Date: 20051017

Docket: T-1937-03

Citation: 2005 FC 1421

Ottawa, Ontario, this 17th day of October, 2005

Present: The Honourable Mr. Justice Richard G. Mosley

BETWEEN:

PFIZER CANADA INC.
and PFIZER INC.

Applicants

and

APOTEX INC.
and THE MINISTER OF HEALTH

Respondents

REASONS FOR ORDER AND ORDER

[1] This application by Pfizer Canada Inc. and Pfizer Inc. (hereafter collectively "Pfizer") under section 6 of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, as amended by SOR/98-166 and SOR/99-379, is for an order of prohibition against the Minister of Health to prevent the issuance of a notice of compliance to Apotex Inc. ("Apotex") until after the expiry of Canadian Letters Patent 2,148,071. The application is in response to a notice of allegation made by Apotex in a letter dated August 29, 2003. Pfizer's notice of application was served on the Minister on October, 17, 2003.

Background

[2] The application addresses Apotex' submission for a notice of compliance with respect to its apo-azithromycin tablets. Pfizer's azithromycin tablets are marketed in North America under the brand name ZITHROMAX. Apotex proposes to market tablets for oral administration comprising azithromycin isopropanolate monohydrate in a strength equivalent to 250 mg azithromycin. The ZITHROMAX formulation is azithromycin dihydrate.

[3] There is nothing novel about azithromycin itself. It was invented in the early 1980's in Europe and has long been approved for use in Canada. Azithromycin is the first macrolide antibiotic of the azalide group. Other macrolides include erythromycin, from which azithromycin was derived, and clarithromycin. Azithromycin is commonly used in the treatment of upper and lower respiratory infections, pneumonia, strep throat, and genitourinary infections such as chlamydia.

[4] Azithromycin has unique properties that make it a valuable instrument in treating microbial infections. While it has low oral bioavailability (absorption of the drug into the bloodstream for therapeutic effect) producing low blood serum concentrations, azithromycin goes directly to the site of the infection, has a long half-life and does not need to be administered
as long or as often as other antibiotics. In contrast to erythromycin, it is acid stable, has decreased gastrointestinal tolerance and increased absorption capability.

[5] ZITHROMAX was initially marketed in North America in a capsule dosage form, beginning in the early 1990's. Tablets were not approved. It appears to have been available also in suspension form, at least to researchers, and to have been prescribed by physicians in tablet, powder and suspension forms in Europe. In the capsule form, the oral bioavailability of azithromycin was found to be adversely affected by the presence of food in the patient's system. For that reason, ZITHROMAX product labelling required that the capsules should be taken at least one hour before or two hours after a meal. Compliance with the dosage instructions presented difficulties for some patients, particularly the young. Failure to follow them reduced the therapeutic effectiveness of the drug.

[6] Conducting research into the other dosage forms, Pfizer scientists found that azithromycin in tablets, powders or suspensions, could be taken with food without losing approximately 50% of its bioavailability. Pfizer sought protection for this claimed discovery. A patent application was filed in Canada on April 27, 1995 and the '071 patent was issued on October 17, 2000. The priority date, based on the U.S. filing, is April 29, 1994.

[7] The '071 Patent has 33 claims. Certain of the claims are limited to tablets made by wet granulation, a formulation Apotex says it does not use. Others are limited to dosages in the form of powders for oral suspension, or unit doses in packets or sachets, which again Apotex says it does not employ. The claims are set out in full in the attached Annex "A".

[8] The parties are agreed that the only claim at issue in this litigation is number 23 which reads:

Use of a therapeutically effective amount of azithromycin for the preparation of a pharmaceutical dosage form which does not exhibit an adverse food effect for administration, in the treatment of an antimicrobial infection, to a patient that has eaten.

[9] Apotex asserts in its notice of allegations and detailed statement that its product, Apo-azithromycin, won't infringe this claim because 1) its tablets are made in accordance with the prior art and thus satisfy the defence set out in *Gillette Safety Razor Company v. Anglo-American Trading Company Ltd.*, (1913) R.P.C. 465; and 2), that if claim 23 is found to be valid and to cover its tablets, they undertake not to market them as intended for administration to a patient that has eaten.

[10] Apotex further alleges that the invention claimed in the '071 Patent is obvious, anticipated, a method of treatment claim, ambiguous, overbroad, lacking in utility, and improperly on the patent register. Consequently, Apotex asks that I find that the '071 patent is invalid, that it is improperly listed on the register (either in addition to or alternatively to its invalidity), and that there is no bar to the Minister issuing a notice of compliance in respect of its apo-azithromycin product.

Onus and Burden of Proof

[11] As recently reiterated by the Federal Court of Appeal in *Pfizer Canada Inc v. Novopharm Limited* [2005] F.C.J. No. 1318, 2005 FCA 270 at paragraph 20, Apotex has no evidentiary burden to support the allegations in its notice of allegations and detailed statement.

[12] The legal burden in these proceedings is on Pfizer to prove, on a balance of probabilities, that the allegations in Apotex' notice were not justified; *AB Hassle v.Canada (Minister of National Health and Welfare* (2002), 22 C.P.R. (4th) 1, 2002 FCA 421 at paragraph 35 *(AB Hassle 2)* .

[13] In establishing that the allegations of invalidity are not justified, Pfizer is entitled to rely upon the statutory presumption of validity found in subsection 43(2) of the *Patent Act* R.S.C. 1985, c. P-4; *Eli Lilly and Co. v. Apotex Inc.* (1995), 60 C.P.R. (3d) 206 at 216 91 F.T.R. 181 at 216 (F.C.T.D.), aff'd (1996), 66 C.P.R. (3d) 329, 195 N.R. 378 (F.C.A.); *Bayer Inc. v. Canada (Minister of National Health and Welfare)* (2000), 6 C.P.R. (4th) 285, N.R. 238 (F.C.A.). Apotex has the evidentiary burden, on a balance of probabilities, to prove that the patent is invalid; *Procter & Gamble Pharmaceuticals Canada Inc. v. Canada (Minister of Health)* [2005] 2 F.C.R.269, 2004 FCA 393. If the allegations are not justified, the prohibition order is granted.

The Evidence

Pfizer's principal witnesses

[14] **Dr. Robert A. Rapp** is a Professor of Pharmacy and Professor of Surgery at the University of Kentucky Colleges of Pharmacy and Surgery. He was tendered as an expert witness to provide opinion evidence as a person skilled in the art of clinical pharmacy. Dr. Rapp has experience in studying azithromycin in a clinical context, and has published papers related to its therapeutic applications. He is also familiar with food-drug interactions and co-authored his university hospital's food-drug interaction guidelines. He has no direct experience in pharmaceutical formulation but has served as an advisor to drug companies particularly Pfizer.

[15] His opinion is that the subject matter of claim 23 was neither anticipated nor obvious based on the general state of the knowledge among clinicians and researchers as of the priority date. In Dr. Rapp's view the knowledge shared by most persons skilled in

the art was that azithromycin in any dosage form exhibited a food effect. Consequently, the fact that it did not in tablets and suspensions was a surprising result.

[16] **Dr. Vincent Andriole** is a specialist in internal medicine and infectious diseases and Professor of Medicine at Yale University, New Haven, Connecticut. He has been the editor, served on the editorial boards, and acted as a reviewer for a large number of medical journals. He has also served on many advisory committees for pharmaceutical companies, including one related to azithromycin for Pfizer from 1989 until the early 1990s. Dr. Andriole provided opinion evidence on a fairly narrow question regarding the construction of claim 23. That is whether it suffers from overbreadth because, on its face, the claim is not limited to tablets but to all formulations of azithromycin that can be taken with food.

[17] **Madelaine Pesant** is an employee of Pfizer Canada and attaches to her affidavit documents related to the litigation, with a view to establishing that the '071 patent is properly listed on the register in connection with the 250 and 500 mg tablets. She also attests to the commercial success of the ZITHROMAX 250 mg tablets. She was not cross-examined on her affidavit but was asked to respond to written interrogatories.

Apotex's principal witnesses

[18] **Dr. Robert S. Langer** is a Professor of Chemical and Biomedical Engineering at MIT, the Department of Chemical Engineering, Whitaker College of Health Sciences, Technology and Management, and the Harvard-MIT Division of Health Sciences and Technology. He is tendered as an expert in pharmaceutics and pharmaceutical formulation technology. He has been awarded a great number of honours including many of the highest awards in medicine, such as the highest Canadian prize in that field. He has published over 700 articles and is a named inventor of hundreds of patents.

[19] In Dr. Langer's opinion, the Apotex azithromycin tablets made by non-wet granulation will not infringe the '071 claims. He attests that the azithromycin tablets made by Apotex are in accordance with the prior art and will not infringe because of the Gillette defence. Even if claim 23 is valid, the tablets will not be identified as administrable to a patient who has eaten. He also supports Apotex' position that the '071 patent is anticipated and that it was also obvious in light of the state of the knowledge in 1994. He also believes that claim 23 is ambiguous, overbroad, and lacks utility.

[20] **Professor Jonathan S. Dordick** is a Professor of Chemical and Biological Engineering at Rensselaer Polytechnic Institute in Troy, New York. He has conducted research on the delivery of drugs in the body, serves as a consultant to numerous companies in the pharmaceutical and chemical industries and is tendered as an expert in pharmaceutical formulations, biosynthetic chemistry and bioanalytical chemistry.

[21] Dr. Dordick states the opinion that claim 23 is anticipated by the prior art because formulations prepared according to the prior art meet the requirements of claim 23. He discusses dissolution tests and asserts that the formulations tested were anticipated by several north american and european patents. He refers in particular to the Canadian 2,101, 466 patent (the '466 or Catania patent) which taught the use of azithromycin in a taste-masked form by grinding up a tablet or using a powder to sprinkle on food. He thinks that the '071 patent was obvious as well, in light of the '466 patent.

[22] **Dr. Michael Mayersohn** is Professor of Pharmaceutical Sciences in the College of Pharmacy at the University of Arizonan and a former member of the Pharmaceutical Sciences Advisory Committee to the US Federal Drug Administration. Dr. Mayersohn has prior but not recent experience as a pharmacist advising patients. He is tendered as an expert in pharmacokinetics, biopharmaceutics and pharmaceutics.

[23] Dr. Mayersohn also reviewed the results of dissolution tests. He concludes that the '071 patent is anticipated, so does not deal with any of the other allegations. In his view, formulations disclosed in prior art patents anticipate the very same rapid dissolution formulations that are described in the '071 patent. He is also of the opinion that the '466 patent discloses the taking of azithromycin with food.

[24] **Dr. Eli Shefter** is a Doctor of Pharmaceutics and Professor of Pharmacy at the University of Colorado and Adjunct Professor at the University of California at San Diego. He is the Chief Scientific Director for IriSys Research and Development LLC and also works as a consultant to pharmaceutical and biotech companies on matters pertaining to formulation, stability and regulatory issues. He too was a consultant to the FDA for over five years and also served on the USP Committee of Experts. He has experience in formulating antimicrobial dosage forms. Dr. Shefter's evidence was similar to that of Dr. Mayersohn.

