the liver, where cholesterol is excreted or recycled. HDL-C is often referred to as “good cholesterol” and higher levels indicate a decreased risk of heart disease.

(d) Total cholesterol (“**TC**”) refers to cholesterol in all of the lipoprotein-cholesterol complexes in the blood. Total cholesterol is what the lay person understands by their cholesterol level. This includes VLDL-C, LDL-C and HDL-C.

It was also common general knowledge before the claimed priority dates that:

Hypercholesterolemia is an elevated level of cholesterol in the blood. The broadest definition is where cholesterol is too high for a particular patient, taking into account that patient’s risk factors. For example, a TC level of 5.5 mmol/L is excessive for a patient with a previous heart attack but acceptable in somebody with no cardiovascular risk factors. A more traditional definition of hypercholesterolemia is where the patient has a level of cholesterol that his higher than that of the average population by more than two standard deviations from the mean.

Hypercholesterolemia may be defined either by considering the total cholesterol (TC) or, more accurately, by the cholesterol in the low density lipoprotein fraction (the LDL-C). There have been a number of treatment guidelines published which recommend target levels for cholesterol based on LDL-C. These targets vary depending on the risk that high cholesterol will likely pose to a particular patient. This risk assessment takes into account risk factors such as whether the patient has previously had a heart attack, has diabetes, has high blood pressure etc. Essentially, the target levels are adjusted so as to set a level which is desirable for a particular group of patients. If a patient has a LDL-C level higher than the target level then I would define the patient as suffering from hypercholesterolemia.

As Professor O’Brien described:

Guidelines referred to as “**NCEP ATP II**” were produced by the US National Cholesterol Education Program (“**NCEP**”) and published in 1993. … The guidelines express targets both in terms of TC and LDL-C. There were also similar guidelines published by learned Australian bodies although these were published after February 1999.

The most common form of hypercholesterolemia is primary hypercholesterolemia. This is hypercholesterolemia which is not caused by any other illness or disease and may have a number of causes. Patients with other diseases may also have elevated cholesterol levels which is known as secondary hypercholesterolemia. This is where another illness, typically poorly controlled diabetes, hypothyroidism, or renal or liver disease, causes an elevation in cholesterol levels.

As Professor O’Brien said:

Hypercholesterolemia is a problem because elevated cholesterol levels are associated with an increased risk of atherosclerosis. Atherosclerosis is a build-up of cholesterol in the arteries.

Typically, atherosclerosis first occurs in the coronary arteries (the arteries which supply blood to the heart muscles) and then sometimes progresses to the arteries of the brain and legs, and occasionally other areas of the body as well. Cholesterol is the biggest risk factor in damage to the arteries. Generally, the degree of build-up of cholesterol is related to the level of cholesterol in the blood, as well as other risk factors.

Atherosclerosis increases a patient’s risk of coronary heart disease (“**CHD**”), stroke and peripheral vascular disease (“**PVD**”). Consequently, patients with hypercholesterolemia might also suffer from coronary heart disease, peripheral vascular disease and/or stroke. PVD refers to blockages of arteries in the legs such that leg muscles do not get enough blood. PVD is particularly common in patients who smoke and have high cholesterol.

Patients with severe or complicated lipid problems are usually referred to an endocrinologist, although such patients may also be referred to a clinical biochemist or cardiologist. Otherwise, many general practitioners also treat people with elevated cholesterol levels. These practitioners knew that the:

drugs that were available to treat hypercholesterolemia as at February 1999 included the follow classes of drugs, with statins being the most common drug chosen and almost always the first choice:

(a) statins;

(b) fibrates;

(c) bile acid binding resins (such as colestipol and cholestryramine); and

(d) nicotinic acid (niacin).

Medical practitioners knew that the class of compounds known as statins (or HMG CoA Reductase Inhibitors) were useful in lowering low density lipoprotein cholesterol (**LDL-C**) and were commonly used for that purpose in treating patients with cardiovascular disease, patients at risk of cardiovascular disease (including diabetics) or patients with elevated cholesterol levels. Professor O’Brien noted that:

Statins were known to inhibit the process of cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase. HMG-CoA reductase is the rate-limiting step in the pathway of cholesterol synthesis. It converts HMG-CoA to mevalonic acid which is a critical precursor molecule to cholesterol.

The enzyme HMG-CoA reductase, like all enzymes, is a complex three dimensional molecule which has a specific site at which it binds to its substrate, HMG-CoA. This binding site on the enzyme complements the shape of an area of the HMG-CoA molecule so that the enzyme and its substrate “fit” together and this allows a reaction which transforms HMG-CoA to mevalonic acid to take place. The substrate is said to have an “affinity” for the enzyme; that is, the substrate and the enzyme are attracted to one-another by inter-molecular forces which act to hold the two together while the reaction takes place.

Statins are molecules which have a similar structure to HMG-CoA (the natural substrate for the enzyme HMG-CoA reductase) but have greater affinity for the enzyme than HMG-CoA – the statin “competes” for the binding site with HMG-CoA. As a result, a statin molecule will be more likely to bind to the enzyme than an HMG-CoA molecule, and the statin will likely remain bound to the enzyme for longer than HMG-CoA would. When a statin is bound to the enzyme, HMG-CoA is unable to bind to it and thus cannot be converted to mevalonic acid which, in turn, cannot be synthesised into cholesterol.

Statins are all based on the structure of the molecule compactin (which occurs naturally in some fungi), with differing side chains. The differences in the side chains affect the length of time that a statin remains inside a cell. The longer a statin remains inside a liver cell, the greater the reduction in cholesterol it is able to achieve. Differences in side chains also affect the affinity of a statin for the enzyme HMG-CoA reductase and, therefore, the ability of that statin to bind to and inhibit the enzyme. Variations in side chains can also affect the solubility of a statin, which can affect whether a particular statin is able to enter into the brain or a specific type of tissue. All of the above factors will have an effect on the percentage by which a statin is able to reduce a patient’s cholesterol levels and also potentially the side effects of the statin.

Statins and HMG-CoA compete for the binding site of the enzyme HMG-CoA reductase, and although statins have greater affinity for the enzyme, sometimes a molecule of HMG-CoA will successfully bind to the enzyme and be converted into mevalonic acid which, in turn, will go on to become cholesterol. Statins therefore do not completely inhibit the production of cholesterol by the liver, but they do act to decrease the amount of cholesterol produced.

Although statins reduce the production of cholesterol in liver cells, they have only a very minor effect on the release of cholesterol from the liver into the bloodstream. The primary method by which blood cholesterol is reduced is via the increased clearance of cholesterol (LDL-C particles) from the bloodstream. If a liver cell is unable to manufacture sufficient cholesterol (because of statin treatment), it expresses more LDL receptors so that it can take up more cholesterol from the bloodstream, reducing a patient’s LDL-C level. This process is particularly important in the liver because the liver is the main organ which clears cholesterol from the bloodstream. This mechanism was known to me prior to February 1999.

By the late 1990s statins were recognised as the primary class of drug available for lowering LDL cholesterol. Simvastatin had been commonly used for this purpose. Atorvastatin was also released and quickly became known in Australia and throughout the world. Because it is a more potent statin than simvastatin, atorvastatin quickly replaced simvastatin as the most commonly prescribed statin in Australia. Statins available in Australia by 1999 also included fluvastatin and pravastatin. According to the MIMS Annual 1998 the following statins were available in the following doses in Australia:

(a) fluvastatin (Lescol and Vastin) – 20 mg and 40 mg tablets;

(b) pravastatin (Pravachol) – 5 mg, 20 mg and 40 mg tablets;

(c) simvastatin (Lipex and Zocor) – 5 mg, 10 mg, 20 mg and 40 mg tablets; and

(d) atorvastatin (Lipitor) – 10 mg, 20 mg and 40 mg tablets.

The MIMS Annual 1998 also recorded the recommended starting and maximum doses of each statin available in Australia as follows:

|  |  |  |
| --- | --- | --- |
| **STATIN** | **RECOMMENDED STARTING DOSE** | **RECOMMENDED****MAXIMUM DOSE** |
| Fluvastatin | 20 mg or 40 mg | 40 mg |
| Pravastatin | 10 mg or 20 mg | 40 mg |
| Simvastatin | 10 mg or 20 mg | 40 mg |
| Atorvastatin | No starting dose for atorvastatin is listed in MIMS Annual 1998, rather a range of 10 mg to 80 mg is stated. I typically used a starting dose of 10 mg. | 80 mg |

By 2000 cerivastatin was also available in Australia but it was not commonly used.

As Professor Tonkin described, all of the statins available in Australia as at 2000 were in tablet form and were typically dosed once a day at night because most cholesterol is synthesised by the liver during the night.

Between 1996 and 2000 in Australia a study comparing the efficacy of simvastatin and atorvastatin in general practice was carried out, with the clinical trials taking place in 1998 and 1999. The study results were published in 2000. From this and other information medical practitioners with a particular interest in treating hypercholesterolemia knew that the available statins had different efficacy in terms of the drug’s ability to reduce cholesterol across its dosage range, with atorvastatin being the most efficacious, followed by simvastatin, then pravastatin, and then fluvastatin. Also, as Professor O’Brien explained, it was well known that:

For any given statin, the starting dose will result in a significant decrease in LDL-C, which varies depending on the efficacy of the statin. Thereafter, each doubling of the dose produces approximately a further 6% reduction in LDL-C. If this is represented graphically, the dose administered, when compared to reduction in LDL-C levels, produces a curve with a sharp initial fall in LDL-C which then begins to flatten out at subsequent higher doses. All known statins follow this dose-response pattern.

There is a limit to the practical cholesterol reduction that can be achieved with a statin, because side effects increase with dose. Fewer side effects are observed at lower doses of statins. Therefore a balance needs to be achieved between effective cholesterol reduction and the likely side effects of a given dose. The maximum marketed dose of a statin represents the upper limit of efficacy that maintains an acceptable side effect profile.

It was also understood that:

the relationship between the dose administered and the reduction in LDL-C observed is non-linear for statins. This non-linear relationship affects prescribing practices, particularly if a patient’s cholesterol levels are well above target levels when they are prescribed the starting dose of a statin. In such a case one may increase the dose beyond the next dose level in one step. For example, if a patient is on 10 mg and has an LDL-C level well above target, one may increase the dose to 40 mg in one step.

Medical practitioners typically prescribe patients (or at least patients who are not high risk) the lowest dose of statin to begin with so as to minimise the risk of adverse events such as myalgia (muscle pain), liver dysfunction and rhabdomyolysis (more severe muscle toxicity) which are potential side effects associated with statins. If the target level is not reached and the dose has been well-tolerated, the dose will be increased (dose titration) over months. Dose titration aims to increase the dose until the patient reaches their target in as safe a manner as possible but this practice increases costs and adversely affects patient compliance (patients do not wish to repeatedly visit their doctor and have blood tests and/or change their dose). For these reasons dose titration often does not occur and the patient remains on their starting dose even though their target levels have not been achieved. Patients with a significant risk profile are more likely to be placed on a higher dose of statins from the outset.

HeFH

Medical practitioners understood that HeFH is a severe form of hypercholesterolemia caused by one or more mutations in the LDL-C receptor gene which impairs the ability of the LDL-receptor to detect and initiate the absorption of LDL-C. Professor O’Brien said:

There are two types of FH; heterozygous and homozygous.

The heterozygous condition occurs where the patient has inherited one defective LDLR gene from one parent and one normal LDLR gene from the other parent. This condition is also known as heterozygous familial hypercholesterolemia. This condition occurs in about 1 in 500 people in the general population (or approximately 100,000 people in Australia).

The homozygous condition occurs where the patent has inherited two defective LDLR genes, one from each parent. The condition is extremely rare and occurs in approximately one in every one million births in Australia, although in some specific populations the rate can be slightly higher. I have treated two patents in my career that suffer from this condition and these patients suffered from significant health issues. The health issues are so extreme that the present treatment is a liver transplant or a procedure which removes LDL-C from the bloodstream, known as LDL apheresis (conceptually similar to dialysis). Statins are only minimally effective in the treatment of homozygous familial hypercholesterolemia.

HeFH is associated with moderate to severe elevations in cholesterol, especially LDL-C, and a severely elevated risk of cardiovascular disease. HeFH is generally diagnosed by reference to LDL-C levels and family history, although there are other clinical criteria including cholesterol deposits in tendons (tendons xanthomas) and other parts of the body. HeFH can also be diagnosed by gene testing but that was not readily available.

Professor O’Brien, who refers to HeFH as FH, said:

Commonly, patients who suffer from FH will have an LDL-C above 8 mmol/L and a TC above 10 mmo/L. It is possible for patients with levels lower than these to still have FH. The levels which are indicative of FH are age-related and would be much lower in children. A young child could have an LDL-C level of 5 mmol/L which would be regarded as FH, but in an adult this level would not be indicative of FH.

Because there are many different mutations in the LDLR gene, the functionality of LDL receptors varies between patients. The worse the genetic defect, the higher the levels of LDL-C and the more premature the CHD. Severe FH usually refers to FH where a patient presents with CHD at a very young age (usually in their 20s). Severity relates to LCL-C levels but also to other risk factors.

It was generally understood that, as Professor O’Brien described:

It is, and was in November 2000, important to diagnose FH because the hypercholesterolemia caused by FH needs to be treated more aggressively than would otherwise be the case. This is because patients who have hypercholesterolemia caused by FH have had high cholesterol all of their lives. Even by the age of 20 they usually have considerable atherosclerosis present. Therefore it is important to know whether the patient has FH so that more aggressive treatment may be used. Another important reason is that I would vigorously screen family members in that situation. This is so that other members of a patient with FH in family with [the] same condition can be found and treated.

Further, while the treatment of hypercholesterolemia is the same for patients with HeFH (that is, to reduce their LDL-C levels to target), HeFH is a complex condition. Although the biological processes for the synthesis of cholesterol is the same in HeFH and non-HeFH patients, the LDL-C levels of HeFH patients are often more difficult to manage (that is, reduce to appropriate levels) than those of non- HeFH patients as HeFH patients only have only one fully functional LDL-C receptor. It is not possible to predict how a given drug will be metabolised in patients and whether the metabolic pathways will be different in HeFH patients compared to non-HeFH patients. That said, the usual treatment for HeFH was a statin, particularly atorvastatin due to its efficacy. Medical practitioners generally expected that a reduction in LDL-C levels in HeFH patients would be associated with a reduced risk of subsequent adverse events. However, statins were often unsuccessful or only partially successful in bringing the cholesterol levels of HeFH patients to target levels so that HeFH patients often had to be treated by a combination of therapies (a statin and another agent such as ezetimibe or a fibrate). As such, HeFH patients were more likely to be treated by a specialist than general practitioner. This latter fact was also confirmed by the evidence which Dr Hay gave. Dr Hay said that if he encountered a patient with very high cholesterol and a family history of cardiovascular disease he usually suspected HeFH and would refer the patient to a specialist such as a lipidologist.

As Professor Tonkin put it, given the seriousness nature of HeFH the general approach to treatment in 2000 was to use a statin at the highest available dose consistent with a reasonably established safety profile. Professor Tonkin said:

In some cases, treatment of HeFH was with a statin in combination with another type of drug if there was inadequate lowering of cholesterol. However, different statins were not combined to treat hypercholesterolaemia. I am not aware of any drug, prior to or since 2000, that has been used to treat hypercholesterolaemia in patients that do not have HeFH, that has not also been used to treat hypercholesterolaemia in patients that do have HeFH, and vice versa.

Perceived need for statins

In Dr Wilson’s view, although there were a number of statins available, including atorvastatin which was perceived as a very effective cholesterol lowering drug, there was nevertheless an unmet need for more effective treatments of hypercholesterolemia including HeFH. This was (and is) because despite existing therapies a number of patients still die and/or suffer morbidity from cardiovascular disease, many patients do not reach target levels despite therapy, patients who reach target levels still suffer cardiovascular disease events, and the widely held view was that target levels needed to be pushed lower. Clinical evidence indicated that target cholesterol levels needed to be reduced, a trend which has continued as more clinical evidence has become available.

Professor O’Brien said:

In many patients, treatment of hypercholesterolemia with statins enables them to reach the targets in the guidelines. However, at February 1999, there were a number of patients, such as those with familial hypercholesterolemia…, who could not achieve the targets using the drugs then available. This is still the case today. Some patients are also intolerant of statins or intolerant of maximum doses of statin and therefore fail to reach target.

Professor Evans, an expert in pharmaceuticals and not a medical practitioner, readily identified four or five commercially available statins in the late 1990s. He considered the statin market to be “crowded” and “saturated” as a result and perceived the available literature as indicating that “the majority of people appeared to be getting an adequate response from statins”.

On this issue I prefer the evidence of Dr Wilson and Professor O’Brien to that of Dr Evans. There were a number of statins available in Australia before the asserted priority dates and many people were achieving their target cholesterol levels as a result of treatment by statins. However, it is apparent that medical practitioners in the field were aware that a material number of patients did not achieve their target levels because of either inadequate ongoing management of their condition and the need for dose titration or difficulty in achieving the required reduction of their cholesterol levels having regard to their risk profiles. These potentially difficult to treat patients included but were not limited to those suffering from HeFH. Accordingly, medical practitioners recognised before the asserted priority dates that there was room for improvement in the field of statins in terms of the development of new statins or improvement of existing statins so as to enable more patients to achieve their target cholesterol levels at doses where side effects could also be minimised. Further, because it was also recognised that dose titration frequently did not occur because of the ongoing management required medical practitioners in the field also appreciated that it was desirable to have available new or improved statins which enabled more people to achieve their target level at the first dose given which, in accordance with ordinary prescribing practices, would be a dose at the lower end of the approved range unless specific risk factors indicated a higher dose was warranted.

For these reasons, to the extent that AZ framed its defence of the validity of the patents on the basis that the inventions claimed therein met an “unfelt want”, I am satisfied that such a description is inapt in the present case. An “unfelt want” as an indicator of inventiveness was referred to in *Wellcome Foundation Ltd v VR Laboratories (Aust) Pty Ltd* (1981) 148 CLR 262; [1981] HCA 12 at 287 (*Wellcome*). But the facts of the present case cannot be characterised in this way merely because there were a number of existing statins in the market before the asserted priority dates. No-one suggested the existing statins were perceived as incapable of being improved upon whether by a new drug or otherwise. To the contrary, it was clear from the evidence that those involved in the treatment of hypercholesterolemia were aware that the existing statins, while an enormous advancement of previously available treatments, still did not enable all patients to be effectively treated whether due to tolerance issues or the difficulty of ensuring appropriate dose titration or otherwise.

AZ’s submissions to the contrary should not be accepted. Atorvastatin was considered efficacious but, as Professor O’Brien said, it was not effective for all people, there being “a subset that require either other agents or require more potent agents, particularly patients with familial hypercholesterolemia”. There were existing statins and the market for statins might well have warranted the description “crowded” before the asserted priority dates but those involved in the treatment of hypercholesterolemia knew that the existing statins did not effectively treat all patients for the reasons already identified. As noted, Professor Evans was not involved in such treatment at the time. Nor was Dr Reece but, in any event, Dr Reece simply held the view that before proceeding with the development of a new statin one would want to have seen “some discernible competitive advantage” it offered. Dr Reece recalled that “once we established from the animal studies and then humans that it was more potent, then we saw the opportunity”. Insofar as AZ relied on Professor Tonkin it is apparent that, in common with all those who gave evidence and were involved in actually treating patients with hypercholesterolemia, Professor Tonkin did not perceive the existing statins as a discouragement to the development of a new statin; he considered that the existing statins meant that before proceeding far with the development process any new candidate statin should have a potential potency and safety profile better than the existing statins or, as he put it, that it be “possible that you come up with something at least as effective as what is available at the present time, and hopefully more effective and also that it would have at least as favourable a safety profile and ideally, more favourable safety profile”.

AZ submitted that none of the experts who gave evidence were in fact looking for a new statin therapy at the asserted priority dates and there is no documentary evidence of the need for a new therapy. This is true but it does not undermine the consistent theme of the evidence of those involved in the actual treatment of hypercholesterolemia as described above. Moreover, it is unsurprising that the experts who gave evidence were not in fact looking for a new statin therapy at the relevant time. The evidence indicated that large scale clinical trials are time consuming and expensive and not usually initiated in Australia in the ordinary course. The fact that none of the experts involved in treating hypercholesterolemia were looking for a new statin therapy before the asserted priority dates does not mean that those involved in the field, including in Australia, failed to recognise that a new statin therapy, which was better at bringing more patients to their target level without dose titration, would be other than highly desirable.

Insofar as the common general knowledge is concerned, accordingly, it was common general knowledge in those involved in treating hypercholesterolemia before the asserted priority dates that statins were an effective and safe treatment for hypercholesterolemia but, despite the existence of a number of statins, there remained patients who could not be effectively treated by them. It was also common general knowledge at that time that one issue with the prescription of statins is that many patients did not achieve their target cholesterol level because they were not effectively subject to dose titration as this process involves ongoing management and supervision by a medical practitioner. Accordingly, it was common general knowledge in those involved in treating hypercholesterolemia that a statin which could bring more patients to their target level without dose titration than the existing statins would be highly desirable. Such a statin would be considered to be “more effective” than the existing statins and to offer a real “competitive advantage” over those statins. There was no “unfelt want”. To the contrary, there was a conscious perception that a new statin which could bring more patients to their target level without dose titration than the existing statins would be highly desirable.

Clinical trials

As Professor O’Brien described it:

A drug is initially chosen based on its efficacy in treating a specific condition or disease. Once a promising drug candidate has been screened for toxicology and therapeutic potential, pre-clinical trials are conducted. These pre-clinical trials test a drug candidate in order to assess the pharmacological effect and any gross side effects associated with administering the drug candidate. Such tests will be conducted on animals such as mice and rats, and then possibly on primates. These tests may involve testing of a range of doses, including even very high doses, well beyond those that would be administered to humans, to test safety. If the drug is considered to be safe and efficacious then it can then be considered a candidate for clinical trials.

Generally speaking, once the animal studies have been conducted, the researcher has an indication of safety and efficacy. By safety, I mean whether or not the drug is safe to administer and whether or not it has any side effects, as well as the severity of those side effects. When I refer to efficacy I am referring [to] how effectively the drug treats the condition or disease intended to be treated.

Whether or not a drug moves into a clinical trial (on humans) from pre-clinical trials (on animals) involves multiple considerations: not only safety and efficacy but also potential cost-effectiveness. The clinical trial process is very expensive and therefore the decision to go ahead with clinical trials is based on an expectation that the drug is going to be successful, both therapeutically and economically.

A clinical trial is an experiment or series of experiments investigating the use of a promising drug candidate and its use in humans. It was common ground that clinical trials are more often than not time consuming and expensive, with many new drug candidates failing at some or other point in the trial process in terms of safety and/or efficacy.

Pre-clinical and clinical trials are the subject of detailed prescriptive protocols and regulatory requirements including ethical and safety requirements.

Clinical trials of a promising drug candidate occur after pre-clinical tests, including testing in animals. The objective of pre-clinical testing is to obtain an indication of safety and efficacy of the drug candidate including in animal models to support progression to human trials. *In vitro* tests give an indication whether the drug has the desired activity against the drug target and its selectivity to the target. Animal studies are used to establish the margin of safety of the drug which is the dosage or blood plasma concentration at which the first signs of toxicity are seen compared to the dose or plasma concentration required for efficacy. Ideally the margin of safety is at least tenfold.

As pre-clinical tests progress information is gathered about safety and therapeutic efficacy as well as the pharmacokinetics (what the body does to the drug in terms of absorption, distribution, metabolism and excretion) and pharmacodynamics (what the drug does to the body in terms of biochemical and physiological effects) of the drug. Because human doses are not yet known doses in animals often exceed that which would be used in humans to enable comprehensive evaluation of the safety indications of the drug. If the safety and therapeutic efficacy of these tests warranted further examination of the drug, clinical trials would then be considered involving testing in humans.

The object of clinical trials is to establish the safety and efficacy of the drug in humans. Dr Morella described clinical trials as generally involving three phases. Phase I trials for new drugs usually involve a small number of healthy subjects, the purpose being to ensure that the drug is safe in humans and to consider dosage ranges, the pharmacodynamics of the drug being a secondary purpose. Phase I trials for reformulated versions of known drugs focus on the pharmacodynamics of the drug, ensuring that the reformulation interacts with the body in the same way as the original formulation. Phase II trials involve studying the drug in a larger number of patients with the relevant condition, the primary objective being to ascertain the pharmacodynamic effect of the drug. Phase III trials involve studying the effectiveness of the drug in a large number of patients over a long period of time. There is also a fourth phase which involves long-term post-marketing observation of the drug in the target population.

Professor Evans’ description of the clinical trial process was generally consistent with that of Dr Morella. Professor Evans said that Phase I trials are:

essentially to ascertain tolerability and acute toxicity, pharmacokinetic parameters, the pharmacological effect of the drug (if possible), and the bioavailability of certain dosage forms. Therefore, factors such as dose linearity (ie, whether if the dose is doubled, the plasma level is also doubled) proportionality, predictability, variability and side effects are intensely monitored during Phase I clinical trials.

Professor Evans described Phase II trials as:

essentially to establish clinical efficacy and adverse effects in the target group, to define concentrations and dosage schedules, and to provide detailed pharmacological and metabolic data to allow planning of Phase III. Checking the safety of the product in the intended population is important because they may have different responses to healthy volunteers, and these early studies are sometimes called Phase IIa studies. Looking for indicative efficacy in the target population and proving that the drug works reliably in slightly larger populations (eg, of anywhere between 50 and 1000 patients) is sometimes called Phase IIb studies. Phase II studies inform the decision about whether to invest time and money into Phase III trials. This will only occur if the Phase II studies have demonstrated efficacy and that safety can be controlled.

Professor Evans described Phase III clinical trials as “pivotal”, the purpose of which is:

essentially to identify less common and unpredictable side effects, to establish ideal dosing regimens, and to explore the place of the new drug in the treatment of the target disease (eg, by comparing it with existing drugs). In most circumstances, there will be two or three multicentre Phase III studies, in which patients with the relevant condition administer the product for a significantly longer period of time than that of Phase II studies. However, this is not always the case.

Professor Evans also noted that:

Although there is linearity in terms of when the initial phases of clinical trials begin, they can often overlap and end at different times. …

This is because there might be two or three studies looking at different formulations and different drug interactions, which are classified as Phase I trials. …

Similarly, there may be several Phase II studies in people with different indications.

Professor Evans said that a new drug is not considered to have been proven as a treatment until appropriate clinical trials have shown that it is safe and effective. It is for this reason that Professor Evans described Phase III trials as “pivotal” because:

generally this is the first time that efficacy can be demonstrated in the long term and in a statistically significant number of participants.

Professor Evans said:

In my experience, clinical trials also involve a great deal of uncertainty, so a drug is not considered to be successful until the later stages of clinical trials because any number of things may go wrong and the product may have to be either abandoned or significantly reworked. One of the main problems at each stage of the clinical trial process is that the drug simply may not work. Although early studies (eg, Phase I and Phase IIa) may give an indication of efficacy, this generally cannot be proven until there are sufficiently large numbers of participants to provide statistically significant results (usually in Phase III).

Professor Evans also noted that:

Because early clinical trials like Phase I and Phase II usually involve smaller populations, where an adverse event is rare and will occur in (for example) only one in 10,000 people, the number of participants may not be large enough to present that adverse event until Phase III or later.

Professor O’Brien also described clinical trials as involving the three phases set out above with the fourth phase occurring after the drug had entered the market. Professor O’Brien said that as clinical trials involve testing on humans, clinical trials would not be commenced “unless there was solid data from the pre-trial studies to indicate safety and efficacy”.

The description which Dr Reece gave of the clinical trial process generally accorded with that of the other experts. Dr Reece said:

Phase I clinical trials are designed to assess tolerability to the drug in humans and to establish that the drug is sufficiently safe to proceed to further development. At the end of Phase I trials, relationships between dose and, where possible, plasma concentrations and toxicity should be known, including the margin of safety over the expected therapeutic dose and the maximum tolerated dose. Using this information and information from animal studies of efficacy it should be possible to define a dose that is sufficiently safe and, at which it can be expected that efficacy will be seen in patients with the disease of interest at that dose.

Dr Reece also said:

I would not generally expect to see any efficacy in Phase I trials because the drug is being tested on healthy volunteers who do not have the disease of interest. Further, the primary objective of Phase I trials is to assess the safety of the drug in humans and determine the maximum tolerate dose. However, depending on the drug being tested it may be possible to obtain an indication of efficacy of the drug in Phase I trials, for example where an actual endpoint can be measured in healthy volunteers, such as plasma cholesterol levels.

Dr Reece described Phase II trials as follows:

Phase II trials are the first studies of the drug in patients with the disease for which the drug is intended to be used as a treatment. The objectives of Phase II are to determine whether the drug candidate has efficacy against the target disease, establish safety in patients and to assist in determining dose sizes and the dosing frequency for Phase III Studies.

As to Phase III trials, Dr Reece said:

The object of Phase III studies is to determine the safety and efficacy of the drug in a larger number of patients and to establish that the drug’s efficacy is statistically significant when compared with the control group. On the basis of Phase III studies, regulatory approval to market the drug may be given.

Dr Reece also noted that:

Phase IV trails are undertaken after the drug has been launched onto the market. One objective of Phase IV trials is to address issues not resolved in Phase III trials including, for example, effects in patients with concurrent disease and effects in different age groups. Another objective is to monitor side-effects associated with long-term use in a larger number of patients than in Phase III studies. Phase IV trials can be several years in duration.

In terms of statins, Professor O’Brien noted (and it was not in dispute that) short term efficacy can be confirmed in Phase I trials because statins have an effect even in healthy humans. Professor O’Brien described Phase I trials as confirming whether or not the drug is well-tolerated, the likely useful dosage range and whether there is efficacy in humans. He described Phase II trials as assessing “the effectiveness of the drug in treating the relevant condition” and gathering further evidence relating to side effects and optimal dosing. Phase III studies “aim to determine whether the drug has its intended therapeutic effect in a larger population as well as testing that population for side effects associated with the use of the drug”.

Dr Wilson said that new drugs need to be extensively tested before they can be shown to be safe and effective in treating human patients. It is not uncommon for drugs which appeared to have potential in Phase I and II trials to fail in later phases. Phase I and II trials may be insufficient to detect safety issues due to the small sample size. For cardiovascular drugs in particular, which are generally taken by patients for life, late stage trials are critical. Toxic effects of cardiovascular drugs which become apparent during late phase trials are generally fatal to the drug’s development. Cerivastatin, a statin, was launched in Australia in the late 1990s and was a most potent drug for reducing cholesterol on a per mg basis. Later, in 2001, cerivastatin was withdrawn from the market because at higher doses (0.8mg) it was associated with an unacceptable increase in severe muscle effects including 52 cases of fatal rhabdomyolysis. According to Dr Wilson “drug development is an unpredictable process” so it is “very difficult, if not impossible, to accurately assess a drug’s safety and efficacy before the drug has been rigorously tested in extensive clinical trials, including late stage clinical trials”.

Dr Morella also said that “generally (but not necessarily) it cannot be known whether a new therapy is in fact a safe and effective treatment for the target population until the Phase III or other appropriate studies have been completed”.

Drug formulation

As Dr Rowe explained:

Pharmaceutical formulations contain at least one active pharmaceutical ingredient (ie, the pharmaceutical compound), combined with other ingredients (excipients) that are generally inert in the body. Excipients are used to ensure that the pharmaceutical formulation has appropriate characteristics and is suitable for administration in the desired dosage form. For example, excipients may be used to control where in the body a pharmaceutical is released (such as in the stomach or in the small intestine), or the rate at which a pharmaceutical is released into the body (ie, a controlled release formulation). Another use of excipients is to stabilise a pharmaceutical (such as by preventing a hygroscopic drug from absorbing water from the environment prior to its administration). … In order to effectively design a pharmaceutical formulation, knowledge of pharmacology and organic chemistry is necessary. Pharmacology is the study of the interactions between pharmaceutical compounds and the human body, ie, how pharmaceuticals affect the human body, and how the various biological systems of the human body affect pharmaceuticals. Organic chemistry is the chemistry of organic, or carbon based, compounds. Organic chemistry is a key component of dosage form design as many of the biological compounds found in the human body (for example, proteins, DNA, carbohydrates, lipids and vitamins) and the majority of pharmaceutical compounds are organic compounds.

An active pharmaceutical ingredient may be able to be delivered in many ways including in liquid form (able to be taken in oral, injectable and/or intravenous forms) and in the form of creams, gels, powders, inhalants, tablets and capsules (amongst others).

Excipients are pharmacologically inactive materials that are combined with an active pharmaceutical ingredient in order to prepare a drug product. There are many classes of excipients including acidifying agents, alkalising agents, antioxidants, diluents/fillers, binders, buffering agents, chelating agents, lubricants, glidants, disintegrating agents, solubilising agents, and tablet coatings. Pharmaceutical excipients are also often used multi-functionally (that is, they serve more than one purpose in the formulation). Well-known fillers included calcium phosphate salts.

A tablet is a compressed unit dosage form.

Dry blending is a standard mixing technique in which no solvent is used. Dry blending involves a simple physical mixture of solid materials where the molecular interaction between the components is likely to be much less than in wet granulation. After blending, the formula is physically compressed into the dosage form such as a tablet. Wet granulation is also a standard mixing technique in which a solvent is used, along with other possible excipients, to form a granulate which is then compressed into the tablet. Professor Kibbe said:

Whatever method is used to formulate the dosage form, homogeneous mixing or blending is a critical, fundamental part of pharmaceutical formulation and production. In a tablet it is essential that each of the ingredients is uniformly distributed throughout the tablet. It is only by such uniformity that each tablet is reproducibly the same as every other tablet and that for a patient the biological effect is the same for every tablet.

Degradation of solid pharmaceutical compositions, such as tablets, is a well-known phenomenon including degradation by water or light which catalyse oxidation and lactonisation reactions. As Professor Kibbe said:

… it is important that a pharmaceutical product be stable, but some amount of degradation of the active pharmaceutical ingredient over time is usual and acceptable provided the degradation products are not toxic and/or do not adversely impact on the delivery of the correct dose of the active pharmaceutical ingredient. Subject to those provisos, for a marketed pharmaceutical less than 5% degradation of the active ingredient in 24 months is a typical rule of thumb for an acceptable specification.

