Date: 20081211

Docket: T-135-07

Citation: 2008 FC 1359

BETWEEN:

ABBOTT LABORATORIES and
ABBOTT LABORATORIES LIMITED

Applicants

and

THE MINISTER OF HEALTH and
SANDOZ CANADA INC.

Respondents

PUBLIC REASONS FOR ORDER AND JUDGMENT
(Confidential Reasons for Order and Judgment issued December 8, 2008)

HUGHES J.:

[1] This is an application made by Abbott Laboratories and Abbott Laboratories Limited (collectively Abbott) under the provisions of section 6 of the *Patented Medicines (Notice of Compliance Regulations*), SOR 93-133 as amended (*PMNOC Regulations)* to prohibit the Respondent Minister of Health from issuing a Notice of Compliance to the Respondent Sandoz Canada Inc. until the expiry of Canadian Letters Patent Number 2,386,527 ('527). For the reasons that follow, I find that the allegations as to invalidity are justified and that the allegations as to non-infringement are not justified. The application is dismissed with costs to Sandoz.

THE PARTIES AND PROCEEDINGS

[2] The Applicant Abbott Laboratories owns the ’527 patent and can be referred to as the patentee. The other Applicant Abbott Laboratories Limited is a Canadian subsidiary of Abbott Laboratories and has regulatory approval (NOC) from the Minister of Health to sell in Canada a drug containing clarithromycin as an antibiotic which it does under the name BIAXIN XL. The two companies are referred to as “first parties” in the *PMNOC Regulations*.

[3] The Respondent, Minister of Health is charged with certain duties under the *PMNOC Regulations* and the *Food and Drug Act*, R.S.C. 1985, c. F-27 as amended and its *Regulations* including the issuances of Notices of Compliance (NOC) to those applying to the Minister for approval to sell certain drugs in Canada. The Minister was not represented at the hearing of this proceeding.

[4] The other Respondent Sandoz Canada Inc. is what is commonly called a “generic” drug company and is referred to as a “second person” in the *PMNOC Regulations*. Sandoz applied to the Minister for an NOC to sell a drug product containing clarithromycin in Canada using an Abbreviated New Drug Submission (ANDS) which meant that it simply referenced the previous NOC granted to Abbott thereby limiting greatly the amount of testing and technical date that it was required to submit. On the other hand, Sandoz was required to engage the *PMNOC Regulations* under which Abbott had listed a number of patents including the ’527 patent.

[5] In accordance with the *PMNOC Regulations*, Sandoz served on Abbott on or about December 8, 2006 a Notice of Allegation, alleging, among other things, that claim 5 of the '527 patent was invalid for a number of reasons and that the claim would not be infringed by Sandoz. Abbott instituted this present proceeding by filing a Notice of Application on January 22, 2007, in which it requested that the Minister be prohibited from issuing an NOC to Sandoz until the expiry of the '527 patent.

MOTION TO STRIKE

[6] Just a few days before the hearing of this proceeding was scheduled to begin, the Applicants filed a motion to strike certain portions of Sandoz's Memorandum of Fact and Law and for an order prohibiting Sandoz from relying on prior art references other than what were identified as documents 62 and 65, or "evidence relating thereto" in support of its allegations that claim 5 of the '527 Patent was invalid for obviousness and for anticipation. The motion was to be heard at the opening of the hearing.

[7] The basis for the Applicants' motion was that in Sandoz's Notice of Allegation it placed specific reliance only on documents identified as 62 and 65 when alleging invalidity of claim 5 thus, the Applicants assert, Sandoz cannot go beyond reliance upon those two documents in supporting its allegation in evidence and in argument. Reliance is placed on decisions such as *ABHassle v. Canada (MNR)* (2000), 7 C.P.R. (4th) 272, [2000] F.C.J. No. 855 (FCA) at paragraph 17 where the Federal Court of Appeal said: "*...the detailed statement must be such as to make the patentee fully aware of the grounds...*"

[8] Sandoz argues that the Applicants were fully aware of the grounds, they received Sandoz evidence without complaint or moving to strike, the Applicants cross-examined upon that evidence without complaint, the Applicants led evidence of their own on the matters addressed by Sandoz in its evidence without complaint. The written argument of the Applicants addresses the evidence and argument of Sandoz.

[9] When asked the Applicants why they waited so long to bring this motion and why no earlier objection had been raised, Applicants' counsel could only point to the Reasons of the Federal Court of Appeal in *Aventis Pharma Inc. v. Mayne Pharma (Canada) Inc.* (2005), 38 C.P.R. (4th) 1, 2005 FCA 50, at paragraph 16 where that Court said that such motions should preferably be brought before the hearing judge, but added that it was not wrong for a motions judge to deal with the matter. It said at paragraph 16:

> ***16*** *Although this Court has stated in unequivocal terms that this type of motion should preferably be deferred to the hearing judge, it has not held, as a matter of principle, that Motions Judges must defer such motions to the hearing judge. Thus, a Motions Judge will not be found to have erred in law if he or she decides to deal with the motion. Whether or not, in a given case, the Motions Judge has made a reviewable error will be dealt with on the basis of the applicable standard of review. I should add that this Court has also made it clear that it will rarely interfere with a Motions Judge's decision to defer the matter to the hearing judge.*

[10] This decision does not say that a party must wait to bring a motion such as this before the hearing judge at the outset of the hearing. In fact in the present case the parties were aware for several weeks that I would be the hearing judge yet there was no suggestion that such a motion would be brought.

[11] The Applicants were fully aware of the case they had to meet and did meet that case by cross-examination, by their own evidence and in argument. The merits of the motion, if any, rest only on slender technical grounds. Sandoz has not relied upon documents beyond those listed in its Notice of Allegation where the nature of the attacks on validity of claim 5 was set out. While specific reliance was placed on two documents in the Notice of Allegation, the other prior art was also listed. If the Applicants had felt surprised or disadvantaged the time to object and make a motion was upon receipt of Sandoz evidence, and not to raise the matter a few days before the trial when it is clear that the Applicants were fully prepared on the evidence and in argument to meet the challenge.