[25] **Stephen Levine** is a formulation scientist at Emerson Pharma Services. He prepared three formulations based on the US 4,963,531 (Remington) patent for azithromycin suspension
and two weights of tablets. He contracted an analytical laboratory (Chemir Pharma Services) to conduct dissolution tests (as described in the '071 patent) comparing the formulations. The tests showed that for each dosage form, at least 90% of the azithromycin dissolved within 30 minutes and also within 15 minutes. He includes as Exhibit 4 the results of the tests. **Lev Fridman** is the employee of Chemir Pharma Services who conducted the dissolution tests. He also attaches the results of the tests. He attests that the instructions he followed were the same as those in the '071 patent. Neither Mr. Levine nor Mr. Fridman were cross-examined.

[26] Pfizer's experts, Dr's Rapp and Andriole, have expertise in the clinical applications of drugs such as azithromycin and both were involved in its development in a consultative capacity.They do not have expertise in drug formulation. Pfizer submits that their evidence, as that of a practising pharmacist and physician with direct experience with the drug should be given greater weight than that of the Apotex witnesses. Apotex claims, in turn, that the opinions of pharmaceutical scientists such as Dr. Mayersohn and drug formulation experts such as Drs Langer and Dordick should be preferred over that of clinicians, however eminent they may be.

[27] While all of the experts tendered by the parties in this case have impressive qualifications, I do have reservations about Dr. Rapp's evidence. It is clear from his evidence that, despite his long experience with the therapeutic applications of azithromycin, he did not become fully aware of the revised dosing instructions until he was instructed for this litigation in 2003. His university's drug interaction guidelines, of which he is co-author, did not reflect the change until that year. As stated by Justice Binnie in *Camco Inc.et al v. Whirlpool Corp.et al*,
[2000] 2 S.C.R. 1067, (2000) 9 C.P.R. (4th) 129 at paragraph 74 [*Camco*],, the skilled worker is thought to be reasonably diligent in keeping up with advances in the field to

which the patent relates. It is open to question how diligent Dr. Rapp was in keeping up with advances in the field.

[28] On cross-examination, it emerged that Dr. Rapp has significant ties to Pfizer, including owning stock in the company, doing promotional talks for it, serving on consulting boards and receiving research grants that, indirectly at least, contribute to the level of compensation he receives from the university. He stated that this is typical of those in his position, at least at his university. While that may be the case, in my view such close links to one of the parties compromises the independence expected of a witness tendered as an expert by that party in litigation. I have also concluded from reviewing his cross-examination that Dr. Rapp seemed defensive and appeared to cross the line at times from independent expert to advocate for the Pfizer position.

[29] I had no difficulty with the manner in which Dr. Andriole and the Apotex experts provided their evidence. While Pfizer counsel took me to several portions of the transcript of Dr. Langer's cross-examination where he stated a lack of knowledge or that he would need to review the evidence in question, I was satisfied that was entirely consistent with what is to be expected from an independent and objective expert.

[30] Having carefully reviewed the experts' affidavits and cross-examinations, where there is a conflict between Dr. Rapp's evidence and that of the Apotex experts, I generally preferred the latter as appearing to be more thorough, objective and grounded in the scientific literature.

Issues

[31] At issue in these proceedings is whether the Court should grant an order prohibiting the Minister from issuing a notice of compliance to Apotex. That requires a determination of whether the allegations of invalidity and non-infringement set out in Apotex' notice of allegation and detailed statement are justified. Following construction of the claim at issue, the specific questions I will address are whether the '071 Patent is invalid on the grounds that the invention claimed was anticipated or obvious by reason of the prior art, whether claim 23 is ambiguous or overbroad, whether the claimed invention is not properly the subject of a patent and, as further alleged by the respondent, whether the patent was improperly listed and whether the Apotex product will not infringe.

Claim Construction

[32] The first step before addressing the issues is to construe the claims through eyes educated by a person or persons skilled in the art. In conducting my analysis, I have had regard to the principles enunciated by the Supreme Court of Canada decisions in *Free World Trust v. Électro-Santé Inc.*, [2000] 2 S.C.R. 1024, 2000 SCC 66 [*Free World Trust*] and *Camco*, supra.

[33] The object of claim construction is to fairly and reasonably define the purpose of the invention. The assistance of experts may be necessary, but is not determinative. I am not bound by the suggested constructions put forward by the parties or their experts. The words of the claims themselves are to be the focus of the analysis: *Novartis Pharmaceuticals Canada Inc. v. RhoxalPharma Inc.* (2005) 38 C.P.R. (4th) 193, 2005 FCA 11 at para. 45, 53.

[34] As noted above, Claim 23 is the contentious portion of the '071 patent. It reads as follows:

Use of a therapeutically effective amount of azithromycin for the preparation of a pharmaceutical dosage form which does not exhibit an adverse food effect for administration, in the treatment of an antimicrobial infection, to a patient that has eaten.

[35] Claims 1-22 are claims to dosage forms, that is tablets, powders for oral suspension and unit dose packets. Claims 24 to 27 are formulation claims for specific tablets. Claims 28 and 32 are a therapeutic package claim. Claims 29-31 refer to powders, 32 to a unit dose packet. The claims are set out in full in Annex "A" to these reasons.

[36] There is some common ground between the parties as to the appropriate construction of Claim 23. For instance, they agree that the reference to "antimicrobial" infections is simply a typographical error and is of no moment. Clearly, the intended wording was "microbial". There is also no serious argument about the meaning of the words "a patient that has eaten." These words are understood by the skilled person to be a patient who has eaten in the hour prior to taking the dose of oral azithromycin or who will eat in the two hours following taking that dose. There is also general agreement that none of the dosage forms contain a significant amount of an alkaline earth oxide or hydroxide (referred to in the claims), and, finally, that capsules are excluded from the claim.

[37] I interpret the words "a therapeutically effective amount of azithromycin" in claim 23 to mean simply, as several of the experts suggested, "enough of the drug to treat the infection". Nothing of importance in these proceedings turns on this in my view.

[38] Pfizer's position is that claim 23 is a "use to treat" claim. Pfizer's reading emphasises the following parts of the claim:

Use of a therapeutically effective amount of azithromycin for the preparation of a pharmaceutical dosage form which does not exhibit an adverse food effect for administration, in the treatment of an antimicrobial infection, to a patient that has eaten. [Emphasis added]

[39] In other words, Pfizer's position is that the claim is for a new use of azithromycin (in particular dosage forms) in a particular manner – the treatment of microbial infections in a patient who has eaten. In its submission, the essential elements in claim 23 are:

(I) the oral administration of a dosage form of azithromycin;
(ii) to treat a microbial infection;
(iii) where the oral dosage form does not exhibit an adverse food effect in a patient who has eaten.

[40] Apotex criticises this reading of claim 23 because it says it ignores a large part of the language of the claim. Apotex emphasises the importance of the words underlined below:

Use of a therapeutically effective amount of azithromycin for the preparation of a pharmaceutical dosage form which does not exhibit an adverse food effect for administration, in the treatment of an antimicrobial infection, to a patient that has eaten.

[41] The words regarding the preparation of the dosage form should not have been included if their meaning was simply going to be ignored, Apotex contends. Experts cannot read in words, and neither should they be able to read them out of a claim: *GlaxoSmithKline Inc. v. Canada (Attorney General)* (2005) 40 C.P.R.(4th) 93, 2005 FCA 197 at paragraph 13.

[42] Apotex's position on claim construction, therefore, is that the emphasis in construing the essential elements of claim 23 must be placed on the formulation of azithromycin dosage forms (that can then be used in a particular way) rather than for the use of the dosage form itself.

[43] Apotex finds support for this position in the terms of claim 27:

A tablet as defined in any one of claims 22 to 26, which is coated with a film of hydroxypropylmethylcellulose, hydroxypropylcellulose or acrylate-methacrylate copolymer.

If claim 23 defines a tablet (rather than the use of a tablet), as suggested by claim 27, this gives some support to Apotex's theory that claim 23 is a formulation claim. However, I do not find this to be conclusive.

[44] Pfizer submits that the experts also read claim 23 as a use to treat claim. Its witness, Dr. Rapp, deposes that a person skilled in the art would understand that the invention described in claim 23 is to administer a pharmaceutical form of azithromycin to a patient who has eaten in a way to overcome the adverse food effect observed with capsules. Dr. Andriole provided a similar opinion.

[45] Pfizer also finds support for its interpretation in the evidence of Apotex' witnesses. In Dr. Dordick's affidavit, at paragraph 40, he states that the key issue in respect of Claim 23 is "...the use of an azithromycin formulation which does not exhibit an adverse food effect and administration of such to a mammal that has eaten" (emphasis added). Further, at paragraph 41 where he breaks down the elements of claim 23 for an anticipation analysis, his description is similar to that urged on the court by Pfizer.

[46] While Dr. Mayersohn initially stated that one of ordinary skill in the art would have no way of interpreting what was disclosed in claim 23, the scope of the claim or the invention that it reflects, he agreed on cross-examination that one aspect disclosed was a method of treating a microbial infection.

[47] On the other hand, Pfizer' s witness Dr. Andriole, at paragraph 47 of his affidavit, seems to have agreed with Apotex' position in stating that "...what was claimed in claim 23 is the use of 'pharmaceutical formulations' ..." Dr. Rapp also, at paragraph 61 of his affidavit, seems to put the emphasis in construing claim 23 on the making of the dosage form.

[48] Dr. Langer, Apotex' expert pharmaceutical chemist, was clear in his evidence at paragraphs 11 and 64 that he reads claim 23 as claiming the use of azithromycin in pharmaceutical dosage forms that do not exhibit an adverse food effect upon administration to fed patients.

[49] Notwithstanding the assistance of the experts, I do not find that the correct reading of claim 23 is plain on its face, as argued by both Pfizer and Apotex. A purposive construction thus requires that it be interpreted in light of the whole of the disclosure: *Schmeiser v.Monsanto Canada Inc*., [2004] 1 S.C.R. 902, 2004 SCC 34 at paragraph 18.

[50] The title of the Patent is "Method of Administering Azithromycin". The first paragraph of the disclosure section reads:

This invention relates to a dosage form of azithromycin, and also to a method of treating a microbial infection which involves administering azithromycin in the fed state to a mammal, including a human patient, in need of such treatment. [emphasis added]

Thus, it is reasonable to expect that the individual claims of the patent will apply to either the dosage form of azithromycin or the administration of azithromycin as a method of treatment.

[51] The "Summary of the Invention" section of the patent disclosure provides for four aspects of the invention: an oral dosage form of azithromycin that does not exhibit an adverse food effect, specific oral azithromycin dosage forms (i.e., tablets, powders), a method for treating a microbial infection, and a therapeutic package containing the dosage forms.

[52] An oral dosage form that does not exhibit an adverse food effect, paraphrasing the disclosure, would be one in which there is substantially no inhibition of the rate at which the azithromycin is absorbed into the blood stream for therapeutic purposes**.**

[53] The inventors assert at page 5 of the patent that they found it surprising that a dosage form of azithromycin did not exhibit an adverse food effect because, they state, azithromycin is unstable at low acid levels such as are found in stomach acid. Apotex argues that this is clearly erroneous as the literature does not support that conclusion with respect to azithromycin as opposed to other related azalide antibiotics. Pfizer did not dispute this.