Professor Kibbe explained aspects of lactonisation. A lactone is a closed ring consisting of two or more carbon atoms and a single oxygen atom, where one of the carbon atoms is a carbonyl group (-C=O) group. Lactones are formed by lactonisation. Lactonisation is the process in which a lactone is formed by an intramolecular reaction between a hydroxyl (-OH) group and an activated carbonyl group (-C=O). To undergo lactonisation, the molecule must have a carboxylic acid functional group and a hydroxyl functional group that is located close, but not too close, to the carboxylic acid functional group. In addition to the lactone, the process of lactonisation releases a molecule of water for every molecule of the lactone produced. To undergo lactonisation, the molecule has to be in solution. Lactonisation does not occur spontaneously, it is caused by acid (H+) attack on the oxygen atom of the carbonyl group (-C=O) of the carboxylic acid (-C(=O)OH) functionality. For a molecule to undergo lactonisation it must be exposed to an acidic aqueous environment (including a micro-environment inside a tablet). Lactonisation is reversible in the presence of water. As lactonisation is a reversible process, small changes in the environment (including micro-environment) can push the equilibrium reaction in either direction. That is, the environment may favour the formation of the lactone degradation product or it may favour the conversion of the lactone degradation product. Temperature and pH can mediate the rate of the lactonisation reaction. For example, reactions generally proceed faster at higher temperatures. Both the lactonisation reaction and the reverse reaction (hydrolysis) would proceed faster at elevated temperature. Also, the more acidic the environment (or micro-environment), the faster lactonisation is likely to occur. pH can also mediate the direction of the reaction. For example, in a basic (alkaline) environment the equilibrium reaction will shift in favour of the lactone degradation product opening up (with the addition of a water molecule) to form open chain rosuvastatin molecules (hydrolysis). The amount of water present in a system can also mediate the rate of lactonisation, with the presence of more water expected to decrease the rate. Lactonisation can also be mediated by an interaction between the molecule and a large blocking functional group. Such a group can physically interfere with the ability of the open chain molecule to curl around so that the hydroxyl group (OH) and the carboxylic acid group (-C=O) cannot get close enough to react and form the closed ring lactone. Exposure to light does not trigger lactonisation and Professor Kibbe was not aware that light has any direct impact on the process or rate of lactonisation. Generally, reactions proceed faster at elevated temperature, so to the extent that incident light serves to increase the temperature of a system it could, by the indirect effect of elevating temperature, cause both the lactonisation and hydrolysis reactions to proceed faster.

Professor Kibbe also explained aspects of oxidation. Oxidation is a common and important mechanism of drug degradation. The mechanism of oxidative degradation is complex. However, oxidation is broadly defined as the loss of electrons from a molecule. Oxidation reactions may be catalysed by, for example, oxygen and heavy metal ions. However not all oxidative degradation reactions require a catalyst. Oxygen may be activated by incident light to become a free radical with an unpaired electron (O2). Free radicals are chemically reactive and can cause oxidation of molecules.

Dr Rowe explained the potential effects of light as follows:

Decomposition resulting from exposure to ultraviolet light can occur in a wide variety of ways and it is therefore difficult to predict what precise degradation products would be formed. Conjugated double bonds between carbon atoms (ie, double bonds alternating with single bonds in a chemical structure or part thereof) absorb ultraviolet light, and if sufficient light is absorbed this can result in those bonds being broken and reforming. Heat can also caused this process to occur, and ultraviolet light and heat can act synergistically in causing this type of degradation. …

Ultraviolet light, which is part of sunlight and has a wavelength shorter than the visible light spectrum, is more energetic and penetrative than visible light. Ultraviolet light can cause degradation of molecules in a tablet that are not present at the surface of the tablet, although with increasing depth the ultraviolet light will be attenuated, and so be progressively less likely to provide sufficient energy to the Formula I molecule to break the bonds.

Any step that reduces the exposure of the pharmaceutical formulation to ultraviolet light will serve to decrease the risk and rate of any such degradation. Steps … to address ultraviolet light include storing the tablets in foil or a blister pack, using an opaque coating on the tablet, and storing the tablets in opaque bottles or jars.

Although a shelf life of 24 months is required for pharmaceutical products it is not efficient to conduct stability studies for this period. Hence, stability of a drug is often tested under accelerated conditions such as 30ºC (Celsius)/65 RH (relative humidity) for 6 months or more, 40ºC/75 RH for 6 months or more, and 60ºC at both ambient and high (eg, 75%) RH, compared to ambient conditions of 25ºC/60RH conducted for 12 months or longer. Samples from stability studies are tested by high performance liquid chromatography (**HPLC**) to measure the amount of the active pharmaceutical ingredient remaining and the formation of degradation products. The degradation products can then be isolated and characterised using nuclear magnetic resonance (**NMR**) and liquid chromatography mass spectroscopy (**LCMS**). Identification of degradation products may enable appropriate excipients, coatings and packaging to be ascertained to ensure that degradation does not exceed relevant guidelines for degradation over time.

A tablet may be uncoated or coated. The coating of a tablet may perform different functions including providing colour, masking an unpleasant taste, providing smoothness, protecting against moisture, air and light, enhancing tablet stability, and modifying the release of the drug after ingestion. Ferric oxide and titanium dioxide are compounds commonly used in tablet coatings, often as colourants. Ferric oxide and titanium dioxide are also practically insoluble in water and form a wax-like barrier when used in a coating.

Dr Rowe gave this information about tablet coatings:

Coatings are sprayed onto tablets. As at January 2000, water-based coatings were normally used. These replaced the old organic based coatings comprising methylene chloride and alcohol. That is, the majority of the material sprayed onto the tablet was water. This water was usually evaporated nearly instantaneously following application to the tablet.

The coating left on the tablet (that is, after evaporation of water) typically contained the following components:

(a) Cellulose derivative; these were either water soluble (for example, HPMC (hydroxypropylmethylcellulose) and PVA (polyvinyl alcohol)), or water insoluble, (for example, ethyl cellulose). The cellulose derivatives were the major component of the coating. The cellulose derivatives form a protective film around the tablet which prevents the passage of external oxygen and water into the formulation, thereby preventing external oxygen and water from causing degradation reactions in the tablet. As at January 2000, water soluble coats were generally used unless the coating was also being used for the purpose of preparing a sustained release or controlled release formulation.

(b) A plasticiser; which was added to make the coating film more flexible and resilient. For example, castor oil was commonly used as a plasticiser (typically making up around 1% of the applied coating).

(c) A pigment or pigments; which were commonly added to make the tablet opaque preventing exposure to ultraviolet light (and any degradation caused by that exposure). Titanium dioxide (TiO2) was (and remains) the most commonly used opacifier.

Prior to 26 January 2000, different coatings were commercially available, or they could be readily prepared from their constituent ingredients. At this time, I used both commercially available coatings, and prepared coatings from their constituent ingredients. Commercially available coatings were supplied in concentrated form. In order to use these coatings, water was added to dilute the concentrate to the appropriate concentration prior to use. Manufacturers of coatings at this time included Shin Etsu, Pharmacon, Dow Corning and Rohm Haas. Commercially available products included products in ranges named Sure Release, Aquacoat, Aquateric, Aqualon, Opadry and Eudragit.

In addition to their protective functions coatings were, before 26 January 2000 (and today) commonly used for a variety of other functions. These functions include:

(a) Improved robustness in transit; in addition to its protective function, the cellulose film also improves the friability of the tablet (ie, the susceptibility to breakage). Improved friability means that the tablet is less susceptible to breakage during transit.

(b) Improving appearance; in my experience, tablets that have coatings have a more attractive appearance than tablets that are not coated. Uncoated tablets are often white or off white, whereas a coating will normally contain a pigment or pigments to give the tablet a more attractive glossy white appearance, or they can be used to add colour.

(c) Addition of colour; in addition to improving the appearance of the tablet, colour may also be added for placebo effects. For example, I am aware of studies that have indicated that yellow tablets are more effective in the treatment of depression. If the pharmaceutical product has been formulated into different doses (ie, formulations containing different amounts of the pharmaceutical compound), coloured coatings may also be used to differentiate between the different doses.

(d) Improve the ease with which tablets may be swallowed.

(e) Sustained release coatings; which control the rate at which the pharmaceutical compound is released into the patient’s gastrointestinal tract. For example, a sustained release coating may ensure that the pharmaceutical compound is released from the tablet over a 12 hour period.

(f) Site directed release coatings; which control the location in the patient’s gastrointestinal tract at which the pharmaceutical compound is released. For example, some formulations are prepared with coatings that are broken down by an enzyme present in the colon. Use of this coating allows targeted delivery of the pharmaceutical compound to the colon.

(g) Enteric release coatings; these prevent the pharmaceutical compound from being released in a patients stomach. As the stomach is highly acidic (has a low pH), some pharmaceutical compounds will be degraded by the pH if they are released from the formulation into the stomach. Enteric coatings ensure that the pharmaceutical compound is not released from the formulation until after the formulation has passed through the patient’s stomach (as other areas of the gastrointestinal tract are not highly acidic).

Inorganic salt

Formulators of pharmaceutical compositions, being the hypothetical skilled addressees of the 842 or cation patent, understood the traditional meaning of a “salt” to be the compounds formed by the neutralisation of an acid and a base. In this traditional meaning the salt is the product of a reaction in solution in which a disassociated hydroxide (OH‾) ion is neutralised by a disassociated hydrogen (H+), that is, the classic acid + base = salt + water reaction. On this traditional meaning, oxides, including ferric oxide and titanium dioxide would not be considered to be a salt. Calcium sulphate, however, would be a salt within this traditional meaning.

Inorganic acids and inorganic bases are distinguished from organic acids and organic bases in that inorganic acids and inorganic bases do not contain within their structure carbon atoms covalently bonded to hydrogen atoms.

Carbonate, silicate and metasilicate are counter anions of inorganic salts on the traditional meaning of a “salt” as the product of an acid-base reaction.

Professor Charman considered that “inorganic salt” could mean not only a compound formed by the neutralisation of an acid and a base (the traditional meaning of a “salt”) but also an inorganic compound which is electrically neutral. This is a compositional definition of “salt”. Calcium sulphate thus would be a salt within both the traditional meaning and this other compositional meaning of “inorganic salt”. However, as noted, ferric oxide and titanium dioxide would not be salts under the traditional meaning but are “inorganic salts” under the compositional definition (that is, they are an inorganic compound with a neutral net ionic charge) in which the cation is multivalent. A multivalent cation is one with more than one positive charge.

This compositional meaning of “inorganic salt” is set out in the International Union of Pure and Applied Chemistry (IUPAC), *Nomenclature of Inorganic Chemistry*, 1990 (GJ Leigh ed.) in which “salt” is defined as:

…a chemical compound consisting of cations and anions.

Definitions published by IUPAC are:

…drafted by international committees of experts in the appropriate chemistry sub-disciplines, and ratified by IUPAC’s Interdivisional Committee on Nomenclature and Symbols. In this edition of the Compendium these IUPAC-approved definitions are supplemented with some definitions from ISO and from the International Vocabulary of Basic and General Terms in Metrology; both these sources are recognised by IUPAC as authoritative. The result is a collection of nearly 7000 terms, with authoritative definitions, spanning the whole range of chemistry.

Dr Morella also understood the term “salt” in this compositional sense as referring to a class of compounds in which a negatively charged ion (an anion) is ionically bonded to a positively charged ion (a cation) to form an electronically neutral molecule. Hence, in Dr Morella’s view while a salt may be formed by the reaction of an acid and a base it could equally include compounds created by oxidation-reduction reactions or thermal decomposition. On this basis, magnesium oxide is an inorganic salt in which the cation is multivalent. So too, according to Dr Morella, are ferric oxide and titanium dioxide.

Dr Oppenheim, Professor Pitman, Dr Rowe and Professor Kibbe disagreed with Professor Charman and Dr Morella about this compositional definition of a “salt” and considered that the traditional meaning was the true meaning of a “salt”. On this basis, as an oxide is formed by the reaction of an element with oxygen, oxides would not be considered to be an inorganic salt or a counter anion of an inorganic salt. The reasons for disagreement of these experts were much the same. In Professor Kibbe’s words:

As at 2000, I, and in my experience other persons skilled in the art of pharmaceutical formulation, had no difficulty recognising what constituted a salt. A salt is the result of the combination of an acid + base reaction. Once formed, all salts are soluble to some extent in water. That is, in the presence of water, they will separate or disassociate into their respective cations and anions. The extent to which they will readily separate into ions in the presence of water depends on the strength of their bonds, but all will separate to some degree without further manipulation or the requirement for a chemical reaction with water or other components of the solutions.

Dr Rowe said that if the compositional definition of “salt” were to be accepted then:

simply requiring that it be a compound in which a cation (positively charged ion) has bonded with an anion (negatively charged ion), with an electrically neutral net charge – a ‘salt’ would include an incredibly broad range of compounds, and would include compounds that are fundamentally considered to be covalent (and not ionic) compounds.

Dr Rowe also noted that ferric oxide and titanium dioxide are insoluble in water whereas salts as traditionally understood (as formed from the reaction of an acid and a base) are typically soluble to some extent in water. Professor Kibbe agreed observing that:

In my opinion ferric oxide and titanium dioxide are not salts. They are not produced by a salt forming reaction and once produced are not soluble in water. … Neither ferric oxide nor titanium dioxide can change or control the pH of a solution because they are not soluble and don’t ionise in water. They therefore cannot affect the hydrogen ion concentration of a solution and change the pH.

Professor Kibbe also said:

… unlike phosphates, carbonates, silicates and metasilicates, an oxide does not exist as a counter anion *per se*. For example, aluminium oxide is *the* oxide. It is not a salt in which aluminium is the cation and oxide is the counter anion. Similarly, iron oxide is not a salt in which iron is the cation and oxide is the counter anion. Iron oxide is *the* oxide. Titanium dioxide is not a salt in which titanium is the cation and oxide is the counter anion. Titanium dioxide is *the* oxide. Looking more broadly at compounds that can be classed as oxides, there are two classes. First, there are those that are electrically neutral and therefore cannot act as an anion as part of a salt. Secondly, there are those that carry a negative charge and can act as an anion as part of a salt. The neutral oxides include, for example, ferric oxide (Fe2O3), titanium dioxide (TiO2), aluminium oxide, copper oxide (and others). The oxides that carry an electrical charge and can act as an anion as part of a salt include, for example, carbonate (CO32-), phosphate (PO43-), metasilicate (H2SiO32-) and sulphate (SO42-). Carbonates, phosphates, metasilicates and sulphates are actually oxides of carbon, phosphorus, silicon and sulphur respectively. Only the second class of oxides can be the anion component of a salt. This second class of oxides does form inorganic salts with metal cations by the traditional acid + base = salt and water reaction. … I am not aware of any neutral oxide that can raise the pH of an aqueous solution when dispersed in it. Salts of oxides in the second class that I describe above can however change the pH of an aqueous solution, because they carry with them a metal cation that can raise pH.

Professor Kibbe noted that:

Sodium and potassium bicarbonate are bicarbonate salts that have been used in pharmaceutical formulations since well before 2000. Calcium carbonate and magnesium carbonate are carbonate salts that have been used in, for example, antacid therapeutic formulations since well before 2000. These compounds are conventionally classified as inorganic salts, even though they contain carbon. Calcium and magnesium are multivalent cations.

Rosuvastatin - awareness

There was a separate issue between the parties described as the “starting point” issue by reason of which the generic parties contended that it was appropriate to assume either that rosuvastatin would have been known to the hypothetical addressee of the patents or that the addressee would have been presented with a problem to solve in terms consistent with problems said to be solved by the patents. This issue involves a question of legal principle different from the essentially factual enquiry associated with common general knowledge

Leaving aside the starting point issue and its resolution (as to which see below) the question remains whether rosuvastatin, whether under the name ZD4522 or rosuvastatin, was part of the common general knowledge of the hypothetical addressees of the patents in 1999 to 2000.

Dr Wilson first became aware of rosuvastatin in about 2003 when the drug was released in the United States, after the asserted priority date for each patent. Although I do not accept that Dr Wilson’s evidence in this regard should be given little or no weight because he was too junior at the asserted priority dates to have been aware of rosuvastatin, Dr Wilson was at a less advanced stage of his career than, for example, Professors Tonkin and O’Brien (who seem to have been clinical leaders in treating hypercholesterolemia from well before 1999). Dr Colquhoun was also more advanced in his career at the asserted priority dates than Dr Wilson. Accordingly, although by 1999 Dr Wilson was a cardiology registrar and had been in practice in a large hospital for nearly six years and despite statins being a fundamental part of the cardiologist’s arsenal I do not find it particularly surprising that Dr Wilson was unaware of rosuvastatin until its commercial release. The same might be said of Dr Hay. There was no suggestion Dr Hay was aware of rosuvastatin in 1999 or 2000, although he plainly was aware of other statins at this time. Dr Hay had been in a large general practice since 1984 and had a particular research interest in cardiovascular diseases but he was not involved in the treatment of hypercholesterolemia at the same advanced level as Professors Tonkin and O’Brien and Dr Colquhoun in 1999 and 2000.

Given the nature of the 051 or low dose patent and the 165 or HeFH patent, which are specifically concerned with hypercholesterolemia, I consider that the skilled addressees of those patents are not general practitioners or general cardiologists. The skilled addressees are those with a particular expertise in lipidology. As at 1999 and 2000 in Australia those persons included Professors Tonkin and O’Brien and Dr Colquhoun but not Dr Wilson (who was then a general cardiology registrar) or Dr Hay (who was a general practitioner). This is consistent with Dr Colquhoun’s evidence that in Australia there were few clinicians with particular expertise in lipidology at that time but the few in number included Professor Tonkin. I consider Professor O’Brien also met this description at the time. Accordingly, it is the knowledge of such persons that is relevant.

Professor Tonkin said that he probably would have been aware of rosuvastatin in 2000 because there was “preliminary data about it, and there had been discussions about the development of another statin” at the time but he could not recall if the information was in the public domain. However, Professor Tonkin was not involved in any investigations for AZ and could not recall being provided by AZ with any information on a confidential basis. It is clear, moreover, that Professor Tonkin attended and presented a paper at the International Society of Atherosclerosis meeting in Stockholm (the 12th International Symposium on Atherosclerosis) in June/July 2000. At that meeting a paper was also presented by Olsson et al. The abstract for the article (coincidentally) was posted next to the abstract of the paper in which Professor Tonkin was involved. Professor Tonkin said that although he did not recall doing so he reviewed abstracts posted on notice boards at such meetings and he expects he would have read the Olsson article during the symposium (and, I infer heard the paper being presented as well).

The Olsson article published at the Stockholm symposium is in these terms:

**ZD4522 – a new HMG-CoA reductase inhibitor – causes rapid and profound reductions in plasma LDL-C levels in patients with primary hypercholesterolaemia**

…

Effects of once-daily oral doses of ZD4522 (rosuvastatin) and atorvastatin – both synthetic inhibitors of HMG-CoA reductase – on plasma LDL-C levels were assessed in patients with mild-to-moderate hypercholesterolaemia.

**Design/Methods:** randomised, placebo-controlled, parallel-group dose-ranging trial (4522|L/0008). After a 6-wk dietary run-in, men (18-70yr) and post-menopausal women (50-70yr) received double-blind placebo or ZD4522 (1, 2.5, 5, 10, 20 or 40mg) or open-label atorvastatin (10 or 80 mg) during a 6 wk treatment period. Percentage change in LDL-C from baseline to wk 6 was analysed by ANOVA for ZD4522 and placebo groups only.

**Results:** 142 patients entered the 6-wk treatment period (124 provided data in efficacy analysis). Compared with placebo, all doses of ZD4522 significantly lowered LDL-C in a dose-dependent manner (p<0.001). At wk 6, reductions in LDL-C from baseline ranged from 36% (1mg) to 63% (40mg) after treatment with ZD4522; reductions of 44% (10mg) and 59% (80mg) were seen with atorvastatin. Informal comparisons showed ZD4522 produced numerically greater reductions in LDL-C than did atorvastatin on a mg-per-mg basis. Approximately 90% of LDL-C reduction occurred within the first 2 wks of randomised treatment with ZD4522 (Figure), indicating ZD4522 had a rapid onset of efficacy. ZD4522 was well tolerated across all doses; occurrence of adverse events was similar across placebo and active treatments, with no increase in adverse events or withdrawals noted with increasing doses of ZD4522. No patients had clinically significant elevations in ALT (>3xULN) or CK (>10xULN).

A version of this article was subsequently published in the European Heart Journal in 2000 which contains the additional statement:

**ZD4522 – a new HMG-CoA reductase inhibitor – causes rapid and profound reductions in plasma LDL-C levels in patients with primary hypercholesterolaemia**

…

…

ZD4522 showed rapid, clinically relevant, dose-related reductions in LDL-C. The safety profile of ZD4522 compared favourably with those of atorvastatin and placebo.

**[European Heart Journal** 2000;21 Suppl p156 Abs P975].

Professor Tonkin said he read the European Heart Journal at that time and continues to do so regarding it as a very credible journal widely read by cardiologists including in Australia.

AZ attempted to diminish the significance of this evidence from Professor Tonkin, submitting that “Professor Tonkin did not give evidence that he had such knowledge before 6 February 1999, and was not able to say whether the knowledge he did acquire, when he later acquired it, was publicly available”. This submission, however, does not reflect the full effect of Professor Tonkin’s evidence as set out above.

Dr Colquhoun also attended and presented a paper at the 12th International Symposium on Atherosclerosis in Stockholm in 2000 but it is not clear whether he became aware of rosuvastatin in so doing. Dr Colquhoun did explain that “in Australia and indeed in the world, there is a very small proportion of people who have an interest in lipids and lipid experts are involved in the basic metabolic studies and the treatment of hyperlipidaemia” which I accept. As at 1999 and 2000 Drs Wilson and Hay probably would not have warranted the characterisation of lipid experts although Professors Tonkin and O’Brien, as well as Dr Colquhoun, would have done so. This is relevant because, as noted, I consider that the non-inventive but skilled addressees of the 051 or low dose patent and the 165 or HeFH patent would have had this particular expertise in the treatment of hyperlipidaemia (or hypercholesterolemia) at the asserted priority dates.

Dr Colquhoun also gave evidence that during the trials which AZ conducted and in which he was involved as an investigator between July 1999 and June 2000 he and others involved in the trials called the drug being tested a “superstatin”. At that time the drug was not called rosuvastatin (it had not yet been named, the earliest public reference to rosuvastatin seeming to be 29 June 2000 in a Heartwire publication referred to below) and was referred to in this period as ZD4522 or, as Dr Colquhoun said, a “superstatin”. Dr Colquhoun said the description “superstatin” was used because of the potency of the drug which was perceived as similar to that of atorvastatin which was also called a superstatin at this time.

Professor O’Brien gave evidence that:

As at 6 February 1999, I recall that I was aware that there was a new statin in development and that this statin was substantially more effective than anything then on the market. I recall that I first heard this information from colleagues, possibly reporting on presentations that they had heard at scientific meetings, although I cannot be completely sure as to how I first heard about this statin under development. I often hear information about a new drug in this manner several years before the drug comes to market.

Before personally reading any scientific papers on the new statin, I recall considerable excitement amongst colleagues relating to the efficacy of the new statin. I recall hearing that it was described as a “superstatin” or a “turbostatin” and that it was able to achieve much greater LDL-C reductions than could be achieved with atorvastatin, such that it was at least twice as effective as atorvastatin. At that time, I was very hopeful that this would be a major advantage in treating patients with familial hypercholesterolemia, and from discussions with fellow clinical lipidologists, I believe that they were also similarly hopeful. I later learnt that the name of this new statin was rosuvastatin.

In that part of his first affidavit describing experience in the field of clinical lipidology, Professor O’Brien said:

I was also asked to and did sit on various lipid advisory boards for pharmaceutical companies that were producing, developing and marketing statins. I was on the advisory board for Merck in relation to simvastatin in the early 1990s. I was also on the lipid advisory board for Parke-Davis (later Pfizer), initially for gemfibrozil and later for atorvastatin, prior to 1998. I was also on an international advisory board for [AZ] for rosuvastatin leading up to the worldwide launch of rosuvastatin. My participation on these advisory boards generally required me to provide answers to specific questions and to provide scientific and educational advice to the company.

AZ attacked the credibility of Professor O’Brien because, in AZ’s view, the reference to Professor O’Brien’s involvement on the AZ advisory board for rosuvastatin leading up to the worldwide launch of the drug was insufficiently detailed. Further, according to AZ Professor O’Brien’s involvement in that advisory board (a process which subjected Professor O’Brien to stringent confidentiality obligations) meant that he could not possibly provide evidence about his awareness of rosuvastatin unaffected by the information which he obtained on a confidential basis. In AZ’s words Professor O’Brien’s “intimate involvement on [AZ]’s national and international advisory boards before the November 2000 priority date hopelessly compromises his ability to provide evidence that is not tainted by hindsight and/or specialist inside knowledge”.

There is force in AZ’s submission that it could not be reasonably expected that Professor O’Brien would now be in a position to identify and separate information he obtained as a result of involvement in the AZ advisory panel for ZD4522 (which was subject to confidentiality obligations meaning such knowledge could not be relevant to the common general knowledge) and information he obtained other than from that source. The fact that at the time he prepared his affidavit Professor O’Brien could not “be completely sure as to how [he] first heard about this statin under development” indicates that, unsurprisingly given the passage of time, his memory of the nature and level of his involvement with the AZ advisory board had diminished over time. I do not accept any part of the attack on Professor O’Brien’s credit. I have no doubt that had he recalled more when he prepared his affidavit he would have disclosed more about his involvement in the AZ advisory board. I also see nothing wrong with Professor O’Brien having been on the AZ advisory board and been willing to give expert evidence in these proceedings. The material effect of AZ’s disclosure of the nature and extent of Professor O’Brien’s involvement on the AZ advisory board (where he would have learnt a great deal about ZD4522 but on a confidential basis) is that weight should not be placed on Professor O’Brien’s present recollection of what he knew when or how he knew it about the drug.

Dr Oppenheim was aware at the asserted priority dates of the general class of compounds known as statins which lowered cholesterol but was not aware of the compound rosuvastatin. Professor Evans also was not aware of rosuvastatin at the asserted priority dates. Nor were Drs Oppenheim, Pitman, Rowe and Morella or Professors Kibbe and Charman. This is unsurprising as these were all pharmaceutical experts and were not involved in the treatment of hypercholesterolemia and thus had no reason to be aware of rosuvastatin other than in the context of these proceedings. As such I do not find the state of their knowledge material to the identification of the common general knowledge of the skilled addressees of the 051 or low dose patent or the 165 or HeFH patent.

Leaving aside material confidential to AZ at the time, it is apparent that before the 12th International Symposium on Atherosclerosis in Stockholm in June 2000 AZ thought it had good reason to describe the drug, then known as ZD4522, as a “superstatin” because of its much greater potential to lower LDL-cholesterol than so-called “first generation” statins at well-tolerated doses. The predecessor of AZ, Zeneca Ltd, publicised its licence with the inventor of ZD4522, Shionogi & Co Ltd (**Shionogi**), for the “world-wide development, marketing and commercialization of this very promising lipid-lowering agent to be known as ZD4522…with a “superstatin” profile” in April 1998. A year later, in April 1999, AZ was created from a merger between Zeneca Ltd and Astra Ltd. At that time AZ’s new Executive Director of research and development gave an interview to Reuters in which he referred to “Zeneca’s superstatin used in heart disease”. On 6 December 1999 AZ issued its first R&D presentation referring to Phase II trials data for “ZD4522 superstatin confirms better lipid lowering efficacy than any existing product and tolerability equivalent to the best in the class”.

The very fact that the results of AZ’s research into rosuvastatin were presented at the 12th International Symposium on Athersclerosis in Stockholm in 2000 is also relevant evidence that the drug was part of the common general knowledge of the hypothetical addressees of the patents (or, at least, the 051 or low dose patent and the 165 or HeFH patent). This includes that two of three experts who could fairly be characterised as experts in lipids at that time, Professor Tonkin and Dr Colquhoun, attended the symposium. This is consistent with AZ’s own records, which show that half of the experts it had on the advisory panel for rosuvastatin (who thus would have been privy to the same confidential information as Professor O’Brien) attended the Stockholm symposium and thus must also be inferred to have obtained the information that AZ permitted to be published by Olsson and others at that time.

The presentation of the results at the 12th International Symposium on Atherosclerosis in Stockholm gained attention. One article, published the same day as the presentation on 28 June 2000, referred to AZ’s trials showing a 65% reduction in LDL cholesterol. Another, published the following day on 29 June 2000 in Heartwire, was headed “Rosuvastatin – the most potent statin yet”. This article referred to Dr Olsson as having reported that the 65% reduction of LDL cholesterol achieved by rosuvastatin “surpasses the maximum responses of all other statins when used as monotherapy”. These results were reported under the by-line in bold “Faster than a speeding bullet? More powerful than a locomotive?” The article also reported that the drug showed “adverse events similar to placebo, [with a] lower risk of interactions with other drugs”. Another AZ researcher, Dr McTaggert, was reported as saying that rosuvastatin is more lipophilic than any of the other statins and, as it is not metabolised in the liver as with other statins, it should be free of interactions with other drugs. Dr Wilson described Heartwire as a free newsletter containing information of interest to cardiologists and any clinician interested in that area. Dr Wilson could not recall if he subscribed to Heartwire when a cardiology registrar but knew that it used to be issued in print and was now issued electronically. He plainly read it to keep up to date on issues including summaries of important clinical trials in the cardiology area. A similar article appeared on the same day in the UK newspaper The Guardian which was available online. And on 31 July 2000 AZ issued a statement about its decision to spend £28.5m to construct a new plant to manufacture ZD4522 following the “recent publication of clinical data from Phase II trials demonstrating the potential of ZD4522, a HMG-CoA reductase inhibitor, to be a highly effective and well-tolerated alternative to currently available statins”.

Although AZ objected to all of the material in the form of newspaper articles and AZ’s own press releases, the fact is that AZ and its predecessor chose for its own commercial reasons to make public announcements about the drug, its potential and characteristics from 1998 when it obtained the licence from Shionogi and after the merger creating AZ. I am satisfied that AZ itself, or its predecessor, used the term “superstatin” to describe the drug as part and parcel of its commercial objectives at the time which apparently included making the market aware that it had an important new drug under development which appeared to be the best statin yet discovered in terms of efficacy and tolerability and which, by 31 July 2000, was sufficiently well demonstrated to warrant building a new multi-million pound plant for manufacturing purposes.

This evidence provides the context for the evidence of Professor Tonkin and Dr Colquhoun, both of whom attended the Stockholm symposium in June 2000. Professor Tonkin believed he would have been aware of rosuvastatin (even if under the name ZD4522) as a result of the symposium and Dr Colquhoun was aware that the drug was called a superstatin. The evidence also provides a context for the evidence of Professor O’Brien. Although Professor O’Brien was privy to confidential information from AZ about rosuvastatin it is highly unlikely that he was not also aware of the information about the drug that AZ had chosen to make public at and after the Stockholm symposium.

I am satisfied that clinicians such as Professors Tonkin and O’Brien, and Dr Colquhoun, who had practices focusing on lipid reducing therapies, were aware by the time of the Stockholm symposium that there was a new statin which had been the subject of Phase II clinical trials. They were aware, due to the results presented at the symposium and subsequent publicity, that the trials showed the drug’s potential to be the most potent statin yet in terms of capacity to reduce LDL cholesterol at doses which were as well-tolerated as the best of the existing statins. This awareness on and from 30 June 2000 was part of the common general knowledge of the skilled addressee of the 150 or low dose patent and the 165 or HeFH patent.

Despite the earlier press releases by AZ and its predecessors I am not satisfied that this awareness formed part of the common general knowledge of the skilled addressees of the 150 or low dose patent and the 165 or HeFH patent before the Stockholm symposium. Apart from Professor O’Brien’s evidence there is no proper basis upon which it may be inferred that people otherwise in his position, such as Professor Tonkin and Dr Colquhoun, became aware of the information which AZ and its predecessor disseminated about the drug in 1998 and 1999. Professor O’Brien’s evidence that he was aware of the drug as at 6 February 1999 cannot be accepted at face value due to his access to confidential information. In contrast to the Stockholm symposium it is difficult to accept that a person in Professor O’Brien’s position would have become aware of the press releases in 1998 and 1999 which appear to be directed more at the pharmaceutical market than clinicians.

For these reasons although I am satisfied that the existence of a new statin with a so-called “superstatin” profile (in terms of its potency in reducing LDL cholesterol levels to a materially greater extent than the existing statins and at doses as well tolerated as the best of the existing statins) was part of the common general knowledge of the skilled addressee of the 051 or low dose patent and the 165 or HeFH patent by 30 June 2000, I am not satisfied that this was so at any time before that date. As AZ submitted, in contrast to the evidence about the Stockholm symposium, there is no basis upon which it should be inferred that the earlier press releases and articles “came to the notice of skilled persons in Australia, let alone that the information in them was actually assimilated into common general knowledge”.

Although the drug was referred to as ZD4522 at the Stockholm symposium and in some articles about the symposium, it was called “rosuvastatin” in the Heartwire article of 29 June 2000. The earliest date by which a skilled addressee could have known of the name “rosuvastatin” is thus 29 June 2000. Given the prevalence of references to ZD4522 at and around this time it is more likely that the new “superstatin” was known by this name as at 30 June 2000.

I do not accept the characterisation of this awareness as a mere “buzz” about a possible new statin. It is possible that such a “buzz” existed as a result of the AZ press releases in 1998 and 1999 but, for the reasons given, I am not satisfied that any such “buzz” had become part of the common general knowledge of the skilled addressees of the patents at that time. The information AZ published at the Stockholm symposium was relatively detailed and based on apparently sound science. The skilled addresses would not have treated this information as other than seriously considered and soundly based. Any caution with which people might have approached AZ’s own earlier press releases would not have applied to the information published at and as a result of the Stockholm symposium.

Rosuvastatin – chemical name and structure

The chemical name and structure of rosuvastatin were not part of the common general knowledge as at the asserted priority dates. None of the evidence referred to above disclosed the chemical name and structure of rosuvastatin other than it was a drug of the statin class with the qualities identified.

A formulator presented with the chemical structure of rosuvastatin would be able to predict potential issues about the compound from the structure including the potential for lactonisation (as a result of the seven member carbon tail) and oxidation (by reason of a free radical attack of conjugated carbon atoms). As Dr Rowe noted:

… it is often possible to predict the types of degradation a compound will be susceptible to from the chemical structure of that compound. The study of potential degradation reactions of pharmaceutical compounds is a significant part of pharmaceutics, which is based on the application of principles of organic chemistry and physical chemistry to pharmaceutical systems..