[12] The motion was dismissed at the hearing.

WITNESSES AND EVIDENCE

[13] The evidence in this proceeding was, as is usual, provided by way of affidavits and cross-examination transcripts. Since the scope of this proceeding was reduced from the consideration of several claims of several patents to just one claim of one patent, claim 5 of the ’527 patent, the parties, following a request from the Court, filed an amended Record containing only the evidence said to be pertinent to that claim of that patent. As a result the evidence of record includes evidence from the following :

1. For the Applicants Abbott:

    a. Affidavit of Sonia Atwell, a law clerk employed by Abbott’s solicitors which exhibited, among other matters, the patent at issue, the Notice of Allegation, certain

Orders and correspondence. She also testified that Abbott Canada makes tablets known as BIAXIN XL containing clarithromycin as the active ingredient pursuant to a Notice of Compliance granted by the Minister. That notice is not in evidence however it is common ground between the parties that the Notice does not specify any particular crystalline form of clarithromycin.

Atwell was not cross-examined.

b. Affidavit of Dr. Jerry Atwood a professor of chemistry at the University of Missouri-Columbia. He claimed expertise in crystal growth, crystal engineering, X-ray crystalography and polymer chemistry. No serious challenge to his expertise was raised.

Dr. Atwood was cross-examined.

c. Dr. Stephen R. Byrn, a professor of medicinal chemistry at Purdue University, Indiana. He claims expertise in solid-state chemistry including polymorphism. His expertise was not seriously challenged.

Dr. Byrn was cross-examined.

d. Loretta Del Bosco who is employed by Abbott Canada as Director of Regulatory Affairs and Quality Assurance. She does not claim to be an expert.

She was cross-examined.

2. For the Respondent Sandoz:

    a. Dr. Craig Eckhardt a professor of Chemistry at the University of Nebraska at Lincoln. He claims expertise in crystals and polymorphs. His expertise was not seriously challenged.

        Dr. Eckhardt was cross-examined.

    b. Dr. Edward Lee-Ruff a Professor of Chemistry at York University, Toronto. He claims expertise in synthetic and mechanistic organic chemistry. His expertise was not seriously challenged.

        Dr. Lee-Ruff was cross-examined.

    c. Dr. Sohrab Rohani a Professor of Chemical and Biochemical Engineering at the University of Western Ontario, London. He claims expertise in the areas of crystallization, crystallization processes, solid state chemistry and polymorphism. His expertise was not seriously challenged.

        Dr. Rohani was cross-examined.

    d. Dr. Martyn Brown a PhD. chemist claiming experience in crystallization. His expertise was not seriously challenged. He performed experiments said to be designed to emulate certain prior art.

        Dr. Brown was cross-examined.

e. Dr. Srebai Petrov a research associate at the Department of Chemistry, University of Toronto claiming considerable experience in analytical methods for studying crystalline substances. His experience was not seriously challenged. He analyzed samples prepared by Dr. Brown.

Dr. Petrov was cross-examined.

f. Pamela Christoforakis, a law clerk with Sandoz's firm of solicitors. She attaches as exhibits copies of the Notice of Allegation and of the prior art referred to in that Notice. She was not cross-examined. No challenge was raised in respect of any of the copies of the prior art documents or the Notice.

[14] Certain portions of the evidence, largely that directed to the processes used to manufacture the Sandoz and Abbott products, were claimed as confidential and, pursuant to an Order of this Court dated March 8, 2007, such documents and evidence relating thereto has been filed with this Court as confidential. Counsel for the parties have endeavoured to restrict their claims to confidentiality to only those documents and materials dealing with processes for producing their versions of clarithromycin.

[15] A consent Order of this Court was issued on April 25, 2007, wherein Sandoz was required to disclose to Abbott certain information, including information that Sandoz provided to the Minister in respect of its product. Included were such documents as would be contained in what is called a Drug Master File (DMF) and samples of any product as supplied to the Minister. Sandoz complied with this Order, no samples were provided since none had been provided to the Minister.

ISSUES

[16] The parties have restricted themselves to issues involving claim 5 of the ’527 patent only. Those issues are:

1. Construction of the claim.

2. Are the following allegations as to invalidity justified:

    a. Anticipation;

    b. Obviousness?

3. Are the allegations as to non-infringement justified?

[17] Before addressing these issues it will be useful to provide a brief scientific background drawn from the non-controversial evidence of the experts and exhibits provided by them.

SCIENTIFIC BACKGROUND

[18] The scientific background has to do with solid state chemistry and, as the ’527 patent says in its opening words at page 1, crystal forms of chemical compounds.

[19] Chemical compounds for use as pharmaceuticals generally must be in solution, that is, dissolved in some liquid for administration as a liquid or intravenously or by becoming liquid such as when a tablet or pellet in a capsule dissolves in the fluids of the stomach or intestine. Once dissolved the chemical has no particular structure, it is a molecule to be found together with other molecules in the liquid environment.

[20] In solid form, such as in a tablet or pellet, before swallowed the pharmaceutical may, depending on a variety of factors assume various forms or no form at all. An amorphous form means that there is no particular regular form assumed by the material. A crystalline form means that the molecules are in a regular ordered arrangement in a lattice or three dimensional patterns. The same molecule may assume a variety of crystalline forms depending on a variety of factors such as the nature of the molecule, how the substance was prepared, stored or handled and, if prepared by drying, the heat, pressure and time of drying among other matters. A polymorph is a molecular material that can crystallize in a variety of different forms.

[21] As to crystals in particular, it is known that the same molecule can exhibit different properties when it assumes different crystal structures, coal, graphite and diamonds, all of which are carbon crystals are used as common examples of these differing properties.