[54] The inventors further say in the detailed description at page 7 that "[it] is believed that the dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract, essentially immediately following ingestion (suspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution."

[55] They conclude, on page 7, that "[w]hile not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution in the GI tract, or at least...within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect."

[56] The disclosure discusses how the rate of absorption into the blood stream is measured and how to determine whether there is no food effect. For an adequate rate of absorption to occur, at least 90% of the azithromycin in the dosage form should dissolve within 30 minutes of ingestion, preferably within 15 minutes. Rapid dissolution alone, however, is not enough to establish bio-availability. There are fast-dissolving capsule formulations which continue to exhibit an adverse food effect in testing of the blood samples of human subjects. The object, according to the disclosure, is to strive for a high degree of statistical confidence that the mean rate of absorption in the general population would fall within specified values. The evidence of the expert witnesses was generally in agreement with this proposition.

[57] An adverse food effect is said not to exist if the ratio of the areas under the azithromycin plasma concentration-time curve in a subject ingesting the drug orally in the fed state (AUC_{fed}) compared to the fasted state (AUC_{fast}), AUC_{fed}/AUC_{fast}, is less than 0.8 and the lower 90% confidence limit for this ratio is not less than 0.75. According to the '071' patent disclosure, an adverse food effect will not occur as measured in *in vitro*

dissolution tests if at least 90% of the azithromycin in the dosage form dissolves within about 30 minutes and, preferably, within about 15 minutes.

[58] The parameters required for dissolution are set out in claims 1, 3, and 6 for the different dosage forms as follows:

...the dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37^{o}C, with paddles turning at 100 rpm, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

[59] The inventors state, at page 7 line 9-10 of the detailed description, that if a non-capsule dosage form of azithromycin satisfies the *in vitro* dissolution requirements specified, they consider it to fall within the scope of the claims. Thus you can determine whether a particular non-capsule dosage form exhibits an adverse food effect in two ways. Either through absorption testing or through dissolution testing.

[60] This conflicts with Dr. Rapp's evidence, at paragraph 63 of his affidavit, in which he says that dissolution alone cannot be used to predict food effect. The patent disclosure is supported by Dr. Shefter's affidavit in which he states at paragraph 31 that

It was well established that prior to 1995 that in vitro dissolution provides a correlation with in vivo dissolution. In other words, the rate at which a dosage form dissolves in a dissolution test is a reflection of how that dosage form will perform in the gastrointestinal tract fluids. The '071 Patent was clearly aware that this type of correlation existed for tablets...

[61] Having carefully reviewed the whole of the specifications and the evidence of the expert witnesses, I conclude that the purpose of the invention claimed in the '071 patent was to offer a solution to the problem of the adverse food effect caused by azithromycin capsules. It was not a new use for azithromycin but a new method of administering azithromycin. The essential elements are:

1. the use of "enough" azithromycin
2. in an oral pharmaceutical dosage form, excluding capsules**;**
3. to treat microbial infections;
4. in patients who have eaten;
5. which does not result in an adverse food effect;
6. as measured within the parameters of standard scientific tests for dissolution or absorption.

Validity of the patent

Anticipation

[62] Apotex alleges anticipation by prior publication and by prior use and sale. As anticipatory prior art, the notice of allegation cites United States Patents No. 4, 963,531 (the '531 or Remington patent), No.4,474, 768 (the Bright or ' 768 patent), Canadian Patent No. 2,101,466 (the '466 or Catania patent), European Patent EP-A-307128 (equivalent to the '531 patent), excerpts from the *Gazetta Ufficiale Della Repubblica Italiana*, an Italian data sheet on ZITHROMAX dated in 1992 and a Spanish invoice for a 250 mg azithromycin formulation dated December 1993.

[63] In asserting that a patent claim has been anticipated, the argument is that the invention has already been disclosed to the public and is therefore not novel. The well-established approach to anticipation is found in Justice Hugessen's decision in

Beloit Canada Ltd.,v. Valmet Oy, (1986) 8 C.P.R. (3d) 289, [1986] F.C.J. No. 87 at page 297 [*Beloit* cited to C.P.R.]:

It will be recalled that **anticipation, or lack of novelty**, **asserts that the invention has been made known to the public prior to the relevant time.** The inquiry is directed to the very invention in suit and not, as in the case of obviousness, to the state of the art and to common general knowledge. Also...anticipation must be found in a specific patent or other published document; it is **not enough to pick bits and pieces from a variety of prior publications and to meld them together so as to come up with the claimed invention**. **One must**, **in effect, be able to look at a prior, single publication and find in it all the information which, for practical purposes, is needed to produce the claimed invention without the exercise of any inventive skill**. The prior publication must contain **so clear a direction** that a skilled person **reading and following it would in every case and without possibility of error be led to the claimed invention**. Where, as here, the invention consists of a combination of several known elements, any publication which does not teach the combination of all the elements claimed cannot possibly be anticipatory.

[Emphasis added]

[64] This approach was cited with approval by the Supreme Court of Canada in *Free World Trust, supra* at paragraph 26. Justice Binnie, in that decision, also cautioned against the use of *ex post facto* deduction in evaluating whether an invention was anticipated by a particular publication, since assembling a dossier of prior art with the benefit of hindsight is "all too easy after an invention has been disclosed" *(Free World Trust, supra* at para. 25).

[65] The priority date for the assessment of anticipation as determined by subsection 28.2 of the *Patent Act*, is a year before the Canadian filing date, hence April 27, 1994. Nothing turns on the two day difference between that date and the date of the US filing, April 29, 1994.

Disclosure by publication

[66] The Remington or ‘531 patent, cited as prior art, was issued in 1990 and assigned to Pfizer. The abstract describes it as a method of use of azithromycin or its derivatives in the treatment of a microbial infection (toxoplasma gondii). Apotex argues that two of the examples provided in Remington are of formulations that fall within the scope of claim 23 of the ‘071 patent as they are identical in all significant respects to two examples in the ‘071 patent and must therefore, exhibit the same properties. Further, formulations made by Apotex’ experts following the two Remington examples were shown to meet the *in vitro* dissolution criteria specified in the ‘071 patent.

[67] Apotex submits that the Remington patent anticipates the ‘071 patent as it teaches and discloses powders for suspension and fast-dissolving tablets made using azithromycin that, upon administration to fed patients, would not exhibit adverse food effects as defined in the ‘071 patent. This was supported by and addressed at length by Dr. Langer in his affidavit at paragraphs 77-81, by Dr. Shefter at paragraphs 21-24 to his affidavit, by Dr. Dordick at paragraphs 61 - 66 and by Dr. Mayersohn at paragraphs 13-18.

[68] Shefter and Langer both agreed on cross-examination that there is no mention in Remington that any of these oral dosage forms exhibit an adverse food effect. Further, there is no discussion of dissolution rates.

[69] The base azithromycin patent for antibacterial use is the ‘768 patent issued in 1984 to Gene Bright, a Pfizer research scientist. Related to the ‘768 patent, for the purpose of Apotex’ prior art submission, is a 1989 international patent application by Allen et al for a new form of azithromycin. The Allen application, also assigned to Pfizer,

incorporates Bright. There is no restriction in either to the administration of the formulations disclosed with or without food. However, neither discuss a food effect.

[70] In his affidavit, Dr. Langer states at paragraph 71 that the inventors of the ‘768 patent (referred to as the ‘071 patent in error) teach the formulation of azithromycin with pharmaceutically acceptable carriers by conventional methods for the production of tablets, suspensions and solutions. A person skilled in the art would understand that to mean, among other things, fast dissolving tablets made via direct compression, dry or wet granulation containing azithromycin and a disintegrant. As a result, Langer says, while the ‘768 tablet does not explicitly discuss the absence of adverse food effects, it teaches the use of azithromycin for the production of oral dosage forms that include solution, suspension and fast-dissolving tablet dosage forms that would not exhibit an adverse food effect when administered to a fed patient. He reaches a similar conclusion with respect to the Allen application.

[71] Further cited as anticipatory prior art is the Canadian ‘466 or Catania patent. Catania has a priority date of July 30, 1992 and a publication date of January 31, 1994. Catania addresses the reduction of the bitter taste of pharmaceutical compositions, including azithromycin, through the addition of a taste masking component. Azithromycin, apparently, has a particularly bitter
flavour. Catania discusses the use of chewable tablets or suspension oral dosage forms for azithromycin. It suggests that the tablets may be ground up, mixed with, placed in or sprinkled on cereals, ice cream or other food and drinks. Alternatively they may be swallowed whole without chewing or mixing. The suspension may be mixed with food and drinks. No concern about an adverse food effect is mentioned. What it teaches, Apotex submits, is the use of azithromycin in a dosage form to be administered to a patient who has eaten with no food effect to treat microbial infections. Precisely one of the alternative constructions for claim 23 of the ‘ 071 patent.

[72] Again, Apotex relies on the evidence of Drs. Langer, Shefter, Mayersohn and Dordick in support of this interpretation of Catania. They all say that the formulations being virtually identical in both Catania and the ‘071 patent, the results should be identical. The only difference being the inclusion of taste-masking agents in the formulations disclosed in the Catania patent. Dr. Langer, at paragraph 99 of his affidavit, says that in his experience he would not expect those agents to make any difference on the dissolution behaviour of the dosage forms or the lack of a food effect.

[73] Dr. Dordick notes first at paragraph 51 of his affidavit that the taste-masking agent in Catania would have no effect on dissolution rates as its purpose is solely to mask the taste in the mouth. He goes on to say, at paragraphs 57, that it is clear to anyone skilled in the art of drug formulation, that Catania teaches that azithromycin can be used in conjunction with food. He concludes at 59 that it is clear that rapidly dissolvable azithromycin formulations existing as powders for oral suspension or tablets were known and formed part of the state of the art prior to
the priority date of the ‘071 patent. Further, because there were teachings correlating *in vitro* dissolution to *in vivo* bio-availability, claims in the ‘071 patent directed towards bio-availability are also anticipated by the prior art. Finally, because azithromycin could be administered with solid food, its use as a purported new medical indication was anticipated by the prior art. Again, there is no specific reference to whether the dosage

forms referenced exhibit an adverse food effect. Dr. Mayersohn stated on cross that he knew they would not because of the results of the tests disclosed in the ‘071 patent.

[74] Incidentally, all of the claims in the ‘071 patent, save for claim 23, exclude a taste-masking amount of an oxide. There is no exclusion in claim 23.

[75] Dr. Rapp, at paragraph 53 of his affidavit, states that it had always been possible to administer an azithromycin compound that does exhibit a food effect (such as capsules) with food. He suggests that a person skilled in the art would know to administer a higher dose because of the food effect. But that is not what Catania teaches. There is no suggestion in the patent that excessive amounts of the drug be administered to counter a food effect. On cross-examination, Dr. Rapp conceded that there was nothing in Catania to support his hypothesis (p.1481 of the record) of higher doses.

[76] Apotex acknowledges that the patents described as prior art for anticipation by publication in its notice of allegation do not speak of solving the food effect problem with tablets. But, Apotex argues, the tablets were a known, obvious alternative to capsules and that the
skilled person reading and following a cited patent would have gone directly to the tablets using routine workshop activity and no inventive skill.