For the sake of clarity all matters other than the drug, its chemical name and structure were part of the common general knowledge by the earliest asserted priority date of 6 February 1999, with the drug and its qualities as identified at the Stockholm symposium being part of the common general knowledge of the skilled addressee by 30 June 2000.

##### The “starting point” issue

###### The competing positions

There was an issue between the parties which they described as the identification of the relevant “starting point”. When dealing with the ground of obviousness resulting in invalidity of the patents, the generic parties submitted that for each patent the starting point is knowledge of rosuvastatin, a known agent. Watson and Ascent submitted that:

The starting point for the determination of obviousness resides in the problem identified on the face of the specification. A hypothetical skilled worker is taken to know the nature of the problem to be solved.

Apotex noted that AZ’s approach, which denies knowledge of rosuvastatin for the purpose of determining the validity of each of the patents, attempts to “rebadge the inventiveness associated with the discovery of rosuvastatin itself (that is, the invention made by Shionogi and which is the subject matter of the 471 Patent) as inventiveness associated with the” inventions claimed in each patent – in the case of the 051 or low dose patent an obvious dosing regime of a known compound, in the case of the 165 or HeFH patent the use of a known compound for a known purpose, and in the case of the 842 or cation patent, the use of a known technique to stabilise the known compound.

Apotex submitted that for AZ’s approach to be accepted, that rosuvastatin cannot form part of the starting point for the stated problems in each patent unless rosuvastatin can be shown to be part of the common general knowledge, would be inconsistent with decisions binding on this court. In Apotex’s words:

The correctness of a “starting point” approach was confirmed by the Full Court in *Apotex Pty Ltd v Sanofi-Aventis* [(2009) 82 IPR 416 at [152]-[153]] (clopidogrel), applying the approach taken by the High Court in [Aktiebolaget]That approach was not merely the concession of counsel. It was the way in which the High Court analysed obviousness. In Apotex the relevant patent claims were to an enantiomer of clopidogrel. Knowledge of the relevant racemate was not part of the common general knowledge in Australia, but the Full Court said that this racemate could be taken as part of the starting point for considering inventive step. The Full Court said that the patent made it clear that selection of the racemate to be resolved into its enantiomers did not form part of the invention.

Similarly, in *Alphapharm* [*Aktiebolaget Hassle v Alphapharm Pty Ltd* (2000) 51 IPR 375; [2000] FCA 1303 at [75] and [80]], the compound omeprazole was not part of the common general knowledge in Australia, but the Full Court said that because the problem to be solved was the instability of omeprazole, this had to be the starting point from which to test the inventive step of the particular formulation of omeprazole claimed in the patent. The High Court applied the same approach.

Such an approach is consistent with, for example [*Wellcome*]where Aickin J set out the following test, [at 262]:

The test is whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they be the steps of the inventor or not.

See also *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* [(2007) 235 CLR 173; [2007] HCA 21] and *Allsop Inc v Bintang Pty Ltd* [(1989) 15 IPR 686].

See the argument before the High Court in *Sanofi-Aventis v Apotex Pty Ltd* at HCA Trans 59 (12 March 2010). See also the analysis by Gyles J. in *Apotex Pty Ltd v Sanofi-Aventis* (2008) 78 IPR 485 [2008] FCA 1194], [96]-[107]. Each of *Alphapharm* and *Apotex v Sanofi-Aventis* was decided under the 1990 Act. The clopidogrel patent was revoked under s138(3) for obviousness. Because they were “old Act” patents, by s233(4), the ground had also to be available under the Patents Act 1952.

…

It is plain that (apart from the extension of common general knowledge by the reference to s7 (3)), s7 (2) is intended to express the earlier law on the assessment of inventive step. To assess the step, one must postulate a starting point and a finishing point. The finishing point is clearly the invention as claimed. The assessment of whether the step is inventive is carried out through the eyes of “a person skilled in the relevant art in the light of the common general knowledge as it existed in the patent area before the priority date of the relevant claim … [and, where relevant, the s7(3) information]”.

The ratio of *Minnesota Mining and Manufacturing Co. v Beiersdorf* (1980) 144 CLR 253 [[1980] HCA 9] is that that assessment must be made in the light of common general knowledge and not in the light of a number of prior specifications. These were “not capable of sustaining [the argument that the invention was obvious] without evidence that they were part of common general knowledge of that time”. Aickin J. referred to some evidence of the kind of surgical tapes in use by the priority date [at 295]:

This evidence showed what kind of products would have been the common general knowledge in Australia as well as the nature of the problem awaiting solution .

As noted and applied in *Alphapharm* the High Court returned to the question of the problem solved by the inventor in [*Wellcome*],286.

Each of the above authorities take the starting point of the asserted inventive step (to the claim) as the problem that the invention addresses.

As the High Court points out in *Alphapharm* and *Lockwood (No. 2)*, a problem/solution analysis can be but might not always be suitable. Here on the face of the specification, it plainly is: a need or problem or objective is stated – “it is important to find dosages of [the Agent] …”.

The existence of s7(3) and the reference to it in s7(2) does not change this analysis. The remaining possibility is that the introductory words of s7(2) have changed the law. Apotex wishes respectfully to maintain the point that they have, and by reference to the prior art base, the definition in Schedule 1 is invoked and information in a document publicly available in or outside the patent area may be taken into account whether or not it is common general knowledge. That is what IPAC recommended, what the Intellectual Property Laws Amendment (Raising the Bar) Act 2012 has made more clear, and what has been the law in the UK since the Patents Act 1977 .

This argument was rejected by the Court in *Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No. 3)* (2011) 92 IPR 320; [[2011] FCA 846] [229]-[230]. In short, the Court treated the introduction words “taken to involve an inventive step when compared with the prior art base” as a composite phase [there is no dispute that it is a deeming provision] “that operates directly upon s.18(1) (b)” – at [230]. The effect of that direct operation is to decline to allow the sub-section to operate via the definition. Apotex respectfully submits that that is incorrect.

In the alternative, if s7(2) does not invoke the definition of prior art base, then (subject to the extension to s7(3)) the effect of s7(2) is precisely the same as s100(e) of the Patents Act 1952. In that event, Apotex respectfully submits that the judgments in *Aphapharm*, *Lockwood (No. 2)* and *Apotex v Sanofi-Aventis* are binding: the problem-solution starting point approach is appropriate here. *Lockwood (No. 2)* concerned a 1990 Act patent. The argument based on the definition of “prior art base” could not be advanced in *Alphapharm* or *Apotex v Sanofi-Aventis* (clopidogrel) because the ground was not available under the 1952 Act. It is here.

AZ’s primary response is that:

…the “starting point” approach is incompatible with the provisions of the Act and thus incorrect as a matter of principle. As noted, inventive step is to be assessed in accordance with s 7(2). That provision deems an inventive step to be present “unless the invention would have been obvious to a person skilled in the relevant art” in the light of the common general knowledge with any available s 7(3) information. There is no room for any resort to information which is not either part of common general knowledge or available under s 7(3). In particular, there is no room for any resort to information simply because it is referred to in the specification of the patent, whether it be expressed as a “starting point” or problem to be addressed or otherwise [citing *Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No 3)* (2011) 196 FCR 1 [[2011] FCA 846;] at [230]; *Wake Forest University Health Sciences v Smith & Nephew Pty Ltd (No 2)* (2011) 92 IPR 496 [[2011] FCA 1002] at [701]-[717]].

According to AZ, the decision of the Full Court in *Apotex Pty Ltd v Sanofi-Aventis* (2009) 82 IPR 416; [2009] FCAFC 134 (*Apotex*) is irrelevant because it proceeded on an agreed basis under the *Patents Act 1952* (Cth) and, in any event, the Full Court’s reasons were concerned with the particular facts of that case based on the specification in suit. Further, no endorsement of the approach is to be found in the decision of the High Court in *Aktiebolaget Hassle* *Pty Ltd v Alphapharm* (2002) 212 CLR 411; [2002] HCA 59] (*Aktiebolaget*) which proceeded on the basis of a concession by Senior Counsel for the patentee that the hypothetical skilled worker was to be “taken to know the nature of the problem to be solved” (at 415). AZ also said:

Statements about the hypothetical skilled person being “faced with the same problem” as the inventor do not indicate any warrant for expanding the prior art base. If the problem itself is part of the common general knowledge, then there is nothing objectionable or unorthodox in that proposition. If the problem is not part of the common general knowledge then the hypothetical skilled person would not be facing it because the hypothetical skilled person only has access to the common general knowledge.

AZ also submitted that, irrespective of this issue, the generic parties’ approach involved the wrong starting point at least for the 051 or low dose patent. In AZ’s words, the “problem” identified in the specification:

does not assume rosuvastatin as a starting point. It is not a problem about what to do with rosuvastatin. The reference to “currently marketed statins” contemplates drugs that were currently on the market as pharmaceutical products, which did not include rosuvastatin. The “problem”, as stated, is to find “dosages of alternative statins”. The claimed method of treatment involving the administration of rosuvastatin is presented as the solution to that problem. The generic parties’ submissions and questions in cross-examination repeatedly ignore the expression “alternative statins” (plural).

The fact that the specification elsewhere states that rosuvastatin is disclosed in EP 0521471 and Watanabe is not to the point. This is simply a means of identifying rosuvastatin as the compound which the inventor selected or chose to use for what ultimately became a new method of treatment. It does not make rosuvastatin part of the problem or “starting point”. Further, there is no admission that rosuvastatin was part of the common general knowledge.

According to AZ the present case is analogous to that considered by Bennett J in *Danisco A/S v Novozymes A/S (No 2)* (2011) 91 IPR 209; [2011] FCA 282 (*Danisco*) (but note also *Novozymes A/S v Danisco A/S* [2013] FCAFC 6) in which Bennett J rejected the submission of the party challenging validity that an enzyme identified in the specification had to be considered as part of the “starting point” for the assessment of obviousness because (at [345]):

Even if the Poulsen enzyme was not part of the invention, the problem was not what to do with the Poulsen enzyme. The problem was the in situ creation of functional ingredients in the foodstuff so as to eliminate the need to list additives.

AZ said that in the present case

to the extent that there is a problem identified in the specification, it was the need for dosages of alternative statins which beneficially alter lipid levels to a significantly greater extent than similar dosages of currently used statins and which have a similar or greater safety profile. The identification, appreciation, development and use of rosuvastatin in the method of the invention is presented as the solution to that problem, not as part of the problem itself, or the “starting point”.

It should also be noted that the generic parties and AZ each maintained that if their competing approaches were not accepted then, in any event, their competing arguments as to invalidity nevertheless should succeed on other bases. In other words, resolution of these issues is not determinative of any party’s case.

###### The cases

Analysis of the cases indicates that the parties’ submissions sought to elevate to a question of principle an issue which must be determined on a case-by-case basis having regard to the terms of the particular patent in suit. For example, in *Danisco* at [326] one principle which Bennett J identified as orthodox having regard to the reasons “as enunciated by the High Court in *Aktiebolaget*, *Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 2)* (2007) 235 CLR 173 [(*Lockwood v Doric (No 2)*] and *Wellcome* and by the Full Court in *Lundbeck* [*H Lundbeck A/S v Alphapharm Pty Ltd* (2009) 177 FCR 151; [2009] FCAFC 70] and *Apotex*”, and which was not disturbed in *Novozymes A/S v Danisco A/S* [2013] FCAFC 6, is that:

In assessing obviousness, it is necessary first to determine the nature of the claimed invention and the inventive step described in the Patent. This may involve ascertaining the “starting point” of the inventive step, sometimes described in terms of an existing problem for which the inventor found a solution. The obviousness of the invention as claimed is then assessed by reference to common general knowledge in Australia at the priority date.

Further, and as Bennett J said at [329] in *Danisco*:

The fact that a specification makes reference to earlier patents or patent applications does not necessarily amount to an admission that those documents were part of common general knowledge. It depends on the description of the invention in the patent under consideration. It may also reflect the inventor’s own journey, especially where the references are to the inventor’s own work (*Apotex* at [162], discussing *Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20 [2008 FCAFC 139).

At [344] as well, Bennett J made a similar point, saying “[a]scertaining a starting point is particularly apposite where the specification is drafted to describe a problem and a solution to that problem”.

In other words, the terms of the specification and claims inform the identification of the relevant starting point for the assessment of obviousness. Contrary to AZ’s submission, this does not involve placing an impermissible gloss on the statutory provisions. Sections 7(2) and (3) of the Act (in their applicable form) pre-suppose the existence of “an invention”. Characterisation of the invention depends on the terms of the claims construed in the context of the specification as a whole. This point was made in *Apotex* at [152] in which the Full Court said the question “whether the invention, so far as claimed in the particular claim, is obvious and does not involve an inventive step…requires a determination of the invention, as described in the specification” (recognising that the claims may claim something less than the whole of the invention in the specification). Although this approach to the question of obviousness was involved in the provisions of the *Patents Act 1952* (Cth), the versions of ss 7(2) and (3) applicable in the present case also focus on the invention compared to the prior art base. It thus remains the case that, as the Full Court said at [152], “[t]he invention to be assessed for obviousness is ascertained from the patent and the obviousness or inventive step of the invention as claimed is then assessed by reference to common general knowledge in Australia at the priority date”.

This approach accords with *Aktiebolaget*. At [21] the High Court made the general point that:

It is worth repeating what was said by Lord Diplock in *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [[1972] RPC 346 at 362]:

"Once an invention has been made it is generally possible to postulate a combination of steps by which the inventor might have arrived at the invention that he claims in his specification if he started from something that was already known. But it is only because the invention has been made and has proved successful that it is possible to postulate from what starting point and by what particular combination of steps the inventor could have arrived at his invention. It may be that taken in isolation none of the steps which it is now possible to postulate, if taken in isolation, appears to call for any inventive ingenuity. It is improbable that this reconstruction a posteriori represents the mental process by which the inventor in fact arrived at his invention, but, even if it were, inventive ingenuity lay in perceiving that the final result which it was the object of the inventor to achieve was attainable from the particular starting point and in his selection of the particular combination of steps which would lead to that result."

Whether the particular starting point is or is not part of the invention cannot be considered in isolation from the terms of the particular patent.

Similarly, in *Lockwood v Doric (No 2*) the High Court at [59] acknowledged that for a particular patent it may be instructive to start with reference to the statement in Fletcher Moulton, *The Present Law and Practice Relating to Letters Patent for Inventions*, (1913) at 24 that:

An invention may, and usually does, involve three processes. Firstly, the definition of the problem to be solved or the difficulties to be overcome; secondly, the choice of the general principle to be applied in solving this problem or overcoming these difficulties; and thirdly, the choice of the particular means used. Merit in any one of these stages, or in the whole combined, may support the invention…

This is not to say that the assessment of inventiveness is limited by the “problem-solution” approach. The terms of the patent must be examined to ascertain whether the approach is appropriate. Moreover, as the High Court said at [65] in *Lockwood v Doric (No 2* the approach may not reflect the fact that “a small amount of ingenuity can sustain a patent in Australia”. This is the basis for the observation of the Full Court in *Apotex* at [159] that:

The High Court now makes it apparent that it does not reject such an approach, where appropriate. The question of obviousness is not confined to a problem/solution approach. It may not be appropriate or sufficient where, for example, no skilled person in the art had thought of a general idea or general method of solving a known difficulty with respect to a known product or where the appreciation that there was a problem with a known product was itself part of the inventive concept. As the High Court [in Lockwood] said at [105], while not every invention constitutes a solution to a problem, it is commonplace so to describe an invention where it is appropriate to do so. However, admissions about a problem in a specification need to be weighed with evidence of the perception of any problem by the person of skill in the relevant art, before exposure to the solution contained in the invention.

It follows that references to the correct “starting point” and the “problem-solution” approach, expressed at the level of principle, are not particularly helpful. As the terms of the statute and the cases disclose close attention to the terms of the specification is required in order to characterise the invention. The relevant comparison is between the invention and the prior art base in order to determine obviousness.

I do not accept Apotex’s additional argument that the introductory words of s 7(2) of the Act changed the law so that information in a document publicly available may be taken into account whether or not it is common general knowledge. The argument was considered and rejected in *Sanofi-Aventis Australia Pty Ltd v Apotex Pty Ltd (No. 3)* (2011) 196 FCR 1; [2011] FCA 846 at [229]-[230] (*Apotex No. 3)* and *Wake Forest University Health Sciences v Smith & Nephew Pty Ltd (No 2)* (2011) 92 IPR 496 [2011] FCA 1002 at [701]-[717]. As Dodds-Streeton J said in the latter case:

[712] [This] construction may be open on a literal reading of s 7(2), which by the words “when compared with the prior art base” picks up the s 18(1)(b) requirement for a comparison with the prior art base. It was, however, ultimately unpersuasive.

[713] Section 7(3) sets out with precision the information to which the skilled person may have access and imposes multiple restrictive preconditions. [This] construction would render s 7(3) largely irrelevant (but not otiose, as s 7(3) potentially allows items to be combined). It is improbable that a radical assimilation to the UK position, which the High Court recognises as divergent, would be effected so obliquely. The position which would result was not recommended by IPAC and is inconsistent with the relevant authority.

[714] [This] construction also appears inconsistent with that adopted by the Full Federal Court in *Insta Image* …at 35–36 [*Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* ; [2008] FCAFC 139].

I find this reasoning persuasive.

###### The inventions

The 051 or low dose patent

The asserted priority date of the 051 or low dose patent is 6 February 1999. As discussed, I do not consider that as at 6 February 1999 the existence of the compound rosuvastatin was part of the common general knowledge of the skilled addressee of this patent (such awareness entered the common general knowledge, in my view, on or about 30 June 2000).

This is not a case involving any concession that rosuvastatin is a “given”. As AZ correctly said, in this sense, the case is not analogous to *Aktiebolaget Hässle v Alphapharm Pty Ltd* (2000) 51 IPR 375; [2000] FCA 1303 in which it was said at [75] that:

Astra accepted the proposition that the hypothetical formulator must be assumed to have had access to the Compound Patent. The rationale of this acceptance must be that it is possible to postulate the existence of a skilled person, concerned at the priority date to formulate omeprazole, only in the context of that person having decided, or been instructed, to formulate the drug. As such a decision or instruction would be unimaginable in the absence of the decider or instructor having information about the basic characteristics of omeprazole, it must be assumed the hypothetical formulator has found, or been given, that information, or, at least, been told where it may be obtained. So it makes sense to assume access to the Compound Patent.

However, the statute requires the invention as claimed to be compared with the common general knowledge. The invention is defined by the terms of the patent. In the case of the 051 or low dose patent AZ’s position that by reason of the terms of ss 7(2) and (3) the invention can somehow include discovering the existence of rosuvastatin is inconsistent with the terms of the patent. The specification identifies the invention in a manner that pre-supposes the existence of rosuvastatin. It is not necessary to make use of the prior art disclosing the existence of rosuvastatin referred to in the specification to reach this conclusion. It is apparent from the terms of the specification as a whole. The invention relates to the dosage range for rosuvastatin. The inventive concept is in the dosage range alone. So much is plain from the opening paragraph of the specification. The subsequent reference to it being important to find dosages of alternative statins does not make knowledge of rosuvastatin any part of the inventive concept. For the purposes of the invention as disclosed the specification itself makes rosuvastatin a given and locates the inventive concept in the discovery of a dosage range. If the language of problem-solution is apt, the problem is not finding dosages of alternative statins and rosuvastatin is not the answer to that problem. The problem is the dosage range of rosuvastatin itself to achieve the objective of lowering cholesterol without significant side effects and the answer to that problem is the dosage range of 5 to 80mg of rosuvastatin. Claim 1, for example, then claims as an invention part only of that dosage range as a starting dose, being a single once daily dose of 5 to 10mg of rosuvastatin.

Contrary to AZ’s submissions I do not find it absurd to treat rosuvastatin as a given in respect of this invention when, as noted, I consider that knowledge of rosuvastatin did not become common place for the hypothetical skilled addressee of the patent in Australia until nearly 18 months after the asserted priority date. This is because the statute focuses on the invention and the invention is defined by the terms of the patent. In the case of the 051 or low dose patent the invention is the discovery of a dosage range of a compound assuming that the existence and nature of the compound is known. Nothing in the patent suggests any inventive activity in respect of rosuvastatin itself or its nature as a HMG-CoA reductase inhibitor. It is not possible to posit the claimed invention without knowing about the existence of rosuvastatin as an HMG-CoA reductase inhibitor.

The reasoning in *Danisco*, on which AZ relied, supports this conclusion rather than AZ’s case. This because Bennett J in *Danisco* stressed that it is necessary first to determine the nature of the claimed invention and the inventive step described in the patent.

AZ’s submission that the “identification, appreciation, development and use of rosuvastatin in the method of the invention is presented as the solution to that problem, not as part of the problem itself, or the “starting point””, the problem being “the need for dosages of alternative statins which beneficially alter lipid levels to a significantly greater extent than similar dosages of currently used statins and which have a similar or greater safety profile”, cannot stand with the terms of the patent. The patent recognises a fact that was part of the common general knowledge at the time, namely, that finding dosages of alternative statins is important because not all patients respond well to existing statins. But nothing suggests anything inventive about the identification of rosuvastatin as an HMG-CoA reducatase inhibitor. The invention, as noted, lies in the identification of a dosage range of a compound assumed by the patent to be a known HMG-CoA reducatase inhibitor.

The 165 or HeFH patent

The invention disclosed in the 165 or HeFh patent also pre-supposes the existence of rosuvastatin as a statin (that is, as an HMG-CoA reductase inhibitor). The invention is the use of that known compound to treat HeFH. The discovery or inventive concept is said to be that rosuvastatin is particularly good at treating HeFH, particularly severe HeFH when existing statins typically have to be used in combination with other therapies to treat HeFH.

It should also be noted in respect of the 165 or HeFH patent that the asserted priority date is 22 November 2000. For the reasons already given, I am satisfied that rosuvastatin and its performance as an HMG-CoA reducatase inhibitor as disclosed at the 12th International Symposium on Atherosclerosis in June/July 2000 was part of the common general knowledge of the skilled addressee of the 165 or HeFH patent before the asserted priority date.

The 842 or cation patent

The asserted priority date of the 842 or cation patent is 26 January 2000. As set out above, I do not accept that rosuvastatin was part of the common general knowledge of the skilled addressee of the 842 or cation patent at this time.

However, the invention claimed in the 842 or cation patent has nothing to do with the discovery or, as AZ would have it, the synthesis of rosuvastatin. The invention is a pharmaceutical composition containing rosuvastatin as its active ingredient. The idea that finding or synthesising rosuvastatin has anything to do with the invention claimed is without foundation. Accordingly, the submission of AZ that the statute mandates the notion that obviousness is to be tested assuming that the skilled addressee has no knowledge of rosuvastatin or its chemical formula is misconceived. As discussed, AZ’s approach seems to disregard the actual invention claimed, contrary to the terms of the statute. If the invention is not disregarded on AZ’s approach then, at the least, it is fundamentally recreated as an invention different from that actually claimed. For the 842 or cation patent, the invention becomes or includes discovering rosuvastatin and its chemical structure and being able to synthesise rosuvastatin. Yet, from the terms of the 842 or cation patent, it is clear that the discovery or synthesis of rosuvastatin has nothing to do with the claimed invention. The invention lies in the formulation of a particular pharmaceutical composition of rosuvastatin. The formulation, which requires the addition of an inorganic salt in which the cation is multivalent, involves improved stability than achieved for other similar compounds by raising the pH. It is that formulation and nothing else which constitutes the invention claimed.

Conclusions about inventions

As should be apparent, I consider AZ’s approach to the inventions in each patent to be untenable. Whilst on the one hand stressing that strict observance must be paid to the terms of the statute (specifically, the common general knowledge requirements as defined in ss 7(2) and (3)) AZ also on the other hand disregarded the other key requirement of these provisions which involve the invention as claimed. Comparison between the inventions as claimed and the version of the inventions which underlies AZ’s submissions exposes the discrepancy. Hence, on AZ’s case, for the 051 or low dose and the 165 or HeFH patents, the invention becomes or includes discovering rosuvastatin as an HMG-CoA reducatase inhibitor when the claimed invention suggests no such thing. For the 842 or cation patent, the invention becomes or includes discovering rosuvastatin and its chemical structure and being able to synthesise rosuvastatin.

I have referred to the version of the inventions which underlies AZ’s submissions because AZ has described its argument as a result of the terms of ss 7(2) and (3). For this purpose, assume rosuvastatin never formed part of the common general knowledge as referred to in s 7(2). AZ would have it that it necessarily follows that in performing the task s 7(2) requires, knowledge of rosuvastatin must be assumed not to exist because it did not form part of the common general knowledge. But the common general knowledge is only part of the statutory equation. Section 7(2) requires the invention to be compared with the prior art base. If, as here, the invention pre-supposes the existence of rosuvastatin as an HMG-CoA reductase inhibitor the required comparison would be distorted by assuming out of existence the factual predicate for the invention. The effect of doing so is necessarily to transform the invention into something which includes the discovery of rosuvastatin as an HMG-CoA reductase inhibitor when no such invention was claimed. In other words, the approach of the generic parties does not undermine the statutory element of the common general knowledge. AZ’s approach undermines the statutory element of the invention.

##### CONSTRUCTION ISSUES

###### Construction principles

The principles relating to the construction of patents are well settled. Those principles include that:

* a specification should be given a purposive construction rather than a purely literal one;
* the hypothetical addressee of the specification is the non-inventive person skilled in the art before the priority date;
* the words used in a specification are to be given the meaning the hypothetical addressee would attach to them, both in the light of the addressee’s own general knowledge and in the light of what is disclosed in the body of the specification;
* as a general rule, the terms of the specification should be accorded their ordinary English meaning;
* evidence can be given by experts on the meaning those skilled in the art would give to technical or scientific terms and phrases, and on unusual or special meanings given by such persons to words which might otherwise bear their ordinary meaning;
* however, the construction of the specification is for the court, not for the expert. In so far as a view expressed by an expert depends upon a reading of the patent, it cannot carry the day unless the court reads the patent in the same way.

(*Flexible Steel Lacing Co v Beltreco Ltd* (2000) 49 IPR 331; [2000] FCA 890 at [81] as cited in *PAC Mining Pty Ltd v Esco Corporation* (2009) 80 IPR 1; [2009] FCAFC 18 at [29]).

In addition to the basic principle that the claims of a patent are to be construed as they would be by the skilled addressee based on the common general knowledge available to that person and in light of the information in the specification, some other principles are also material to the issues of construction in these proceedings. Those principles were succinctly identified by Bennett J in *Danisco* at [37]-[38] in these terms:

[37] …

* A patent is not a written instrument operating inter partes but a public instrument which must, if it is to be valid, define a monopoly in such a way that is not reasonably capable of being misunderstood: *Welch Perrin and Co Pty Ltd v Worrel* (1961) 106 CLR 588 at 610 (*Welch Perrin*).
* The invention is ascertained from a fair reading of the specification of a whole. If it is impossible to do so that “is an end of the matter”: *Welch Perrin* at 610.
* If a verbal or grammatical question can be resolved according to the ordinary rules of construction, that does not leave uncertain the ambit of the monopoly claimed: *Welch Perrin* at 610.
* It is not legitimate to narrow or expand the boundaries of monopoly as fixed by the words of a claim by adding to those words glosses drawn from other parts of the specification: *Welch Perrin* at 610.
* If a claim is clear it is not to be made obscure simply because obscurities can be found in particular sentences in other parts of the document: *Welch Perrin* at 610.
* The meaning of the claims and the terms used in the claims may be made clear by using the specification as a dictionary of the jargon of the claims: *Welch Perrin* at 616.
* Once the nature of the invention has been appreciated, it is not to be “demolished” by finding that particular phrases used could, out of context, be ambiguous: *Welch Perrin* at 617.
* The specification must be read as a whole: *Welch Perrin* at 610; *Decor Corporation Pty Ltd v Dart Industries Inc* (1988) 13 IPR 385 at 410 (*Decor Corporation*).
* If words are used in a particular way in a specification whether or not by way of a formal dictionary and thereby it is shown that the draftsman used such words to have a particular meaning, that meaning must be given to those words in the claims: *Decor Corporation* at 410; *Flexible Steel Lacing Company v Beltreco* (2000) 49 IPR 331 ; [2000] FCA 890 at [76]–[77].
* There is a fine line between reading down the words of a patent claim to reflect how a person skilled in the art would understand it in a practical and common sense way and impermissibly limiting the clear words of the claim because the reader skilled in the art would be likely to apply those wide words only in a limited range of all of the situations that they would describe: *Sachtler GmbH & Co KG v RE Miller Pty Ltd* (2005) 221 ALR 373; 65 IPR 605 ; [2005] FCA 788 at [42].
* An essential part of the process of construction involves understanding the nature of the invention described and claimed and the way in which the patentee has used words or phrases describing and then claiming the invention. It is appropriate to try to understand what the patentee seeks to convey by the words used, especially where those words convey matters of biological or technological complexity: *Inverness Medical Switzerland GmbH v MDS Diagnostics Pty Ltd* (2010) 85 IPR 525; [2010] FCA 108 at [15] (*Inverness*).
* The patentee must define the invention with sufficient precision to permit the monopoly to be determined and to allow the general public to identify from the words of the claims the conduct prohibited: *British United Shoe Machinery Co Ltd v A Fussell & Sons Ltd* (1908) 25 RPC 631 at 650–1; *Clorox Australia Pty Ltd v International Consolidated Business Pty Ltd* (2006) 68 IPR 254; [2006] FCA 261 at [18].
* If the monopoly as defined by the claims is reasonably capable of being misunderstood, it is open to the court to conclude that the terms of the specification are so ambiguous that a proper construction must always remain a matter of doubt. In such circumstances the duty of the court would be to declare the patent void: *Martin v Scribal Pty Ltd* (1954) 92 CLR 17 at 59 per Dixon CJ.
* The fact that there are alternative constructions of a claim does not mean that the claim is invalid for want of clarity: *Welcome Real-Time SA v Catuity Inc* (2001) 113 FCR 210; 51 IPR 327 ; [2001] FCA 445 at [167]–[168].

[38] It is accepted that a claim is not to be construed with an eye to the infringing article, nor should it be construed with an eye to the prior art. However, it is a fact and is well understood that patentees may draft a claim with knowledge of the prior art and in order to avoid anticipation.

The Full Court’s observations in *Kinabalu Investments Pty Ltd v Barron & Rawson Pty Ltd* [2008] FCAFC 178 at [44] are also important. Accordingly:

When determining the nature and extent of the monopoly claimed, the specification must be read as a whole. But as a whole it is made up of several parts which have different functions. The claims mark out the legal limits of the monopoly granted. The specification describes how to carry out the process claimed and the best method known to the patentee of doing that. Although the claims are construed in the context of the specification as a whole, it is not legitimate to narrow or expand the boundaries of monopoly as fixed by the words of a claim, by adding to those words glosses drawn from other parts of the specification. If a claim is clear and unambiguous, it is not to be varied, qualified or made obscure by statements found in other parts of the document. It is legitimate, however, to refer to the rest of the specification to explain the background of the claims, to ascertain the meaning of technical terms and resolve ambiguities in the construction of the claims.

Watson and Ascent also referred to the observations of Middleton J in *Britax Childcare Pty Ltd v Infa-Secure Pty Ltd* (2012) 290 ALR 47; [2012] FCA 467 at [273] as follows:

Furthermore, in reading the claims, it must be borne in mind that “a claim is a description of an invention which it is intended to be put to practical use.” (*Stanway Oyster* at 582) [*Stanway Oyster Cylinders Pty Ltd v Marks* (1996) 66 FCR 577]. In *Ranbaxy Australia v Warner-Lambert* [*Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC (No 2)* (2006) 71 IPR 46; [2006] FCA 1787] at first instance, Young J said at [126] in relation to the claim in issue that it “must be construed in a practical, common sense manner, with an eye to the utility of the invention, and avoiding a construction which is overly meticulous or unduly technical …”. So, if on one construction, an embodiment of the invention would be absurd or surprising, and on another construction — read with a measure of common sense — the embodied invention is plainly practical, the latter construction is to be preferred: *Stanway Oyster* at 583.

This followed his Honour’s comment at [272] that:

There are two oft-cited dangers associated with the purposive approach. The first is reading down, or expanding the plain words of the patent claims by drawing an impermissible gloss from the specification in an attempt to read in the claims in context: *Inverness Medical Switzerland GmbH v MDS Diagnostics Pty Ltd* (2010) 85 IPR 525 ; [2010] FCA 108 at [15]; and *Sachtler* [*Sachtler GmbH & Co KG v RE Miller Pty Ltd* (2005) 65 IPR 605 ; [2005] FCA 788] at [42]. The second is crossing the fine distinction between reading down the words of a patent to reflect how the skilled addressee would understand them in a practical common sense way, and impermissibly limiting the words of the claim because a person skilled in the art would likely to apply those words only in a limited range of situations*: Stanway Oyster Cylinders Pty Ltd v Marks* (1996) 66 FCR 577 at 585; *Inverness* at [15]; *Sachtler* at [42]; *Norton & Gregory Ltd v Jacobs* (1937) 54 RPC 271. As the Full Court noted recently, there is no warrant for adopting a method of construction giving the patentee what they may have wished to claim, rather than what the words of the claim actually say: see the Full Court in *Australian Mud Co* [*Australian Mud Co Pty Ltd v Coretell Pty Ltd* (2011) 93 IPR 188 ; [2011] FCAFC 121]. Further, as the Full Court reminded us recently, a patentee may have good reason for introducing a limitation into a claim: see *Kimberly-Clark v Multigate Medical Products*[(2011) 92 IPR 21; [2011] FCAFC 86] at [45] per Greenwood and Nicholas JJ.