[22] Identification of a particular crystal structure can rarely be done by eye or touch. Instead a variety of testing techniques are commonly used. Three common techniques are powder x-ray diffraction (PXRD), infra-red (IR) and differential scanning calorimetry (DSC). Each technique produces graphical data which can be read and analyzed by persons skilled in the art. Important identifying features in the graph are noted in respect of samples tested and compared with known graphical features for known crystal forms of the molecule. If they match, then skilled persons recognize the sample as being a known crystal form. If they do not match, then probably a hitherto unknown or previously unidentified form may be present. There is no standard protocol for naming known forms of a crystal structure or new ones as they become identified. Often the first form of a particular molecule to become identified is simply called Form I, the next Form II and so forth. The

Forms are related to the identifying characteristics observed from graphs produced by tests such as PXRD or IR or DSC.

[23] In performing a test known as PXRD the sample being tested is prepared in powder form and spread on a flat surface. X-Rays are impringed on the sample in the shape of a cone emanating from the outlet of the X-Ray which is essentially a point. The angle of the outside of the cone measured against the direction in which the x-rays are emanated is called two theta (2 θ). A graph of the scatter of the x-ray beams bouncing off the sample is produced which shows various peaks corresponding to particular ways that the x-rays are scattered. Those peaks vary in intensity depending on how much of the material being studied is present in the sample. Sometimes, the sample tested includes a variety of materials in which case the peaks created by one material may be masked by peaks created by another material. A skilled person will read the graph or, nowadays, a computer may be used, and the important peaks identified. A particular crystal form of a material may be identified by the peaks created by the PXRD technique. Thus it is common scientific language to say something like Form III of chemical x is identified using PXRD with 2 θ values of (say) 2.2, 4.3, 7.8, 9.2 and 15.7. Another sample tested the same way which exhibits the same peaks is said to be Form III also.

[24] In the present case we are dealing with crystalline forms of a pharmaceutical chemical, a molecule known as clarithromycin. The ’527 patent discusses crystalline forms which Abbott has chosen to call Form I and Form II. There is reference elsewhere in the evidence to another form identified as Form 0. The ’527 patent provides graphs showing the result of testing Form I and Form II by each of PXRD, IR and DSC. The claims of the ’527 patent however speak only of Form

I and clarithromycin in Form I substantially free of Form II and in identifying Form I the claims speak only of the identification provided by one of those techniques RXRD and the 2 θ values detected at 8 peaks, using recorded figures, at 2 θ values, 5.2, 6.7, 10.2, 12.3, 14.2, 15.4, 15.7 and 16.4 (rounded off).

THE ’527 PATENT – CLAIM 5

a) General

[25] The ’527 patent is the only patent now at issue. Originally several more patents were involved in this application. The parties have reduced the number of patents to this one and the only claim of that patent at issue is claim 5.

[26] The application for the ’527 patent was filed with the Canadian Patent Office on July 25, 1997 which means that the patent is governed by the post October 1, 1989 and, in particular, the post October 1, 1996 version of the *Patent Act*, R.S.C. 1985, c. P-4.

[27] The application claims priority from a similar application filed in the United States Patent Office on July 29, 1996. The Canadian application was laid open for public inspection on February 5, 1998. The ’527 patent was ultimately issued and granted to Abbott Laboratories on May 27, 2003. The patent will endure for a term of 20 years from its Canadian filing date that is until July 25, 2017, unless earlier held to be invalid in an action (not this proceeding) brought for that purpose in this Court.

b) Description of the patent

[28] The descriptive portion of the ’527 patent comprises the first seventeen pages (the last two are numbered 15a and 15b) together six graphs at the end identified as Figures 1a, b and c and 2 a, b and c. Figure 1a is a graph illustrating a PXRD graph of Form I clarithromycin, 1b is an IR graph, and 1c is a DCS graph. Figures 2 a, b and c are similar graphs for Form II clarithromycin. The descriptive position of the ’527 patent is similar in many respects to that of another Canadian Patent 2,258,606 (’606) which patent has been considered in other NOC proceedings in the Court and the Federal Court of Appeal. The ’606 patent has claims directed to Form II clarithromycin while the claims of the ’527 patent are directed to Form I clarithromycin. Both patents claim priority from the same United States patent application, 08/681, 723 filed July 29, 1996. The application for the ’527 patent was filed directly with the Canadian Patent Office on July 25, 1997 whereas the application for the ’606 patent was filed under the provisions of the Patent Co-Operation Treaty (PCT) on July 25, 1997 and entered the “national phase” in Canada on December 16, 1998. For purposes of considering construction both were laid open for public inspection on February 5, 1998 and for purposes of anticipation and obviousness, both have a “claim date” of the claimed priority filing date of the Untied States application, July 29, 1996. I set out this identity because other Courts have considered the ’606 patent.

[29] The ’527 patent at issue begins with a description of the technical field which description includes both Form I and II:

Technical Field

> *This invention relates to compounds having therapeutic utility and to methods for their preparation. More particularly, the present invention concerns the novel compounds 6-O-methylerythromycin A*

> *crystal Form I and Form II, a process for their preparation pharmaceutical compositions comprising these compounds and methods for use as a therapeutic agent.*

[30] Following that the '527 patent acknowledges that clarithromycin and its use as an antibiotic in humans form the background of what is later discussed as being the invention. In other words, clarithromycin and its use is prior art. It says (without reproducing the picture of the molecule):

> *6-O-methylerythromycin A (Clarithromycin) is a semisynthetic microlide antibiotic of formula*
>
> ...
>
> *Which exhibits excellent antibacterial activity against gram-positive bacteria, some gram-negative bacteria, anaerobic bacteria, Mycoplasma, and Chlamidia. It is stable under acidic conditions and is efficacious when administered orally. Clarithromycin is a useful therapy for infections of the upper respiratory tract in children and adults.*

[31] Page 2 of the '527 patent sets out a summary of the alleged invention, in brief, it says that the inventors have discovered that clarithromycin can exist in and at least two crystal forms which they call Form I and Form II, that these forms have an "identical spectrum of antibacterial activity" but that Form I dissolves more quickly. It is stated that Form I exclusively can be found when clarithromycin is recrystallized from a solution containing certain solvents. In other words, Form I and Form II have the same antibacterial properties, Form I dissolves more quickly:

> *<u>Summary of the Invention</u>*
>
> *We have discovered that 6-O-methylerythromycin A can exist in at least two distinct crystalline forms, which for the sake of identification are designated "Form I" and "Form II". The crystal forms are identified by their infrared spectrum, differential scanning calorimetric thermogram and powder x-ray diffraction patterns. Form I and Form II crystals have an identical spectrum of*

> *antibacterial activity, but Form I crystals unexpectedly have an intrinsic rate of dissolution about three times that of Form II crystals. Investigations in our laboratory have revealed that 6-O-methylerythromycin A when recrystallized from ethanol, tetrahydrofuran, isopropyl acetate, and isopropanol, or mixtures of ethanol, tetrahydrofuran, isopropyl acetate, or isopropanol with other common organic solvents result in exclusive formation of Form I crystals, not identified hitherto before.*

[32] The summary goes on at page 2 of the '527 patent to say that "Drugs currently on the market" utilize Form II crystals. It is asserted by Abbott and not disputed by Sandoz that this is a reference to Abbott's BIAXIN product (not the later product BIAXIN XL) and that while BIAXIN contained essentially only Form II as an active ingredient, the public was not aware as to what the crystal form was. It says:

> *Drugs currently on the market are formulated from the thermodynamically more stable Form II crystals. Therefore, preparation of the current commercial entity requires converting the Form I crystals to Form II. Typically this is done by heating the Form I crystals under vacuum at a temperature greater than 80°C. Therefore, the discovery of a novel form of 6-O-methylerythromycin A which can be prepared without the high temperature treatment results in substantial processing cost savings. In addition, the favourable dissolution characteristics of Form I relative to Form II increases bioavailability of the antibiotic and provides significant formulation advantages.*

[33] What is being said is that Form I is cheaper to make and, because it dissolves more quickly, can be more advantageously formulated into a drug.

[34] The summary at page 2 of the '527 patent describes the characteristics of Form I crystals with reference to the 2 θ values obtained by the PXRD technique:

> *Accordingly, the present invention in its principle embodiment provides a novel crystalline antibiotic designated 6-O-*

> *methylerythromycin A Form I. This novel crystalline antibiotic may be characterized by peaks in the powder x-ray diffraction pattern having the following 2 θ values (not repeated here, they are the same as set out in claim 1 which is repeated in full subsequently in those reasons).*

[35] The summary distinguishes between Form I and Form I "substantially free" of Form II.

> *In another embodiment, the present invention provides a novel crystalline antibiotic designated 6-O-methylerythromycin A Form I substantially free of 6-O-methylerythromycin A Form II. This novel crystalline antibiotic may be characterized by peaks in the powder x-ray diffraction 2 θ (same values as in claim 1).*

[36] The summary of the '527 patent at page 2 and over to page 3 states that the alleged invention also includes pharmaceutical compositions including Form I, to a method of treating mammals by administering Form I and to a process of making Form I.

> *The present invention also provides pharmaceutical compositions which comprise a therapeutically effective amount of 6-O-methylerythromycin A Form I in combination with a pharmaceutically acceptable carrier and such compositions for use in the treatment of bacterial inventions or in the preparation of an antibiotic medicament.*
>
> *The invention further relates to a method of treating bacterial infections in a host mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of 6-O-methylerythromycin A Form I.*
>
> *In another embodiment, the present invention provides a process for preparing 6-O-methylerythromycin A Form I comprising…*

[37] In the process described at page 3 the steps of drying the crystals out of solution is described as being carried on between ambient temperature (later described at page 8 as being about between 20°C to about 25°C) and about 70°C. At lines 19 and 20 on page 3 the patent says:

> *(d) drying 6-O-methylerythromycin A is isolated in step (c) at a temperature of between ambient temperature and about 70°C to form 6-O-methylerythromycin A Form I.*

[38] In what is described as a "preferred route" at pages 7 to 9 of the patent the drying step is more particularly described:

> *For purposes of this specification, ambient temperature is from about 20°C to about 25°C. Crystalline 6-O-methylerythromycin A is then isolated, preferably by filtration, and the wet solid is converted to 6-O-methylerythromycin A Form I by drying in a vacuum oven at a temperature of between ambient temperature and about 70°C, preferably from about 40 to about 50°C and a pressure of between about 2 inches of mercury and atmospheric pressure to remove any remaining solvent.*

[39] The Form I clarithromycin is said at pages 9 to 12 as being capable of formulation into a pharmaceutical composition in solid or liquid form:

> *The present invention also provides pharmaceutical compositions which comprise 6-O-methylerythromycin A Form I formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.*
>
> ...
>
> *Solid dosage forms for oral administration include capsules, tablets, pills, powder and granules.*
>
> ...
>
> *Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs.*

[40] The reference to liquid forms is peculiar because a crystal such as Form I is no longer a crystal once it is in solution, it loses its crystalline identity. There can be no liquid dosage forms which includes Form I crystals. When asked about this at the hearing Abbott's counsel had no explanation. Perhaps it was an overzealous or careless patent draughtsman.

[41] The dosage levels for administration are described at page 12 and 13 as levels that "may be varied" depending on several conditions and that it is "within the skill of the art" to start with lower doses then increase the level:

> *Actual dosages levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.*
>
> *Generally dosage levels of about 1 to about 1000, more preferably of about 5 to about 200mg of 6-O-methylerythromycin A Form I per kilogram of body weight per day are administered to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.*

[42] Nowhere is it set out whether the fact that Form I is the crystalline form used to do the formulations of the pharmaceutical composition makes a difference or is in any way different from,

for instance, Form II formulations. The *"significant formulation advantages"* promised at page 2 are not described or exemplified anywhere.