[77] Apotex relies upon *SmithKline Beecham Pharma Inc.et al.v. Apotex Inc.et al.*, (2001) 14 C.P.R. (4th) 76 (F.C.T.D.), aff’d (2002) 21 C.P.R. (4th)129, 2002 FCA 216 in support of this position. In *SmithKline*, the patent in suit addressed a problem which resulted from the formulation of paroxetine tablets by a wet granulation process (they turned pink). Justice Gibson held that the claimed invention was anticipated by the parent patent which provided for alternative formulation methods that did not involve water. Thus a logical first step for a person skilled in the art would be to turn to those alternative formulations. All the information required to produce the claimed invention could be found in the prior patent without the aid of inventive genius but purely mechanical skill.

[78] In a subsequent decision involving paroxetine, *GlaxoSmithKline Inc. v.Apotex Inc.*, (2003) 27 C.P.R. (4th) 114, 2003 FCT 687. . Justice Kelen reached the conclusion, as had Justice Gibson, that the divisional patent at issue was anticipated by its parent as it was merely an application of one of the alternatives taught in the parent. It was further invalid for evergreening or double patenting. That the use of a dry formulation was the solution to the pink hue problem would be obvious to a skilled formulator.

[79] Pfizer argues that the ultimate difficulty with any and each of the cited prior art references, as Apotex witnesses Langer and Shefter conceded on cross-examination, is that none
of them refer to the 90 per cent confidence limit for no food effect set out in the ‘071 patent disclosure. There is no demonstration that any dosage form of azithromycin administered to a patient that had eaten food in the three hour window would not have an adverse food effect.

Disclosure by sale or use

[80] For the purpose of analysing anticipation in the context of disclosure by prior sale or use under paragraph 28.2(1)(a) of the *Patent Act*, the Federal Court of Appeal has observed that the *Beloit* principles may need to be "tailored to fit the particular circumstances": *Baker Petrolite Corp.v. Canwell Enviro-Industries Ltd.*,(2002) 17 C.P.R. (4th) 478 at 494, 2002 FCA 158. . At paragraph 35 of *Baker*, Justice Rothstein notes by

way of example that anticipation by publication involves the skilled person reading the prior art. With anticipation by sale or use, reading may not be relevant.

[81] At paragraph 42 of *Baker*, Justice Rothstein identifies a number of principles or factors relevant to disclosure by prior sale or use. First is that sale or use by the public alone is insufficient; there must be disclosure of the invention. Use makes the invention part of the state of the art only so far as the necessary information is disclosed. The second principle is that the prior use or sale must amount to an enabling disclosure such as to allow the public to make or obtain the invention.

[82] The third principle identified by Justice Rothstein is that the prior sale or use of a chemical product will constitute enabling disclosure if its composition or internal structure can be discovered through analysis of the product. Apotex contends that this means that if an analysis of the product sold revealed that it did not have an adverse food effect, that would constitute disclosure by prior sale or use. But that would be disclosure of the properties or effects of the chemical, not its composition or internal structure.

[83] The fourth principle addresses disclosure where reverse engineering is available of products sold to the public, the sixth says that it is not necessary for any member of the public to actually analyse the product, the seventh says that the amount of time and work is not determinative and the eighth, that it is not necessary that the product be capable of exact reproduction. It is the subject matter of the patent claims that must be disclosed through analysis.

[84] Apotex alleges that there was prior disclosure by the sale and use of tablets containing azithromycin which were publically available before the priority date. It asserts that the evidence establishes that these formulations, when analysed, show that they would have no food effect.

[85] The evidence relied upon by Apotex for this allegation relates primarily to the sale of azithromycin tablets in Italy. The first evidence tendered in support are extracts from the *Gazetta* or Official Journal of the Italian Republic dated May 5, 1992. Reproduced at pages 3199 to 3248 of the record are translations of pages from the journal containing references to four products RIBOTREX, ZITHROMAX, AZITROCIN and TREZID relating to 250 mg capsules, pediatric use powder for oral suspension and 500 mg splittable tablets of azithromycin dihydrate manufactured by Pfizer Italiana S.p.A. . The therapeutic indications provided for these products are similar to those described for the ZITHROMAX product sold in North America.

[86] Apotex submits that the powder for oral suspension cited in the *Gazetta* is essentially the same as referenced in Example 2 of the prior ‘531 patent and referable to that in Example 6 of the ‘071 patent and tables XII and XIII. The tablets are virtually identical to Examples 3-5 of the ‘071 patent. At page 26 of the ‘071 patent, Table VII, there is a listing of 500 mg tablets that do not exhibit a food effect. Support for this interpretation of the formulations described in the *Gazetta* is found in Dr. Langer’s evidence at paragraph 42 where he states that such dosage forms, upon routine testing, meet the dissolution constraints defined in the ‘071 patent. Further he states at paragraphs 88-91, that the *Gazetta* references are essentially the same with minor non-material differences. Similar evidence was provided by Drs Shefter, Dordick and Mayersohn.

[87] Also tendered in evidence was an extract from an Italian data sheet entitled "GioFil" which bears the year 1992 and contains information on the composition and properties of ZITROMAX 500 mg splittable tablets consistent with the *Gazetta*

references described above. I note that it also contains a warning not to administer the drug after an "abundant meal" as that would reduce the bioavailability of azithromycin by 50%.

[88] It appears from a document, submitted by Apotex, purporting to be an invoice from a Barcelona pharmacy and reproduced in translation at page 1917 of the record, that a product described as 250 mg packets of ZITROMAX was being sold in Spain in December 1993. There is no direct evidence of the nature of the formulation employed in these packets.

[89] Apotex sought, over Pfizer's objections, to rely upon evidence filed in European opposition proceedings to the equivalent of the '071 patent to establish the composition of the Spanish formulation. As I was not satisfied that the evidence in those proceedings was properly before the Court, I have given it no consideration.

[90] However, Pfizer refused to answer written interrogatories concerning the manufacturing and marketing of Pfizer branded products in Europe put to its corporate witness Madeleine Pesant, except to the extent that they related to Canada, on the grounds that they were not relevant to her affidavit. Apotex submits that the objections were improper as the questions were within the scope of proper cross-examination and the witness could easily have obtained the information from Pfizer Canada Inc.' parent company. I am asked to draw the inference that the answers would have been unfavourable to Pfizer and would have established that Pfizer manufactured and sold azithromycin tablets and powders in Italy and Spain, in the formulations shown in the *Gazetta* pages.

[91] Apotex submits that support for this proposition can be found in a decision by Justice Wetson, *Pharmacia Inc.v. Canada (Minister of National Health and Welfare),*(1995) , 60 C.P.R. (3d) 328, 92 F.T.R. 253 [*Pharmacia* cited to C.P.R.] in which he refers to a common law principle that where the subject matter of an allegation lies particularly within the knowledge of one of the parties, that party must prove it. In that case, only the respondent knew the precise composition of their product. Apotex argues that the same is true here. Only Pfizer knows exactly what it was manufacturing and selling in Europe prior to 1994. See also *Hoffman-LaRoche Ltd.v.Apotex Inc.*, (1983) 41 O.R (2d) 84, 71 C.P.R. (2nd) 20 (Ont.H.C.)at 25, aff'd (1984) 47 O.R. (2d) 287, 1 C.P.R. (3rd) 507 (Ont. C.A.) and *Eli Lilly and Co. v. Nu-Pharm Inc*, (1996), 69 C.P.R. (3d) 1 at 18, [1997] 1 F.C. 3. Pfizer submits that the scope of cross-examination in these PM(NOC) proceedings is limited and they were not obliged to answer the question.

[92] I am satisfied that Pfizer could and should have answered the interrogatories as the information was properly the subject matter of cross-examination upon Ms. Pesant's affidavit and the information could easily have been obtained from within the Pfizer family of companies. I accept that an inference may be drawn that is unfavourable to Pfizer respecting the manufacture and sale of azithromycin products in Europe prior to 1994. However, that doesn't add much to the case that Apotex has made through other evidence that Pfizer was selling azithromycin tablets of an essentially identical formulation to those in the '071 patent in Europe prior to 1994.

[93] The GioFil document indicates that the 500 splittable tablets were marketed, at least in Italy, with a warning respecting reduced bioavailability if taken with a substantial meal. Pfizer contends that this shows that the invention claimed in the ‘071 patent was not disclosed through prior use and sale in Europe. Apotex argues that the warnings in themselves don’t establish a
food effect for tablets. That can only be determined by looking at the tablet formulations and by testing. Dr. Shefter addressed that point in paragraph 79 of his affidavit in which he attests that whether or not the tablets were sold with a warning, the tablets themselves do not inherently exhibit a food effect. Dr. Rapp conceded this in cross-examination (pages 1312 and 1483 of the record).

[94] Apotex has put forward an Italian doctor named Giovanni Donadio who attests that before April 1994, he prescribed azithromycin by suspension and tablets to patients without any restrictions or warnings as to whether it was to be taken on a full or empty stomach. He attests that this was the standard practice among Italian physicians and that pharmacists distributed azithromycin without any instructions as that is the domain of physicians in Italy.

[95] Dr. Donadio was cross-examined on his affidavit and taken to references which did not support his understanding. Charitably, the confusion he exhibits in the cross examination may be attributable to the poor quality of the simultaneous translation. In sum, his evidence, at best, establishes that medical practitioners in Italy may not have been aware of or may have disregarded Pfizer’s instructions that the drug should be taken in the fasted state for the best effect.

Conclusion on Anticipation

[96] As stated in *Beloit, supra* the test for anticipation is a very strict one. A patent will be found to be invalid on the ground of anticipation where there exists a prior disclosure which contains sufficient information to enable a person of ordinary skill and knowledge in the art to understand, without access to the patent in issue, the nature of the invention and to carry it into practical use without the use of inventive genius but purely by mechanical skill. As stated in *Baker, supra*, sale or usage is not enough to satisfy the test for anticipation, there must be actual disclosure of the nature of the invention.

[97] The Catania patent comes the closest, in my view, to establishing anticipation through publication. But to conclude that the tablets disclosed in that patent do not exhibit a food effect, one has to have reference to the test results obtained for the dosage forms disclosed in the ‘071 patent. This was conceded by Apotex’ witness Dr. Mayersohn in cross-examination. Thus Catania alone does not lead directly to the claimed invention. Nor, in the absence of clear undisputed evidence to satisfy the *Baker* analysis am I satisfied that anticipation through sale or use has been established.

[98] Thus, I am unable to conclude that the ‘071 patent was anticipated. However, the prior art cited for anticipation is relevant to the question of obviousness and on that question, I reach a different conclusion.

Obviousness

[99] Section 28.3 of the *Patent Act* requires that the subject-matter defined by a claim in an application for a patent in Canada must not have been obvious on the claim date to a person skilled in the art or science to which it pertains. As noted above, the priority date for assessing obviousness with respect to the '071 Patent is April 29, 1994, the date of the filing of the U.S. application.

[100] As a preliminary matter with respect to this issue, I would note that Pfizer contended at paragraph 28 of its memorandum of argument that the prior art relied upon by Apotex for obviousness was not readily accessible to persons of ordinary skill in the art at the relevant time. This was not pressed by counsel for Pfizer at the hearing and properly so as it was not raised as an issue by Pfizer in its Notice of Application. As provided for in Rule 301(e) of the *Federal Court Rules, 1998* an application shall set out a complete statement of the grounds intended to be argued. As noted by Wetson J., in *Pharmacia, supra* at page 339, it also flows from the legal burden on the applicants under section 6 of the regulations to inform the respondent as to what "vexes" the patentee so that it may, if necessary, tender evidence in response.