Middleton J explained the purposive approach to construction at [270], noting that there is often a:

delicate balance that is to be struck between confining a patentee to their claims, and recognising that there is often more than one possible construction of the language used. The principles of “purposive construction”, now widely accepted in Australia, attempt to meet this task. Of particular relevance…are the following comments of Lord Hoffmann in *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* (2004) 64 IPR 444 ; [2004] UKHL 46 beginning at [32]:

Construction, whether of a patent or any other document, is of course not directly concerned with what the author meant to say. There is no window into the mind of the patentee or author of any other document. Construction is objective in the sense that it is concerned with what a reasonable person to whom the utterance was addressed would have understood the author to be using the words to mean. Notice, however, that it is not, as is sometimes said, “the meaning of the words the author used”, but rather what the notional addressee would have understood the author to mean by using those words. The meaning of words is a matter of convention, governed by rules, which can be found in dictionaries and grammars. What the author would have been understood to mean by using those words is not simply a matter of rules. It is highly sensitive to the context of, and background to, the particular utterance. It depends not only upon the words the author has chosen but also upon the identity of the audience he is taken to have been addressing and the knowledge and assumptions which one attributes to that audience …

###### Starting dose

The generic parties said the starting dose is just the first dose given to a patient. Further, that the expert evidence otherwise indicated (as I accept it did) that it was common practice of clinicians treating hypercholesterolemia to prescribe a starting dose at the lower end of the range consistent with efficacy and thereafter to raise the dose as necessary (dose titration) unless some specific risk factor warranted a more aggressive approach to the starting dose. As some of the clinicians who gave evidence, such as Professor Tonkin, tended to see patients with those specific risk factors more often than others, Professor Tonkin’s practice often involves a higher starting dose than might otherwise be the case for patients with a lower risk profile. AZ said that the “starting dose” may be the continuing dose. Without the dose being increased, the patients would thereafter remain on the “starting dose” on a continuing basis.

In the context of claim 1 of the 051 or low dose patent I do not accept that the reference to a “starting dose” includes a continuing dose merely because the patient may remain on the starting dose. It is not apparent to me that, in context, “starting dose”, has anything other than its ordinary meaning of initial dose. Claim 1 refers to a method of treatment which comprises administration “as a starting dose” of the drug. “As a starting dose” means precisely that – the initial dose which the patient is prescribed. No doubt a dose continues to be a “starting dose” for some period of time, but I do not accept that a dose retains this character indefinitely merely because the patient’s dose is never increased. At some point, which would need to be determined on a patient-by-patient basis, the starting dose becomes the dose. If expert evidence is relevant to this issue then the opinion of Professor Tonkin accords with common sense. Professor Tonkin said:

It’s a matter of nomenclature. I think at one stage - some stage patients transfer, if you like, from being on a starting dose to being on a maintenance dose. And if you have gone through a process whereby you might have assessed that patient for their response and you’ve made the decision not to increase that dose I think it becomes a maintenance dose at some stage. That is what I was referring to, which may be the same as the starting dose.

…

It is the same as the starting dose, but I think two years down the track I would certainly think it’s the maintenance dose, which I think would be in many patients inappropriately low.

Accordingly, where used in claim 1 of the 051 or low dose patent “a starting dose” means the initial dose prescribed to a patient. If the dose is thereafter increased, the patient is no longer on the starting dose. If the dose is thereafter not increased, then the patient may or may not be on the starting dose depending on the circumstances including, in particular, the length of time for which the patient has been on the dose. At some point, to be determined on a case-by-case basis, all patients who continue to take the medication move from taking a starting dose to taking a dose or a maintenance dose as Professor Tonkin described it. Claim 1 is concerned only with the starting dose.

###### Pharmaceutical composition

The phrase “pharmaceutical composition” is used in the claims of both the 051 or low dose patent and the 842 or cation patent, including in claim 1 of each of these patents. The phrase does not necessarily take the same meaning in each of the patents as the context is different, but the real dispute between the parties concerned the 842 or cation patent.

Claim 1 of the 842 or cation patent refers to “[a] pharmaceutical composition comprising [the Agent] or a pharmaceutically acceptable salt thereof as the active ingredient and an inorganic salt in which the cation is multivalent, provided that…”. The real controversy between the parties related to the phrase as it appears in claim 1 of the 842 or cation patent.

AZ’s case is that “pharmaceutical composition”, as it appears in claim 1 of the 842 or cation patent (and, for that matter, in the 051 or low dose patent), simply means the means by which the active pharmaceutical ingredient (in this case, rosuvastatin) is administered or delivered to the patient, in whatever form. Accordingly, if the form of the pharmaceutical composition is a coated tablet then the tablet as coated is the pharmaceutical composition.

The generic parties submitted that in the context of the 842 or cation patent “pharmaceutical composition” should be construed as excluding the mere coating on a tablet, with the consequence that the inorganic salt in which the cation is multivalent must be admixed with or in intimate contact with the active pharmaceutical ingredient, being the rosuvastatin. The generic parties put this submission in multiple ways.

Apotex said that:

When read in the context of the specification, it is clear that:

• The term “pharmaceutical composition” refers to a mix or blend of rosuvastatin and an inorganic salt in which the cation is multivalent which is then made into the desired dosage form;

• The word “and” further conveys the notion that the inorganic salt in which the cation is multivalent is mixed or blended together with rosuvastatin in the pharmaceutical composition.

According to Apotex, AZ’s construction, in which “the claim does not require any mixing or blending of the rosuvastatin (being the agent sought to be stabilised) and the inorganic salt with the multivalent cation (being the stabilising agent), with the consequence that they can be present in separate and distinct parts of a formulation (i.e. rosuvastatin in the tablet core and ferric oxide or titanium dioxide in the tablet coating)” is untenable for nine reasons.

First, it is said that AZ’s construction “ignores the description of the “invention” in the specification”. This argument relies on the fact that the specification refers to the pharmaceutical composition on numerous occasions before any reference is made to a coating. The concept of a coating appears on p 6, after the preparation of the “pharmaceutical composition of the invention” is described on p 5. The specification says “[a] tablet coating may then be applied”. The generic parties emphasised the words “may then” as reinforcing the fact that the pharmaceutical composition exists before the coating, which is optional, is applied. The specification also says “[a]ccordingly we present as a feature of the invention a pharmaceutical composition comprising the Agent, the composition having a ferric oxide light protective coating.” The generic parties stressed that this formula of words shows that composition exists separately from the coating. It follows, they submitted, that pharmaceutical composition in claim 1 of the 842 or cation patent must mean the pharmaceutical composition excluding any coating. They also submitted that although there is no reference to stability in claim 1 of the 842 or cation patent, the claim should be construed as if it required the stability of rosuvastatin to be achieved.

These submissions appear to involve an attempt to narrow the clear scope of the claim by reference to parts of the specification, contrary to the accepted principles of construction. The construction for which the generic parties contend also operates with an eye to the infringements alleged against them which is similarly impermissible. But for the facts of the present case (on which AZ too no doubt has its eye in respect of its own preferred construction) there would be no warrant for construing “pharmaceutical composition” as it appears in claim 1 of the 842 or cation patent as meaning anything other than the means, method or mode of delivery of the defined agent and the inorganic salt, whatever be that means, method or mode. Nor is any basis apparent for reading into claim 1 a stability requirement.

As the expert evidence, unaffected by considerations of potential infringements disclosed, a pharmaceutical composition may take a multiplicity of forms (gels, emulsions, powders, capsules, tablets and many others). If in the form of a tablet the tablet may be coated in many different ways or a coating may be unnecessary. The pharmaceutical composition, however, is the whole of the means, method or mode of delivery. Nothing in the language of claim 1 suggests in any way that the pharmaceutical composition does not include a coating if the composition happens to be coated. Nor does it suggest that the agent and the inorganic salt must be mixed together by any particular method.

Nor does the principle that the claims must be read in a practical common sense way as the skilled addressee would read them provide support for the approach of the generic parties to this issue. As noted, but for the alleged infringements in this particular case, the experts seemed to accept that a pharmaceutical composition was nothing more than the form in which an active pharmaceutical ingredient was delivered or administered to the patient, the forms being many and varied, including coated and uncoated tablets. Only the facts of this case which (as we shall see) involve the inorganic salt being present only in the coating of the tablets the generic parties wish to supply, caused a different and more limited meaning to be given to the expression “pharmaceutical composition” as it appears in claim 1 of the 842 or cation patent.

Insofar as the justification for the limitation on the ordinary meaning is said to arise from the context which the specification provides, the language of the specification is by no means as supportive as the generic parties assume. The specification discloses that the pharmaceutical composition will include tablets and that the tablets may be coated or uncoated. What the specification does not say is that if there is a tablet that is coated the pharmaceutical composition excludes the coating. A more natural reading of the specification is that it contemplates that the pharmaceutical composition may be a tablet which is coated or uncoated. Either way, the integers of the claim remain. There must be a pharmaceutical composition comprising the agent as defined and an inorganic salt in which the cation is multivalent provided that the inorganic salt is not hydrotalcite or synthetic hydrotalcite and the counter anion to the inorganic salt is not a phosphate.

The references throughout the specification on which the generic parties relied, such as the improvement of stability by selection of an inorganic salt “to be added to the composition”, do not dictate that the addition must be other than by inclusion of the inorganic salt in a coating. Nor does the fact that the specification contemplates that the coating may or may not be used in a tablet assist. If there is no coating then no doubt the inorganic salt will be added to the tablet, howsoever the tablet might be prepared. If there is a coating, then the inorganic salt might be added either in the coating or in the tablet. The concept of an inorganic salt being “added to” the composition might be achieved either way. At the least the concept of being “added to” does not exclude the addition by way of a coating if there is a coating. Similarly, the fact that one preferred embodiment of the invention might exist without a coating does not exclude the fact that another might include a coating. Hence, the reference to “such a composition” having a good flow rate (which is inconsistent with the composition being in tablet form) simply supports the conclusion, which all of the evidence supported, that a pharmaceutical composition may take one of many forms. The references on which the generic parties relied are to one form of composition but do not exclude others, as the terms of the specification, including the references to the preparation of tablets without or with coatings, disclose. Moreover, once it is accepted that a pharmaceutical composition in claim 1 includes a tablet uncoated or coated, the references to an inorganic salt being “in the” composition in the specification make sense. The inorganic salt may be in the composition either by being in the tablet before coating or in the coating.

The fact that the four examples in the specification all include an inorganic salt which is blended with the other ingredients and then prepared into tablets (both coated and uncoated, including a coating with an inorganic salt) does not lead to the construction for which the generic parties contend. By definition, an example is merely one way of performing the invention. Although tribasic calcium phosphate is an inorganic salt in which the cation is multivalent and is blended with the other ingredients in each example, two examples involve a coating in which there is also present (arguably) an inorganic salt. Even if this latter fact is ignored, the examples remain mere examples. Hence, the submission that there is no hint in the examples that “the ferric oxide or titanium dioxide in the coating satisfies the requirement that an inorganic salt in which the cation is multivalent be present in the pharmaceutical composition containing rosuvastatin” may be accepted without advancing the task of the proper construction of the claims, particularly claim 1. Further, the assertion (which, for this purpose, may be assumed to be correct) that the “conditions for the stability tests were extreme and do not provide a reliable basis for determining whether commercially useful stability has been achieved” does not impinge on the proper construction of the claims. Equally, the possible lack of utility of the examples because they involve too many variations in formulation (which also may be assumed to be correct for current purposes) says nothing about construction of the claims.

The same considerations apply to each of the other references in the specification to which the generic parties referred as supporting their construction. Once the basic proposition that a “pharmaceutical composition” in claim 1 is simply whatever form has been chosen to enable delivery or administration of the active pharmaceutical ingredient and that such a form includes tables, be they coated or uncoated, is accepted the references all support the construction for which AZ contends. This approach also has the benefit of starting with the language of the claim in context and giving the claim its apparent meaning without regard to the alleged infringements in this particular case.

Accordingly, the assertion that the words “added to” “do **not** mean that the inorganic salt in which the cation is multivalent is suspended in a layer of cellulose placed on top of a composition containing rosuvastatin” finds no support in the words themselves. To the contrary, something being placed on top of something else, whether suspended in cellulose or otherwise, ordinarily would be considered to involve “adding to”.

Other matters to which the generic parties referred in this context, even if assumed to be correct, seem to have nothing to do with the proper construction of the claims. It may be assumed, for example, that “there is no evidence whatsoever presented in the patent to show that an inorganic salt has any benefit over an organic salt”. It may also be assumed that “there is no evidence whatsoever presented in the patent to show that an inorganic salt in which the cation is multivalent has any benefit over one in which the cation is monovalent”. How these assumed facts might affect the proper construction of the claims remains obscure.

Equally, given that claim 1 says nothing about stability, it is difficult to see how the evidence of a number of the experts hypothesising that stability might be improved by “intimate interaction between the inorganic salt and rosuvastatin and therefore close proximity through mixing or blending” leads to a construction of the claim excluding the presence of an inorganic salt in a coating of a tablet if the tablet happens to be coated.

The submissions in this regard involve arbitrary assertions. On the one hand there is said to be no evidence that adding an inorganic salt does anything to improve stability. On the other hand it is said that a claim which makes no mention of stability should be read as if it required stability to be achieved. This is required not because of anything in the language of the claim but because a number of experts, whose primary position is that adding an inorganic salt does nothing to improve stability over and above the effect achieved by raising the pH, hypothesise that if (contrary to their primary position) adding an inorganic salt does anything, it could have that effect only if admixed with the rosuvastatin and not in a coating on top of the rosuvastatin. Hence, to achieve this (illusory) stability the phrase “and an inorganic salt” in the claim must be read as meaning “and an inorganic salt provided it is not merely in any coating”. The points which the generic parties are making in this regard may be relevant to other issues in the case, but they do not assist in the task of construction. For these reasons the assertion that the “coating on the Apotex tablets will not reduce oxidation and lactonisation of rosuvastatin throughout the tablet” because “only a miniscule amount of the surface of any Apotex tablet will contain particles of rosuvastatin in contact with particles of ferric oxide or titanium dioxide that are in the tablet coating”, if assumed to be true, provides no assistance to the issue of the meaning of the claims, particularly claim 1 of the 842 or cation patent. For the same reasons evidence about the possible stability of Apotex’s tablets by reason of the presence of ferric oxide or titanium dioxide only in the coating is immaterial to the issue of construction. All of this evidence overlooks the basic fact that claim 1 of the 842 or cation patent says nothing about stability.

Second, it is said that AZ’s construction is “contrary to the common sense of a formulation chemist – chemical components cannot be separated from one another and be expected to have the same interaction”. The latter part of this proposition may be accepted but does not assist. The argument seems to be that because the experts either did not believe that presence of an inorganic salt in which the cation is multivalent in a tablet coating could have any beneficial effect on the stability of a tablet containing rosuvastatin or could not adequately explain how it might do so, it must follow that the claimed invention is a pharmaceutical composition in which the rosuvastatin and the inorganic salt are admixed and in intimate contact with each other. In this regard, let it be acknowledged that Professor Kibbe and Drs Oppenheim, Pitman and Rowe did not accept that presence of an inorganic salt in which the cation is multivalent in a tablet coating could have any beneficial effect on the stability of a tablet containing rosuvastatin. Let it also be accepted that Professor Charman and Dr Morella effectively acknowledged that their explanations of how the inorganic salt in the tablet coating might provide a stability benefit involved a hypothesis only (and not one readily understandable by any of the experts propounding them). The fact remains that the language of the claim is clear and provides no justification for construing “pharmaceutical composition” as including a tablet (which it plainly does) but not the coating of the tablet if it happens to be coated. The evidence does not assist in construing the claims.

Third, it is said that AZ’s construction is “contrary to conventional formulation approach, which involves mixing all relevant excipients together”. The problem with this argument is that it overlooks the fact that pharmaceutical compositions also conventionally include tablets which may or may not be coated. It also ignores the fact that coatings perform a range of functions and are often multi-functional. A conventional function of a coating, moreover, includes improving stability of a tablet.

Fourth, it is said that AZ’s construction is “contrary to the invention described in the priority document”. The essence of this submission is that the priority document “disclosed the invention as the use of tribasic phosphate salt – it did not disclose the use of any other inorganic salt in which the cation is multivalent, whether in a tablet core or a tablet coating”. The priority document is UK Patent Application GB 0001621 filed on 26 January 2000. The priority document, however, refers to tribasic phosphate salt as a preferred inorganic salt only. It also does refer to an inorganic salt in which the cation is multivalent. Otherwise the same considerations relevant to the 842 or cation patent apply as set out above. As a result it cannot be said that AZ’s construction is contrary to the invention described in the priority document.

Fifth, it is said that AZ’s construction is “contrary to [AZ]’s discovered documents, in which the relevant ‘inorganic salt’ is always mixed with the rosuvastatin”. The generic parties contend that AZ’s discovered documents are relevant “in that they provide an objective view as to whether a skilled addressee would understand ferric oxide or titanium dioxide in a coating only as being a relevant stabilising inorganic salt with a multivalent cation”. Again, the submission fails to confront the fact that claim 1 says nothing about stability.

Sixth, it is said that AZ’s construction is contrary to AZ’s own commercial product, Crestor, “which has both a coating with ferric oxide and titanium dioxide, as well as tribasic calcium phosphate mixed with rosuvastatin in the tablet core”. AZ’s own commercial product is as immaterial to the proper construction of the 842 or cation patent as the products of the generic parties.

Seventh, it is said that AZ’s construction is contrary to AZ’s position in respect of the divisional application. According to this submission if AZ “had intended to include a ferric oxide coating as being within the pharmaceutical composition in claim 1 of the Cation Patent, it would have done so expressly”. This submission seeks to by-pass the ordinary process of constriction in accordance with established principles. The submission is not aided by the proposition that in a related application, a divisional of the 842 or cation patent, AZ claimed a ferric oxide coating. Patent Application AU 2005202392 filed 2 June 2005 does claim a pharmaceutical composition comprising rosuvastatin as the active ingredient “the composition having a ferric oxide light protecting coating”. How it is that an application filed some five years after the 842 or cation patent might be relevant to construction remains obscure. For the same reasons the assertion, if it be true, that AZ has taken a position before the Patent Office with respect to the divisional application inconsistent with its position in this case cannot be relevant to the proper construction of the patent. The notion that any issue with the consequences of AZ’s construction in the present case for the divisional application is somehow relevant so that, as it is put, AZ “cannot have it both ways” is not grounded in any identified or identifiable principle of construction.

Eighth, it is said that AZ’s construction is absurd because “it leads to the conclusion that the invention lacks an inventive step…or in the alternative, the specification does not describe a manner of new manufacture”. It is not apparent that this consequence, if assumed to be the consequence, means that the construction for which AZ contends is absurd. If that were so the consequence of invalidity might always be avoided.

Ninth, it is said that AZ’s construction is “merely a contrivance that [AZ] has been forced to devise in an attempt to bring the former formulation of the” generic products within the claims of the 842 or cation patent. This might be so but is immaterial. Whether a contrivance or not from AZ’s perspective the claims must be given meaning.

Watson and Ascent put the same contentions. Referring to the principle that a patent is to be construed through the eyes of a person skilled in the art to reflect how a person skilled in the art would understand the invention defined by the claims in a practical and common sense way, they also submitted that “the claims do not encompass a situation where the claimed invention merely resides in rosuvastatin plus a known coating”. This is a variant of the argument that AZ’s construction is absurd because it leads to invalidity. It seems to me that the argument, however put, crosses the “fine line” between reading down a claim in the manner it would be understood by the skilled addressee and impermissibly limiting the clear words of the claim. I am unable to see how the clear words of claim 1 of the 842 or cation patent involve the limitation on the location of the inorganic salt (that is, that the inorganic salt may not be present only in the coating of a tablet) as the generic parties contend.

For these reasons I do not accept the submissions of the generic parties about these issues. Claim 1 of the 842 or cation patent, in referring to a pharmaceutical composition comprising rosuvastatin and an inorganic salt in which the cation is multivalent includes a pharmaceutical composition in any form. If the form is a tablet and the tablet is not coated the integers of the claim will be present if the composition comprises rosuvastatin and an inorganic salt in which the cation is multivalent (not being otherwise excluded). If the form is a tablet and coated, the pharmaceutical composition comprises the tablet as coated. The rosuvastatin and inorganic salt in which the cation is multivalent (not being otherwise excluded) may be present in any part of the composition, be it the coating or otherwise. Whether the composition is stable or not is immaterial to claim 1.

###### Inorganic salt

The generic parties contend that ferric oxide and titanium dioxide cannot be considered inorganic salts in which the cation is multivalent within the meaning of claim 1 of the 842 or cation patent. As Apotex put it:

* Ferric oxide and titanium dioxide are not “salts” within the traditional understanding of the term “salts” since they are not the product of an acid and base reaction ;
* The traditional meaning of a salt is the one taught to pharmaceutical formulators, and is further the meaning that has practical utility to a formulator in that it provides them with information about the likely impact of the salt on the pH of the formulation;
* The specification does not displace the traditional understanding of “salts” that the skilled addressee brings to bear when reading the Cation Patent;
* [AZ] and its experts rely on the lists of cation and anions in the Patent to say that the Patent specifically contemplates that ferric oxide is an inorganic salt in which the cation is multivalent and, by extension, so too is titanium dioxide. This is the sole basis for [AZ] seeking to apply a very broad, non-traditional, meaning of the term “inorganic salt”. This approach fails to recognise that the overriding requirement is the presence of an “inorganic salt”, and these lists only specify examples of cations and anions that may be “found in” the inorganic salt…

…

* In fact, [AZ]’s ‘construction’ of the word ‘salt’ gives that word no practical meaning, and makes ‘inorganic salt’ essentially equivalent to ‘inorganic compound’. …
* The word ‘salt’ is a word of the patentee’s ‘own choosing’ (*Catnic Components Ltd v Hill & Smith Ltd* [1982] RPC 183 at 243) and a construction that gives that word a practical sphere of operation ought to be preferred to one that does not. Such an approach is well-established as a principle of construction in the United Kingdom: ‘if the patentee has included what is obviously a deliberate limitation in his claims, it must have a meaning. One cannot disregard obviously intentional elements’. See further *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* (2004) 64 IPR 444; [2004] UKHL 46 at [35], in a passage widely cited with approval in Australian decisions.
* Although the list of anions at page 3, lines 1 to 4, specifically includes oxides (and the list of cations specifically includes iron), oxides are compounds, not ions. They are not “salts” because they are not composed of an anion and cation. “Oxides” are the product of a reaction of oxygen and another element, which may itself be an anion. The patent itself gives examples of two such oxides, namely titanium dioxide and ferric oxide, which it lists as ingredients of a separate coating (page 6).
* Further the word ‘oxide’ as used in this context in the patent could sensibly be understood as referring to ions that are themselves negatively charged oxides, including phosphate ions and carbonate ions, which is consistent with the traditional meaning of ‘inorganic salt’.

To the extent that Apotex referred to AZ’s onus of proof it must be said that issues of construction do not involve any onus. AZ bears the onus to prove infringement but the meaning of the claims is not to be resolved by reference to any notion of onus.

Otherwise the submissions of the generic parties fail to confront one telling piece of evidence. The evidence was given by Dr Morella. Dr Morella said that the chemical nomenclature used in the specification of the 842 or cation patent is IUPAC nomenclature: (referring in particular to the chemical name of rosuvastatin on p 1A of the specification). None of the other experts disagreed with this proposition. As AZ submitted, if IUPAC terminology is used to define one integer of the invention, namely rosuvastatin, it follows naturally that it would apply in relation to the definition of the other integers, including that of “inorganic salt”. And as AZ also said, the patent is the Australian version of international patent protection, filed by an international company. The fact that some of the experts were unfamiliar with IUPAC or the IUPAC definition of “salt” is immaterial. In the context of the patent, to this extent, those experts are not representative of the hypothetical skilled addressee whereas Dr Morella and Professor Charman were in this respect representative of the hypothetical skilled addressee.

Even without this evidence the reference to an inorganic salt in which the cation is multivalent provided that the inorganic salt is not hydrotalcite or synthetic hydrotalcite and the counter anion to the inorganic salt is not a phosphate” in claim 1 of the 842 or cation patent, in the context of the specification as a whole, cannot be limited to the product of an acid and base reaction as the generic parties contend. It is plain from the evidence that there is a broader meaning of salt than the product of a reaction between an acid and a base which is known at least to those with expertise in inorganic chemistry, as the definition of “salt” given by IUPAC discloses. It is equally plain from the specification as a whole that the skilled reader was expected to have this broader definition in mind when construing the patent. AS AZ put it:

(a) both the description and various claims (see, eg, claims 4 and 5) expressly state that the counter anion of the inorganic salt may be an “oxide” (which is not produced by the neutralising reaction of an acid and a base), amongst other possibilities. This is incompatible with the narrow definition of salt, which excludes the possibility of oxide as an anion;

(b) the description and claims also state that the cation may be “iron” (with iron oxide included in the preferred embodiments); and

(c) the 842 Patent contains no reference to an acid-base reaction as a qualification on or requirement for the formation of a salt.

…

Professor Kibbe advanced an alternative view, which was apparently not shared by Dr Oppenheim or Dr Pitman but might have been by Dr Rowe, to the effect that the references to “oxide” could be read as referring to anions comprising oxygen atoms with other atoms, such as carbonates, phosphates, metasilicates (and silicates) and sulfates. This does not resolve the difficulties associated with the broader context. Aside from being an awkward use of the term “oxide” which is not supported by the evidence, it would mean that various terms used in the passages and claims identified above would be redundant.

For these reasons AZ’s construction of the reference to “inorganic salt” in the claims of the 842 or cation patent is to be preferred. Those words mean the class of compounds in which a negatively charged ion (an anion) is ionically bonded to a positively charged ion (a cation) to form an electronically neutral molecule. As such, ferric oxide and titanium dioxide are inorganic salts in which the cation is multivalent.

##### VALIDITY OF THE 051 OR LOW DOSE PATENT

###### Reference to generic parties

In the subsequent sections of these reasons for judgment I do not distinguish between arguments by one but not another of the generic parties. I deal with all arguments put by any generic party referring to the generic parties.

###### Entitlement

The generic parties contended that the invention in the low dose patent, the use of a 5 to 10mg dose of rosuvastatin as described was invented by employees of Shionogi, none of whom are named as an inventor. The sole named inventor, Ali Raza, through whom AZ claims entitlement was thus not the inventor. Accordingly, under s 138(3)(a) of the Act, the patent may be revoked (see also s 15 which identifies who is entitled to apply for a patent).

Certain facts are relevant to this argument. There is no dispute that Shionogi invented the compound rosuvastatin. Shionogi granted AZ a licence in respect of rosuvastatin. A so-called “inventorship record” for the 051 or low dose patent records that:

During the licence negotiations for ZD4522, Shionogi provided Zeneca with data from a Japanese Phase IIa study (dose of ZD4522 up to 4 mg) in hyperlipidaemic patients, showing 41% lowering at the 4 mg dose level. However, the effect of higher doses of ZD4522 to lower LDL had not been investigated.

At a meeting on 23rd December 1997 at Mereside, Alderley Park, between Ali Raza (AR), Brent Vose, Nigel Finch and Tony Clarke, AR suggested, as part of a proposed clinical plan, that a Phase II clinical trial be carried out to estimate the dose-response relationship between the dose of ZD4522 and the percentage reduction of LDL-C in hyperlipidaemic patients, including two open label arms of atorvastatin start dose of 10 mg and max dose of 80 mg, with secondary objectives of estimating the effects of ZD4522 on other lipoprotein levels, and assessing tolerability and safety.

By April 1998, when the licence negotiations were completed, AZ issued a press release announcing its acquisition of the rights to the compound, then known as ZD4522, referring to the compound as a “superstatin” in the press release. I accept the submission on behalf of the generic parties that this press release should be seen as be a truthful contemporaneous record of the stage that Shionogi had reached in the development of the compound, namely:

(a) that ZD4522 [Shionogi’s S4522] had a “superstatin” profile;

(b) that it “had the potential at well-tolerated doses” [i.e., as to safety] of lowering LDL-C and TG “to a much greater extent than the first generation of ‘statins’” [i.e., as to efficacy];

(c) that “Phase IIa clinical trial results in Japan had shown very encouraging results” [i.e., in dose ranging studies, as to safety and efficacy]; and

(d) that “first regulatory submission is anticipated in approximately 3 years’ time” and that “ZD4522 offers Zeneca the opportunity of entering the market for lipid lowering medicines” [i.e., that a full clinical trial program was contemplated, and was expected to succeed].

This is consistent with the documentary record which shows that by October to December 1993, Shionogi began clinical trials for rosuvastatin. The first “Early Phase single dose tolerance study” involved doses of 0.25 2.5, 5, 10 and 20mg doses with healthy volunteers (a Phase I study). By February to April 1994, Shionogi’s second Phase I study had begun. The doses were:

Doses of 5 mg/day and 10 mg/day which were among the doses administered in the early phase single dose tolerance study and which were within the estimated clinical dose range as well as 20 mg/day which correspond to twice the estimated maximum clinical dose were set in this study.

In June to July 1994, a further Phase I study, or “one-week repeated administration study”, was conducted. The report of this study said:

Estimated from the results of preclinical studies, the usual dose of S-4522 is 5 mg and the maximum dose 10 mg. Since one of the objectives of this study is to evaluate the accumulation of S-4522, the dose was set at 10 mg, a high dose among the estimated clinical doses.

It was common ground between the experts that the efficacy of statins (unlike some other drugs) is disclosed by use in healthy volunteers. In other words, even in a healthy person statins reduce cholesterol levels. This fact underlies another observation in the report of Shionogi’s “one-week repeated administration study” that:

Since about a 20% reduction in total cholesterol has been observed in the one-week repeated administration study of commercially available similar drugs, a comparable reduction in total cholesterol is anticipated with S-4522.

Shionogi conducted another study in September to October 2004, being a “two-week repeated administration study in subjects with mild hyperlipidemia” in which doses of at 0.5, 1, 2 and 4 mg were used.

From June 1995 to June 1996, Shionogi conducted an “Early Phase II clinical study of S-4522”. This tested rosuvastatin’s efficacy at doses from 1 to 4 mg daily. The report concluded:

In the Phase II clinical studies of the existing HMG-CoA reductase inhibitors, about 20% and 30% reductions in TC and LDL-C, respectively, have been reported (Table 14).

In the present study, we expected greater reductions in these lipids than those achieved with the conventional drugs and actually obtained the results as expected.

All of Shionogi’s work was disclosed to AZ as part of the licence arrangement

The generic parties submitted that the asserted (and only possible) invention was Dr Raza’s “suggestion” as set out in this inventorship record. The claims do not refer to the efficacy or safety of the dosage range and “because the claims are not limited to any asserted advantages or benefits, those assertions are irrelevant to questions of validity: *Apotex v Sanofi-Aventis* at [84], per Gyles J (2008) 78 IPR 485; [[2008] FCA 1194] in the Full Court at [89] per Bennett and Middleton JJ, (2009) 82 IPR 416; [[2009] FCAFC 134]”. Yet this invention, as claimed, had been discovered by the employees of Shionogi. The generic parties submitted that:

It is thus clear that Shionogi had not only invented rosuvastatin – which has since apparently been licensed to [AZ] – its scientists had also conceived of a method of treating hypercholesterolaemia comprising administration of 5 mg and 10 mg rosuvastatin, including as a starting dose. That is, they “invented” the “invention” claimed in the claims of the low dose patent. Similarly, they conceived of its use for severe hypocholesterolaemia – which includes HeFH. The Due Diligence report shows, of course that these “inventions” were communicated to AstraZeneca but [AZ] derives no title to them from Shionogi.

…

From the outset, 5 and 10mg per day were considered as being the “clinical range”, with 10mg being the estimated maximum clinical dose.

It follows that [AZ] was not entitled to either invention. Dr Raza’s later “suggestions” for clinical trials did not make him the inventor.

…

The true position is that Dr Raza did not invent rosuvastatin, and he was not the first person to conceive of the use of a 5mg dose or a 10mg dose. He was given this by Shionogi, as was the idea of a conventional series of Phase II trials, including dose ranging studies. All of the experts agreed that this is a standard process.

As such, it was submitted that “Dr Raza is not an inventor at all. In the alternative, he is only one of a number and [AZ] does not derive title from the others. It follows that, in either event, [AZ] is not entitled to the invention and the low dose patent is liable to be revoked”.

AZ’s first answer to this case is that the alleged lack of entitlement by reason of Dr Raza not being an inventor at all was not open on the pleadings, it having been pleaded only that the employees of Shionogi were also inventors. In my view, this aspect of the case is not confined by the pleadings given the conduct of the hearing. It is not possible to conceive of any relevant prejudice that AZ might suffer if the generic parties are permitted to argue that Dr Raza was not an inventor at all. There was never a suggestion that, in such an event, AZ’s position might change and it would call Dr Raza or any other evidence to support its case. All of AZ’s inventorship records for the 051 or low dose patent were apparently made available through discovery. AZ was free to seek to tender any document it possessed to make good its case. There is no rational reason to preclude this argument by reason of AZ’s pleading point.

As to matters of substance, AZ submitted that the true position was that “Shionogi had reached a dead end. It had done nothing for 2 years. Rosuvastatin was on the shelf. There was no “collaborative” effort between Shionogi and [AZ] to achieve the invention.” Further, AZ submitted that:

A useful way to test the proposition is to ponder whether Shionogi could have filed a patent application for the 051 Patent claims at the conclusion of its work. Shionogi had no basis for asserting that it had discovered or made a method of treating hypercholesterolemia by administering 5 to 10mg of rosuvastatin. It had never administered such a treatment. At the most it would have been an untested hypothesis. That is not the making of an invention.

According to AZ, Shionogi’s work stopped in 1996 at the point rosuvastatin had been identified as nothing more than a “promising candidate for development”. AZ’s work began two years later and it is AZ alone which invented the method of treatment claimed in the 051 or low dose patent. The method of treatment and its constituent elements (a patient suffering from a particular condition being hypercholesterolemia, the administration of particular doses of the compound, being 5 to 10mg, once daily, orally, as the starting dose daily in claim 1 or as a single daily dose in claim 2) are the inventive concept (see *Polwood Pty Ltd v Foxworth* (2008) 165 FCR 527; [2008] FCAFC 9 at [13], [42] and [60]). AZ said:

In combination, these elements produce a method of treatment that is efficacious, in the sense of that it is safe and effective in treating the patient’s hypercholesterolemia. The “invention” or “inventive concept” resides in the combining of those elements to produce this effect for the benefit of patients.

It may be accepted that neither Shionogi nor its employees claim any entitlement to the invention claimed in the 051 or low dose patent. But that does not necessarily answer the question whether AZ, though Dr Raza, was so entitled. Similarly, it may be accepted that Shionogi chose to conduct Phase II trials using doses of 1, 2 and 4mg to Japanese patients, although it had conducted Phase I trials at doses of 5 and 10mg. These facts led AZ to submit that:

Shionogi never treated a patient suffering from hypercholesterolemia with a 5 to 10 mg dose of rosuvastatin. Shionogi did not and indeed could not have determined that that was a useful or effective or safe method of treatment.