[43] The intrinsic dissolution rate for Form I in comparison with Form II as promised at page 2 is, however, exemplified in Example 4 at page 19 of the '527 patent:

Example 4

Dissolution Rates of 6-O-methylerythromycin A Forms I and II

Dissolution studies were carried out at 60 rpm in 300mL of 0.05 M phosphate buffer at 37°C using a constant surface area (13/32"diameter) drug compact. Aliquots were removed periodically and assayed directly by HPLC (5cm x 4.6mm 3μ ODS-2 "Little Champ" (Regis) column; 50:50 acetonitrile-0.05 M pH 4.0 phosphate buffer mobile phase; 1.0 mL/min flow rate). As shown in Table 1. 6-O-methylerythromycin A Form I has an intrinsic rate of dissolution about three times grater than Form II.

Table 1

Intrinsic Dissolution Rates of 6-*O*-methylerythromycin A forms I and II

Crystal Form	Dissolution Rate ± S.D. ($\mu g/min/cm^2$)
I	636 ± 2.5
II	203 ± 14

[44] Nowhere, however, does the patent show what advantage, if any, this increased rate gives. Both Form I and Form II dissolve. Form II is acknowledged at page 2 of the patent to be the active ingredient in a commercial product. Thus it is reasonable to infer that Form II is sufficiently soluble for commercial use. What then is the advantage of increased solubility? It is not stated.

c) Claim 5

[45] Claim 5 reads as follows:

> *5. The use of 6-O-methylerythromycin A Form I according to claim 1 or 2 in the treatment of bacterial infections in a host mammal.*

[46] Claims 1 and 2 referred to in claim 5 reads as follows:

> *1. 6-O-methylerythromycin A Form I characterized by peaks in the powder x-ray diffraction pattern having the following 2 θ values: 5.2°±0.2, 6.7°±0.2, 10.2°±0.2, 12.3°±0.2, 14.2°±0.2, 15.4°±0.2, 15.7°±0.2, and 16.4°±0.2.*
>
> *2. 6-O-methylerythromycin A Form I characterized by peaks in the powder x-ray diffraction pattern having the following 2 θ values 5.16°±0.2, 6.68°±0.2, 10.20°±0.2, 12.28°±0.2, 14.20°±0.2, 15.40°±0.2, 15.72°±0.2, and 16.36°±0.2.*

[47] It can be seen that claim 1 differs from claim 2 in that the values for 2 θ are rounded off to one decimal place in claim 1 whereas those values are expressed to two decimal places in claim 2.

[48] Claim 5 can be simplified for purposes of discussing the issues in this proceeding by referring to 6-O-methylerythromycin A simply as clarithromycin and to say simply Form 1 without recitation of the eight 2 θ values.

[49] Thus claim 5 can more cryptically be written as:

> *"5. The use of Form 1 clarithromycin in the treatment of bacterial infections in a host mammal"*

[50] It is common ground between the parties that claim 5 is directed to a particular use of clarithromycin, namely "*…treatment of bacterial infections in a host mammal*". It is also common

ground that claim 5 covers the use of Form I clarithromycin even where Form I may be mixed with other forms of clarithromycin, for example Forms 0 and Form II.

[51] It is to be noted that claim 1 and 2 are directed only to Form I and do not specify any particular use. They are not at issue in this proceeding.

[52] It is also noted that other claims such as 7 and 8 specify that the clarithromycin Form I be "substantially free" of Form II. Again, these claims are not at issue.

[53] It is further to be noted that claim 5 in speaking of Form I references that Form to be "according to claim 1 or 2" and that claim 1 and 2 identify Form I as that identified by 8 specified values determined by the PXRD technique at 2 θ.

[54] In addressing the points in the construction of claim 5 that are relevant to the discussion at hand one must consider what the late Justice Pumfrey of the English Chancery Court (Patent Division) as he then was, said in *Nokia v. Interdigital Technology Corporation,* [2007] E.W.H.C. 3077 (Pat.) at paragraph 25, regard must be had to where the "shoe pinches".

[55] For the purpose of the discussion at hand, therefore, claim 5 can be construed as saying:

> *"5. The use of clarithromycin, at least some of which is Form I, for the treatment of bacterial infections in a host mammal".*

PERSON SKILLED IN THE ART

[56] The parties are in substantial agreement that, when it is necessary to consider who is a person skilled in the art (POSITA) to whom the ’527 patent is addressed, that person is a chemist or chemical engineer having at least a bachelor level degree and at least three to five years experience in the pharmaceutical industry including substantial experience with crystallization processes.

VALIDITY

a) General

[57] This is a proceeding brought under the provisions of section 6 of the *PMNOC Regulations* for a determination of several issues including whether Sandoz’s allegations that claim 5 of the ’527 patent is “not valid” is “justified”. The use of the term “not valid” comes from section 5(b)(iii) of the *PMNOC Regulations* and, as the Supreme Court of Canada (Rothstein J. for the Court) wrote in *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61 (*Sanofi*) at paragraph 17, the inquiry parallels what would otherwise be a defence to an infringement action as referred to in section 59 of the *Patent Act*.

[58] The *Patent Act*, section 43(2), in the case of a post October 1, 1996 patent such as the ’527 patent here, provides that a patent shall, in the absence of evidence to the contrary, be valid. In *Pfizer Canada Inc. v. Canada (Minister of Health)*, 2008 FC 11, I reviewed the recent authorities, including two from the Federal Court of Appeal, on the question as to who had the burden of proof as to validity particularly in NOC proceedings such as this, and concluded that a patentee such as Abbott may rely on the presumption of validity however, if the attacking party, Sandoz, has lead

reliable evidence, then the Court must weight all the evidence on the usual civil burden of proof, if the matter was then seen to be evenly balanced, the attack on validity fails. At paragraph 33 of that decision, I wrote:

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

[59] The attacks made as to the validity of claim 5 of the ’527 patent are those of anticipation (lack of novelty) and obviousness (lack of invention). I reviewed these concepts in detail in *Eli Lilly Canada Inc. v. Apotex Inc.*, 2008 FC 142 at paragraphs 127 to 129 citing the Federal Court of Appeal in *Imperial Tobacco Ltd. v. Rothmans Benson & Hedges Inc.* (1993), 47 C.P.R. (3d) 188, Professor Carl Moy, and Lord Hoffman in *Synthon BV v. SmithKlineBeechman plc*, [2005] UKHL 59 (*Synthon)* a decision relied on heavily by Rothstein J. in *Sanofi*, *supra*. In brief, anticipation and obviousness are both questions of fact, prior art may be considered in respect of both, but the tests are to be used differently. In anticipation, a single document or, for post October 1989 patents, a single disclosure, is to be considered as it would be been considered by a person skilled in the art as of the relevant date to determine if the claimed invention would have been disclosed and enabled to such a person at that time. If so, the claimed invention was anticipated. With respect to obviousness, if there are differences between what was disclosed, was there room left for a person to make an

inventive contribution. If what was not disclosed was something that a person skilled in the art as of the relevant date would have been expected to do without exercising invention ingenuity, hence the claimed invention is obvious.