[101] With obviousness, the invention need not be disclosed in one single patent or piece of prior art, as is the case for anticipation. The Court is entitled to look at all the patents and other publications that a skilled technician would discover in a "reasonable and diligent search" to determine whether the resulting "mosaic" leads directly to the invention: *Illinois Tool Works Inc. v. Cobra Fixations Cie.* (2002), 221 F.T.R. 161, 2002 FCT 829 aff' d on this point, varied only with respect to costs: (2003), 312 N.R. 184, 2003 FCA 358. There is no suggestion before me that the prior art cited by Apotex could not have been found in such a search by such a technician.

[102] The commonly accepted test for obviousness was also set out in *Beloit, supra* by Hugessen, J.A. as he then was, at page 294:

The test for obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right. **The question to be asked is whether this mythical creature** (the man in the Clapham omnibus of patent law) **would, in the light of the state of the art and of common general knowledge as at the claimed date of invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy.**

[Emphasis added]

[103] In determining whether a patent claim is obvious, the Court must avoid using the benefit of hindsight. The question to ask is whether the solution taught by the patent would be "plain as day" to the skilled technician who was searching for something novel, without having to do experimentation or research. Suggestions or signposts in the prior art are not sufficient to make a patent invalid for obviousness: *Apotex Inc. v. Wellcome Foundation Ltd.* (1998), 79 C.P.R. (3d) 193, 145 F.T.R.161 (F.C.T.D.), varied but not on the issue of obviousness, [2001] 1 F.C. 495 (C.A.), (2000) 10 C.P.R. (4th) 65 aff'd [2002] 4 S.C.R. 153, 2002 SCC 77, *Bayer Aktiengesellschaft v. Apotex Inc.* (1995), 60 C.P.R. (3d) 58, [1995] O.J. No. 141 (Ont. Gen. Div.), varied on other grounds (1998), 82 C.P.R. (3d) 526, 11 O.A.C. 1 (O.C.A.), leave to
appeal to the Supreme Court of Canada denied [1998] S.C.C.A. No. 563 (QL) and *Fabwerke Hoechst v. Halocarbon (Ont) Ltd.*, [1979] 2 S.C.R. 929, 42 C.P.R. (2d) 145.

[104] In order to address obviousness, one must have some sense of how the claimed invention represents an advance over the prior art. The azithromycin compound and

function is not claimed in the ‘071 Patent. The structure, function and use of azithromycin were well known in the art and the specific form of azithromycin used, azithromycin dihydrate, was covered by a patent dating back to 1984. Also known was the therapeutically effective amount required to treat humans as an antimicrobial, that azithromycin had a long half-life and that less dosing was required, that azithromycin was acid stable, that it had an increased absorption capability and decreased gastro-intestinal intolerance over erythromycin. The various dosage forms were all known. None of this was disputed in these proceedings.

[105] What is disputed is the scope of the knowledge about adverse food effects. Apotex submits that taking all that was known about the drug, what was known about avoiding adverse food effects, what was known about azithromycin dosage forms already made and used and the knowledge that other closely related macrolides such as clarithromycin were being administered in tablet form with no food effect, the result claimed in the patent was obvious.

[106] Pfizer’s expert Dr. Rapp deposed that as a person skilled in the arts of medicine and pharmacology his understanding of the state of the art prior to publication of the invention claimed in the ‘071 patent was that azithromycin exhibited a food effect. Accordingly, Pfizer contends that the discovery that azithromycin could be administered in tablets, powders or sachets, without an adverse food effect was an advance over the prior art as it was inconsistent with the experts’ understanding of the interaction between food and the drug based on the available scientific literature.

[107] Dr. Rapp attested that this view about the azithromycin food effect persisted even after the publication of the 1996 report by the Pfizer scientists which disclosed their findings regarding the absence of a food effect for tablets and suspension dosage forms. Rapp cited that report in a 1998 paper in which he repeated the food effect caution. Indeed it continued to appear in his university ’s drug interaction guidelines, for which he was co-author, as late as June 2003. Rapp says that he only became aware that the labelling instructions for ZITHROMAX had changed at the outset of this litigation.

[108] As indicated above, I have some difficulty accepting Dr. Rapp’s evidence about what a person of ordinary skill in the art would have known before the priority date when it appears that he was not reasonably diligent in keeping up with the literature in the field in which he professes expertise.

[109] The section of the ‘071 patent disclosure headed "Background" refers to a 1980 review paper by authors Toothaker and Welling of the School of Pharmacy at the University of Wisconsin entitled "The Effect of Food on Drug Bioavailability". Pfizer cites this paper as illustrating the common understanding of persons skilled in the art at that time, that the formulation in which a drug is administered can have a profound effect on the extent of drug-food interaction. At page 176 of the article, 267 of the record, the authors note that "[w]ith capsule and tablet dosage forms, not only is dissolution likely to be affected by the presence of food but also the delay in gastric emptying due to food is likely to have a greater effect when the drug is contained in a single dose." (emphasis added). The study goes on to note, however, that the food effect can vary widely depending on the dosage form and other factors such as disintegration and dissolution rates.

[110] Apotex submits that the Toothaker & Welling paper teaches that you can’t assume that because you have one formulation that has a food effect, a different formulation of

the same medicine will perform in the same way. That, in essence, is what Pfizer scientists demonstrated when they tested the bio-availability of non-capsule oral dosage forms.

[111] The ‘071 patent disclosure states further, at page 2, that at least one unpublished study had shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state. From the evidence, it seems that this study was conducted by Pfizer’s employee, Scott Hopkins, who published a report on the study in a supplement to the American Journal of Medicine in 1991. The report is cited in Dr. Rapp’s affidavit and was produced in evidence. In the Hopkins study, adult patients were treated with azithromycin contained in capsules but those under 15 were given the drug in suspension form. Dr. Hopkins reported that the capsules produced an adverse food effect. His report says nothing with respect to whether a food effect was experienced by the children and youth treated with the suspension dosage form.

[112] It appears from the evidence that Hopkins’ findings that an adverse food effect was associated with the capsules formed the basis for Pfizer’s product labelling caution that ZITHROMAX should not be taken with food. Other scientists, such as Drew and Gallis in their 1992 evaluation of azithromycin, relied upon that information and repeated the food effect warning. But the source of that information related solely to the use of capsule dosage forms and not to the use of azithromycin in tablets or any other dosage forms.

[113] None of the references in the literature cited by Dr. Rapp as supporting his understanding of the conventional wisdom among persons skilled in the art, were based on new testing. Rapp conceded on cross-examination that all of them rely directly or indirectly on Hopkins and Pfizer’s information leaflet. He further conceded that prior to April 1994, the only data that existed on azithromycin in terms of food effect was referable to azithromycin capsules.

[114] Apotex’ expert, Dr. Langer, attested that as of a year prior to the priority date of the ‘071 patent, a person skilled in the art would have been aware of the fact that the occurrence of adverse food effects for oral dosage formulations was often associated with a particular dosage form, with fast-dissolving, suspension or solution dosage forms often exhibiting a lack of food effect as compared to dosage forms such as capsules. Support for this view is also found in Dr. Shefter’s affidavit.

[115] Dr. Rapp says that this general information was superceded by the specific references in the literature addressing azithromycin. As I have noted above, these references were based solely on Pfizer’s testing of the capsules. Dr. Langer’s view, conveyed at paragraph 118 of his affidavit, is that Rapp appears to either ignore or to not fully appreciate or understand the teachings about the relationship between the nature and type of oral dosage forms and the occurrence or lack of an adverse food effect that were available to those skilled in the art in the early 1990's.

[116] Dr. Shefter, citing a 1980 pharmaceutical text on tablet dosage forms referenced in Apotex’ notice, attested that the type of testing described in the ‘071 patent is commonly known and routine in formulation development and that the lack of an adverse food effect of the described fast-dissolving formulations would have been easily demonstrated as an inevitable consequence of routine testing carried out by a person skilled in the art. (Shefter affidavit paragraph 47).

[117] Dr. Langer points out that other macrolide antibiotics in oral dosage forms such as tablets and suspensions that could be administered without regard to meals were commercially available prior to the filing date of the ‘ 071 patent. He cites erythromycin ethylsuccinate suspensions and tablets and clarithromycin tablets (BIAXIN). Both were known not to have an adverse food effect. Langer concludes that these examples of drugs related to azithromycin would have led a person skilled in the art to consider performing routine testing on similar tablet formulations containing azithromycin. (Paragraphs 55-59). Langer’s evidence in this regard was supported by Dr. Dordick (at paragraph 46) and by excerpts from the 1990 and 1993 Physicians’ Desk Reference texts.

[118] In essence, Apotex’ argument on obviousness is that as of the priority date Pfizer had all of the information it required from the state of the art to conclude that if the capsules exhibited an adverse food effect, simply testing the tablets or suspension forms, which they had already produced, would demonstrate whether they too exhibited the same effect, a routine and non-inventive step. As Dr. Rapp conceded on cross-examination, the means or techniques to do this *in vivo* or *in vitro* were known as of April 1994.

[119] Pfizer says, on the other hand, that prior to the claimed invention, there existed a prejudice in the art with respect to the association of an adverse food effect with oral azithromycin dosage forms and teachings in the literature that would have dissuaded a person skilled in the art from testing non-capsule dosage forms of azithromycin for a lack of an adverse food effect.

[120] Pfizer, in effect, is asking the court to conclude that because it proceeded on the assumption, based on Dr. Hopkin’s 1991 study of the effects of its capsules, that all oral dosage forms of azithromycin would exhibit the same adverse food effect, that this reflects the state of the art prior to the testing it later conducted that demonstrated otherwise. In my view, that is not supported by the evidence.

Commercial Success

[121] As stated by the Federal Court of Appeal in *Diversified Products Corp v. Tye-sil Corp.*(1991), 35 C.P.R. (3d) 350 at 367-368, 125 N.R.218, evidence of commercial success in the introduction of a patented product is not to be disregarded but is not determinative of obviousness.

[122] Pfizer offered the evidence of Ms. Pesant who attested that ZITHROMAX 250 mg tablets are successful in the marketplace. Shortly after their introduction, Pfizer discontinued marketing the capsule version. Sales of the tablets have grown steadily. Ms. Pesant attaches a graph indicating the prescription sales of the capsules and tablets respectively between 1993 and 2003. Ms. Pesant acknowledges that part of the sales since the introduction of the tablets simply reflects substitution for the capsules but asserts that the tablet form has added to the market beyond the substitution effect. This assertion is based entirely upon Pfizer’s sales projections for the capsules and their conclusion that they have sold considerably more tablets than they had expected to do with the capsules.

[123] In response, Apotex has tendered the affidavit of Aslam H. Anis, Associate Professor of Health Economics in the Department of Health Care and Epidemiology at the University of British Columbia. Professor Anis claims expertise in all areas of the

pharmaceutical industry, especially in the interface between government regulation and corporate behaviour. He disagrees with Ms. Pesant's assertion that the ZITHROMAX tablets were a commercial success. Rather, he finds that there has been no more growth in the sale of tablets than would have been expected of capsule sales (had they not been phased out) based on data related to the previous sales for capsules.