It cannot be concluded that Shionogi was ever in possession of the invention, being a method of treatment involving (inter alia) the administration of 5 or 10 mg of rosuvastatin, in these circumstances. To the contrary the choice of Shionogi to test only lower (1 mg, 2 mg and 4 mg) doses in Phase II trials involving patients suffering from hypercholesterolemia proves positively that Shionogi was not in possession of the invention at the time it concluded its own clinical work in 1996.

Shionogi plainly never conceived of the significant therapeutic and consequent commercial benefits of a 5 to 10 mg dose of rosuvastatin for treating hypercholesterolemia.

AZ also noted that Shionogi’s work had left open issues of safety, with the results of its Phase II work recording that the “dose-response relationship of adverse reactions will need to be further investigated in a greater number of cases”, the overall position being that the compound would “deserve further evaluations for its efficacy and safety in a greater number of cases”. This, AZ said, is also reflected in the Watanabe article which identified the compound as one of several “promising candidates for development of antiarteriosclerotic agents”. AZ’s work thereafter involved seven Phase I trials which were the first to introduce rosuvastatin to the western world at a time when the difference between Japanese and Western populations, in their clinical response, was not well understood. The pivotal Phase II study, Study 8 conducted between August 1998 and January 1999, compared the lipid lowering effects of 1, 2.5, 5, 19, 20 and 40mg of rosuvastatin with 10 and 80mg doses of atorvastatin. This study, submitted AZ (which is referred to at some length in the 051 or low dose patent), is the foundation for the statement in the specification “that rosuvastatin “has now been found” surprisingly, when administered in accordance with the disclosed methods of treatment, to alter lipid levels to an unexpected degree, without significant adverse effects.”

One difficulty with these submissions is that they place too much of a load on the reference to a “method of treatment” in the claims. AZ appears to equate the reference to a “method of treatment” to a promise of efficacy and safety. Yet analysis of this exposes the difficulty. It cannot be the case that absolute efficacy and safety is inherent in the assumed promise. Nor is there a proper basis to assume efficacy and safety relative to existing therapies in the sense that the method will be as efficacious and as safe as existing therapies. As it was put for the generic parties (albeit in a different context):

… that safety will never be assured or completely verified… The assessment of safety is a continuous process and even now rosuvastatin is marketed with a range of safety warnings in its product information including rhabdomyolysis.

It may be acknowledged that the claims do assert a “method of treating” hypercholesterolemia which must involve notions of at least some degree of efficacy and safety; otherwise there would be no method of “treating” at all. AZ’s case, however, appears to depend on efficacy and safety having been proved to a standard equivalent to that sufficient for regulatory approval before it can be said that the method of treatment exists. Nothing to that effect appears in the claims and it cannot be sustained merely by the invention being a method of treating hypercholesterolemia.

Whatever the contemporaneous debate about potential differences between Japanese and Western responses to statins (which I accept did exist at the time, it apparently being thought that Japanese were less tolerant of statins than Westerners) the work conducted by Shionogi had involved the discovery that rosuvastatin, at 5 and 10mg once a day doses, reduced lipid levels by a significant extent and was tolerated by humans for that purpose, even if its safety at various doses required further work. Given that the reference to a “method of treating” cannot mean anything more than some degree of efficacy and safety, if there is any invention claimed by the patent, it was invented by Shionogi not Dr Raza. This conclusion applies to both claims 1 and 2 and as claim 3 is dependent on either of those claims it too must fail.

It follows that I accept the argument for revocation based on lack of entitlement to the invention claimed in the 051 or low dose patent.

###### Novelty

Introduction

By s 138(3)(b) of the Act a patent may be revoked on the ground that the invention is not patentable. Section 18(1)(b)(i) requires an invention as claimed to be novel when compared with the prior art base as it existed before the priority date of the claim in order for it to be patentable. The assessment of novelty is regulated by s 7(1), the terms of which as applicable to the patents in this case are set out above.

The principles relating to the assessment of novelty were not in dispute. The generic parties summarised the essential principles in these terms:

The relevant authorities for determining whether the Low Dose Patent lacks novelty in light of a citation are usefully set out in [*Apotex Pty Ltd (No 3)* at [175]-[192]] which, in turn, relays the law as elaborated by the Full Federal Court in *H Lundbeck A/S v Alphapharm Pty Ltd* [2009) 177 FCR 151; [2009] FCAFC 70 at [170]-[190]]. The question is whether an invention is novel when compared to prior art information made publicly available. The test is not whether the invention has been made publicly available. The prior publication is to be read through the eyes of the skilled addressee having regard to the state of knowledge at the date of publication of the document.

The question to be determined by the Court, as discussed by the Full Court in *Faulding* [*Bristol-Myers Squibb Co v FH Faulding & Co Ltd* (2000) 97 FCR 524; [2000] FCA 316 at [67]] is aptly put in the following terms:

What all those authorities contemplate, in our view, is that a prior publication, if it is to destroy novelty, must give a direction or make a recommendation or suggestion which will result, if the skilled reader follows it, in the claimed invention. A direction, recommendation or suggestion may often, of course, be implicit in what is described and commonly the only question may be whether the publication describes with sufficient clarity the claimed invention, or in the case of a combination, each integer of it…

Apotex emphasised the observations of Bennett J in *Lundbeck*; as follows:

[181] If the prior art discloses some but not all integers of a claimed patent to a product, such as a combination, there is anticipation if the skilled addressee would add the missing information as a matter of course and without the application of inventive ingenuity or undue experimentation (*Nicaro* 91 ALR at 530-531 [*Nicaro Holdings Pty Ltd v Martin Engineering Co* (1990) 91 ALR 513]).

[183] It is these last two examples that, in Australia, could be said to be within a shorthand description of “enabling disclosure”. That is, the disclosure is not complete but it is sufficient to enable the skilled addressee, in the ordinary course and without invention, to add what is missing in the prior publication to obtain the claimed invention. The term “enabling disclosure” may also be apposite to disclosure to the skilled addressee of an asserted prior use; whether what the skilled addressee observes on inspection is sufficient to enable him or her to comprehend the complete invention (eg *Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20 [[2008] FCAFC 139]; *Jupiters* [*Jupiters Ltd v Neurizon Pty Ltd* (2005) 222 ALR 155; [2005] FCAFC 90]), that is, sufficient to amount to a disclosure of the invention.

…

[190] It follows that, where the prior publication is of the subsequently claimed invention, that is sufficient. Where the prior disclosure falls short of a complete disclosure, the question of the sufficiency of that disclosure arises. It is there that consideration must be given to the quality of a disclosure to the skilled addressee armed with common general knowledge. It is in that context that, in a limited fashion, questions of “enablement” can be said to arise. The use of that expression tends to cause confusion between anticipation and sufficiency. Rather, the Court, armed with the evidence of the skilled addressee as to terms of art and the nature and extent of the disclosure in the prior art document, must determine whether the prior disclosure is sufficient to enable the skilled addressee to perceive, understand and, where appropriate, apply the prior disclosure necessarily to obtain the invention.

AZ stressed that:

A prior publication will only anticipate if it discloses all of the essential integers of the claimed invention; it must contain “clear and unmistakable directions” to carry out the invention in order to render it not novel [*General Tire & Rubber Company v Firestone Tyre and Rubber Company Ltd* (1971) 1A IPR 121 at 137-138]. Thus, it has been said that anticipation “is deadly but requires the accuracy of a sniper, not the firing of a 12 gauge shotgun” [*Apotex Pty Ltd v Sanofi-Aventis* (2008) 78 IPR 485 at [91], approved in *Lundbeck* at [170].]. Further, it is not sufficient that a prior publication merely “includes” or “encompasses” the claimed invention; a broad disclosure will not necessarily anticipate a later, more specific claim [*Apotex Pty Ltd (No 3)* at [180]-[181] and the authorities cited, esp *ICI Chemicals & Polymers Ltd v Lubrizol Corp Inc* (2000) 106 FCR 214 [[2000] FCA 1349] at [51] and *IGT (Australia) Pty Ltd v Aristocrat Technologies Australia Ltd* (2008) 77 IPR 482 [2008] FCAFC 131 at [56]]. A metaphor that has been used in the cases to illustrate the concept is that “the prior inventor must clearly be shown to have planted his flag at the precise destination before the patentee” [*General Tire* 485-486.].

AZ also noted that “it is not permissible to supplement a prior publication by reference to some other disclosure, forming part of the common general knowledge, in order to assess whether the publication truly amounts to an anticipation”, because the prior publication “is to be assessed by reference to what it would disclose to the skilled addressee”, not what the skilled addressee might add to it in light of the common general knowledge (*ICI Chemicals & Polymers Ltd v Lubrizol Corporation Inc* (2000) 106 FCR 214; [2000] FCA 1349 at [43]) (*ICI Chemicals*). To the extent that the last element of this submission suggests that the skilled addressee must be assumed to be forbidden from reading the particular prior publication in question without regard to the common general knowledge, I do not accept it. The prior publication in issue is to be construed through the eyes of the skilled addressee with the benefit of the common general knowledge in the art; it is reference to other publications, in order to create a mosaic, which is not permissible.

The two pieces of prior art which support the primary argument of lack of novelty are the 471 patent and the Watanabe article. It is common ground that both were publicly available before the asserted priority date of the 051 or low dose patent.

The 471 patent

The 471 patent (a European patent application which has an equivalent US patent on which the generic parties also relied for this purpose), filed by Shionogi, is the European patent for the compound rosuvastatin. It is convenient to deal with the terms of the 471 patent in the context of the competing arguments about whether the document destroys the novelty of the 051 or low dose patent.

AZ submitted that:

First, so far as the active agent is concerned, what EP 0521471 discloses is a class of compounds identified by way of a general structural formula. While rosuvastatin is a compound encompassed by that formula, it is one among a practically infinite number of other compounds,

Notably, there is no specific claim to rosuvastatin in EP 0521471. Claim 1, which contains the general structural formula, covers over 57 trillion compounds, only one of which is rosuvastatin; claims 2 to 4 exclude rosuvastatin whereas claims 5 and 6 encompass rosuvastatin, but along with a very large number of other compounds. Examples 1 and 7 relate to salts of rosuvastatin (though not referred to by that name) whereas Examples 2 to 6 are not related to rosuvastatin. At best for the generic parties, EP 0521471 thus merely includes or encompasses rosuvastatin along with many other compounds. That is not sufficient for novelty purposes.

It is true that invention disclosed in the 471 patent is a class of HMG CoA reductase inhibitors of which rosuvastatin is but one member of the class. Hence, the invention relates to “compounds” of the formula which includes rosuvastatin. However, specific examples are given, two of which constitute salts of rosuvastatin. There cannot be any real doubt that the 471 patent is a sufficient disclosure of the compound rosuvastatin given the terms of the patent as a whole. The fact that many other compounds might also fall within the class, at least insofar as the sufficiency of disclosure of rosuvastatin is concerned, is immaterial given the examples. Hence, to the extent that AZ’s submission might suggest that the 471 patent does not disclose the integer rosuvastatin by reason of the breadth of the class of compounds disclosed, the submission cannot be accepted.

AZ then said:

Secondly, as noted in the context of the interlocutory application, EP 0521471 describes the compounds as useful to treat three different diseases, only one of which is hypercholesterolemia. What compound should be used to treat which disease is not identified. The absence of any teaching of this reflects, no doubt, the fact that the focus of EP 0521417 is the identification and characterisation of compounds, rather than describing methods of treatment.

Again, it is true that the 471 patent discloses that the compounds are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. However, the sufficiency of the disclosure must be assessed by reference to the terms of the 471 patent as a whole. The document refers to the compounds (which must include the specific examples and thus must include rosuvastatin) as being HMG – CoA reductase inhibitors and that, by inhibiting the HMG-CoA reductase, “which plays a major role in the synthesis of cholesterol, and thus…suppress the biosynthesis of cholesterol”, the compounds “are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis”. The document also says that the compounds (which, again, at least must include the specific examples even if not all compounds within the class) may be administered orally or parenterally in various forms. Hypercholesterolemia, hyperlipoproteinemia and atherosclerosis are diseases in humans as the skilled addressee would know. The fact of administration discloses what the patent otherwise makes clear, that the compounds, specifically the examples, are useful for the purposes of treating these diseases in humans and can be administered to humans for this purpose. So much is confirmed by the reference that follows to the fact that:

The dosages may vary with the administration route, age, weight, condition, and the kind of disease of the patients, but are usually 0.5-200mg/day, preferably 1-100mg/day for oral administration and 0.1-100mg/day, preferably 0.5-50mg/day for parenteral administration. They may be used in single or divided doses.

This is a clear disclosure that the compounds, or at least the specific examples given, are useful for treating each of the three diseases in the dosage ranges identified. The fact that the dosage range may vary depending on each of the factors described (disease, age, weight etc) does not undermine the sufficiency of this disclosure. It is a specific disclosure, and would be understood as such by the skilled addressee, of the usefulness of rosuvastatin (a specific example given of the compound) for treating hypercholesterolemia (a specific disease identified in the context of compounds which are HMG – CoA reductase inhibitors, itself indicative of usefulness of treating hypercholesterolemia to the skilled addressee), in specific dosage ranges (preferably 0.1-100mg per day for oral administration) in either a single daily dose or a split daily dose.

AZ said that:

Thirdly, EP 0521471 also provides no indication as to which, if any, of the compounds can be safely administered to humans. More specifically, there is no mention of the testing of rosuvastatin (or any other compound encompassed by the EP 0521471) in any humans, let alone humans suffering from hypercholesterolemia. Safety and efficacy of administration cannot be predicted in the absence of appropriate and extensive human testing. EP 0521471 addresses the question of biological activity by reference to in vitro testing on rat liver microsomes, but there are no in vivo tests, even in animals. The generalised assertion in EP 0521471 that the compounds are “useful in … treatment” cannot make up for this lack of disclosure.

I do not accept that the skilled addressee would read the 471 patent as not indicating which of the compounds can be safely administered to humans. As noted, safety is a relative and not an absolute concept. Once that is recognised, it is apparent that the lack of reference to testing in humans in the 471 patent does not undermine the disclosure that at least the compounds identified in the specific examples are useful for treating the three nominated diseases, which are diseases in humans. To be useful in treating these diseases, the nominated compounds are disclosed not as safe in any absolute sense, but as relatively safe having regard to their degree of efficacy. The skilled addressee would know this not only from the references to the compounds being useful for treating the identified diseases but also from the fact that the compounds are part of a class, statins, which from the expert evidence I am satisfied had known side effects before the priority date, primarily myalgia (muscle pain), liver dysfunction and rhabdomyolysis (more severe muscle toxicity)) and a known dose-efficacy-side effect relationship (in that lower doses were associated with fewer side effects and achieved the greatest reduction in LDL-C levels, which thereafter flattened out with increased doses.

Hence, although it may be accepted as a general proposition that “[s]afety and efficacy of administration cannot be predicted in the absence of appropriate and extensive human testing”, as AZ submitted, this general proposition is not determinative of the sufficiency of disclosure of the relevant integers in the 471 patent. As the protocols for drug development explained by the experts discloses, there is usually extensive animal testing before testing in humans commences. Testing in humans occurs in stages designed to minimise the chance of adverse effects. Drugs which appear promising in terms of efficacy and safety may be proved to the contrary through the testing process at any stage and, indeed, after the drug has been approved and marketed (such as occurred in the case of cerivastatin; although after the asserted priority dates the withdrawal of a drug due to unacceptable side effects compared to other available drugs would have been well known to the skilled addressee). In this sense, safety and efficacy can never be predicted in the absence of extensive use by people over the long term.

The question remains, however, whether the “prior disclosure is sufficient to enable the skilled addressee to perceive, understand and, where appropriate, apply the prior disclosure necessarily to obtain the invention” (*Lundbeck* at [190]). In the face of a document which specifically identifies rosuvastatin as useful for treating three diseases in humans, where rosuvastatin belongs to a known drug class with a known set of side effects and dose profile, the submissions of AZ lack persuasive force.

AZ also said that:

Fourthly, the document does not identify how any of the broad class of compounds should be administered to humans, including the appropriate dose. There is a generalised statement that the compounds can be administered in dosages which “may vary with the administration route, age, weight, condition and the kind of disease of the patients, but are usually 0.5-200 mg/day, preferably 1-100 mg/day for oral administration”. However, this does not tell the reader what dose within that range should be administered of which compound, by what route and at what frequency, in order to treat which of the three diseases in a way that is safe and efficacious. Further, the very fact that the statement is made by reference to each and every member of the class of compounds disclosed, of which the authors had synthesised only a handful, confirms that the statement was and could not have been understood as providing a teaching of any specific method of medical treatment in respect of any individual compound.

The submissions do not accurately reflect the actual terms of the 471 patent about doses, which are set out above. Read as a whole it is clear that the 471 patent at least discloses that the identified compounds of the broader class, which specifically include rosuvastatin, are useful in treating all three identified diseases (one of which is hypercholesterolemia) by, relevantly, oral administration in a preferred dosage range of 1 to 100mg, either once or twice daily. As such, AZ’s contention that the 471 patent is “far from a disclosure, for novelty purposes, of the invention in the 051 Patent, which claims a method of treatment involving, amongst other matters, the safe and efficacious treatment of hypercholesterolemia by administering a particular dose (5 mg to 10 mg of rosuvastatin) at a particular frequency (one daily) to treat a particular condition (hypercholesterolemia)” cannot be accepted. The 471 patent discloses precisely the method of treatment claimed in the 051 or low dose patent.

Contrary to AZ’s submissions I do not find that any of the expert evidence, other than that referred to above, provides support to the contrary. Dr Reece, a formulator and not a physician, agreed that the general formula contains millions, perhaps trillions (it hardly matters at those sort of numbers), of compounds. But this misses the point that of those millions, or trillions, a very small number of specific compounds are expressly identified as examples of the class. By the ordinary processes of construction, it is apparent that at least those compounds are specifically identified as examples of the invention which are useful in treating the nominated diseases by the nominated doses. The fact that Dr Reece, and others, also read the 471 patent as saying that all of the potential compounds are useful in the same way is not to the point. It is not to the point because in this case the integer is rosuvastatin and there is no escaping the fact that rosuvastatin is specifically disclosed in the examples of the invention in the 471 patent. AZ’s argument might carry some weight if, for example, this case related to another compound, which was within the general class in the 471 patent but not specifically disclosed in the examples, In such a case issues of the sufficiency of the disclosure might arise. But that is not the present case. Dr O’Brien’s evidence to the same effect as that of Dr Reece also did not assist AZ. And for the same reasons as set out above, the fact that Dr Reece would not actually give anybody any of these compounds is also beside the point. Of course he would not do so. One, he is not a physician and cannot prescribe anything. Two, the drug was not approved in Australia. But more to the point, the question is not whether having read the 471 patent Dr Reece or anyone else would give someone with hypercholesterolemia rosuvastatin. It is whether the 471 patent contains a clear direction which, if followed, would result in the invention.

Contrary to AZ’s submissions this is not a case where the 471 patent would have the skilled addressee “rummage through the flag locker with the blindfold of no safety and efficacy data in humans and try and cobble together the elements of a method of treatment”. That cannot be so when the integers of claim 1 of the 051 or low dose patent (and the other claims relied upon), are all clearly disclosed in the 471 patent. The only real issue which AZ can point to is that the 471 patent does not disclose human trials. But for the reasons given, that does not undermine the sufficiency of the disclosure that in fact appears in the 471 patent given that it discloses the precise compound (rosuvastatin), the nature of the compound as a statin or HMG-CoA reductase inhibitor (a class which has known qualities), the fact that the compound or at least the identified examples are useful for treating three diseases which are diseases in humans, one of which is hypercholesterolemia, a dosage range for oral doses, and the fact that the dose may be given once or twice daily.

To the extent that AZ attempted to rely on variations in the dosage range by reference to Dr O’Brien’s evidence (he agreed that he did not understand that the 471 patent was “telling you that this is an effective and safe medical treatment and every single one of those dosages for each of those diseases regardless of the age, gender, etcetera of any patient”) a number of answers may be given. One, the 051 or low dose patent does not and cannot give any promise in any claim that the doses it directs are an effective and safe medical treatment regardless of the age, gender, etcetera of any patient. Two, the dosage range in the 471 patent is clearly stated and the mere fact that variation may be required does not alter the substance of the disclosure of, at the least, rosuvastatin as useful in treating all three diseases at the doses specified. Three, the dosage range includes the dosage ranges in the claims of the 051 or low dose patent. Construed in context, there is a clear direction in the 471 patent that rosuvastatin at a dose of anywhere between 0.5 to 200mg (which includes doses as specified in the 051 or low dose patent) will be useful in treating hypercholesterolemia in an oral once or twice daily administration. This necessarily encompasses the integer of a starting dose in claim 1 of the 051 or low dose patent as there will always be a starting dose to treat a disease by oral administration and the 471 patent directs the starting dose and the continuing doses to be in the range specified.

As to safety and efficacy, AZ’s proposition that it is inherent in a method of treatment that its performance will treat the condition to which it is directed without unacceptable side effects recognises the relative nature of efficacy and safety. Just as this relativity is inherent in a method of treatment so too it is inherent in a compound being useful in treating. There is no material difference between the two concepts.

For these reasons I am satisfied that each of the integers of claims 1 and 2 of the 051 or low dose patent are disclosed in and anticipated by the 471 patent. Claim 3 is a dependent claim. Accordingly, the invention was not novel and the 051 or low dose patent is liable to revocation on this basis.

The Watanabe article

It is common ground that the Watanabe article was published before the asserted priority date. Again, I will deal with the terms of the Watanabe article in the context of the competing arguments about whether the article anticipates the claims of the 051 or low dose patent so as to destroy novelty.

AZ submitted that the Watanabe article does not describe a method of treatment but “describes the synthesis and characterisation of a range of compounds, including rosuvastatin (referred to as S-4522, or compound 3a), by reference to certain in vitro tests and in vivo animal tests by which biological activity was assessed”, there being “no disclosure of any in vivo testing conducted in humans, let alone humans suffering from hypercholesterolemia”.

In fact, the Watanabe article starts from the premise that hypercholesterolemia is a serious disease associated with coronary heart disease which is widely treated by a number of well-known statins including lovastatin, pravastatin and fluvastatin. The article explains the mechanisms by which these statins work within the body and how they can be modified to create a more potent HMG- CoA reductase inhibitor. The article reports on the synthesis of statins in this modified form, one of which is specifically identified, being rosuvastatin (referred to as S-4522). S-4522 is also reported in the article as being the subject of a study the results of which show the compound to possess greater enzyme inhibitory activity than lovastatin and pravastatin. Hence, although a range of new compounds is identified in the Watanabe article (3a to 3g), it is S-4522, or rosuvastatin, which is reported on the first page of the article as having greater enzyme inhibitory activity than lovastatin and pravastatin. S-4522 is thereafter referred to as the “selected compound”, which was further evaluated for its capacity to inhibit rat liver HMG-CoA reductase, as well as testing in beagle dogs and monkeys, which all showed the greater potency of S-4522, or rosuvastatin, compared to lovastatin and pravastatin. It is also reported that S-4522 acted more potently in liver than peripheral tissue or “liver selectivity” indicating, for S-4522, “potent cholesterol lowering and, moreover, reduced side effects in clinical use because the liver is a major site of cholesterol biosynthesis”. The reference to “clinical use” and “side effects”, in this context, is a reference to what the animal trials indicate to the skilled addressee for use in humans – namely, more potent cholesterol lowering and reduced side effects compared to existing statins.

The conclusion in the Watanabe article, emphasised by AZ, that the compounds (that is, all of 3a to 38) “are promising candidates for development of antiarteriosclerotic agents”, with the “clinical trials” of S-4522 “in progress”, is to be read in this context. While it is true that the experimental section of the Watanabe article identifies the potency of all of the compounds 3a to 3g and all are encompassed by the “promising candidates” reference, it is only one which is described as the “selected compound” and which is reported in detail in the text and said to be in clinical trials. Read against the common knowledge that the skilled addressee would have about how statins function, available statins, the dose range and response activity of statins, and their dose-side effect relationships, Watanabe is an effective disclosure of a new statin capable of treating hypercholesterolemia having greater potency than existing statins (the dose-response range of existing statins being well-known), albeit without safety and efficacy having been proven by the extensive clinical trials and ongoing monitoring required to obtain regulatory approval. In terms of the doses of existing statins, it should be noted that cerivastatin, which involved far smaller doses than all other statins, was not available in Australia until 2000 and was not commonly prescribed. The commonly prescribed statins involved a dosage range of between 10mg and 80mg, with dose titration from a lower starting dose to a higher dose a well-understood process.

AZ said that the “data presented from animal testing is also hopelessly incomplete and insufficiently detailed to be of any use to provide any guidance when moving from animals to humans”. It is correct that the Watanabe article does not disclose the maximum tolerated dose in any animal, toxicological effects, if any, that were observed in any animals and at what dose or the minimum effect dose that first caused plasma cholesterol lowering in any animal model. But the Watanabe article does report on relative potency of compound 3a, the relativity measured against known compounds with (to the skilled addressee) a known dose-response range in humans. In this regard, the cross-examination of Dr Reece, a formulator, about the lack of information in the Watanabe article was not particularly helpful. Dr Reece (or at the least Dr Reece alone) is not the skilled addressee. Dr O’Brien is representative of the skilled addressee and on his reading of the Watanabe article he expected S-4522 to have similar or better efficacy than atorvastatin and to be effective in doses lower than the commonly used doses of pravastatin (10 to 40 mg). Given what the skilled addressee knew about statins at the time and what the Watanabe article reports as set out above, this expectation is unsurprising. Read against the common general knowledge of the skilled addressee the Watanabe does teach that there is a new statin, rosuvastatin, which is a class of drugs used to treat hypercholesterolemia, which due to its structure, is relatively more potent than the nominated existing statins in reducing cholesterol (that is, by inference, greater cholesterol lowering effect at the same doses) and exhibits liver selectivity which indicates a potential for reduced side effects in clinical use compared to the existing statins. Given common knowledge of the dose-response range of existing statins, including the frequent administration of a starting dose within a fairly narrow dosage range for the then existing statins which is then dose-titrated, the Watanabe article teaches each of the integers of the 051 or low dose patent. As Apotex submitted:

A piece of prior art does not have to persuade the reader to abandon his or her currently preferred drug. It has to disclose something within the claims “with sufficient clarity”.

The Watanabe article, read by the skilled addressee, does so. The facts are not analogous to those discussed in *Pfizer Overseas Pharmaceuticals v Eli Lilly & Co* (2005) 68 IPR 1; [2005] FCAFC 224 at [319]-[322], in which the breadth and generality of the discussion in the prior art undermined the submission of anticipation.

AZ’s references to Professor O’Brien’s evidence concerning the potency of rosuvastatin as compared to atorvastatin do not undermine these conclusions. Given the results reported in respect of lovastatin and pravastatin, and the common knowledge of the skilled addressee about the relative potency of statins, it is hardly surprising that on reading the Watanabe article Professor O’Brien expected rosuvastatin to be more potent than atorvastatin. The results overwhelmingly pointed in that direction.

For these reasons I am satisfied that each of the integers of claims 1 and 2 of the 051 or low dose patent are disclosed in and anticipated by the Watanabe article. Claim 3 is dependent on the validity of claims 1 or 2. Accordingly, the invention was not novel and the 051 or low dose patent is liable to revocation on this basis.

###### Inventive step/obviousness

Section 18(1)(b)(ii) requires an invention as claimed to involve an inventive step when compared with the prior art base as it existed before the priority date of the claim in order for it to be patentable. The assessment of inventive step is regulated by ss 7(2) and (3), the terms of which as applicable to the patents in this case are set out above.

I have considered the invention claimed in the 051 or low dose patent in the context of the so-called “starting point” issue resolved above. In the case of the 051 or low dose patent the invention is the discovery of a dosage range of a compound assuming that the existence and nature of the compound is known, the compound being rosuvastatin. On this basis the invention in the 051 or low dose patent would have been obvious to a person skilled in the relevant art in light of the common general knowledge in the patent area as it existed before the asserted priority date. The invention would have been obvious because, against the common general knowledge, the invention involved nothing more than the identification of a conventional starting dose for a compound within a known class for a known purpose. As Apotex submitted:

The selection of a 5 to 10 mg dose is no more than the selection of a relatively low (but conventional) dose of rosuvastatin, by reference to the preferred prescribing practice of some, but not all, doctors - of starting patients on a relatively low dose and then titrating the dose upward.

On this basis, the invention claimed in claim 1 of the 051 or low dose patent is not a patentable invention. Claim 2 provides a small dosage variation which is immaterial to inventiveness in the circumstances. Claim 3 is dependent on claims 1 or 2. Accordingly, the patent is liable to revocation on this basis.

All of the expert evidence assumed that the invention involved more than the discovery of a dosage range of a compound assuming that the existence and nature of the compound is known, the compound being rosuvastatin. The experts all assumed, at the least, that some part of the invention involved unearthing the existence of rosuvastatin itself. I say “at the least” because some of the expert evidence also appeared to assume that the invention went still further, and involved conceiving of the very existence of a need for a new drug to treat hypercholesterolemia, which might be a new drug of a previously known or unknown class. I have already said that I do not accept that the skilled addressee would have done other than recognise that statins were the drug of choice to treat hypercholesterolemia and despite the existence of a number of statins there remained a real need for the development of new statins which had greater efficacy at lower doses to remove or reduce the need for dose titration. Accordingly, that part of AZ’s case which relied on evidence to this effect (particularly that of Dr Evans) is not accepted. Otherwise, it is appropriate to consider further this alternative case put by the generic parties and denied by AZ.

Insofar as AZ’s case in response relied on the proposition that none of the experts in fact took any step at the time to solve the problem they said they perceived (that is, the need to find dosages of alternative statins which beneficially altered lipid levels to a significantly greater extent than similar dosages of then currently used statins and which had a similar or improved safety profile), the reliance was misplaced. As discussed, I have no doubt that the experts who said they perceived this need before the asserted priority date did do so. None of them took steps to fulfil the need for the simple reason that they were not in a position to do so. The relevant experts in this regard, Professors O’Brien and Tonkin and Dr Colquhoun in particular, were treating physicians and, while involved in trials for drug companies, not in the business of finding alternative statins to those then available. Their evidence about the steps they would have taken had they had the task of finding dosages of alternative statins which beneficially altered lipid levels to a significantly greater extent than similar dosages of then currently used statins and which had a similar or improved safety profile was necessarily hypothetical. Given the nature of drug development, which involves time consuming and expensive trials, the case is not similar to *Lockwood v Doric (No 2)* in this respect. The evidence is necessarily hypothetical, but it is not mere speculation given the extensive information available as part of the common general knowledge of the skilled addressee in respect of clinical trials, hypercholesterolemia and statins. The skilled addressee, attempting to find dosages of alternative statins, would have discovered the 471 patent (or its US equivalent as Professor O’Brien found) and the Watanabe article by routine and conventional literature searches that necessarily would have been carried out by reason of the posited attempt. AZ’s arguments to the contrary are not well-founded. Each document, on the evidence, would have been ascertained, understood and regarded as relevant to the skilled addressee as required by s 7(3) as applicable to the 051 or low dose patent. Each document, considered separately, would have led the skilled addressee as a matter of course to try the claimed invention in the expectation that it might well produce a useful alternative to or a better result than currently achieved in the field (*Aktiebolaget* at [53]).

I do not accept AZ’s submission that these documents would not have been found by the skilled addressee without hindsight and in the ordinary course of events. That is not to say that there were no issues with the evidence about finding these documents. Many of the issues AZ identified, however, are more a product of the hypothetical nature of the exercise which the experts undertook than any impermissible process of amalgamation of non common general knowledge. Whatever the issues with parts of the evidence, what the evidence did establish was that a skilled addressee would have readily found each of these two documents, understood each and regarded each as relevant. In this regard, the fact that Dr Wilson and Dr Evans did not locate either document, in contrast to Professor O’Brien and Dr Reece, does not persuade me to the contrary.

The fact that there were other potential statin candidates (eleven according to AZ) for development at the time, including cerivastatin and a compound NK-104, which the skilled addressee would also have located as a matter of course, does not detract from the fact that the information in each of the 471 patent and the Watanabe article would have led the skilled addressee as a matter of course to try the claimed invention in the expectation that it might well produce a useful alternative to or a better result than currently achieved in the field. As Watson and Ascent submitted in respect of the extensive clinical trials which AZ conducted:

The dosages identified in the Low Dose Patent were said by [AZ] to have been identified following a clinical trial where patients were administered those dosages. The undertaking of such a trial is a perfectly ordinary, albeit expensive, step taken to confirm efficacy and safety and achieve regulatory approval.

Further, the fact that, as AZ put it, the “vast majority of development projects involving new chemical entities fail following clinical trials for reasons which include a lack of efficacy or an unacceptable safety profile” does not undermine the expectation of success in this case. The skilled addressee would have had the benefit of common general knowledge as described and the information in the 471 patent or the Watanabe article. While the skilled addressee would have known, as Professor Tonkin did, that the non-LDL lowering actions of agents within this class may differ so that “a similar effect between agents in the absence of trials …cannot be assumed”, they also would have understood what each of the 471 patent or the Watanabe article was telling them about rosuvastatin. Professor Tonkin’s (and the other expert’s) proper concerns about long-term safety do not alter the fact that, based on either the 471 patent or the Watanabe article in light of the common general knowledge, what AZ claimed to have invented in the 051 or low dose patent was obvious. Professor Tonkin’s prescribing practices (to choose a particular dose depending on any data that was available showing effects in clinical trials in similar patients, and what was known about the anticipated effect on cholesterol levels, and safety data) are one thing; the claimed invention of a method of treatment in which there is and could never be any promise of any absolute level of safety and efficacy is another.

AZ also referred to the criteria of commercial success, as evidence of inventiveness. The problem with this approach in the present case is that the commercial success of AZ’s rosuvastatin product, on the evidence, is due to its potency at lower doses than other statins. But as the generic parties pointed out, these are qualities of the compound rosuvastatin. AZ did not invent rosuvastatin. As Apotex put it, “the commercial success of Crestor is due to the quality of the drug itself, not to the entirely conventional doses of 5 mg and 10 mg”. Watson and Ascent made the same point in these terms:

Whilst [AZ] have shown that rosuvastatin is a successful drug, it has not shown how that success is attributed to the actual inventions claimed in the Patents as distinct from the initial discovery by Shionogi and its commercial decision to licence that compound from it.

And as Watson and Ascent also submitted, AZ had banked on the commercial success of rosuvastatin as a “superstatin” before it conducted any of the clinical trials on which AZ relies to defend the validity of the 051 or low dose patent.