[60] In the case of a post October 1, 1996 patent such as the ’527 patent the relevant date for consideration of novelty, where a disclosure has been made by someone other than the inventor or person deriving knowledge from the inventor, is the “claim date” which, in the case of the ’527 patent which claims priority from the United States patent application filed July 29, 1996, is that date of filing that United States application (sections 28, 28.1 and 28.2 of the post-October 1, 1996 version of the *Patent Act*). In respect of obviousness, the relevant date, in this case since no disclosure was made by the inventors or other persons gaining knowledge from the inventors, is also the “claim date”, July 29, 1996 (section 28.3 of the *Patent Act*, *supra*).

[61] Chemical patents, including those directed to pharmaceuticals, present particular concerns. Complex molecules are often involved. A prior art disclosure, such as an earlier patent may disclose a particular molecular structure with instruction that, at certain locations other molecules may be added or substituted or left out. Often the reader is left to select from classes or groups of molecules from which those choices may be made. Often the number of possible choices can number in the thousands or hundreds of thousands and more. Where different choices are made the resulting molecules are sometimes referred to as analogues of each other. A subsequent patent may claim one such analogue or a group of them and the Court may be asked if such claim is anticipated or obvious.

[62] Another situation may present itself where the molecular structure can be twisted, when viewed three dimensionally, this way or that. A molecule may be twisted around what are called chiral centres within the structure, and depending upon how many such centres exist in a molecule, there can be several differently twisted versions of the molecule. A mixture of such molecules with equal amounts of each twisted version is called a racemic mixture, and each individual twisted version is often called enantiomer. In *Sanofi* the Courts had to consider whether the selection of one of these enantiomers was anticipated or obvious.

[63] A third situation is one present in this case. In solution a molecule simply floats around with other molecules in the solution. When the molecules in solution dried out, they may assume one or another crystalline shape. The molecule however, remains chemically the same. The solidified shape of the crystals may vary. Whether the selection of one such crystalline shape was anticipated or obvious is the question here.

b) <u>Prior Knowledge</u>

[64] It is not contested that there was considerable prior knowledge that a person skilled in the art would have had before the "claim date", July 29, 1996. From the Memoranda and written submissions filed and from statements made by counsel for the parties during the hearing, as well as from what has been set out at pages 1 and 2 of the description of the '527 patent previously reviewed, at least the following can be accepted as prior knowledge:

1. Clarithromycin and its molecular structure were known

2. The use of clarithromycin in the treatment of bacterial infections in a host mammal such as a human was known. This was the only known use of clarithromycin.
3. Clarithromycin existed in a crystalline form. Such a form was not publicly described, for instance no 2 θ PXRD data was known. Nor was it known whether one or more crystalline forms existed.
4. Standard techniques for identifying crystal forms such as PXRD, IR and DSC were known and used.
5. Standard techniques for measuring solubility and solubility rates were known and used.
6. A commercial product called BIAXIN was sold by Abbott. That product included clarithromycin as an active ingredient. However there was no public knowledge as to whether such clarithromycin was crystalline or, if so, what form or forms it took.

In addition, certain other facts are not contested:

7. Abbott currently sells a commercial product known as BIAXIN XL. This product contains a mixture of Form I and Form II clarithromycin.
8. Abbott has an NOC from the Minister to sell BIAXIN XL in Canada. That NOC simply states that the active ingredient is clarithromycin without specifying any particular form. It is this NOC which Sandoz has referenced thus giving rise to these proceedings.

c) Anticipation

i) Legal Test

[65] The law as to anticipation was very recently reviewed and restated by the Supreme Court of Canada in *Sanofi, supra*, particularly at paragraphs 18 to 50. That Court at paragraphs 20 to 22 reviewed the legal test for anticipation used by the Trial Judge namely "*that the exact invention has already been made and publicly disclosed"*. This test, the Supreme Court wrote at paragraph 23, was overstated:

> ***23*** *For the reasons that follow, and in light of recent jurisprudence, I am of the respectful opinion that the applications judge overstated the stringency of the test for anticipation that the "exact invention" has already been made and publicly disclosed.*

[66] The Supreme Court discussed with approval at paragraph 24 to 37 the decision of the House of Lords in the *Synthon* case, *supra*. Two separate requirements are necessary for there to be anticipation, prior disclosure and enablement.

[67] Prior disclosure means that the prior patent (publication, use or other disclosure) must disclose subject matter which, if performed, would necessarily result in infringement of the patent (claim at issue). The person skilled in the art looking at the disclosure must be taken to be trying to understand what the prior patent (or other disclosure) meant. There is no room for trial and error, the prior art is simply to be read for the purposes of understanding.