[124] Pfizer argues that Apotex has not laid a proper foundation for the reception of Professor Anis' opinion evidence in that the reliability of the data he used to form that opinion, including drug store and hospital sales figures and the prices paid by government drug plans for azithromycin capsules and tablets, as hearsay, was not proven through admissible evidence in these proceedings. On cross-examination, Professor Anis indicated that this was the data he usually relied upon in his work and that he did logical checks to verify its consistency. However, he received the data employed for this analysis from Apotex counsel.

[125] It is well established in the jurisprudence that experts can rely upon hearsay information as background knowledge in forming their opinions. The fact that the opinion is based on information that is not before the court does not render the opinion inadmissible. The weight to be given to the opinion will however depend on the extent to which the facts upon which the opinion is based are proven. In the absence of proof of any of the underlying factual basis for the opinion, it is appropriate for a trier of fact to give no weight to the opinion: *R. v. Abbey*, [1982] 2 S.C.R. 24.

[126] Accordingly, I am unable to give any weight to Professor Anis' opinion notwithstanding that it appears to have been formed in an appropriately scientific manner.

[127] However, it is not clear to me that the commercial success described by Ms. Pesant should be accorded much weight in the determination of the question of obviousness. That success is based solely on Pfizer's own sales projections for the capsules and does not allow for other variables. The growing recognition of the value of azithromycin by clinicians and other factors may have accounted for the increased sales. I am not satisfied that Pfizer's sales projections on their own serve as an adequate basis for concluding that the discovery claimed in the '071 patent was the cause. Accordingly, while I have considered it, I give little weight to Ms. Pesant's evidence in this respect.

Conclusion on obviousness

[128] Pfizer does not dispute that azithromycin was a known drug, that there were known suspension and tablet dosage forms for it before 1994 and disintegrants that could be used in the tablet formulations. Despite all of that, its argument goes, there was a long-held sense of "resignation" that the drug, otherwise exceptionally useful, came with a known and accepted downside, namely the adverse food effect. No one solved the problem until the inventors added and advanced the state of the art with the '071 patent. There is no discussion in the literature that suggested that the tablets and other non-capsule dosage forms used with azithromycin earlier might not have a food effect.

[129] But was it open to others to experiment with and address the problem while the base patents, all of them held by Pfizer, were still active? While the *Patent Act* subsection 55(2) permits experimental use there has to be some incentive for conducting the research. The capsules came out in 1992, the '071 patent application was filed in 1994. There was not was not much time to conduct research on the food effect problem. In

those circumstances, I find it difficult to accept the argument that if it wasn't novel, why didn't someone else do it?

[130] It is clear from the evidence that some persons treating patients with azithromycin, including Dr. Rapp, acted inconsistently with the development of the art and continued to believe that there was a food effect with the tablets and the suspensions even after that had been shown to be wrong by Pfizer's scientists. Pfizer counsel describes this as a "prejudice" in the art in favour of the food effect. On the evidence as to how the literature was influenced by Pfizer's own information leaflets, that should be taken as no more than an indication that some persons skilled in the art did not question that information. It does not mean that an ordinary skilled technician, familiar with the art, would not be led directly to the invention.

[131] In my view, the test for obviousness does not exclude routine testing to determine the characteristics of known compounds. I conclude that testing the tablet and other non-capsule dosage forms to verify that they did not exhibit an adverse food effect was an entirely obvious and routine step for the unimaginative skilled drug formulator to take and did not constitute undue experimentation. The evidence of the applicant's subsequent commercial success with its 250 mg tablets does not convince me that the claimed invention was truly novel. Accordingly, I
am satisfied that the respondent has established on a balance of probabilities that the subject matter of the '071 patent was obvious and the patent is invalid for that reason.

Ambiguity

[132]

Subsection 27(4) of the *Patent Act* provides that patent specifications must end with a claim or claims defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed.

[133] Apotex alleges that the phrase in claim 23 "which does not exhibit an adverse food effect for administration in the treatment of an antimicrobial infection, to a patient that has eaten" is ambiguous because it can be read as meaning (a) that it is infringed only when a dosage form of azithromycin is administered without a food effect in a patient that has eaten or (b) that it is infringed by any dosage form of azithromycin. Apotex argues that the claim is thus ambiguous under the first interpretation as not being sufficiently explicit to inform the reader as to what is within and what is not within the claim, and in the second instance to claiming more than the alleged new use the inventor discovered for the known dosage form. Apotex relies on *Hoffman-LaRoche Ltd.v. Apotex Inc.*, (1989), 24 C.P.R. (3d) 289, 23 C.I.P.R. 1 (F.C.A.)in support of its ambiguity submissions.

[134] Pfizer contends that a claim is not ambiguous simply because one part of it is capable of more than one construction. But, in any event, the impugned phrase is not ambiguous as claim 23 would be infringed only when a dosage form of azithromycin, which does not exhibit a food effect, is administered to treat a microbial infection in a fed patient. A dosage form has no food effect if, when tested, it meets the minimum confidence levels discussed above. *Hoffman*, Pfizer says, doesn't assist Apotex as it dealt with a claim for a therapeutic composition. Here, claim 23 is for a new use of azithromycin.

[135] In *Hoffman, supra*, the questioned phrase was "effective in the treatment of smx-resistant bacterial infections". I think it is irrelevant that it was in a combination claim. The Court of Appeal found that the phrase could be read in at least two ways. One could read the words as limiting the scope of the claim to the combination when and only when it was effective in treating such infections. If read in that manner, it would be impossible to know whether use of the combination would infringe the claim until its effectiveness had been demonstrated. Alternatively, the phrase says that such a combination is effective for treating infections but does not restrict the claim to the combination when made or sold for that purpose. Thus it was held to be ambiguous and invalid for not being sufficiently explicit to inform the reader of what was within or not within the claim.
[136] In this case, claim 23 is limited to dosage forms that do not produce a food effect when azithromycin is administered to a fed patient for the treatment of an infection. But whether there is or is not a food effect can be determined through standard *in vivo* or *in vitro* testing of the dosage form. As the Apotex witnesses have stated, that would be standard preformulation work. I don't, therefore, find that claim 23 is ambiguous or invalid for insufficiency.

Overbreadth
[137] A claim will be considered overbroad and, therefore, invalid if it asserts an exclusive property or privilege in something the inventor did not actually invent, or, something the inventor claimed exceeding that which was disclosed in the patent: *Farbwerke Hoechst AG.v Canada (Commissioner of Patents)*, (1965, 50 C.P.R. 220 at 222, [1966] Ex. C.R. 91, aff'd (1966), 50 C.P.R. 220, [1966] S.C.R. 604.
[138] Apotex contends that claim 23 is broader than the invention disclosed which is limited by the restrictions set out in the patent disclosure. These include the use of disintegrants, the use of less than a taste-masking amount of an alkaline oxide, the exclusion of capsules and for suspensions, thickening agents and that it is limited to oral dosage forms. The claim itself does not include any of these restrictions. While the disclosure purports to invent a new use for azithromycin formulations that do not exhibit a food effect, the claim itself covers any formulation that does not have that effect. As conceded by Dr. Rapp on cross-examination (AR, pp. 1280, 1286), claim 23 would cover any and every formulation of an azithromycin tablet that does not exhibit a food effect. Further the claim is silent as to the ingredients that would be necessary for the dosage form and the processing details for making the dosage forms.
[139] Pfizer concedes that there are no restrictions in claim 23 on the type of oral dosage forms, excepting capsules, that could be used to treat a fed patient for a microbial infection with azithromycin. The applicant argues that to have any practical value, the patent has to cover every embodiment that can yield the desirable result, otherwise anyone could use the invention in the "unfenced" area and it would be as worthless as if invalid: *Burton Parsons Chemicals, Inc.v. Hewlett-Packard (Canada) Ltd.*, [1976] 1 S.C.R. 555, (1974) 17 C.P.R. (2d) 97.
[140] The patent states, at page 8, that in addition to azithromycin, a necessary ingredient of the tablets for the invention would be a disintegrant. This is to facilitate dissolution in the GI tract. Apotex argues that claim 23 covers any tablet form of

azithromycin, including those which can be made without a disintegrant. The claim is also silent as to whether the dosage form has to be oral or whether you can use a capsule.
[141] As I read the claim with the aid of the disclosure, it is clear that the dosage forms have to be oral and that capsules are excluded. Dr. Mayersohn was cross-examined on the statements in his affidavit that the nature of the dosage forms in claim 23 could not be determined or limited. He conceded that a food effect would be inconsistent with methods of administration other than oral dosage forms. As I have construed the patent, the purpose was to deal with the problem caused by capsules. It is conceivable that a capsule or tablet without a disintegrant could be developed that would have no food effect. Dr. Rapp suggested as much in his cross-examination.
[142] I acknowledge the force of the argument that claim 23 by purporting to assert a claim for all azithromycin dosage forms that do not exhibit a food effect is overreaching. But this is not such a case, in my view, to warrant invoking Justice Binnie's felicitous phrase from *Camco,*
supra about claiming anything that grows hair. I would not find the claim invalid solely by reason of overbreadth.

Improper Subject Matter

Method to Treat

[143] In Canada, as in other Commonwealth countries, methods of medical treatment have been held not to fall within the definition of "invention" in s. 2 of the *Patent Act*. The authority most frequently cited for that proposition is *Tennessee Eastman Co. et al v. Commissioner of Patents* [1974] S.C.R. 111, (1972), 8 C.P.R. (2nd) 202.
[144] Apotex submits that claim 23 simply amounts to a method for instructing doctors and pharmacists in how to treat patients with azithromycin and, is therefore, not patentable under the *Tennessee Eastman* principle. The rest of the components of the claim are old, namely the use of azithromycin in the treatment of microbial infections and the formation of azithromycin in various dosage forms.
[145] Pfizer counsel submits that the conclusion reached in *Tennessee Eastman* stemmed from a repealed provision of the *Patent Act*. Subsection 41(1) of the *Act* as it read in 1972 provided that a substance intended for food or medicine could not be claimed except as part of a product by process claim. With the repeal of that provision, it should be an open question as to whether the method of treatment exception should remain. In any event, Pfizer submits, the recent jurisprudence is clear that a new use for an old drug is patentable: *Apotex Inc.v. Wellcome Foundation Ltd.*,[2001] 1F.C. 495, (2000) 10 C.P.R. (4th) 65 (F.C.A.) aff'd [2002] 4 S.C.R. 153, [2002] SCC 77.