For these reasons, if my conclusions on the nature of the invention are incorrect, the invention claimed in all three claims of the 051 or low dose patent (which are variants of claim 1, the differences not being material for present purposes) nevertheless lacks any inventive step and is liable to be revoked.

###### Manner of manufacture

To be a patentable invention, s 18(1)(a) of the Act requires the claimed invention to be a manner of manufacture.

According to Apotex:

the use of a known compound for a purpose stated on the face of the specification of treating a medical condition as taught in the prior art cannot be patentable subject matter (it is not a “manner of manufacture”).

Apotex submitted that:

In *Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) [154 FCR 31; [2006] FCAFC 91] the Full Court found that there was no manner of manufacture in circumstances where the prior art documents referred to on the face of the specification disclosed weekly administration of alendronate, but only disclosed a dosage range, and not the precise doses specified in the claims in suit. The facts were therefore directly analogous to the facts in this proceeding. The Full Court concluded:

The claims in the patent are analogous to the use of alendronate as taught in those documents. The patent specification discloses no new substance, no new characteristic of a known substance, no new use and no new method. There is, therefore, no manner of new manufacture.

In *Advanced Building Systems Pty Ltd v Ramset Fasteners (Aust) Pty Ltd* (1998) 194 CLR 171, the majority stated, at 192-193 [39]-[40]”

In *Philips*, the appellant failed in its attempt to establish that although a claimed use was noting but a new use of an old substance this could still be a proper subject of letters patent under the 1990 Act where this character of the claimed use was apparent on the face of the specification. Rather, Brennan, Deane and Toohey JJ decided that “if it is apparent on the face of the specification that the quality of inventiveness necessary for there to be a proper subject of letters patent under the Statute of Monopolies is absent, one need go no further”. It was unnecessary to adduce evidence of the prior art base and to compare the invention claimed with the prior art base for the purposes of s18(1)(b) if the absence of inventiveness appeared on the fact of the specification. Their Honours also said that “it would border upon the irrational if a process which was in fact but a new use of an old substance could be a ‘patentable invention’ under s18 if, but only if, that fact were not disclosed by the specification.”

The present case is not in that category of cases, considered in *Philips*, where the lack of an inventive step appears on the face of the specification.

Apotex submits that the proposition remains the law – but confined to matters apparent on the face of the specification. See also *Lockwood v Doric (No. 2)* (2007) 235 at 173.

Apotex also reserved its right to argue that each of the claims is not a manner of manufacture because they claim methods of treatment of the human body. This submission cannot be accepted given the current state of authority (see *Anaesthetic Supplies Pty Ltd v Rescare Ltd* (1994) 50 FCR 1; *Bristol-Myers Squibb Co v FH Faulding & Co Ltd* (2000) 97 FCR 524; [2000] FCA 316;).

Watson and Ascent made the same points, saying:

The decision of the High Court in *Advanced Building Systems Pty Ltd v Ramset Fastners (Aust) Pty Ltd* [(1998) 194 CLR 171; [1998] HCA 19] made it clear that the lack of invention must appear on the face of the specification. The specification includes documents referred to therein and which are incorporated and read as part of the specification. It is a matter of assessing, from the face of the specification and documents incorporated, and with reference to the common general knowledge, what is the alleged invention disclosed.

Watson and Ascent also submitted that the passage in the specification which uses the words “surprisingly” and “unexpected” (see para 3 of the 051 or low dose patent) do not take the patent outside the scope of these principles. Watson and Ascent said:

The aforementioned assertions are scrutinised in terms of the promise made in light of the information revealed on the face of the specification when read as a whole. It is not merely sufficient that the specification state that there is promise if, in context, that promise is not new and inventive. See *Merck* at 52 [*Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) 154 FCR 31; [2006] FCAFC 91]; and *Phillips* at 665 [*NV Philips Gloeilampenfabrieken v Mirabella International Pty Lt*d (1995) 183 CLR 655; [1995] HCA 15]. It is necessary for the Court to assess the face of the specification, including the documents referred to therein, and assess newness and inventiveness

…

Given the aforementioned disclosures, it follows that when read by the person skilled in the art it is apparent that there is insufficient newness or inventiveness to sustain the grant of a patent. There is no new manner of manufacture. There is no invention. The Low Dose Patent is, on the face of the specification, nothing more than a claim to a known dosage range of a known substance in the treatment of a condition that the substance was taught as useful to treat.

AZ submitted that the specification does not admit that a method of treating hypercholesterolemia comprising the administration as a starting dose of a single, once daily oral dose of 5 to 10 mg of rosuvastatin was known or was obvious. The specification asserts, to the contrary, that this method surprisingly reduces cholesterol to an unexpected degree without significant adverse side effects AZ further submitted that:

[T]he general introductory statement that “the Agent is taught as useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis” must be read in context. The evidence shows that this is not read by the skilled addressee to suggest a method of treatment is already known that is safe, effective and able to be administered to a patient is known and available. The statement also says nothing to about the combination of elements that is needed to administer the agent in a way that is safe and effective, including the method of administration, the dose range, the start dose and dosage form that sould be used. There is no place in the specification that admits these matters are known.

AZ submitted that the contents of the 471 patent and Watanabe article are not incorporated in the specification in whole or part, but rather that “these documents are referred to briefly… to assist in identifying the compound rosuvastatin rather than to describe the invention”.

It is true that, unlike in *Merck & Co Inc v Arrow Pharmaceuticals Ltd* (2006) 154 FCR 31; [2006] FCAFC 91, there is no express statement of incorporation of the 471 patent or Watanabe article. The terms of the specification are thus similar to those considered in *Apotex Pty Ltd v Sanofi-Aventis* (2008) 78 IPR 485; [2008] FCA 1194. In that case, Gyles J found that a reference to a previous French specification did not destroy the quality of “newness” by reason of incorporation. The earlier specification was “incorporated sufficiently to understand the reference to the racemic compound in the specification in the suit” (at [121]).

By parity of reasoning, the Watanabe article and the 471 patent are properly considered external to the specification the conclusion of lack of a manner of manufacture can not be reached in the present case.

###### Fair basis

Section 138(3)(f) of the Act provides that it is a ground of revocation if a specification does not comply with s 40 (3), which provides that the claims must be fairly based on the specification.

Apotex contended that:

The body of the specification of the low dose patent places no emphasis or focus on a 5 to 10mg dose of rosuvastatin. Nowhere does it disclose that there is any benefit to be obtained by using a 5 to 10 mg dose of rosuvastatin over using some other dose of rosuvastatin. In terms of *Lockwood v Doric No. 1* (2004) 217 CLR 274 [[2004] HCA 58] at 301 [69], the passage at p10 lines 14-16 is “stray in nature” if it is relied on to provide a basis for 5 or 10 mg as a starting dose, not tied to an improvement in efficacy.

This is because the entire focus of the specification is the attempt to link dosage levels of rosuvastatin “which beneficially alter lipid levels to a significantly greater extent than similar dosages of currently used statins”. That approach was only abandoned when the claims in their current form were amended on 12 December 2003.

Page 10 lines 14 to 16 of the specification say that “[a] starting dose of 5 or 10 mg per day of the Agent unexpectedly has a superior efficacy and a comparable or better safety profile compared to the starting doses of other statins, and is therefore particularly advantageous.”

The amendments in 2003 to the specification deleted the claims of various permutations of dosage ranges and the combination of these dosages with various cholesterol-related parameters. According to Apotex, the “claims are now broader than the disclosure because they are no longer limited to combinations that link dosage ranges to cholesterol-related parameters – the only advance asserted by the specification over the disclosures in the admitted prior art.”

I do not accept that the specification fails to disclose the claimed invention. The specification identifies the invention as including a starting dose of 5 to 10mg per day. The disclosure is not confined to a particular result or cholesterol-related parameter, although that too is disclosed. The claims thus do not travel beyond the specification. As AZ said:

it is not to the point that additional matter is disclosed in the description of the 051 Patent, in the form of methods of treatment involving the use of doses greater than 5 to 10 mg of rosuvastatin. It is apparent that, of the total field described, the patentee has claimed only that portion involving the use of 5 to 10 mg of rosuvastatin, being a preferred embodiment which is described and addressed in the examples. This does not give rise to any lack of fair basis for the narrower claims.

For these reasons also the argument that the priority date of the 051 or low dose patent is deferred cannot be sustained on this basis. As AZ explained by reference to the priority document (GB 9902590), which contains the statement that “[a] particularly suitable starting dose of the Agent [ie, rosuvastatin] in the methods referred herein is 5 to 10 mg per day, especially 10 mg per day”:

there is no basis for concluding that the claims of the 051 Patent are not fairly based on matter disclosed in the priority document, or that they claim matter in substance disclosed by the later amendments to the specification. The assessment of fair basis and “in substance disclosure” depends on substance rather than form. An “over-meticulous verbal analysis” is to be avoided [*Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 1)* (2004) 217 CLR 274; [2004] HCA 58 at [68]]. What is needed is a “real and reasonably clear disclosure” of what is claimed [*Lockwood Security Products Pty Ltd v Doric Products Pty Ltd (No 1)* (2004) 217 CLR 274; [2004] HCA 58 at [69]; *Pfizer Inc v Commissioner of Patents* (2005) 141 FCR 413; [2005] FCA 137 at [75].]. The disclosures in the priority document and the specification of the 051 Patent as filed plainly provide this.

###### Utility

Section 18(1)(c) of the Act requires a patentable invention to be useful. If an invention is not useful it is liable to revocation under s 138(3)(b). Apotex did not press its challenges on this ground.

To the extent that Watson and Ascent pressed the issue, AZ conveniently identified the applicable principles:

Section 18(1)(c) requires that an invention be “useful”. This will be the case if the claimed invention does what it is intended by the patentee to do, in the sense of meeting the object or promise in the specification, and the end result obtained is itself useful [*Ranbaxy Australia Pty Ltd v Warner-Lambert Co LLC* (2008) 77 IPR 449; [2008] FCAFC 82 at [141]]. For this purpose, the claims must be construed from the perspective of a skilled person in a commonsense way, and not in a way that any such addressee would appreciate would lead to an unworkable result [*SNF (Australia) Pty Ltd v Ciba Specialty Chemicals Water Treatments Ltd* (2011) 92 IPR 46; [2011] FCA 452 at [293]].

It is not necessary for the description in the specification to spell out matters which the skilled person could supply without the exercise of any inventive faculty in order to achieve the promise of the invention. The patentee is entitled to assume that the reader has a reasonably competent knowledge of what was known before and reasonably competent skill in the practical mode of doing what was then known. A purposeful adoption of an embodiment that would obviously lead to an unworkable or inferior result is not an appropriate way of testing utility. It is also relevant to pay attention to the nature of the alleged “promise” in the specification. See, by way of analogy, *Austal Ships Pty Ltd v Stena Rederi Aktiebolag* (2005) 66 IPR 420; [[2005] FCA 805] at [254]-[255]. Ultimately, an asserted lack of utility must be established by appropriate evidence, not by mere speculation that the invention will not work or meet the promise set out in the specification.

As noted elsewhere (and against AZ in other contexts) the claims do not (indeed, cannot) promise absolute efficacy or safety for any patient. That said, it cannot be doubted that the claimed invention is useful, albeit as a product of the qualities of rosuvastatin rather than the method of treatment. This ground of challenge, accordingly, must fail.

###### False suggestion

Section 138(3)(d) of the Act provides that a patent may be revoked on the ground that it was obtained by fraud, false suggestion or misrepresentation.

The first false suggestion alleged concerns the statement that “[s]urprisingly it has now been found that when dosed orally to patients with hypercholesterolemia at particular dosages or in a particular dosage range the Agent lowers total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) by an unexpected degree… to an unexpected and beneficial extent, without any significant adverse side effects”. The contention is that these statements are false, because it would not have been surprising or unexpected that, when administered to patients in the doses described, rosuvastatin achieved the benefits referred to.

It may be accepted that statements to the effect that results are surprising or unexpected are inherently vague, whether read subjectively or objectively, and thus difficult to falsify. Moreover, as AZ said, the clinical trials which are referred to and form the basis for this statement show that administering a 5 mg dose of rosuvastatin is approximately twice as effective as administering 10 mg of atorvastatin, which was the then market leading statin. Even with all of the information it had as part of the licensing arrangement with Shionogi AZ (and the skilled addressee) might well still have been surprised by the potency of rosuvastatin. Whilst this is an inherent quality of rosuvastatin rather than the result of any invention by AZ, the false suggestion allegation is confounded by the evidence of rosuvastatin’s actual performance in the clinical trials; AZ had bought a superstatin that was not just demonstrably more potent than atorvastatin (as Shionogi’s work showed) but substantially more potent at the lower doses at which statins were conventionally prescribed. The weight of the expert evidence confirms that rosuvastatin turned out to be better than even AZ expected.

The second alleged false suggestion arises from statements made in correspondence sent to the Commissioner in February and November 2003, in connection with the prosecution of the application for the patent. These statements too are to the effect that the results achieved by the claimed method of treatment were surprising or unexpected or could not have been predicted. For the same reasons as set out above the allegation of falsity cannot be sustained. And as AZ also said in this regard it is apparent that these statements were made in the context of a debate with the examiner about the novelty and inventiveness of the invention against prior art cited by the examiner. As such, they constitute submissions about the effect of the prior art and cannot be demonstrated to be false, even if incorrect (see in *ICI Chemicals & Polymers Ltd v Lubrizol Corp Inc* (1999) 45 IPR 577; [1999] FCA 345 at [183]).

The third alleged false suggestion arises from a statement made in further correspondence sent to the Commissioner in December 2003 that “[t]he claims have also been amended to refer to the dosage as the starting dose” when, in fact, only claim 1 had been so amended.

As AZ said it can hardly be imagined that the statement was material to the grant of the patent. The same letter contained the claims as amended and thus the form of amendment sought was clear. It cannot be inferred that the Commissioner did not read the actual amendments given that the Commissioner effected them. Moreover, the letter did not say that every claim had been so amended. Claim 1 was so amended and, to the extent dependent on claim 1, claim 3 was thus also amended. Claim 2 was not amended as the statement of amendments provided to the Commissioner showed. As AZ also said a document from 2010 relating to a re-examination does not support any inference about the Commissioner’s state of mind in respect of the amendments.

The fourth alleged false representation concerns the entitlement of the patent applicant to the grant of a patent for the invention. The representation as to entitlement may have been wrong but it is difficult to characterise it as a false suggestion or misrepresentation such as to found an independent ground of challenge.

###### Conclusions

The 051 or low dose patent is liable to be revoked because the claims did not involve a patentable invention (on the grounds of lack of novelty, lack of inventive step or obviousness, and no manner of manufacture) and AZ lacked entitlement to the claimed invention, such entitlement being that of Shionogi through its employees rather than AZ through Dr Raza.

##### VALIDITY OF THE 165 OR HEFH PATENT

###### Novelty

As noted, the invention disclosed in the 165 or HeFH patent also pre-supposes the existence of rosuvastatin as a statin (that is, as an HMG-CoA reductase inhibitor). The invention is the use of that known compound to treat HeFH. The discovery or inventive concept is said to be that rosuvastatin is particularly good at treating HeFH, particularly severe HeFH when existing statins typically have to be used in combination with other therapies to treat HeFH.

Accordingly, I do not accept AZ’s submissions that prior publications could not anticipate the claimed invention because they did not disclose the chemical structure of rosuvastatin. Rosuvastatin is assumed to exist and have a particular chemical structure (that is, be a compound within the statin class) by the invention in the 165 or HeFH patent.

SCRIP article

The first alleged novelty destroying publication is the SCRIP article published in September 2000. This article reports on a study recommending an aggressive approach to the treatment of HeFH by statins referring to two then currently available statins, atorvastatin and simvastatin. The SCRIP article continues in these terms:

Although Dr Smilde gave no recommendations as to which statin to use as long as it aggressively lowered cholesterol, atorvastatin would be a logical choice because it is so potent. Other so-called “superstatins” in development, such as [AZ]’s rosuvastatin and Negma/Kowa’s [p]itavastatin, which have shown up to 65% reductions in LDL cholesterol (Scrip No 2563, p 21), could also fill this role.

AZ said that this “speculative, second-hand comment by an unidentified author does not amount to the disclosure of a method of treating HeFH within the claims of the 165 [or HeFH]” patent. I disagree. Based on Dr O’Brien’s evidence it is clear that every statin used to treat hypercholesterolemia is also able to be used to treat HeFH. The skilled reader of the SCRIP article would understand it as a clear direction to use statins as available to treat HeFH more aggressively than previously considered, the obvious focus for such treatment being statins with the greatest potency. The article suggests rosuvastatin is such a statin, along with other statins as nominated. The fact that other statins are not nominated does not teach away from rosuvastatin. The teaching is towards potent statins to treat HeFH, including rosuvastatin. The integers of claims 1 and 2 of the 165 or HeFH patent are anticipated. All dependent claims of claims 1 and 2 are also anticipated. Specifically, claims 1 to 10 and 21, relied on by AZ to allege infringement, are liable to revocation on this basis.

Open label extension study

The second alleged novelty destroying publication is the “open label extension” study conducted by AZ from June 2000. As AZ said:

The open label extension study (study 4522IL/0034) was preceded by a Phase III clinical trial (study 4522IL/0030) which compared the effects of rosuvastatin and atorvastatin in patients with HeFH, the results of which were later published in a paper by Stein et al. The Stein paper itself was published after the priority date of the 165 Patent and is not said to be an anticipation. What occurred in the open label extension study was that patients with HeFH who had participated in the clinical trial were given rosuvastatin on an ongoing basis pending the outcome of the results of the clinical trial. In this respect, the open label study is to be distinguished from the clinical trial, which was conducted on a “double blind” basis (meaning that neither the patients nor those acting as investigators were aware what drug was being administered to a particular patient). For ethical reasons, the conduct of an open label extension study is a common practice following the conduct of a clinical trial and provides an opportunity for all patients who participated in the trial to receive the drug being evaluated, pending the outcome of the results of the trial.

Contrary to AZ’s submissions I accept that the fact that the closed label trial had continued as an open label trial and the patients were being prescribed rosuvastatin on an ongoing basis to treat their hypercholesterolaemia amounts to a clear suggestion to use rosuvastatin in that way. I also accept that any statin useful in treating hypercholesterolemia would be understood by the skilled addressee as also useful in treating HeFH. HeFH is a particular cause of hypercholesterolemia but the evidence made plain that the treatment goals are the same, even if more difficult to achieve in HeFH patients. AZ’s points about the compound not being disclosed and no method of treatment being disclosed are not persuasive. The compound was already publicly available and the open label study, by definition, involved a method of treatment of hypercholesterolemia. As the compound was previously disclosed, I do not accept that the open label study could not anticipate the 165 or HeFH patent because it did not disclose the chemical structure of the compound. The compound existed and had a known chemical structure. Public information cannot be confidential information. AZ’s reliance on the statement that the required standard is “what the skilled addressee observes on inspection is sufficient to enable him or her to comprehend the complete invention” (*Lundbeck*) discloses the problem for AZ. The complete invention pre-supposes the existence of rosuvastatin; synthesising rosuvastatin is no part of the invention claimed in the 165 or HeFH patent. The open label study involved a clear direction to use rosuvastatin to treat hypercholesterolemia caused by HeFH. Insofar as the dependent claims 21 and 22 are concerned, which include an integer relating to 20 to 40 mg of rosuvastatin, if it is accepted that the open label study involved doses of 80mg, it can hardly be said that lower doses are not disclosed also.

Insofar as AZ submitted that safety and efficacy of rosuvastatin had not been proved I accept the submission of Watson and Ascent that these:

are not requirements of the claims properly construed. So, for example, claim 1 of the HeFH Patent does not require a particular effect (that is, LDL-C lowering) and simply requires administration to the patient. Likewise, safety is not referred to in the claims defining the invention.

In any event, as Watson and Ascent also pointed out, the open label protocol includes a patient information sheet stating that ZD 4522:

has already been tested on healthy people and patients (approximately 250) and has shown good lowering of cholesterol. Overall, the drug has been well tolerated.

AZ also relied on the “grace period” in s 24(1) of the Act. The relevant part of that provision, said not to be satisfied in this case, is that a patent application for the invention is made within the prescribed period, the prescribed period being 12 months (Regulation 2.2(d) of the Patents Regulations 1991 (Cth)). The problem for AZ is that the HeFH patent application was made on 16 November 2001, more than 12 months after the open label study commenced in mid 2000. AZ submitted, however, that the requirement was satisfied by reason of the filing of UK Patent Application GB 0028429 on 22 November 2000, within the 12 month period.

I do not accept AZ’s submissions that the reference to a “patent application for the invention” in s 24(1) of the Act includes a foreign application. A “patent application” is a defined term (s 3(1) and the Schedule) and means an application for a standard patent or innovation patent. In the context of the Act as a whole, these are Australian patents. AZ’s reference to provisional applications being included (*NSI Dental Pty Ltd v University of Melbourne* (2006) 69 IPR 542; [2006] FCA 1216) and to the policy of the legislation do not assist in expanding the reference to “patent application” so as to include foreign applications. There is no ambiguity about the reference. Its meaning is clear and confined by the definition.

For these reasons I accept that the open label study anticipates and thus destroys the novelty of all of the claims of the 165 or HeFH patent on which AZ relies.

The 051 or low dose patent application

AZ submitted that the 051 or low dose patent application could not anticipate the 165 or HeFH patent as it does not disclose or refer to HeFH. I disagree. And, properly understood, Professor Tonkin’s evidence on which AZ relied does not suggest to the contrary.

I accept that the trial referred to in the 051 or low dose patent application may or may not include patients with HeFH, it being impossible to tell one way or another. I accept also that it was common general knowledge that patients with HeFH were understood to be more difficult to treat than patients without HeFH and that, generally speaking, more aggressive treatment including but not limited to statins was often required to treat HeFH. That said, as Watson and Ascent put it, the 051 or low dose patent application:

teaches the treatment of hypercholesterolemia using a statin, namely rosuvastatin, which treatment is independent of the cause. The direction to use that drug in the treatment of hypercholesterolemia applies whether that hypercholesterolemia is caused by genetic factors (that is, FH) or other factors.

This reflects Professor O’Brien’s evidence, which I accept, that “any statin can be used to treat FH because statins are very effective at reducing LDL-C levels, the primary problem with FH”. The fact, which also was known to the skilled addressee, that HeFH patients might have variable responses, requiring more aggressive treatment, does not change the other basic fact that the first-line aggressive treatment was with statins, the same drug class, the objective of lowering LDL-C also being exactly the same albeit harder to achieve for HeFH patients. Professor Tonkin’s point is that, at the level of an individual patient with HeFH, safety and efficacy of any statin is only demonstrated through testing. So much, of course, is also true of any individual patient with hypercholesterolemia not caused by HeFH. Further, AZ relied on this part of Professor Tonkin’s evidence:

in the absence of being able to make a reasonable assumption that the trials referred to in that 051 patent, if you had read it – that is, inability to make a reasonable assumption that it treated HeFH patients – you would not have understood 051 as telling you to use rosuvastatin in HeFH patients. You certainly wouldn’t have understood that, would you?---No.

Yes. You agree with me?---I agree.

The context of this evidence is important. The context was Professor Tonkin’s actual prescribing practices in 2000. Unsurprisingly, without having to hand all of the safety data about rosuvastatin at that time Professor Tonkin believes he would have continued to prescribe atorvastatin to his HeFH patients. What is apparent from the balance of the expert evidence, that of Professors Tonkin and O’Brien, Drs Wilson and Colquhoun, is that statins are the preferred treatment for hypercholesterolemia and the goal of statin treatment for all patients with hypercholesterolemia, irrespective of its cause, is the same (lowering LDL-C in particular). The relevant point, accordingly, is that no skilled addressee could have read the 051 or low dose patent without also realising that it provided them with a new method of treatment of HeFH as claimed in the 165 or HeFH patent. The skilled addressee would have realised this as a matter of course in the sense that it would never have occurred to the skilled addressee that a statin useful for treating hypercholesterolemia would not also be useful in treating HeFH. And as it was common general knowledge that more aggressive treatment of HeFH patients was often required, the higher doses in the dependent claims of the 165 or HeFH patent are also anticipated.

For these reasons the 051 or low dose patent anticipates and destroys the novelty of the claims of the 165 or HeFH patent on which AZ relies.

Olsson and Pears articles

The content of the Olsson article is set out above. The Pears article is another abstract in substantially the same terms. The articles thus refer to the randomised, placebo-controlled, parallel-group dose-ranging trial (4522IL/0008) conducted by AZ to assess the effects of once daily oral doses of rosuvastatin and atorvastatin, being the same trial as referred to in the 051 or low dos patent. Accordingly, AZ submitted that these articles could not anticipate the 165 or HeFH patent as they make no reference to HeFH or to a method of treating HeFH “as opposed to hyperlipidemia generally”. AZ also made the point that neither publication discloses the chemical compound which is the subject of the 165 or HeFh patent.

For the reasons already given above I do not accept either argument. The articles showed that rosuvastatin effectively reduced LDL-C levels (indeed, more effectively than atorvastatin, the then most potent statin available) and was well tolerated with a safety profile which compared favourably to both atorvastatin and placebo. To the skilled addressee the articles thus also disclosed that rosuvastatin would be an effective and well tolerated treatment for HeFH as particularly the more potent statins were known by the skilled addressee to be the first-line treatment for HeFH, irrespective of the fact that higher doses as part of a more aggressive treatment strategy, and other drugs in combination with statins, might also have to be used. In other words, if it is not apparent already from the discussion above, the expert evidence about the potential different responses of HeFH patients given the cause of their hypercholesterolemia fell far short of any suggestion contrary to the general proposition that all statins capable of reducing LDL-C levels are a useful treatment for patients with HeFH, with the issues of efficacy and safety of statin therapy for such patients required to be considered and assessed on an ongoing basis (as with all patients) but with particular regard to their risk profile. Against this background I find it inconceivable that the skilled addressee could have read the Olsson or Pears articles without immediately recognising that rosuvastatin would be a useful method of treating HeFH at least at all of the doses indicated (1 to 40 mg). The claims of the 165 or HeFH patent, accordingly, are not novel in light of the Olsson and Pears articles. As to AZ’s point about the compound, the same argument is rejected for the reasons already given.

The 471 patent and the Watanabe article

Watson and Ascent submitted that these documents also anticipated the claims of the 165 or HeFH patent asserted against them. Consistent with the reasoning above, I agree with this submission.

###### Inventive step/obviousness

AZ submitted that the contention of the generic parties that the invention claimed in the 165 or HeFH patent was obvious in the light of the common general knowledge alone cannot succeed for the “threshold reason…that rosuvastatin did not form part of the common general knowledge before the 22 November 2000 priority date”. This argument, as discussed, overlooks the nature of the invention in the 165 or HeFH. The question is whether the invention would have been obvious to the skilled addressee in light of the common general knowledge. The invention in the 165 or HeFH patent assumes the existence of rosuvastatin. The invention lies in the claimed method of treatment alone, that is, using the compound which is assumed to exist as a method of treating HeFH. The question is thus whether that method would have been obvious to the skilled addressee in light of the common general knowledge. This question must be answered in the affirmative for the reasons already given. In any event, for the 165 or HeFH patent, unlike the 051 or low dose patent, I am satisfied that rosuvastatin, as disclosed at the Stockholm symposium in the Olsson article, was part of the common general knowledge by 30 June 2000 and thus before the asserted priority date. On both bases, the 165 or HeFH patent cannot be taken to have any inventive step as provided for in s 7(2) of the Act, irrespective of any information of the kind referred to in s 7(3).

Professor Tonkin’s evidence about the Olsson article, referred to by AZ, does not establish the contrary. It is true that Professor Tonkin saw the Olsson article at the Stockholm symposium (it was pinned up next to his own contribution). It is also true that Professor Tonkin did not thereafter seek himself to develop rosuvastatin as a method of treatment for HeFH. AZ said that, as a result:

it cannot be said that Professor Tonkin, as a skilled addressee, would have been directly led, by the knowledge that rosuvastatin was a promising new statin, to take any step to develop a new treatment for HeFH in the expectation that treatment would be effective. He was put in the precise position that the generic parties seek now to recreate by artificial hypothetical evidence, yet did nothing. This is because Professor Tonkin – like Dr O’Brien – simply was not interested in developing any new treatment for HeFH. This is an example of unfelt therapeutic want.

I do not accept this submission. Professor Tonkin did not pursue rosuvastatin as a treatment for HeFH because it was no part of his job to do so at the time. The idea that treating physicians such as Professor O’Brien and Professor Tonkin were not interested in any new treatment for HeFH is untenable in the face of their evidence. To the contrary of AZ’s submission, they knew full well that HeFH patients were more difficult to treat than non-HeFH patients and did not always respond as well to existing statin therapy as non-HeFH patients. This is the reason that HeFH patients often had to be treated far more aggressively than non-HeFH patients by higher doses of statins, atorvastatin being perceived as the most potent available, and combined with other non-statin therapies. There was no “unfelt therapeutic want”. For hypercholesterolemia generally there was a commonly perceived need for more effective statins to enable more patients to be brought to their target LDL-C levels without dose titration or with reduced dose titration and, for HeFH in particular, to enable the more aggressive reduction of these patients’ LDL-C levels given their higher risk profiles.

Similarly, and as also set out above, the fact that Professor Tonkin, if he had read the 051 or low dose patent (which sets out the same information as in the Olsson article), would have preferred to have used the available statins to treat patients with HeFH because, “there was a stronger evidentiary base to support their efficacy” concerns his prescribing practices only. The evidence in no way undermines the clear proposition from the evidence that it was common general knowledge of the skilled addresses that a statin which could reduce LDL-C levels would be useful in treating HeFH. This evidence does not confirm or support the opinion attributed to Professor Evans, who is not a physician treating hypercholesterolemia and HeFH, that “the established success of other statins taught away from pursuing new statins for treating HeFH (and, for that matter, hypercholesterolemia generally)”. First, Professor Evans was commenting only that there were a number of existing statins in the market so it was “congested”, but did not know what Professors Tonkin and O’Brien did about the limitations of existing statins, even atorvastatin the most potent then available. Second, the success of statins as a compound class in fact made it obvious that more potent statins with the same or a reduced side effects profile would be highly desirable which, of course, is the very reason that AZ obtained the rights to rosuvastatin, the so-called “superstatin”, from Shionogi.

AZ said that the “test of obviousness also requires the skilled addressee to have a reasonable expectation the path that he or she pursues will prove to be successful”. AZ itself certainly held such an expectation as its own investment in licensing and developing rosuvastatin shows. Indeed, on 31 July 2000 (before the asserted priority date of the 165 or HeFH patent), AZ issued a statement about its decision to spend £28.5m to construct a new plant to manufacture ZD4522 following the “recent publication of clinical data from Phase II trials demonstrating the potential of ZD4522, a HMG-CoA reductase inhibitor, to be a highly effective and well-tolerated alternative to currently available statins”. Given the disclosure in the Olsson article, this confidence was well-placed and, given the common general knowledge, equally applicable to rosuvastatin being a useful method for treating HeFH.

AZ’s submissions to the contrary take parts of Professor Tonkin’s evidence out of context and elevate them above all other parts of his, and the other experts’ evidence, about HeFH. As discussed, the contextual issue is that Professor Tonkin was considering his own prescribing practices when he gave evidence about the complexities of the interaction between the enzyme, the new statin, and the HeFH condition in the patient. It is hardly surprising that Professor Tonkin would not actually prescribe to a patient a compound that had not yet been approved. But prescribing practices and the conception of the claimed method of treatment are two different things. The conclusion which AZ drew from Professor Tonkin’s evidence, that “the very nature of the HeFH condition is such that the efficacy in terms of potency/safety of a new statin cannot be assumed to be of any benefit to HeFH sufferers without testing. It is an unknown quantity”, simply cannot stand with the other evidence or, indeed, Professor Tonkin’s own approach to treating HeFH patients aggressively with the most potent statin he then had available, being atorvastatin.

The cross-examination of Professor Tonkin referred to by AZ, predicated as it was on an express assumption as to “safe” use in HeFH patients (when any absolute concept of safety is meaningless in this context), does not assist AZ’s case on this issue. To the contrary, Professor Tonkin’s evidence exposed the flaw in AZ’s approach. Professor Tonkin said that he would have expected rosuvastatin, given its potency as shown in the Olsson article and his knowledge of statins, to be more effective in treating HeFH than other statins. When Dr Wilson’s point that such efficacy and safety could not be predicted in HeFH patients from the results for non-HeFH patients was put to him, Professor Tonkin explained the difference for him, as a scientist, between an expectation and a prediction. He accepted that the nature of HeFH was such that he could not predict with “100% confidence” from the Olsson article that rosuvastatin would treat HeFH better than existing statins but he certainly had an expectation to that effect “more likely than not”. Nor did the Olsson article “necessarily indicate” such usefulness in treating HeFH, but Professor Tonkin expected it to be so useful albeit again not with “100% confidence”. Consider, for example, the following (telling) evidence which provides the context to the evidence of Professor Tonkin isolated by AZ in its written submissions:

And the reason why you can’t know without testing is because you understand now, and understood in 2000, that it may well not work – the statin may well not work in an HeFH patient; that’s right, isn’t it? --- It may not. But, on the other hand, my expectation would be that it would be more likely than not to work.

The same point is made in the following exchange:

Because, as you agree – I think you’ve already agreed that the efficacy may depend on the cause of the particular hypercholesterolaemia, that is, the efficacy of a statin on treating hypercholesterolaemia; that’s right? ---Yes, in an individual level, certainly there could be some variation, etcetera. But, on the other hand, if I was taking a group of patients with heterozygous FH I could have, I think, a prediction that it was more likely than not that it would be effective. I cannot make comments about its safety until one has – in terms of its safety across a large group of people, I would want more information.

And again, the point is made in this evidence:

But in the absence of any evidence of safe and effective use in any HeFH patients, you wouldn’t make any prediction, would you? --- I would.

In the absence of any – I thought you’ve indicated that provided you had some evidence of safe use in HeFH patients, you might make a prediction? ---No. What I mentioned was that I would have expected – I would – could make a prediction about safety based on the extent of the exposure there had been to that time. Because some of those things, for example, affecting metabolism of the particular agent might have also disclosed safety signals – adverse ..... signals – in other patients. So I would also, though, want to know specifically there might be some conditions that related to heterozygous FH, but I think if I use expectation as more likely or not but not certainty, I do believe I can make some predictions.