[68] The second requirement is that of enablement which means that the person skilled in the art would have been able to perform what had been disclosed. At this stage the person skilled in the art

is assumed to be willing to make trial and error experiments to get it to work. The Supreme Court at paragraph 37 of *Sanofi* summarized a non-exhaustive list of factors that may be applied in the consideration of enablement:

> ***37*** *Drawing from this jurisprudence, I am of the opinion that the following factors should normally be considered. The list is not exhaustive. The factors will apply in accordance with the evidence in each case.*
>
> > *1. Enablement is to be assessed having regard to the prior patent as a whole including the specification and the claims. There is no reason to limit what the skilled person may consider in the prior patent in order to discover how to perform or make the invention of the subsequent patent. The entire prior patent constitutes prior art.*
> >
> > *2. The skilled person may use his or her common general knowledge to supplement information contained in the prior patent. Common general knowledge means knowledge generally known by persons skilled in the relevant art at the relevant time.*
> >
> > *3. The prior patent must provide enough information to allow the subsequently claimed invention to be performed without undue burden. When considering whether there is undue burden, the nature of the invention must be taken into account. For example, if the invention takes place in a field of technology in which trials and experiments are generally carried out, the threshold for undue burden will tend to be higher than in circumstances in which less effort is normal. If inventive steps are required, the prior art will not be considered as enabling. However, routine trials are acceptable and would not be considered undue burden. But experiments or trials and errors are not to be prolonged even in fields of technology in which trials and experiments are generally carried out. No time limits on exercises of energy can be*

> *laid down; however, prolonged or arduous trial and error would not be considered routine.*
>
> *4. Obvious errors or omissions in the prior patent will not prevent enablement if reasonable skill and knowledge in the art could readily correct the error or find what was omitted.*

[69] To this analysis by the Supreme Court should be added comments by Floyd J. of the English Chancery Court, Patents Division, in a recently decided case, June 30, 2008, *Actavis UK Limited v. Janssen Pharmaceutica N.V.*, [2008] EWHC 1422 (Pat). He was applying the law established in *Synthon, supra*. He was considering an argument to the effect that the prior art must disclose something that, if carried out, must "inevitably result" in what is claimed in the patent at issue and, if there was any room for doubt, then there is no anticipation. Floyd J. rejected that argument, the Court, he held, is required to consider the evidence on the normal civil burden of "balance of probabilities" and not on a "quasi-criminal standard". He wrote at paragraph 85:

> *85. Is that finding good enough for an inevitable result? The legal requirement is that this feature of the claim be the inevitable result of carrying out the prior teaching. Does that mean that if there is something other possibility, even a fairly remote one, that some other result would follow, I should conclude the result is not inevitable? Or am I concerned to establish what, on the balance of probabilities would in fact occur? In my judgment, it is the latter approach which is correct. The inevitable result test does not require proof of individual facts to a quasi-criminal standard. It may be impossible to establish the relevant technical facts to that standard. It is another matter if the evidence establishes that sometimes one result will follow and sometimes another, depending on what conditions are used. But there is nothing of that kind suggested here. It is simply a question of what occurs in fact.*

[70] Adding to this point regard should be had to the recent decision of the Supreme Court of Canada in *F.H. v. McDougall,* 2008 SCC 53 where Rothstein J. for the Court stated at paragraph 40 that in civil proceedings there is only one standard of proof, the balance of probabilities. At paragraph 40, the Court says:

> ***40*** *Like the House of Lords, I think it is time to say, once and for all in Canada, that there is only one civil standard of proof at common law and that is proof on a balance of probabilities. Of course, context is all important and a judge should not be unmindful, where appropriate, of inherent probabilities or improbabilities or the seriousness of the allegations or consequences. However, these considerations do not change the standard of proof. I am of the respectful opinion that the alternatives I have listed above should be rejected for the reasons that follow.*

[71] A further legal consideration arises in cases such as the present. What is the situation where, in practicing the prior art a particular substance was present and doing what it always has done but that substance was not recognized as such or as doing that particular thing. As Floyd J. said at paragraph 99 of *Actavis*, *supra*:

> *99. In my judgement, merely explaining the mechanism which underlies a use already described in the prior art cannot, without more, give rise to novelty.*

[72] It is useful in this regard to have regard to an earlier decision given by Lord Hoffman in the House of Lords in *Merrell Dow Pharmaceuticals Inc. v. H.N. Norton & Co. Ltd.*, [1996] R.P.C. 76. The issue in that case was whether a claimed pharmaceutical had been previously disclosed by use. The previous use was by way of metabolism in the human body, that is, a related but different pharmaceutical composition was swallowed but, in the liver it changed to some extent. It was "metabolized" and became the chemical claimed in the patent at issue. Nobody had conducted an

analysis however at any previous time as to what if anything was happening in the liver. The "metabolite" itself had not been previously identified. Lord Hoffman held that there was sufficient anticipation to invalidate the claimed invention. In doing so, he relied on a case in the European Patent Office which held that a patent claiming a process for making flavour concentrates from vegetable or animal substances by extraction with fat solvents under pressure in the presence of water was anticipated by old cookbook recipes for pressure cooking chicken or stews. Nobody knew that flavour concentrates were being extracted but it was being done, hence the claim was anticipated. As he said at page 90 lines 8 and 9 "*if the recipe which inevitably produces the substance is part of the state of the art, so is the substance*". Later at the same page 90, at lines 49 to 52 he said:

> *The fact that they would not have been able to describe the chemical reaction in these terms does not mean that they were not working the invention. Whether or not a person is working a product invention is an objective fact independent of what he knows or thinks about what he is doing.*

[73] Following that quoted portion, Lord Hoffman at the end of page 90 and over to page 91 considered the situation where a patent claimed a use for the product. If the claimed use is different than the old use of the undetected but nonetheless present product, then the claimed use may not have been anticipated. But, if the old use is the same as the claimed use, the claim is anticipated. He wrote:

> *The position may be different when the invention is a use for a product; in such a case, a person may only be working the invention when he is using it for the patented purpose: see the discussion of the MOBIL/Friction reducing additive case in the next section). The Amazonian Indian who treats himself with powdered bark for fever is using quinine, even if he thinks that the reason why the treatment is effective is that the tree is favoured by the Gods. The teachings of his*

> *traditional medicine contain enough information to enable him to do exactly what a scientist in the forest would have done if he wanted to treat a fever but had no supplies of quinine sulphate. The volunteers in the clinical trials who took terfenadine were doing exactly what they would have done if they had attended Merrell Dow's Strasbourg symposium and decided to try making the acid metabolite in their livers by ingesting terfenadine.*