[146] Apotex points to decisions in the United Kingdom and Australia which dealt with changes to the dosing regimes of known drugs. In a case dealing with the drug taxol, the U.K. Court of Appeal held unpatentable the discovery that a three hour infusion produced the same treatment results with less neutropenia as a 24 hour infusion: *Bristol-Myers Squibb Co.v. Baker Norton Pharmaceuticals Inc.*, [1999] R.P.C. 253 at paragraphs 43-44 [*Bristol-Myers*].
[147] With respect to the drug alendronate, used to treat osteoporosis, 10 mg was prescribed on a daily basis under strict dosing instructions that were difficult to comply with, particularly for the elderly. The daily regime caused significant gastro-intestinal

side effects in some patients. It was discovered that these effects could be significantly reduced and the therapeutic value maintained by a once weekly administration of 70 mg. The Court of Appeal, substituting the word alendronate for that of taxol in its analysis, reached the same conclusion that it had in *Bristol-Myers*, as did also the Australian Federal Court of Appeal: *Instituto Gentili SpA.v. Teva Pharmaceutical Industries Ltd.*, [2003] All E.R. 62 at para.59 (F.C.A.); *Arrow Pharmaceuticals Ltd., v. Merck & Co.,Inc* . [2004] F.C.A. 1282 at paras.80-97 (Austl.).

[148] In *Merck & Co. Inc.v. Apotex Inc.*, (2005) 41 C.P.R. (4th) 35, 2005 FC 755, I declined to find that the Canadian patent for a weekly dose of alendronate was invalid as a method of treatment on the ground that patents are taken out of the reach of *Tennessee Eastman* as long as the claims are distinguishable from the work of a physician which requires the exercise of specialized skill.

[149] As I read claim 23, it merely instructs physicians and pharmacists that the azithromycin tablets can be administered to treat microbial infections without concern as to the patient's fed or fasted state. It doesn't instruct them on how to treat the patient. Accordingly, I see no reason to find that it is invalid on the *Tennessee Eastman* principle.

Mere Discovery

[150] Apotex submits that the purported inventors of the '071 patent merely disclosed the inherent characteristics of fully disclosed prior art tablets and suspension formulations, a non- inventive discovery. The respondent argues that if the discovery was inevitable by following the instructions in the prior art then it does not matter whether it would have been realized by the skilled reader of the prior art.

[151] Pfizer argues that this is simply an attempt to argue obviousness twice. This case is not simply about a tablet claim. It is a new use for azithromycin. It can now be used to treat patients that formerly would have been told they could not take it unless they fasted. Finding a new use
for a known compound is inventive and patentable as a "new and useful art": *Apotex Inc.v. Wellcome Foundation Ltd.*, [2001] 1 F.C. 495 at paras. 64-65, (2000) 10 C.P.R. (4th) 65 (F.C.A.); *Shell Oil Co. v. (Canada)Commissioner of Patents*, [1982] 2 S.C.R. 536 at 548-9 [*Shell Oil*].

[152] Apotex cites *Sharpe & Dohme Inc.v. Boots Pure Drug Co.Ltd*, (1928), 45 R.P.C. 153 at 191-192 (C.A.) in which it was held by the English Court of Appeal that the ascertainment of the valuable properties of certain alkyd chemicals, while important as a useful development in itself, was not a patentable invention but at most verification. Pfizer relies on *Shell Oil., supra* where it was concluded that a new use for an old compound is patentable subject matter.

[153] In *Riello Canada Inc. v. Lambert* (1986), 9 C.P.R. (3d) 324, 8 C.I.P.R. 286 (F.C.T.D.) at 335, Justice Strayer quoted a statement of Lord Buckley in *Reynolds v.Herbert Smith & Co.,Ltd.*(1902), 20 R.P.C. 123 (Ch.D) as the classic distinction between a "discovery" and an "invention":

> Discovery adds to human knowledge, but does so only by lifting the veil and disclosing something which before had been unseen or dimly seen. Invention also adds to human knowledge but not merely by disclosing something. Invention necessarily involves the suggestion of an act to be done, and it must be an act which results in a new product or a new result or a new process or a new combination for producing an old product or an old result.

[154] Here the use is the same. The only difference lies in the condition of the patient who receives the treatment. The evidence does not indicate that food effect was a major problem. At best, there was some inconvenience in avoiding taking the capsules one hour before or two hours after eating. This is not a problem that had waited solution for many years.
[155] In *Bristol-Myers, supra* at paragraph 59, the U.K. Court of Appeal, dealing with the discovery that the three hour taxol infusion would be just as effective as the 24 with less ill effects, stated "this is not a case of second medical use at all.The use is the same. All you have new in the patent is more information about that use."
[156] In my view, the '071 patent is not a case of a new medical use for azithromycin. The use, treatment of a microbial infection remains the same. The dosage forms were known. The therapeutically effective amount of the drug required is the same. The bio-availability of the drug is maintained. All that is new is that it was found that the drug can be taken after eating in tablet or suspension form without adverse effect. That is not a new result, a new product or a new process but a mere discovery of the existing properties of the drug in a different dosage form.

Infringement
[157] As I have found that the '071 patent is invalid as obvious and a mere discovery, it follows that the Apotex product, 250 mg tablets of azithromycin isopropanolate monohydrate, will not infringe.
[158] In the event that I am found to have erred in those conclusions, I will comment briefly on the infringement issues.

Gillette Defence
[159] A Gillette defence as recognized by the House of Lords in *Gillette Safety Razor, supra*, is available when the product alleged to infringe the patent in question is made in accordance with the prior art. If the product infringes the patent as written, then the patent must have been anticipated by the prior art, and is consequently invalid. Apotex' assertion of the defence is based on the claim that it's formulation is the tablet preparation described in Example 4 of the '531 patent.
[160] Pfizer does not question that the Apotex tablet will be formulated as disclosed in the prior art. However, it argues that the *Gillette* defence is irrelevant as the invention in claim 23 is the new *use* of azithromycin to treat a patient who has eaten, not to a tablet formulation in the abstract. As indicated above, I do not accept that construction of claim 23.
[161] Both Pfizer experts, Drs Rapp and Andriole, described claim 23 of the '071 patent as a claim for the use of azithromycin in the preparation of a pharmaceutical formulation that does not exhibit a food effect (Andriole affidavit para. 47, AR p.968; Rapp Affidavit, para.61, AR.pp.51-52). That accords with how I have construed the claim. Accordingly, I would find that as the Apotex formulation falls within the prior art - the '531 patent - that formulation would not infringe claim 23 of the '071 patent or the latter is invalid for claiming the prior art.

No direct or indirect infringement

[162] Apotex says that its product, Apo-azithromycin, will not directly or indirectly infringe the claims of the ‘071 patent. With respect to direct infringement, if claim 23 is as Pfizer contends, a use to treat claim, as a corporation that neither prescribes nor dispenses, Apotex can never directly infringe the patent. Moreover, the tablets will not be specifically identified as intended for administration to a patient who has eaten. The product monograph issued with its NOC will not stipulate that the tablets will be ingested after the patient has eaten, subject to the patent found to be valid. In any event, Apotex says, there is no evidence that its tablets if given to fed patients will not exhibit a food effect. The only testing of its product in the record is the bioequivalence testing which was done in the fasted state. Thus there is no evidence before the court that approval of its version of azithromycin will result in direct infringement of the ‘071 patent.

[163] Pfizer has not directly addressed the direct infringement question but contends that indirect infringement is inevitable. As the Apotex product will be bioequivalent to ZITHROMAX, the undertaking or product monograph will not prevent physicians from prescribing and pharmacists from dispensing Apotex’ azithromycin product for use in patients who have eaten.

[164] In support of the infringement claim, Pfizer offered the evidence of Mr. Spiridon Goussios a licensed pharmacist and Dr. Frank Martino, a family physician, obstetrician, and emergency practitioner, both currently practising in Ontario.

[165] Dr. Martino attested that he frequently prescribes ZITHROMAX, but states that he would readily prescribe a generic equivalent. If the product monograph did not provide directions with respect to food, he would believe that the drug could be taken with food. He could not, of course, speak for all doctors, had not read Apotex’ product monograph, was unfamiliar with the regulatory regime for new drug submissions and conceded on cross-examination that differences in the tablet formulations could have significant effects on how the tablets would function in the presence of food. Ultimately, he agreed with the suggestion put to him on cross that if he was unsure about a generic’s properties, he would not write a prescription for the generic or allow substitution by the pharmacist.

[166] Mr. Goussios attests that Apotex ’s assurance that it will not market its azithromycin specifically for patients who have eaten is a hollow one in light of the practice of pharmacists. The absence of instructions would lead a pharmacist to either assume that there is no food-drug interaction, or turn to the *Compendium of Pharmaceuticals and Specialties* entry for ZITHROMAX. Dr. Goussios was cross-examined on his affidavit in the course of which he acknowledged that if Apotex’s product was approved only for certain uses, he would likely be made aware of that and would not dispense it for unapproved uses.

[167] To successfully prosecute a prohibition application under the Regulations in relation to a "use" patent where indirect infringement is alleged, the patentee would have to prove that third parties would, in fact, use the second person’s product for a claimed use in the first person’s patent, *and* that the second person had actively induced or encouraged such use: *AB Hassle Inc.v.Canada (Minister of National Health and Welfare)* (2002), 22 C.P.R. (4th) 1 at paras. 47-59, 2002 FCA 421. To induce or procure another to infringe a patent, something active must be done. Mere passivity is not sufficient: *Beloit, supra* at 46-47.

[168] There is no evidence on the record that Apotex has or will actively encourage third parties to infringe Pfizer's patent, if it were held to be valid, and assuming Apotex were to be granted a notice of compliance to market its product with the stipulated monograph. One cannot assume that responsible physicians and pharmacists will prescribe or dispense a drug for administration to patients in a fed state if it is not indicated for that use. Therefore, despite my suspicion that there is an air of unreality to Apotex' position, I cannot find that Pfizer has satisfied its burden to establish on a balance of probability that the respondent's intention to sell Apo-azithromycin will infringe the applicant's patent, and must conclude that the allegation of non-infringement is justified.

Eligibility for Listing on the Patent Register

[169] Apotex contends that the '071 patent is improperly listed against 250 mg azithromycin tablets on the Patent Register because the listing was made outside the time requirements of the Regulations and was not relevant to the submissions with which it was listed. Pfizer suggests that, if there is a legitimate concern about the listing, the proper time for bringing it before the court would have been my way of a preliminary motion under subsection 6(5) of the Regulations.

[170] Section 3 of the *Regulations* requires the Minister to maintain a register of patents for drugs containing medicine in respect of which a NOC has been issued. Subsection 4(3) and (4)
govern the timing of listing patents on the registry:

PATENT LIST	LISTE DE BREVETS
4. (1) A person who files or has filed a submission for, or has been issued, a notice of compliance in respect of a drug that contains a medicine may submit to the Minister a patent list certified in accordance with subsection (7) in respect of the drug.... (3) Subject to subsection (4), a person who submits a patent list must do so at the time the person files a submission for a notice of compliance. (4) A first person may, after the date of filing of a submission for a notice of compliance and within 30 days after the issuance of a patent that was issued on the basis of an application that has a filing date that precedes the date of filing of the submission, submit a patent list, or an amendment to an existing patent list...	4. (1) La personne qui dépose ou a déposé une demande d'avis de conformité pour une drogue contenant un médicament ou qui a obtenu un tel avis peut soumettre au ministre une liste de brevets à l'égard de la drogue, accompagnée de l'attestation visée au paragraphe (7).... (3) Sous réserve du paragraphe (4), la personne qui soumet une liste de brevets doit le faire au moment du dé pôt de la demande d'avis de conformité. (4) La première personne peut, après la date de dépôt de la demande d'avis de conformité et dans les 30 jours suivant la délivrance d'un brevet qui est fondée sur une demande de brevet don't la date de dépôt est ant érieure à celle de la demande d'avis de conformité, soumettre une liste de brevets, ou toute modification apportée à une liste de brevets,.....