It is all this which leads up to the evidence relied on by AZ, in these terms:

Well, can I suggest to you your view in 2000 would have been – absent some experience of testing of a new statin in an HeFH patient, you would not have been prepared to make a prediction in the sense of more likely or not as to the safe use of such a treatment in an HeFH patient. Do you agree with that? ---I would be wanting trials to be done to investigate – I – being interested in the scientific process, an expectation might generate a hypothesis, but it doesn’t generate the answer. So you need to go on and do trials, but it’s a matter of whether that expectation is reasonable to generate the hypothesis, and I believe that it was reasonable to generate that.

Can I suggest to you that even if you had knowledge of safe use in non-HeFH patients, you would want more information as to the process of metabolism of the particular compound before you would make any prediction as to the likely safety of the new compound in HeFH patients. Do you agree with that? --- Yes, I would have wanted more information.

This evidence, in context, is concerned with what is needed to make a prediction which is then scientifically proved. What is beyond doubt is that, just like Professor O’Brien, from the Olsson article Professor Tonkin expected that rosuvastatin would be a useful treatment for HeFH. It follows that AZ’s submission that Professor Tonkin’s evidence confirms that “the Cripps question cannot be satisfied unless clinical trial data for patients suffering HeFH when treated with rosuvastatin, together with information about the process of metabolism, were part of the common general knowledge” involves a view of his evidence which is not reasonably open.

I also do not accept AZ’s criticisms of Professor O’Brien’s alleged failure to disclose in his affidavits that he too would have immediately recognised that rosuvastatin was a useful treatment for HeFH from the information in the Olsson article. Professor O’Brien’s evidence that he did not in fact come up with the solution of using rosuvastatin to treat HeFH in November 2000 has to be understood in the context of his limited role as part of the AZ advisory committee at that time. Professor O’Brien did not in fact at that time “come up” with anything because he was not tasked with doing so. But the idea that Professor O’Brien would not immediately recognise from the Olsson article that rosuvastatin would be useful for treating HeFH is untenable.

Insofar as it might be necessary to consider s 7(3) information, I have explained above that I consider that the information disclosed at the Stockholm symposium (in substance, the same as that in the Olsson article which was published there) became part of the common general knowledge of the skilled addressee of the 165 or HeFH patent before the asserted priority date of 22 November 2000. On this basis, the question whether the Olsson article is also relevant under s 7(3) does not arise. Even if my primary conclusions are incorrect, however, I am satisfied that the Olsson article is a document that the skilled person could have been reasonably expected to have ascertained, understood and regarded as relevant to work in the relevant art before 22 November 2000. The fact that there was no evidence of how such a document might have been found by the skilled addressee is beside the point given that Professor Tonkin in fact attended the Stockholm symposium and knew about the Olsson article, Dr Colquhoun attended the Stockholm symposium and may be inferred to have known about it, and Professor O’Brien did not attend but certainly was in routine contact with colleagues who did attend and can be expected to have known about the results reported in the Olsson article without recourse to any AZ confidential information before 22 November 2000. From the perspective of the skilled addressee as at 2000 (recalling Dr Wilson was a registrar at that time and not as far advanced in his career then as Professor Tonkin, Professor O’Brien and Dr Colquhoun), the results reported by the Olsson article would have been perceived as highly significant for the future treatment of hypercholesterolemia and, accordingly, HeFH as well. So much AZ must have known as well when it published its decision to construct a new plant to manufacture rosuvastatin shortly after the Stockholm symposium.

Given the nature of the invention as discussed (that is, an invention which assumes the existence of rosuvastatin and claims an invention relating to a method of treatment of HeFH using rosuvastatin), I also do not accept AZ’s submissions that the skilled addressee would not have ascertained, understood and regarded as relevant each of the SCRIP article, the 051 or low dose patent application, the 471 patent and the Watanabe article. Consistent with the reasoning above, the 165 or HeFH patent was also obvious given the information in each of these documents considered separately as required by s 7(3).

For these reasons the claims of the 165 or HeFH patent on which AZ relies are liable to be revoked on the basis that the invention so claimed does not involve any inventive step and was obvious within the scope of s 7(2) of the Act.

###### Manner of manufacture

The relevant provisions and principles have been set out above.

Consistent with those principles, while it may be acknowledged that the specification refers to a “new use” of a statin, being rosuvastatin, the specification construed in light of the common general knowledge of the skilled addressee discloses no such new use.

First, as Apotex submitted:

The HeFH patent admits on the face of the specification that rosuvastatin (ZD4522) was a known HMG-CoA reductase inhibitor: p4 lines 27-31. Although that is an ungenerous admission by November 2000, it is sufficient for the present submission – in the context of the admissions in the specification.

Second, the 165 or HeFH patent also admits, and in any event it was common general knowledge of the skilled addressee that: - (i) that LDL is atherogenic and that “subjects with hypercholesterolaemia are at increased risk of developing atherosclerosis” with clinical manifestation including CHD and PVD; in HeFH patients these [same] manifestations occur early, (ii) “one important goal in these subjects is to reduce blood cholesterol levels”, (iii) statins are “a breakthrough in treating hypercholesterolaemia”, lowering LDL-C levels by inhibiting HMG-CoA reductase, and (iv) “despite the benefits of statin therapy less than optimal therapeutic results are achieved in patients with HeFH”.

In this context, I accept Apotex’s submissions as follows:

the present case is one “in that category of cases, considered in *Philips*, where the lack of an inventive steps appears on the face of the specification” [*Advanced Building Systems Pty Ltd v Ramset* *Fasteners (Aus) Pty Ltd* (1998) 194 CLR 171; [1998] HCA 19 at [40]]: the use of a known statin to treat the known condition in the known way is even stronger than *Microcell*, *Philips* or *Merck v Arrow*: subject only to one matter. That matter is the assertion of superior efficacy: “particularly good” (at p3 line 11 – p4 line 2), in the context of the disadvantages asserted at p2 line 30 – p3 line 8, in particular that “there is no single drug treatment which may be used on its own which consistently brings a significant number of patients suffering from HeFH within NCEP or EAS guidelines” at p3 lines 6-8.

The phases “particularly good at treating HeFH” and “a significant number of patents” are too vague to define an invention and, more importantly, the claims do not attempt to limit the invention to the superior efficacy described.

…

Each of the claims is, thus, nothing more than a claim for the use of a known pharmaceutical substance for a use for which its known properties make it suitable, namely the treatment of hypercholesterolaemia in any patient.

There was no “hitherto unknown or unsuspected property” of rosuvastatin that made it suitable for treating hypercholesterolaemia in patients with HeFH – the relevant property that made it suitable is precisely the same property that made it suitable for treating hypercholesterolaemia in any patient: it acts to inhibit HMG-CoA reductase.

###### Secret use

Section 18(1)(d) of the Act provides that an invention is a patentable invention if the invention was not secretly used in the patent area before the priority date of the claims. By s 9 certain acts are not to be taken as a secret use.

The generic parties’ contention of secret use of the invention claimed in the 165 or HeFH patent relates to the “open label extension” study associated with AZ’s clinical trial 4522IL/0030. The facts do not support the contention.

As AZ pointed out use for “the purpose of reasonable trial or experiment” or “any purpose other than the purpose of trade or commerce” are excluded by operation of ss 9(a) and (c) of the Act. As AZ submitted:

the open label extension study was a continuation of the clinical trial and was in the nature of research and development activity. It did not involve commercial exploitation of the invention claimed in the 165 Patent.

The arguments to the contrary are unpersuasive. The purpose of the activities of AZ may be inferred. Direct evidence is not essential. The distinction sought to be drawn by the generic parties between trials done for the purpose of determining utility and for the purpose of obtaining regulatory approval is not attractive. The development to market of a drug is different from developing a lorry-pulled seed-harvesting machine as considered in *Longworth v Emerton* (1951) 83 CLR 539.

###### Fair basis

AZ noted that Watson and Ascent challenged the validity of the claims 3 and 13 and their dependent claims of the 165 or HeFH patent on the grounds that the claims were not fairly based on the specification. If so, the challenge was not pressed in any meaningful way and thus I disregard it.

###### False suggestion

The case in relation to false suggestion depends on the contention that AZ, through its employees Dr Raza and Dr Hutchinson, was not entitled to the grant of a patent for the invention in the 165 or HeFH patent. As discussed in the context of the 051 or low dose patent I find it difficult to accept that a lack of entitlement, if established, also founds a separate case of invalidity for false (as opposed to merely incorrect) suggestion. The real issue is that of entitlement to the invention.

###### Entitlement

The fact that AZ has not proved that Dr Raza and Dr Hutchinson are the inventors of the claimed invention in the 165 or HeFH patent is beside the point given that the onus is on the generic parties to prove to the contrary.

I also have difficulty in understanding the argument of lack of entitlement on the basis that the claimed invention was not novel and did not involve any inventive step. To explain, as far as I understand the argument Apotex puts in this regard, it is that Dr Raza and Dr Hutchinson are not the inventors because there is no invention; as any statin that treats hypercholesterolemia is, by definition, also a treatment for HeFH, the claimed invention is no invention at all. Although I accept that the invention claimed is not a patentable invention on the grounds set out above, nothing suggests that Dr Raza and Dr Hutchinson did not have the idea claimed, albeit an idea which was obvious and lacked novelty. The fact that I also accept many, perhaps all, of Apotex’s submissions relating to the relevant facts in this regard does not assist in understanding the real thrust of Apotex’s case on this issue. Hence, I accept:

* The evidence of Dr Wilson [and, I note, all of the other relevant experts in this regard who were involved in treating hypercholesterolemia and HeFH] that there was “an unmet need for more effective treatments for hypercholesterolemia (including HeFH)” – so that it follows that the perception of the need cannot be part of the invention, as it sometimes can.
* That both the Japanese and FDA Guidelines require or suggest that efficacy findings for hyperlipidemia (of which the principal class is hypercholesterolemia) be characterised separately for HeFH, so that a suggestion for such a trial to test the efficacy of a drug in lowering LDL-C in patients with HeFH cannot be part of the invention.
* The evidence shows that it was routine to test the response in HeFH patients when testing a drug for hypercholesterolemia.
* Dr Reece was not challenged on his opinions that the design of such trials was conventional or standard, - it follows that the design of the particular 0030 trial conducted for HeFH is not part of the invention. There is no evidence that even as little as this was done by Dr Raza or Dr Hutchinson. Dr Evans agreed that such trials are standard.
* It was Shionogi who invented the idea of progressing rosuvastatin through a series of conventional trials, in conformity with the Japanese Guidelines.

Nevertheless I do not translate these matters, or the other matters referred to by Apotex, into a lack of entitlement.

For these reasons I do not accept that lack of entitlement is a ground on which the 165 or HeFH patent may be revoked.

###### Clarity

Watson and Ascent submitted that:

Claims 11 to 20, 22 and 23 are not clear and therefore they do not comply with section 40(3) of the Act. The meaning of the word “use” is unclear and ambiguous and the precise extent of the monopoly sought to be claimed is not clear.

Section 40(3) requires claims to be clear. The alleged lack of clarity is itself ambiguous. Accordingly, the submission is unhelpful and unpersuasive.

###### Conclusions

The 165 or HeFH patent is liable to be revoked because the claims did not involve a patentable invention (on the grounds of lack of novelty, lack of inventive step or obviousness, and no manner of manufacture).

##### VALIDITY OF THE 842 OR CATION PATENT

###### The priority date

As noted the 842 or cation patent claims a priority date of 26 January 2000 based on the filing of UK Patent Application GB 0001621 (also referred to by the generic parties as the Salt Patent Priority Document, also referred to below as the priority document).

The generic parties contend on a number of bases that the priority date should be deferred. The bases include “external fair basis” in that the claims of the 842 or cation patent are not fairly based on the priority document (s 43 of the Act) and disclosure in substance of matters in the amendments (s 114(1) of the Act).

External fair basis

As to external fair basis, in *Sigma Pharmaceuticals (Australia) Pty Ltd v Wyeth* [2011] FCAFC 132 at [64]-[66] Bennett J said:

[64] Section 40(3) of the Act provides that the claims of a patent must be fairly based on the matter described in the specification. The test for determining whether a claim is fairly based is determined by the application of the principles set out in *Lockwood (No 1)* at [69]. Section 40(3) requires a “real and reasonably clear disclosure” of what is claimed. The invention must be broadly described in the body of the specification and not travel beyond the matter disclosed. As the High Court emphasised in *Lockwood (No 1)*, s 40(3) does not involve an analysis of the inventor’s rights to the invention but whether, as a matter of drafting, the claims can be said to reflect what is disclosed or stated in the body of the specification.

[65] The same principles apply to a determination of external fair basis (*Inverness Medical Switzerland GmbH v MDS Diagnostics Pty Ltd* (2010) 85 IPR 525 at [142]); the claims must be fairly based on matter disclosed in a parent patent or a priority document. If the patentee asserts an earlier priority date than the filing date of the patent, by reason of the filing of an earlier patent or document in Australia or overseas, the claims of the patent must be supported by the description of the invention in the earlier patent or document. If the patentee changes the claims, the priority date of the claims may be deferred to the date that those changes were made.

[66] In essence, even if an amended patent itself complies with the drafting rules, for example by amendments to add information to the specification to provide support for amended claims, a patentee cannot set forth one basis for and description of the invention to obtain an early priority date and then change the basis and the characterisation and description of the invention while keeping the same earlier priority date.

The priority document identifies a pharmaceutical composition of rosuvastatin said to have advantageous properties in terms of stability. This composition is described as “the first aspect” of the invention comprising “the Agent and a tribasic phosphate salt in which the cation is multivalent”. Another aspect is said to comprise the Agent and a tribasic phosphate salt in which the cation is multivalent with one or more fillers, binders, disintegrants or lubricators, so as to permit formulation into an oral dosage form such as a tablet. There is no reference in the priority document to the composition not including a tribasic phosphate salt. Accordingly, I accept the submission of the generic parties that:

[t]he real and reasonably clear disclosure within the Salt Patent Priority Document is squarely directed to and limited by the pharmaceutical composition where the tribasic phosphate salt is included therein.

As none of the claims of the 842 or cation patent are limited to a composition in which there is the “Agent” and a tribasic phosphate salt, the claims are not fairly based on the priority document. Accordingly, the priority date of the 842 or cation patent cannot be 26 January 2000. The earliest possible priority date is the date of the filing of the application, being 4 August 2000.

This conclusion is potentially relevant for various purposes. One result of this deferral of the priority date is that the date is later than the date by which, in my view, the information in the Olsson article about rosuvastatin had entered the common general knowledge of the skilled addressee of the 842 or cation patent (as such an addressee, as I have found, would constitute a hypothetical team of experts including not only formulators but also persons with the expertise of, for example, Professors Tonkin and O’Brien). Other consequences depend on the resolution of competing submissions about novelty and obviousness which are dealt with separately.

Amendments

As AZ said:

s 114(1) and reg 3.14 apply, and the question is whether the claims of the 842 Patent “claim matter that was in substance disclosed as a result of amending the specification”.

Regulation 3.14 provides that:

If subsection 114 (1) of the Act applies to a claim of a specification, the priority date of the claim is:

…

(b) in any other case - the date of filing of the statement of proposed amendments that resulted in the disclosure referred to in subsection 114(1) of the Act.

The disclosure referred to in s 114(1) is the disclosure in substance of matter as a result of amending the specification.

AZ’s submissions disclose the issue. As AZ said, the effect of the amendments was to incorporate what now appear as exclusions (i) and (ii) in claim 1 of the 842 or cation patent. In other words, by the amendments the required inorganic salt in which the cation is multivalent was confined by the addition of the words “provided that (i) the inorganic salt is not hydrotalcite or synthetic hydrotalcite; and (ii) the counter anion to the inorganic salt is not a phosphate”. These amendments were made on 31 January 2005.

Accordingly, AZ’s case is that this version of the deferred priority date argument must be rejected because the effect of the amendments relied upon by the generic parties was in each case to narrow the scope of the claims of the 842 or cation patent. AZ put it this way:

Once it is understood that the effect of the amendments was to narrow the scope of the claims, there is no basis for any conclusion that the claims “claim matter that was in substance disclosed as a result of amending the specification”. All of the matter that is within the scope of the claims as they stand now was already disclosed, and indeed was already claimed, as and from the date of filing of the specification of the 842 Patent on 4 August 2000. It is just that there is some additional matter (compositions in which the counter anion is phosphate, for example) which is no longer claimed but is nevertheless disclosed in the specification. That circumstance provides no basis for a deferral of the priority date pursuant to s 114(1) and reg 3.14.

AZ cited *ICI Chemicals* at [116]-[119] as supporting this proposition. At [118] the Full Court said that “[t]here is much authority for the proposition that there is a close relationship between the test for fair basing and the question whether matter is in substance disclosed in a specification. It is unnecessary to consider whether it is appropriate to go so far as to say that the two tests are “virtually the same” (*Ethyl Corp's Patent* [1972] RPC 169 at 195)”. This formulation indicates that an exclusion from a claim may or may not result in a matter in substance being disclosed in the amendment containing the exclusion. It does not indicate that, as a matter of principle, an exclusion from a claim can never so result. It indicates that what is required is a case-by-case consideration to ascertain whether the relevant disclosure is in substance disclosed in the specification or in the subsequent amendments. Labelling an amendment as an exclusion only may distract from the required task; inventions may be defined by both inclusion and exclusion and changes to either may change the substance of what is disclosed.

As Watson and Ascent submitted, the application before the amendments did not specify that the inorganic salt in which the cation is multivalent not be a hydrotalcite or synthetic hydrotalcite, did not specify that the counter anion to the inorganic salt not be a phosphate, and otherwise taught that phosphates are the preferred counter anion to the inorganic salt. The limitations (or at least one of them) specified in the amendments are part of the invention as claimed in all of the claims or, as it was put by Watson and Ascent, are essential in defining the alleged invention as claimed in each of the claims.

I do not consider that s 43(3) of the Act assists AZ. Section 43(3) provides that:

Where a claim defines more than one form of an invention, then, for the purposes of determining the priority date of the claim, it must be treated as if it were a separate claim for each form of the invention that is defined.

The section operates in addition to s 43(1) which makes clear that each claim has its own priority date. The problem for AZ is that all of the claims of the 842 or cation patent involve both or one of the limitations. Accordingly, every form of the invention claimed travels beyond the disclosure in the specification before amendment and every form thus takes the priority date of 31 January 2005, being the date of the making of the amendment application.

###### Novelty

Australian Patent No. 200051841

The first alleged novelty destroying document is Australian Patent No. 200051841 (referred to by Watson and Ascent as “AU841A” or “Tribasic Phosphate Patent” and by AZ as the “841 Application”), which is a published specification which has a priority date of 26 January 2000 and was published on 2 August 2001. It was applied for and published in the same form.

First, I do not accept AZ’s assumption that Apotex should be precluded by its pleadings from relying on the arguments Watson and Ascent made in this regard. AZ is not relevantly prejudiced by Apotex doing so and permitting Apotex to do so is consistent with the way in which Apotex conduced the hearing.

Second, it should be noted that the argument depends on the definition of “prior art base” in Sch 1 to the Act, in particular, the inclusion within that definition of not only publicly available information ((a))but also ((b)(ii)):

information contained in a published specification filed in respect of a complete application where:

(A) if the information is, or were to be, the subject of a claim of the specification, the claim has, or would have, a priority date earlier than that of the claim under consideration; and

(B) the specification was published after the priority date of the claim under consideration; and

(C) the information was contained in the specification on its filing date and when it was published.

Watson and Ascent submitted that:

AU841A discloses a pharmaceutical composition of rosuvastatin with a tablet coating comprising titanium dioxide and ferric oxides (see, for example, page 4 lines 29 to 31). Specific examples 2 and 3 at pages 6 and 7 respectively are claimed at claim 22 although the relevant test is whether those examples could be (but not necessarily are) the subject of a claim.

If it were accepted that the claims of the Cation Patent include within their scope, an inorganic salt containing titanium or ferric oxide within the coating (as the inorganic salt) whether or not a phosphate is present, then the disclosure in AU841A anticipates.

It follows that on [AZ]’s interpretation the Cation Patent lacks novelty in light of AU841A. This must naturally extend to all claims said to be infringed.

I agree that the 841 application discloses a pharmaceutical composition of rosuvastatin with a tablet coating comprising titanium dioxide and ferric oxides and this information was contained in the specification on its filing date and when it was published. The question is whether a claim (assumed or otherwise) the subject of this information would have an earlier priority date than the claim under consideration, being the claims of the 842 or cation patent.

AZ’s answer to this is whether the priority date of the claims of the 842 Patent is 26 January 2000 (based on the filing of the priority document) or 4 August 2000 (based on the filing of the complete application), the alleged anticipatory information contained in the 841 Application cannot be entitled to an earlier priority date. This is said to be because:

in order to anticipate pursuant to s 7(1)(b) and sub-para (b)(ii) of the definition of “prior art base”, the information contained in the 841 Application must be the subject of a claim in the 841 Application, or be capable of being the subject of a claim in the 841 Application, which has, or would have, a priority date which is earlier than that of the claims of the 842 Patent. Since both specifications were filed on the same day and claim priority from the same priority document, that cannot be the case.

…

…the priority date of the claims of the 842 Patent, and the notional priority date of the alleged anticipatory information in the 841 Application, are to be determined by reference to each individual form of the invention. In the context of these specifications, any particular pharmaceutical composition is a form of the invention. Thus, to the extent that the 842 Patent claims a form of the invention or composition which is also disclosed in the 841 Application, the priority date associated with each must be the same – whether it is 26 January 2000 (based on the filing of the priority document) or 4 August 2000 (based on the filing of the complete applications). In either case, the information in the 841 Application cannot have an earlier priority date.

There is a problem with this submission in that it seems to demand precise equivalence between the forms of the invention in each document. But application of the provision is one thing and whether novelty is destroyed is another.

The 841 application is said to have a priority date of 26 January 2000 by reason of UK Patent Application GB 0001621, the same document said to found the asserted priority date of the claims of the 842 or cation patent. In contrast to the 842 or cation patent, however, the putative claims of the 841 application would be fairly based on UK Patent Application GB 0001621; that is, such claims would have the priority date of 26 January 2000. Hence, in terms of the definition of “prior art base” the priority date of the putative claims of the 841 application would be 26 January 2000. The priority date of all of the claims of the 842 or cation patent, however, is not 26 January 2000 but a later date on either of the two bases set out above (31 January 2005 or 4 August 2000 if I am incorrect about the effect of the amendments). If the 31 January 2005 date is correct, the definition of “prior art base” in (b)(ii) is inapplicable but (a) applies as the specification for the 841 application was published before that date on 2 August 2001. If the 4 August 2000 date is correct, the definition of “prior art base” in (b)(ii) is inapplicable for the same reason. The question whether, when compared with the prior art base (which includes the 841 application either way), the invention in the 842 patent is novel remains and is to be answered not by reference to a test of each referring to the same “form of the invention”, as AZ’s submissions appear to assume by reference to the terms of s 43(3) of the Act, but by reference to the principles of what the prior art discloses to the skilled addressee.

The 841 application teaches the improved stability of a pharmaceutical composition of rosuvastatin with a tablet coating comprising titanium dioxide and ferric oxides (inorganic salts in which the cation is multivalent not within the terms of the exclusions from the claims of the 842 or cation patent). This is also the invention claimed in the 842 or cation patent, on the construction of the patent as proposed by AZ and as I have accepted.

Accordingly, I accept that the 841 application destroys the novelty of the 842 or cation patent or, at the least, the claims on which AZ relies to assert infringement. The primary claims in this regard are claims 1 and 2 which are not novel for the reasons given. The dependent claims also fail as they are dependent and there is nothing novel is apparent in the more specific integers.

Other documents

The generic parties also submitted that:

If the priority date of the Cation Patent is 31 January 2005 then the Cation Patent lacks novelty in light of each of (a) International Publication No. WO 01/54669 (WO ‘669); (b) European Patent No. 1314425 (EP ‘425); (c) GB 0001621.2 (Salt Patent Priority Document).

Given the terms of the documents, I accept this submission.

Trial 4522IL/0030

AZ’s clinical trial 4522IL/0030 measured the effects of rosuvastatin and atorvastatin in lowering blood LDL levels in HeFH patients. The trial commenced in July 1999 when the first patients were recruited and concluded in June 2000. The commencement of the trial involved a 6 week “wash out” period in which no drugs were administered.

The generic parties contend that the conduct of this trial constituted the doing of an act which made publicly available information that anticipated and thus destroyed the novelty of the invention claimed in the 842 or cation patent. In this regard, there is no doubt that the tablets administered to the trial participants contained rosuvastatin as the active ingredient and, in the coating, titanium dioxide and ferric oxide which are inorganic salts in which the cation is multivalent not being hydrotalcite or synthetic hydrotalcite and the counter anion to the inorganic salt not being a phosphate. In other words, the tablets administered during the trial were a pharmaceutical composition having all of the integers of the claims of the 842 or cation patent.

According to the generic parties:

the provision of tablets containing the relevant composition to such patients is sufficient to anticipate. Where an apparatus, or in this case tablets, have been made available to the public, it is an anticipation. This is not a case where the person skilled in the art could not have been able to identify the composition of the tablet, it being publicly available and persons being free in law and equity to do so. Indeed the evidence of Dr Rowe called by Apotex, establishes that it would be easy to analyse a tablet in order to determine its composition.

[AZ] have not pleaded in its defence that this trial would be a reasonable trial or experiment and, in any event, on the evidence, the use of rosuvastatin was not a trial to test the invention claimed in the Cation Patent. [AZ] have led no evidence to show that section 24 would apply; namely that it was necessary to test the invention in the Cation Patent in those “clinical” trials. It follows that section 24 should not be applied in any event.

AZ’s answer to these contentions is that all of the investigators involved in the trial were subject to obligations of confidentiality. This is true but the point of the generic parties is that the patients were not. AZ’s further answer is that “[p]atients were given tablets and directed to take them, and there is no evidence that anyone ever reverse-engineered or analysed their composition. Indeed, patients were required to return any tablets they did not take” and, further, that “there is no evidence that any person participating in the trial received any information about the nature of the composition that was used, and in particular whether it contained a compound having the formula set out in the claims”. If by this AZ meant that the tablet did not contain a compound having a formula as set out in the claims it is incorrect. What is correct is that patients were given tablets contain a compound having that formula and the required inorganic salt (in the coating) but there is no evidence that the patients were told or knew either of these things. The case of the generic parties depends on the notion that patients were free to have the tablet analysed and, thereby, to know the tablet contained a compound having the required formula and the required inorganic salt, albeit there being no evidence that any patient did so.

If, as is the case, the “requisite degree of publication will be met if the prior publication or act communicates the information to any one member of the public in a manner which left that person free, in law and in equity, to make use of the information” (*JMVB Enterprises Pty Ltd v Camoflag Pty Ltd* (2005) 67 IPR 68; [2005] FCA 1474 at [54]) the circumstances upon which the generic parties relied do not amount to an anticipation. As AZ said, all the patients received were tablets which might or might not have been the relevant tablet containing rosuvastatin and an inorganic salt. Patients were instructed to take the tablets and return any unused tablets. In *Insta Image Pty Ltd v KD Kanopy Australasia Pty Ltd* (2008) 78 IPR 20; [2008] FCAFC 139 at [124] the Full Court identified relevant principles as including that:

* In order to be “available”, information said to destroy novelty must be of a kind that would disclose to a person skilled in the relevant art all of the essential features or integers of the invention: compare *RD Werner & Co Inc v Bailey Aluminium Products Pty Ltd* (1989) 25 FCR 565 at 593–4; 85 ALR 679 at 708 ; 13 IPR 513 at 542.
* In order to be “available”, information said to destroy novelty must “enable” the notional person skilled in the art at once to perceive, to understand, and to be able practically to apply the discovery, without the need to carry out further experiments in order to arrive at that point (*Stanway Oyster* at 581–2).

The evidence of Dr Rowe about the ease with which a skilled addressee could work out that the coating of the tablets contained the relevant inorganic salts and the assumption otherwise that the tablet could be analysed to determine the compound it contained did not indicate that the skilled person, if a patient had given them the tablets, could at once perceive, understand, and be able practically to apply the claimed invention without further experiments. As such, I do not accept that the 4522IL/0030 constitutes an anticipation by prior use.

As to s 24 of the Act, taking the same approach to AZ as I have done to the generic parties on pleading issues, I consider AZ should be able to rely on the section if it is available on the evidence. However, I am not persuaded it is available on the evidence for the reasons given by the generic parties. As Apotex put it the provisions of s 24(1)(a) of the Act and reg 2.2(2)(d) are not engaged because:

The 0030 trial was a trial of a method of treatment, it was not a trial of the stability of a pharmaceutical formulation. It was therefore not a relevant trial of the invention at all, and it was further not reasonably necessary to trial the stability of the formulation (the relevant invention) in public.

###### Secret use

In the alternative to their argument that AZ’s clinical trial 4522IL/0030 destroyed the novelty of the 842 or cation patent the generic parties submitted that the trial constituted a secret use of the invention claimed in the 842 or cation patent, as referred to in s 18(1)(d) of the Act. Apotex put it in these terms:

The 4522IL/0030 trial was a closed label trial of rosuvastatin as administered to patients for the treatment of hypercholesterolemia in patients with HeFH– it was not a trial of the stability of the rosuvastatin formulation. The ‘use’ of the claimed invention, being a method of stabilising rosuvastatin, is not a use that related in any way to the relevant trial. The High Court, considering a related provision under the Patents Act 1903-1946, held that relevant experiments by the patentee must be limited ‘to acts which are reasonably necessary to produce the result embodied in the specification’ [*Longworth v Emerton* (1951) 83 CLR 539 at 548].

Apotex also repeated its contention, not accepted above, that the trial should be characterised as for the purpose of trade or commerce. I do not accept that proposition because as AZ said:

The clinical trial was in the nature of research and development activity. Indeed, this is an inherent characteristic of a clinical trial. Further, the clinical trial was supported and funded by [AZ]. It did not involve commercial exploitation of the invention claimed in the 842 Patent. No investigators or patients paid any money to receive compound ZD4522, and [AZ] provided each investigator with a budget intended to cover trial expenses.

It is apparent from the reference to “any other use” in s 9(c) of the Act that even if it is the case that the trial was not for any purpose associated with the 842 or cation patent (which I accept) the exclusion of use within s 9(c) (use for any purpose other than trade or commerce) is sufficient to take the use outside the scope of a secret use.

For these reasons I do not accept that the 842 or cation patent is liable to revocation on the ground of secret use.

###### Inventive step/obviousness

The generic parties contend that the 842 or cation patent lacks an inventive step and, accordingly, is liable to be revoked on that basis.

As discussed, I have construed the 842 or cation patent so that the claimed invention includes, among other possibilities, the presence of an inorganic salt having certain features in the coating of a pharmaceutical composition containing rosuvastatin. On this basis, the generic parties submitted that the lack of inventive step is exposed by the fact that the person skilled in the art would coat the composition in the ordinary way with a commercially available and commonly used coating such as OpadryTM which contains the inorganic salt (accepting for this purpose, and as I have found, that titanium dioxide and ferric oxide is a salt) without even attempting to solve the stated problem of instability of rosuvastatin. Alternatively, if recourse to s 7(3) documents is required, the generic parties submitted that Kabadi, Mills and Joshi, considered with the common general knowledge, would have made it routine for rosuvastatin to be formulated with a coating including titanium dioxide or ferric oxide.

AZ submitted that the generic parties’ case was misconceived as they attributed to the skilled person knowledge of the compound rosuvastatin, as part of the “problem” to be solved. As discussed, because I consider that the invention lies in the formulation of a particular composition of rosuvastatin, the invention pre-supposes the existence of the compound, with its particular chemical structure. In other words, no part of the invention lies in knowing about rosuvastatin or its chemical structure, it being common general knowledge in the art that such a structure might suffer from instability. Apart from this, as I have also said, I do not accept that 26 January 2000 is the relevant priority date. If, as I consider, the priority date of all of the claims is 31 January 2005 then the common general knowledge of the skilled addressee included the compound and its chemical structure. If the relevant priority date is 4 August 2000 then by that date the common general knowledge of the skilled addressee also included the compound, even if not the chemical structure, by reason of the Stockholm symposium and Olsson article. In this latter regard, it is true that none of the pharmaceutical scientists or formulators who participated in the concurrent evidence session were aware of rosuvastatin in 2000 but, as noted, I do not consider that the hypothetical skilled addressee of the 842 or cation patent would be limited to pharmaceutical scientists or formulators; the hypothetical skilled addressee would include the knowledge of treating physicians such as Professors Tonkin and O’Brien.

AZ submitted that the generic parties are thus driven to rely on s 7(3) of the Act as the skilled person’s means of obtaining rosuvastatin. I do not accept this for the reasons given above. If the above reasoning is incorrect, I accept that the evidence of Dr Rowe and Dr Oppenheim about the documents that would have been ascertained, understood and regarded as relevant for the purposes of s 7(3) of the Act was fraught with conceptual difficulty both because they used the existence of rosuvastatin as their starting point (which would be impermissible assuming my reasoning is incorrect) and because their ultimate ascertainment of relevance depended on an impermissible combination of multiple pieces of prior art information.

The real problem for AZ, leaving aside any issues about s 7(3), is that I do not accept that part of the case reflected in AZ’s submission as follows:

The generic parties also suggest that, in effect, “slapping on a coating” would be enough to make the claimed invention on [AZ]’s construction of the claims. However, that proposition glosses over the evidence, and does not address the relevant question. While the evidence is that coatings containing titanium dioxide and ferric oxide were well known, that does not make their combination in a composition with rosuvastatin obvious. It is necessary to be able to conclude, on the evidence, that the skilled person would directly be led to try that step in the expectation that it may achieve a useful result. The evidence of Dr Rowe and Dr Oppenheim does not seek to address this.

The combination of the well-known coatings containing titanium dioxide and ferric oxide with rosuvastatin would have been obvious to the skilled addressee at and before the earliest asserted priority date of 26 January 2000. The fact that none of the experts could adequately explain how coatings containing titanium dioxide and ferric oxide might stabilise rosuvastatin does not indicate an inventive step. It is equally possible that rosuvastatin is not particularly unstable in various forms particularly, as was also well-known before the earliest possible priority date, in forms involving higher pH. For this reason AZ’s submission that “[n]one of the experts who gave evidence in concurrent session could speak definitively about the mechanism underlying the stabilisation effect” is not an indicator of inventiveness. On the basis of the available evidence it is equally possible that any stability issue was not particularly acute if the pH of the formulation was raised and a coating applied by conventional techniques.