[171] This issue arises because the original new drug submission for Pfizer's 250 mg tablets was filed on or about September 15, 1994 (the notice of compliance was issued on February 21, 1996) but the '071 patent did not issue until October 17, 2000. The 1994 submission was for a five day dosing regime in which 500 mg were taken the first day, comprised of two 250 mg tablets, followed by 250 mg on the second, third, fourth and fifth days. Pfizer subsequently filed a submission for a supplemental NOC in respect of a 500 mg tablet and an accelerated dosage regimen for azithromycin in adults which

provides for daily dosing of 500 mg per day for 3 days. The supplemental NOC was granted on August 5, 2003. On August 13, 2003, the ‘071 patent was listed on the patent register in connection with both the 250 and 500 mg tablets.

[172] Thus, Apotex argues, the ‘071 patent was improperly listed on the register in connection with the 250 mg tablets, because by August 13, 2003, it was out of time. Pfizer should have taken steps to list the patent within 30 days of its issuance in October, 2000. Since the supplemental NOC was not for the 250 mg tablets, but for the 500 mg tablet and the accelerated dosing regime, the ‘071 patent could not be properly listed as part of that submission. This case, Apotex submits, is on all fours with the decision of Justice Huguessen in *Novopharm Ltd.,v.Canada* (1998), 78 C.P.R.(3d) 54 (F.C.T.D.)

[173] Clearly, the 500 mg tablet could be used for either the original dosing regime, as one tablet on the first day instead of two, or for each day of the new three day regime. How does that justify listing the ‘071 patent with respect to the 250 mg tablets so long out of time? It is not clear to me that there was any justification for what appears to have been done. In response to written interrogatories, Ms. Pesant, Pfizer’s employee responded that the 250 mg tablets were listed with respect to the new three day treatment. But those tablets had been approved long before and were not part of the new drug submission. In response to a further question, Pfizer refused to provide the product monograph that existed prior to the August 30, 2001 submission which might have helped to resolve the question.

[174] Should Apotex be allowed to raise this issue at this stage of the PM(NOC) proceedings?

[175] Subsection 6(5) of the Regulations provides that the NOC process may include a motion for dismissal of a Notice of Application under section 6(1) if the patents in question were not eligible for inclusion on the patent register. This allows the respondent to a Notice of Application under 6(1) to apply for a procedural remedy similar to striking out pleadings in appropriate circumstances: *Proctor & Gamble Pharmaceuticals v. Minister of Health* (2003) 26 C.P.R. (4th)180 at para14.

[176] The primary purpose of striking out pleadings under rule 221 of the *Federal Court Rules, 1998* (and similar remedies, such as summary judgment under rule 213) is to prevent the waste of time and resources by the litigants and the courts. Where the process can be streamlined, it should be and these steps should be taken as early as possible. I note that under rule 213 a motion for summary judgment is not available after a trial date has been fixed and that a motion to strike will not be considered if a party unduly delays in bringing its motion: *Radil Bros. Fishing Co. v. Canada (Minister of Fisheries and Oceans)* (2003), 230 F.T.R. 228, 2003 FCT 79..

[177] At any time prior to the hearing of this application, Apotex could have brought a motion under 6(5)(a). Apotex argues, however, that it would have been imprudent to do so and would have likely wasted time and resources because of the high standard required to strike out an application; that the listing was so plainly improper to be bereft of any chance of success : *David Bull Laboratories (Canada) Inc. v. Pharmacia Inc. et al.*, [1995] 1 F.C. 588, 58 C.P.R. (3d) 209 (C.A.). If they can bring it at this stage, they also enjoy the tactical advantage that the burden to disprove the allegations rests with the applicants whereas Apotex would have carried the burden on a preliminary motion to dismiss.

[178] I accept that Apotex can make its allegation as part of these proceedings and is not required to bring a motion under subsection 6(5) in advance of the hearing of the 6(1) application. I am also satisfied that Pfizer has failed to establish on a balance of probabilities that the ‘071 patent was properly listed on the patent register as it was out of time when the NOC for the accelerated dosing regime for the 500 mg tablets was issued.

Conclusion

[179] For the foregoing reasons, I am satisfied that the ‘071 patent is invalid for obviousness and for claiming a mere discovery. I am also satisfied that the Apotex apo-azithromycin product will not infringe. Accordingly, Pfizer has not discharged its burden to establish that the allegations of invalidity and infringement are not justified and this application will be dismissed.

COSTS

[180] The parties agree that there is no reason to deviate from the normal scale of costs in Column III. They ask and I agree that allowance should be made for second counsel at the hearing. The Minister of Health made no representations in these proceedings. Accordingly, there is no order in respect of costs made in the Minister’s favour.

ORDER

THIS COURT ORDERS that the application is dismissed with costs to the respondent in the normal scale with allowance for second counsel at the hearing.

" Richard G. Mosley "
Judge

ANNEX "A"

The Claims

1. An oral dosage of azithromycin in the form of a tablet made by wet granulation and administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant and which exhibits substantially no adverse food effect, the dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37^{o}C, with paddles turning at 100 rpm, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

2. A dosage form as defined in claim 1, wherein the mammal is a human.

3. An oral dosage form of azithromycin in the form of a powder for oral suspension and administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents and an anhydrous buffer and which exhibits substantially no adverse food effect, the dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37^{o}C, with paddles turning at 100 rpm, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

4. A dosage form as defined in claim 3, wherein the mammal is a human.

5. A dosage form as defined in claim 4, in the form of a suspension made from the powder.

6. An oral dosage form of azithromycin in the form of a unit dose packet and administrable to a mammal that has eaten, which comprises azithromycin and a dispersing agent and which exhibits substantially no adverse food effect, the dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as

the following: 900 ml sodium phosphate buffer, pH 6.0, 37^{o}C, with paddles turning a 100 rpm, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

7. A dosage form as defined in claim 6, wherein the mammal is a human.

8. A dosage form as defined in claim 7, in the form of a suspension made from the unit dose packet.

9. An oral dosage form of azithromycin in the form of a tablet made by wet granulation and administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant and which exhibits substantially no adverse food effect, the dosage form exhibiting a value of (AUC_{fed})/AUC_{fst}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

10. A dosage form as defined in claim 9, wherein the mammal is a human.

11. An oral dosage form of azithromycin in the form of a powder for oral suspension and administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents and an anhydrous buffer and which exhibits substantially no adverse food effect, the dosage form exhibiting a value of (AUC_{fed})/AUC_{fst}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

12. A dosage form as defined in claim 11, wherein the mammal is a human.

13. A dosage form as defined in claim 12, in the form of a suspension made from the powder.

14. An oral dosage form of azithromycin in the form of a unit dose packet and administrable to a mammal that has eaten, which comprises azithromycin and a dispersing agent and which exhibits substantially no adverse food effect, the dosage form exhibiting a value of (AUC_{fed})/AUC_{fst}) of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided

that the dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

15. A dosage form as defined in claim 14, wherein the mammal is a human.

16. A dosage form as defined in claim 15, in the form of a suspension made from the unit dose packet.

17. A therapeutic package, comprising a container, an oral dosage form of azithromycin which is defined in any one of claims 1 to 16 contained therein, and, associated with the package, written matter non-limited as to whether the dosage form can be taken with or without food.

18. A therapeutic package as defined in claim 17, wherein the dosage form is in the form of a tablet.

19. A therapeutic package as defined in claim 17, wherein the dosage form is in the form of a powder for oral suspension.

20. A therapeutic package as defined in claim 19, wherein the dosage form is in the form of a suspension made from the powder.

21. A therapeutic package as defined in claim 17, wherein the dosage form is in the form of a unit dose packet.

22. A therapeutic package as defined in claim 21, wherein the dosage form is in the form of a suspension made from the unit dose packet.

23. Use of a therapeutically effective amount of azithromycin for the preparation of a pharmaceutical dosage form which does not exhibit an adverse food effect for administration, in the treatment of an antimicrobial infection, to a patient that has eaten.

24. A tablet of azithromycin for administration to a human patient that has or has not eaten food, which comprises:

azithromycin in an amount of from 25 mg to 3 g,

a disintegrant in an amount of from 1 to 25% by weight

based on the total tablet, and

at least one pharmaceutically acceptable excipient, provided that the tablet contains

no or less than a taste-masking amount of an alkaline earth metal oxide or hydroxide,

wherein the tablet exhibits substantially no adverse food effect and exhibits a value of $(AUC_{fed})/AUC_{fst}$ of 0.80 to 1.25 with a lower 90% confidence limit of 0.75 to 1.40 and is made by wet granulation.

25. A tablet as defined in claim 24, which contains at least one member selected from the group consisting of sodium croscarmellose, sodium starch glycolate, microcrystalline cellulose and cross-linked polyvinylpyrrolidone in an amount of 3 to 15% by weight based on the total weight of the tablet as the disintegrant.

26. A tablet as defined in claim 25, which contains sodium croscarmellose and pregelatinized starch as the disintegrants.

27. A tablet as defined in any one of claims 22 to 26, which is coated with a film of hydroxypropylmethylcellulose, hydroxypropylcellulose or acrylate-methacrylate copolymer.

28. A therapeutic package for commercial sale, comprising a container, the tablet as defined in any one of claims 24 to 27, contained therein, and, associated with the package, a written message that the tablet can be taken with or without food.

29. A non-caking free-flowing powder of azithromycin adapted to be made up by a pharmacist into an oral suspension which is to be administered to a human patient that has or has not eaten food, wherein the powder comprises an antimicrobial effective amount of azithromycin, at least one thickening agent in an amount of 0.1 to 2% and in anhydrous buffer or pH-alterning agent for providing a pH of approximately 10 in the suspension in an amount of 0.1 to 2.5%, all by weight based on the total weight of the powder, and wherein the powder contains no or less than a taste-masking amount of an alkaline earth metal oxide or hydroxide and exhibits substantially no adverse food effect and exhibits a value of $(AUC_{fed})/AUC_{fst})$ of 0.80 to 1.25 with a lower 90% confidence limit of 0.75 to 1.40.

30. A powder as defined in claim 29, wherein the thickening agent is at least one member selected from the group consisting of xanthan gum, guar gum, locust bean gum, gum tragacanth, sodium carboxymethylcellulose, polyvinylpyrrolidone and hydroxypropylcellulose.

31. A powder as defined in claim 30, which contains colloidal silicon dioxide as a dispersing agent in an amount of 0.2 to 2.0% by weight based on the total weight of the powder.

32. A unit dosage packet or sachet containing therein the powder as defined in claim 29, 30 or 31 and being designed to be emptied into water or a natural or artificial fruit beverage to constitute the oral suspension.

33. A therapeutic package for commercial sale, comprising a container, the packet or sachet as defined in claim 32 contained therein and, associated with the package, a written message that the suspension can be taken with or without food.

FEDERAL COURT

SOLICITORS OF RECORD

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and
THE MINISTER OF HEALTH and APOTEX INC.

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