To the extent that AZ relied on dependent claims such as claim 5 (which provides that the anion must be a silicate, an oxide or a metasilicate) it is not apparent to me how the conclusion of obviousness is avoided by reference to Dr Rowe’s evidence.

The hypothetical skilled addressee, faced with the same problem disclosed in the 842 or cation patent, immediately would have taken the routine step of applying a conventional coating containing titanium dioxide and ferric oxide to a pharmaceutical composition containing rosuvastatin in the expectation that stability would be improved because improving shelf life, providing protection from degradation by external agents and enhancing tablet stability were three of the recognised potential functions of coatings at all material times. On the evidence, the skilled person would directly be led to try the step of stabilising a pharmaceutical composition of rosuvastatin by “slapping on a coating” containing titanium dioxide and ferric oxide in the expectation that it may achieve a useful result in terms of improved stability. The uninventive worker in the field would have taken such a step as a matter of course.

Nor can the inventive step lie in perceiving the rosuvastatin might have an instability problem. On the evidence, faced with the chemical structure of rosuvastatin, the skilled addressee would immediately perceive the potential of that structure for lactonisation and oxidation. Whether, as might have been in dispute between the experts, the stability issue included also photodegradation, is immaterial. If it included photodegradation then that would have been merely an additional reason to try a coating containing titanium dioxide and ferric oxide in the expectation of improving the stability of the rosuvastatin tablets. As Apotex said, if the stability issue included photodegradation, as Professor Charman and Dr Morella suggested, then:

it is beyond doubt that it is obvious to address a problem of photodegradation by using a standard light-protective coating that includes titanium dioxide and/or ferric oxide. The experts agreed that such coatings were well known as at the priority date, and indeed the most widely used component in such a coating to impart opacity is titanium dioxide, and the most widely used component to impart colour in a coating is ferric oxide.

###### Manner of manufacture

As AZ said, the specification for the 842 or cation patent does not contain any express admission that the claimed invention, being a composition comprising rosuvastatin or a pharmaceutically acceptable salt thereof and an inorganic salt in which the cation is multivalent, is not new or inventive. The specification asserts to the contrary. Watson and Ascent submitted that applying a common coating to a tablet of rosuvastatin cannot be new or inventive and the specification acknowledges this to be so by identifying coatings comprising titanium dioxide and ferric oxides as commercially available and, by inference at least, routinely applied:

If the claims of the Cation Patent are so broad as to encompass a situation where merely rosuvstatin (a known substance) is coated with a commercially available known coating, such as SpectrablendTM or OpadryTM, then the invention as defined by the claims is not, as is disclosed on the face of the specification, a manner of new manufacture. It is not an invention to take a known substance and apply a known pharmaceutical tablet coating.

However, I accept that, as submitted by AZ, the specification “does not admit or disclose on its face that it was known, before the priority date, that such coatings could be used to address the stability issues with rosuvastatin which are discussed in the specification”. The patent therefore discloses a manner of manufacture.

###### Fair basis

The contention that the claims of the 842 or cation patent are not fairly based on the specification as required by s 40(3) of the Act is said to arise because what is disclosed and stated in the body of the specification does not include the use of an inorganic salt in which the cation is multivalent in the tablet coating only. To the contrary, every disclosure is of an inorganic salt in which the cation is multivalent being admixed or blended with the rosuvastatin in the formulation. Although the specification says that a coating containing ferric oxide or titanium dioxide may be applied (which, on my construction of the patent, are an inorganic salt in which the cation is multivalent) the specification does not suggest this to be the invention. Apotex thus submitted:

The only real and reasonably clear disclosure is of the inorganic salt and the rosuvastatin being mixed or blended together in the pharmaceutical composition. There is no disclosure whatsoever of a formulation in which the inorganic salt is a component of the coating only (which [AZ]’s own witness considers would be a separate invention). Accordingly, if the claims are broad enough to include a pharmaceutical composition in which the inorganic salt is only in the coating, then the claims are not fairly based on the specification.

Further, the generic parties contend that as specification teaches the use of phosphate salts, yet the claims exclude phosphate salts, each of the claims of the 842 or cation patent is not fairly based. In addition it is argued that the claims are not fairly based if they are “not limited to pharmaceutical compositions which are stable.”

The first aspect of this contention depends on construing the specification as if it limited relevant pharmaceutical compositions to those in which the inorganic salt is present in the tablet core when, as discussed in the context of the construction issues above, this limitation is not apparent from the specification.

The second aspect of this contention also cannot be accepted. Although a consistory clause is not determinative, as the specification must be construed as a whole, it is not apparent why the disclosure of precisely what is claimed in the consistory clauses in this case is insufficient read in the overall context. The consistory clause expressly provides that the counter anion to the inorganic salt is not to be a phosphate. The examples which use tribasic calcium phosphate are examples only. As AZ said:

the statements of preferments that follow are plainly subject to the consistory statement. There is nothing in the balance of the description which indicates that the invention is narrower than what is set out in the statement.

The third aspect is difficult to understand. As AZ put it, stability is the object of the claimed invention but not an essential integer of the invention claimed or as described in the specification.

For these reasons I do not accept the challenges to validity based on lack of fair basis.

###### Utility

Despite the fact that it seems equally plausible on the evidence that any stability issue with a pharmaceutical composition of rosuvastatin was not particularly acute if the pH of the formulation was raised and a coating applied by conventional techniques and, indeed, if such a problem did exist could be solved by those conventional methods, AZ identified the difficulty for the generic parties on the issue of alleged lack of usefulness. First, the generic parties have the onus of proof. Second, without testing what might or might not be happening in terms of the stability of particular compositions, the evidence left the various possibilities equally likely. One possibility is that while rosuvastatin has a potential stability issue, that potential is not borne out in the process of actual composition. Another is that a pharmaceutically acceptable salt of rosuvastatin might have increased pH sufficient itself to resolve any stability issue. Another is that a coating containing titanium dioxide or ferric oxide is sufficient to resolve any stability issue by means that could not be adequately explained by the experts. If the latter, then the claimed invention is useful. All of the evidence involved hypothesis and speculation. As such, it might reasonably be suspected that one or both of the first two possibilities is more likely than the last, but suspicion is not inference and does not prove lack of utility. Ultimately, as AZ submitted:

No direct evidence of the alleged inutility, such as evidence based on testing of compositions, was brought forward by the generic parties. In the absence of such evidence, it is not possible to conclude that the inclusion of the “inorganic salt” in the tablet coating cannot achieve the promised result.

As to the argument that the invention is not useful because the claims are not limited to compositions which are stable and do not specify any minimum amount of inorganic salt but rather “include trace amounts of inorganic salt which can be expected to have no effect on stability”, I accept AZ’s submission that this “argument also entails the purposeful adoption of an embodiment which the skilled person would appreciate would lead to an unworkable or inferior result”, which is inappropriate.

Another argument is that the invention claimed is not useful because the specification of the 842 or cation patent promises improved stability over that achieved by solely controlling pH in accordance with the method disclosed in GB 2262229 whereas the claims encompass compositions which are stabilised in accordance with that method. However, as AZ said, the 842 or cation patent requires something different from the method disclosed in GB 2262229 to improve stability. The 842 or cation patent also does not promise that the claimed compositions will have improved stability over all of the formulations encompassed by GB 2262229. It says only that stability is improved by selection of an inorganic salt to be added to the composition which contains one or more multivalent inorganic cations.

A further argument is that the invention claimed in the 842 or cation patent is not useful because “the promise of improved stability is not achieved for tablets containing higher doses, including about 20 mg or more”. Again, as AZ said the problem is evidentiary. In AZ’s words:

Reliance is placed on laboratory notebooks discovered by [AZ]. Such reliance is misconceived. Taking the notebooks and Dr Rowe’s comments on them at face value, all that they reveal is that in a particular test environment the stability of some tablets was not significantly different with an without an inorganic salt with a multivalent cation. This does not prove lack of stability.

###### Best method

This ground of challenge relates to s 40(2)(a) and s 138(3)(f) of the Act. Section 40(2)(a) provides that a complete specification must describe the invention fully including the best method known to the applicant of performing the invention. Section 138(3)(f) provides that a patent may be revoked on the ground that the specification does not comply with s 40(2).

The contention starts from the record in a notebook of one of the named inventors in 1998 that if the ratio of the tribasic calcium phosphate to rosuvastatin was too high, then that reduced the amount of rosuvastatin recovered in a stability trial. Then it is said that the specification does not indicate that if the ratio of inorganic salt to rosuvastatin becomes too high then that may negative the very benefit promised by the 842 or cation patent, being improved stability. The problem with this argument is that the claims exclude phosphate as the anion of the “inorganic salt” with a multivalent cation.

As AZ said the applicant is not required to identify which of the embodiments of the invention it believes to be the best method. The requirement is only that the best method known to the applicant in fact be disclosed. It is not apparent from the evidence that the best method known to the applicant is not disclosed in the specification, irrespective of what might be said in a notebook recording the results of a test using one substance, a phosphate, which is excluded from the claimed invention.

###### Clarity

The arguments of lack of clarity do not meet the required standard. Ambiguity is one thing; the impossibility of ascertaining the invention is another. It will be apparent from the resolution of the construction issues associated with the 842 or cation patent that I do not accept that the claims are not clear within the meaning of s 40(3) of the Act.

Accordingly, mere potential ambiguity in the meaning of “pharmaceutical composition” is insufficient. The need to construe the meaning of “inorganic salt” does not expose any lack of clarity. The exclusion of certain nominated inorganic salts and phosphates is clear. The example provided by Apotex does not indicate to the contrary. The preferred construction of the claims is that which Apotex described as “option 1”, namely, that “the words ‘provided that’ in claim 1 only describe the necessary characteristics of the relevant inorganic salt in which the cation is multivalent”.

###### False suggestion

The generic parties contend that the 842 or cation patent falsely represents that rosuvastatin is “particularly sensitive to degradation under certain conditions” which “makes it difficult to formulate and provide a pharmaceutical composition with acceptable storage life for a marketed product”, and that “it is not sufficient to improve stability by solely controlling pH in the formulation”. These are said to be proved to be false by reference to AZ’s development of the drug, described as follows:

(a) The inventors/patentee started their development of a formulation in February 1999;

(b) The inventors/patentee achieved a commercially acceptable formulation of rosuvastatin in March 1999;

(c) This formulation was the same as in Example 3 of the Cation Patent;

(d) The stability of the rosuvastatin formulation was not significantly different with, or without, the relevant inorganic salt with a multivalent cation (that is, tribasic calcium phosphate or TBCP), as shown by the report by Mr Wiggins dated 6 June 1999. The conclusion of Mr Wiggins in a follow up report on 17 June 1999 was ‘TBCP is not hurting the formulation so keep it’. No subsequent report or experiment conducted by Mr Creekmore or Mr Wiggins sets out any different evidence.

..

…previous experiments by Mr Creekmore and Mr Wiggins had showed was that there was some positive impact on stability of rosuvastatin with TBCP at very high temperatures (about 70˚C), however such conditions can favour different chemical reactions to those occurring under normal storage conditions, and are not necessarily reflective of the stability under normal conditions.

Apotex described this as “unexplained evidence” consistent with:

(a) The examples in the UK Patent which show that adequate stability is achieved by controlling pH alone.

(b) The examples in the Pravastatin Patent which also show that adequate stability is achieved by controlling pH alone.

(c) Dr Rowe’s understanding that the Cation Patent only discloses the use of an alkaline reacting compound to stabilise rosuvastatin.

I accept AZ’s submissions to the contrary.

First, the statements in question are not precise statements of scientific fact, but rather are in the nature of statements of opinion by the patentee.

Second, the evidence relied upon does not show the statements to be false. The inferences sought to be drawn from the evidence to that effect are not sufficiently supported. They raise a suspicion about the accuracy of the statements, which it is correct to say is not necessarily dispelled by Professor Charman’s evidence, but nothing more. The evidence is not such as to cast any persuasive or other burden on AZ to prove the truth of the assertions. Hence, the submissions about AZ’s alleged failure to call the inventors or others are immaterial.

###### Conclusions

The 842 or cation patent is liable to be revoked because the claims did not involve a patentable invention (on the grounds of lack of novelty, lack of inventive step or obviousness, and no manner of manufacture).

##### INFRINGEMENT OF THE 051 OR LOW DOSE PATENT

###### AZ’s case

It is common ground that the generic parties intend to supply rosuvastatin products to the market that include the active ingredient rosuvastatin in 5 mg, 10 mg, 20 mg or 40 mg doses.

AZ relies on s 117 of the Act to establish infringement. The section provides as follows:

(1) If the use of a product by a person would infringe a patent, the supply of that product by one person to another is an infringement of the patent by the supplier unless the supplier is the patentee or licensee of the patent.

(2) A reference in subsection (1) to the use of a product by a person is a reference to:

(a) if the product is capable of only one reasonable use, having regard to its nature or design - that use; or

(b) if the product is not a staple commercial product - any use of the product, if the supplier had reason to believe that the person would put it to that use; or

(c) in any case - the use of the product in accordance with any instructions for the use of the product, or any inducement to use the product, given to the person by the supplier or contained in an advertisement published by or with the authority of the supplier.

AZ also relies on the principles of joint tortfeasorship, on the basis that the generic parties, by the act of supply, would be aiding, inducing or procuring the infringement of the patent by patients who used the products in issue.

Finally, AZ contends that the generic parties threaten to infringe the patents by authorising the use in circumstances where s 13 of the Act gives the patentee the exclusive right to authorise other persons to exploit an invention during the term of a patent.

AZ submitted that:

There can be no real doubt that use of the generic products in accordance with the instructions contained in the respective PI documents of the generic parties (including to administer once daily, oral doses of 5 or 10 mg rosuvastatin as a starting dose for the treatment of hypercholesterolemia) would result in “persons” infringing claims 1 and 2 of the 051 Patent. Indeed, the matter is effectively admitted, at least by Apotex for the 5 and 10 mg doses. Threatened infringement is established pursuant to s 117(1), by force of s 117(2)(c).

Further, there can be no dispute that the generic parties, as suppliers, have reason to believe (and, indeed, know) that the 5 and 10 mg dosage forms of their generic products will be used in methods of treatment having the integers of each claim of the 051 Patent.

…

In this respect, the knowledge of the generic parties is established, amongst other matters, by the PI documents for their proposed generic products and the evidence of Drs Hay and Wilson, who each explain that 5 and 10 mg doses of rosuvastatin are prescribed and administered for the purpose of treating hypercholesterolemia in accordance with the methods of treatment in claims 1 to 3 of the 051 Patent.

As to the proposed supply by the generic parties of the 20 and 40 mg dosage forms of rosuvastatin, AZ said:

The same position applies to the 20 and 40 mg dosage forms of the generics' products, which will be split by patients (both at the direction or with the knowledge of their doctors and at their own initiation) to obtain 5 and 10 mg doses for use in the methods of treatment claimed in claims 1 to 3.

…

Indeed, Watson’s PI and its Consumer Medicine Information expressly contemplate, and encourage, the splitting of such tablets [the product information says “The 10, 20 and 40 mg tablets can be divided into equal halves. The 5 mg tablets are NOT intended for 2.5 mg dosing.”].

AZ referred to the evidence of Dr Hay and Dr Wilson to the effect that they prescribe AZ’s product, Crestor:

in the knowledge that their patients will split the tablets into smaller doses, and in many cases specifically instruct their patients to do so, including so that patients will save money when purchasing their prescriptions. As each prescription costs patients the same, regardless of the dose, patients can significantly reduce their medication costs by splitting tablets and making each prescription last longer.

AZ referred to the evidence of Mr Divesh Sanghvi, an experienced pharmacist who was not required for cross-examination, who said rosuvastatin is among the medicines for which patients are most likely to engage in pill splitting, as well as the evidence about readily available pill splitting devices, including one for splitting into quarters, and that:

IMS Health (IMS) data further confirms the existence of tablet splitting including in respect of 20 and 40 mg CRESTOR tablets. For the purposes of its business, IMS relevantly collects, stores and utilises data obtained from a rolling panel of general practitioners, which includes information recorded on prescriptions. For the 24 month period ending 30 March 2012, IMS data records some 22,220 prescriptions for 20 mg CRESTOR tablets that included a recorded direction to take “half a tablet”. This equated to 2.75% of total prescriptions for 20 mg CRESTOR. The figure of 22,220 prescriptions is necessarily under-representative of the extent of tablet splitting since, for example, IMS data will not pick up tablet splitting that occurs other than as may be recorded on a written prescription, for example pursuant to oral directions or advice provided by a doctor, or where the tablet splitting occurs at the patient’s own volition.

AZ observed that:

the prevalence of the practice of splitting rosuvastatin tablets will inevitably further increase if 20 and 40 mg generic products are marketed, because such products will be supplied to patients at substantially less cost (in some instances, possibly even at no cost) compared to the price of [AZ]’s 5 and 10 mg CRESTOR product, thereby creating a significantly stronger price incentive to split larger doses.

According to AZ, and contrary to the generic parties’ case, rosuvastatin is not a staple commercial product. It is rather “a specialised product that is used for a specific medical purpose”. As AZ put it:

The reference in s 117(2)(b) to the supply of a "staple commercial product" means a product that is supplied commercially for various uses: *Northern Territory v Collins* (2008) 235 CLR 619 [[2008] HCA 49;] at [27], [41], [48], [50] and [145]; [*Apotex Pty Ltd (No 3)*] at [270]. As submitted below, specific pharmaceutical products that are supplied for the purpose of oral administration to treat disease fall outside the scope of the concept of a product that is supplied commercially for various uses.

AZ also noted that:

The product at issue in *Collins*, unmilled timber, readily fits the description of a “staple”, within the plain English and dictionary definitions noted above. Timber is also clearly a product (being a raw material) that is supplied for a vast multitude of commercial uses. It comfortably fits within the description of a “staple commercial product” within the meaning of s 117(2)(b).

By contrast, the generic rosuvastatin product the subject of the generic parties’ PIs is very far removed from unmilled timber, or any similar raw material. Rather, the generic rosuvastatin product (claiming bioequivalence to the CRESTOR product) is a complex, synthesised pharmaceutical formulation that is relevantly designed for the two medical treatment uses specified in the generic parties’ PIs. To speak about such an article as being a “staple commercial product” runs counter to common sense. Such an article is not within the ordinary meaning of the word “staple”. A "staple" commercial product is something such as timber, iron ore, rice or wheat, each of which has a number of uses and can be used to make a variety of other things.

AZ also submitted that the generic parties cannot properly call in aid alleged uses beyond those contemplated in their respective product information (which is directed in each case to the treatment of hypercholesterolemia). AZ said: - (i) the questions asked in cross-examination of Dr Hay and Dr Wilson were non-specific and related to “statins” generally, rather than to rosuvastatin, (ii) the generic products are not indicated for any conditions additional to those specified in their product information, and (iii) properly viewed, the generic party is (in each instance) the only relevant supplier.

AZ also put an argument in these terms:

[AZ] does not license medical practitioners or the generic parties to practise a method of treatment that involves administering 5 to 10 mg of its CRESTOR product as the “starting dose”, followed by a higher dose of a competitor’s generic product.

…

The instructions given by the generic parties to doctors to administer a 5 or 10 mg starting dose thus constitute an inducement or permission to practise the claimed invention in a way that is not authorised by [AZ]. [AZ] respectfully maintains the submission, not accepted by the Court at the interlocutory level, that such conduct amounts to infringement under s 13 (by authorisation) or by applying the principles of joint tortfeasorship.

###### Generic parties’ case

The generic parties submitted that the supply of 20 mg and 40 mg tablets of rosuvastatin would not fall within the scope of the 051 or low dose patent.

As to the factual question of tablet splitting, Watson and Ascent said that is no evidence to suggest that 40 mg tablets will be divided to make 4 x 10 mg doses. Dr Wilson had not heard of this happening for rosuvastatin. Indeed:

The dividing of doses of 40 mg rosuvastatin into 10 mg doses has not been proven as a reality much less to the requisite extent to show the generic parties reason to believe.

In terms of the splitting of the proposed 20 mg tablets of the generic parties into two doses of 10 mg each, The generic parties noted: - (i) it is clear that the vast majority of patients do not split tablets and that patients take the dosage supplied to them by the manufacturer without adulteration by pill splitting, and (ii) it is also clear that while some, a small proportion of patients, split tablets, most practitioners do not encourage the practice due to compliance and degradation concerns. Given these facts, there is an insufficient evidentiary foundation for the generic parties to have reason to believe that a patient prescribed their products will split the 20 mg dose into two 10 mg doses in order to treat their hypercholesterolemia.

Further, the generic parties characterised s 117(2)(b) of the Act as imputing infringement “where a product is supplied in the circumstance of a reason to believe by the supplier about the use to which a particular primary infringer (“the person” in paragraph (b)) would put the product to the infringing use”. AZ’s case, however, involves a general proposition that “some unidentifiable persons within the class of persons supplied with generic rosuvastatin will split tablets of 20 mg (and 40 mg)”. Watson and Ascent submitted:

It is not sufficient that a person supplied the “product” by Watson and Ascent may split the rosuvastatin and put it to an infringing use. To make Watson and Ascent liable for any infringement under section 117 of the Act it must be shown that the reason to believe relates to the fact that the person being supplied would, in fact, put it to that use.

Furthermore, even if the tablet is split, it must still be shown that there is a reason to believe that the split tablet would be used in the treatment of hypercholesterolemia to be within the scope of the claims; a split tablet may just as well be used to treat diabetes or another condition discussed by Drs Wilson and Hay. This provides another reason why it cannot be said the 20 mg tablet would be put to an infringing use.

The generic parties also contended that as they would be supplying a product of 20 and 40 mg of rosuvastatin, the act of a patient in splitting such a tablet so as to create 5 and 10 mg has the effect of creating a new product. They submitted:

Section 117 of the Act does not encompass such a situation where the product supplied is different to the product actually used.

…

The allegation of infringement made against Watson and Ascent does not relate to the use of 20 mg dosage of rosuvastatin - it is clear that such a dosage would not infringe the patent under the clear wording of section 117 of the Act. Section 117 of the Act does not by its wording cover a situation where a product is supplied, modified or adulterated by the person (for example, by pill splitting) to change it into a new dosage and then used in an infringing manner.

In any event, the generic parties contend that rosuvastatin is a staple commercial product. Rosuvastatin, on the evidence, is “used to treat various different conditions or for other effects including (i) pleomorphic (anti-inflammatory) effects to reduce the incidence of plaque rupture and heart attacks; (ii) treatment of diabetes; (iii) treatment of stroke; (iv) treatment of chronic renal disease; and (v) coronary artery disease or peripheral vascular disease”. Further, the “most common group of patients seen by Dr Wilson appear not to be hypercholesterolemia patients but those requiring secondary prevention such patients with coronary artery disease or peripheral vascular disease and diabetes independent of their cholesterol level”. As rosuvastatin can be used in various non-infringing ways, it is a staple commercial product by analogy to the reasoning in *Northern Territory v Collins* (2008) 235 CLR 619; [2008] HCA 49 (*Collins*).

The generic parties also referred to an observation of Keane CJ in *Apotex Pty Ltd v Sanofi-Aventis Australia Pty Ltd (No 2)* (2012) 204 FCR 494; [2012] FCAFC 102 at [56] that s 117 of the Act is not engaged where the patent is in respect of a method of treatment. Keane CJ noted that in such a case the medical practitioner may not be doing any act within the meaning of the definition of “exploit” in s 13, “[i]n particular, the medical practitioner would neither be using a product (as opposed to a method) or doing any act in respect of a product “resulting from” the use of the patented method. One attraction of this argument would be that it prevents the effective renewal of the expired patent for the product”. As an argument to this effect was disclaimed in the hearing in *Apotex (No 2)*, the Court did not need to resolve it. In the present case, the argument is pressed on the basis that:

if the Low Dose Patent is valid and there is invention in the administration of 5 to 10 mg dosages that monopoly resides in the method of treating hypercholesterolemia using that dosage. It does not reside in the 5 mg or 10 mg dosages per se and, even further removed, the operation of section 117 of the Act should not be available to restrict the supply of 20 mg and 40 mg dosages.

The generic parties also challenged the legal and factual foundation of the claim of joint tortfeasorship. As the generic parties have proposed measures (in effect, instructions to medical practitioners not to permit tablet splitting) it cannot be said that the generic parties have engaged in an agreed or common action with persons who may choose to split tablets. Finally, the mere supply of a product does not amount to authorisation.

###### Discussion

I have found that all of the claims of the 051 or low dose patent are liable to revocation on various grounds. Accordingly, the question of infringement does not arise. It is nevertheless appropriate to deal with the issues in any event, albeit in an abbreviated form in recognition of the conclusions I have reached as to invalidity of this patent.

Apart from the argument based on the observations of Keane CJ in *Apotex (No. 2)*, there is no real question on the evidence that the proposed supply of the 5 and 10 mg doses of the generic rosuvastatin products of each of Apotex, Watson and Ascent would involve exploitation of the method of treatment claimed in the 051 or low dose patent. Apotex effectively admits as such, as AZ said. This is because the product information for each generic rosuvastatin product directs such use, so that s 117(c), at the least, is engaged.

Although I can see the attraction of the argument which was considered by Keane CJ in *Apotex (No. 2)*, in particular that it would ensure that AZ cannot claim a monopoly over rosuvastatin in Australia when there has never been a patent for rosuvastatin in Australia, I have difficulty in reconciling this approach with the words of s 117. The difficulty is that there is still use of the product (being the generic parties’ rosuvastatin products in 5 and 10 mg doses) within the meaning of s 117(1) even though that use is part only of the claimed method of treatment. As such, I do not accept this argument. It follows that, if the 051 or low dose patent were valid, AZ would have proved threatened infringement in respect of the proposed supply of the 5 and 10 mg doses by each of the generic parties.

The 20 and 40 mg doses involve other issues. I will deal with the 40 mg dose first because this can be resolved at the level of fact. I am aware of that the evidence includes one pill splitter that indicates it can be used to cut tablets into quarters. I am aware also of the real economic incentives that a patient might have to make their medication go further because they will pay no more for a 40 mg dose compared to lower doses. Ultimately, however, whether a person would use the product (the 40 mg generic products) within the claims of the 051 or low dose patent which is limited to 5 and 10 mg is an issue for AZ to prove. I am not satisfied on the evidence that any person could, let alone would, attempt to divide a single tablet into four in order to obtain four 10 mg doses irrespective of the size of the economic incentive to do so. I cannot say the same for the 20 mg tablet which I infer could readily be divided into two 10 mg doses using a pill splitter. I am also satisfied given the ease of tablet splitting by using a pill cutter, whether the tablet be scored or unscored, and the economic incentives, that there is a risk that some people will obtain the 20 mg dose of the generic tablets for the purpose of dividing them into two 10 mg doses. I also infer that this risk will exist irrespective of any instructions the generic parties might send to medical practitioners and pharmacists not to endorse tablet splitting in any way because, ultimately, the obligation of medical practitioners and pharmacists is to their patients and not to drug companies who want to try to avoid patent infringements. The risk also remains despite Apotex’s product information directing against tablet splitting.

All of this said, the question of infringement (assuming validity) remains. As to this question, I am not satisfied the generic parties’ products are “capable” of only one reasonable use within the meaning of s 117(2)(a). On the evidence rosuvastatin has a range of medical uses. Whatever the product information of the generic parties, which focuses on hypercholesterolemia, medical practitioners prescribe and thus patients use rosuvastatin for a variety of uses, albeit all uses associated with disease states in humans, either actual or prospective. I do not accept AZ’s submission that the evidence of those other uses should not be inferred to relate to rosuvastatin just as much as any other statin or is irrelevant due to the product information. Hence, s 117(2)(a) is not engaged.

Section 117(2)(c) is also not engaged. Despite the reference to the tablets being able to be divided in the Watson and Ascent product information, on the whole of the evidence, including the proposed communications with medical practitioners and pharmacists, it cannot be said that the generic parties will instruct or induce any person to split a 20 or 40 mg tablet into two or four.

This leaves s 117(2)(b). Despite the fact that I accept that rosuvastatin has a number of medical uses, not just the treatment of hypercholesterolemia, I cannot accept that it should be characterised as a “staple commercial product”. The difficulty I have arises from the word “staple”, which does indicate something more than merely a “commercial product”. The reasoning in *Collins* does not lead me to the view that the fact that a product can be used in one or even a number of non-infringing ways is itself sufficient to make the product a staple commercial product. While “staple” is not concerned with the economic significance of uses, it is concerned with the variety of uses. The variety of uses in this case is confined by the nature of the product to a limited class, being the treatment of diseases of a particular kind or class (albeit different diseases) in humans. Rosuvastatin, despite its usefulness for a variety of disease conditions, is not able to be compared to timber (as in *Collins*) or, for example, types of pharmaceutical products which might be useful for many human conditions. It is for these reasons I conclude that the rosuvastatin products proposed to be supplied by the generic parties are not staple commercial products.

I do not accept that s 117(1) and (2)(b) requires AZ to prove that any particular person will split a 20 mg tablet into two 10 mg doses. In the present case the evidence is sufficient to infer that whatever the instructions the generic parties give to medical practitioners and pharmacists there remains a risk that some people will obtain the 20 mg dose of the generic tablets for the purpose of dividing them into two 10 mg doses. Risk, however, is one thing. Proof on the balance of probabilities that any person “would” infringe the 051 or low dose patent is another. Given the steps proposed by the generic parties to instruct medical practitioners and pharmacists not to endorse or encourage tablet splitting, it is a long stretch on the currently available evidence to conclude that any person would split the tablets into 10 mg doses and thereby infringe the patent. I accept that AZ has proved a real risk that it might occur, given the economic incentives. But in terms of proof that is insufficient.

As to the additional arguments, joint tortfeasorhip, authorisation and directions to use AZ’s low dose products and then swap (the last argument), it is sufficient to say that they are not established on the facts. The generic parties propose to do what they can to stop infringement and thus are not joint tortfeasors and do not authorise any infringement. The last argument is one which I cannot grasp. It remains unclear to me how any use of AZ’s own product could ever constitute an infringement of AZ’s patent.

For these reasons, if the 051 or low dose patent is valid (contrary to my view), I am satisfied that AZ has established that the generic parties threaten infringement of the patent to the extent that they propose to supply the 5 and 10 mg doses of their products. I do not accept that AZ has established any threatened infringement in respect of the 20 or 40 mg doses for the reasons given above.

##### INFRINGEMENT OF THE 165 OR HEFH PATENT

It is not in dispute that the rosuvastatin products of the generic parties will be therapeutically appropriate to treat HeFH. As discussed, it is part of the case of the generic parties (which I have accepted) that all statins treat HeFH to some extent and rosuvastatin, as a powerful statin, is particularly well-suited to treat HeFH.

AZ contended that the generic parties threaten to infringe claims 1 to 10 and 21 of the 165 or HeFH patent. The generic parties propose to exclude HeFH from the indications for their products and to notify medical practitioners and pharmacists to this effect. That said, it is also the case that the generic products will remain suitable for use to treat HeFH and medical practitioners do not always, or even often, prescribe by brand name as opposed to compound when different brands of the same compound are on the market.

In respect of this issue (in common with the conclusions I have reached about the 20 and 40 mg doses of the generic products as set out above) I do not in the ultimate analysis find AZ’s case for infringement as persuasive as I did at the interlocutory stage. First, s 117(2)(a) is not engaged as the generic parties’ rosuvastatin products will have more than one reasonable use, as described. Second, s 117(2)(c) is not engaged as the generic parties (or Apotex and Watson in any event) have excluded the treatment of HeFH from the product information for their products and thus can hardly be said to be instructing or inducing infringement. As to s 117(2)(b), I remain of the view that “doctors and pharmacists should not be burdened by court-mandated instructions from a pharmaceutical company that have no therapeutic efficacy or safety purpose and which are intended to do nothing other than to aid the pharmaceutical company to avoid an alleged patent infringement” (*Apotex Pty Ltd v AstraZeneca AB (No 3)* (2012) 95 IPR 581; [2012] FCA 265 at [20]). But this is a policy view and the question is not whether the generic parties have proved that their will be no infringement, but whether AZ has proved that, in the face of the product information, a generic rosuvastatin product will be used by some person to treat HeFH. In the case of Apotex and Watson that inference cannot be drawn given the terms of their product information.

Ascent’s case may be different in that the product information for the Ascent product includes HeFH. As the question is hypothetical, given my conclusions that the claims of this patent (specifically, claims 1 to 10 and claim 21, but also all claims dependent on claim 1) are invalid, this is an issue where, if necessary, I would seek further clarification from Ascent as to its position, the result of which if Ascent adopted a position common to that of Apotex and Watson) would result in my conclusion of non-infringement also for Ascent. This is unnecessary given my conclusions as to invalidity.

For these reasons I am not satisfied that AZ has proved threatened infringement of the 165 or HeFH patent on any of the bases argued.

##### INFRINGEMENT OF THE 842 OR CATION PATENT

For the reasons already given I have also concluded that claim 1 of the 842 or cation patent and all dependent claims are invalid and liable to be revoked. In the course of reaching this conclusion I preferred AZ’s construction of the integers of claim 1. Accordingly, I did not, and for the purpose of infringement do not, accept the generic parties’ construction of claim 1 of this patent.

On the basis of this preferred construction it is apparent that, if claim 1 and the dependent claims of the 842 or cation patent are valid, then the generic rosuvastatin products, excluding only the alternative product proposed by Apotex which does not use titanium dioxide or ferric oxide in the coating, would infringe claim 1 and the dependent claims.

##### CONCLUSIONS

For the reasons given I consider that all of the claims of the 051 or low dose patent are invalid and that the patent should be revoked. The claims on which AZ relies to assert infringement of the 165 or HeFH patent (claims 1 to 10 and 21) and the 842 or cation patent (claims 1 to 5, 7 to 9 and 10 to 18) are also invalid and liable to be revoked, although there is a question whether any of the claims of these patents can be sustained given the conclusions I have reached as set out above.

The generic parties should immediately be released from any undertakings and interlocutory injunctions that they have given or by which they are bound. AZ’s applications for relief against infringement should be dismissed. The invalid claims of the patents in question should be revoked but it is also appropriate that I hear the parties further on the form of orders for revocation that should be made in all of the circumstances. Costs may be resolved pursuant to other directions that can be made as required.

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| I certify that the preceding five hundred and twenty three (523) numbered paragraphs are a true copy of the Reasons for Judgment herein of the Honourable Justice Jagot. |

Associate:

Dated: 5 March 2013