[74] Lord Hoffman further addressed this point in *Synthon, supra,* at paragraph 22*:*

> *22. If I may summarise the effect of these two well-known statements, the matter relied upon as prior art must disclose subject-matter which, if performed, would necessarily result in an infringement of the patent. That may be because the prior art discloses the same invention. In that case there will be no question that performance of the earlier invention would infringe and usually it will be apparent to someone who is aware of both the prior art and the patent that it will do so. But patent infringement does not require that one should be aware that one is infringing: "whether or not a person is working [an] ... invention is an objective fact independent of what he knows or thinks about what he is doing": Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd [1996] RPC 76, 90. It follows that, whether or not it would be apparent to anyone at the time, whenever subject-matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied. The flag has been planted, even though the author or maker of the prior art was not aware that he was doing so.*

[75] To summarise the legal requirements for anticipation as they apply to the circumstances of this case:

1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.
2. The disclosure does not have to be an "exact description" of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.

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

ii) Application to the Facts

[76] The claimed invention must be kept clearly in mind since it must be the invention, as claimed, that is to be the subject of the anticipation inquiry. Claim 5 as cryptically written reads:

> *"5. The use of Form I clarithromycin in the treatment of bacterial infections in a host mammal"*

and as construed previously reads:

> *"5. The use of clarithromycin, at least some of which is Form I, for the treatment of bacterial infections in a host mammal".*

[77] In the Notice of Allegation, Sandoz states that claims 1 to 38 of the ’527 patent, which is now reduced for those purposes to claim 5 of the ’527 patent, are invalid as anticipated and obvious. For purposes of these reasons it is only necessary to focus on the allegations directed to United States Patent No. 4,990,602 (’602 patent). Those allegations are, as taken from page 53 of the Notice of Allegation:

> *290. Claims 1 to 38 concerning Form I are invalid as anticipated and obvious. Form I was known prior to the claim date, as set out in the prior art set out below,*
>
> ...
>
> *291. Form I is also admitted to be produced by the method set out in prior art U.S. Patent no. 4,990,602 (Sandoz Document 65) at p. 10, lines 1-6 of the disclosure of the 732 patent: "6-O-methylerythromycin A was prepared from erythromycin…according to the method of the U.S. Patent No. 4,990,602 to give 6-O-methylerythromycin A Form I." Identifying and characterizing an existing compound does not confer novelty.*
>
> ...
>
> *293. Form I and its use as an antibiotic were known prior to the claim date of the ’527 patent, as set out above, and thus the claims to Form I in the treatment of a bacterial infection or as an antibiotic are invalid as anticipated and obvious.*

[78] It is to be noted that in the following discussion, no reference will be made to material sought to be struck out of Sandoz’s evidence and argument in the Abbott motion which I dismissed.

[79] The ’602 patent is a prior disclosure which was issued February 5, 1991, that is, over five years prior to the claim date of July 29, 1996. Hence it is timely in terms of prior art.

[80] The ’602 patent begins by stating at the beginning of column I what the parties acknowledge was already previously known, that is that clarithromycin (6-O-methylerythromycin A) was already known as was its use as an antibacterial agent and that there were several known methods for preparing it:

> *BACKGROUND OF THE INVENTION*
>
> *1. Field of the Invention*
>
> *The present invention relates to erythromycin A derivatives and a method of the preparation of the same.*
>
> *2. Description of the Prior Art*
>
> *6-O-Alkylerythromycins are useful as anti-bacterial agents or intermediates for synthesis of the antibacterial agents. For examples, 6-O-methylerythromycin A is not only stable under acidic conditions but also has a strong antibacterial activity when compared with erythromycin A. Especially, this compound shows an excellent effect in treatment of infections by oral administration, and therefore it is a useful antibacterial agent.*
>
> *There are known in the past several methods for preparing 6-O-methylerythromycin A, for example…*

[81] An example for the preparation of clarithromycin is provided at column 22 and called Referential Example 1. I will reproduce only the last part:

> *(2) To a solution of 2 g of the compound, obtained above, and 1.1 g of sodium hydrogen sulfite in 20ml of ethanol/water (1/1) was added 0.25 ml of 99% formic acid, and the mixture was refluxed for 100 minutes. To the reaction solution was added 30 ml of water, 5 ml of 2N aqueous sodium hydroxide solution was added dropwise, and then the mixture was stirred under ice-cooling for 2 hours. The precipitate which formed was collected by filtration and recrystallized from ethanol to give 1.51 g of 6-O-methylerythromycin A. m.p. 223^{o}-225^{o}C.*

[82] It is shown in this Example that clarithromycin is recrystallized, that is, that the resulting product is in a crystal form and that the melting point (m.p.) is 223-225^{o}C. This melting point corresponds with the melting point for Form I indicated in the DSC chart figure 1c of the ’527 patent.

[83] Thus the ’602 patent discloses a crystalline form of clarithromycin useful in the treatment of infections by oral administration that is useful as an antibacterial agent. The crystal form is not identified by 2 θ values, only a melting point. The name “Form I” as previously discussed is simply arbitrary, the important point to note here is that the product is identified as crystalline and has a melting point the same as what later was called Form I. Thus just like the metabolite case or the fried chicken case, we have an unidentified substance performing the same use as the use as claimed in Claim 5 the ‘527 patent.

[84] The evidence is that Abbott itself identified the crystalline form present as Form I in a patent issued to Abbott several years later. In Canadian Patent 2,261,732 (’732 patent) issued to Abbott Laboratories published on February 5, 1998 Abbott acknowledged that the process described in the ’602 patent produces Form I clarithromycin. It does not matter that the ’732 patent was made public after the “claim date” of the ’527 patent. What matters is that Abbott itself has acknowledged that the unidentified crystalline form of the ’602 patent is that which is now identified as Form I. at page 10 of the ’732 patent Abbott says:

Reference Example

> *6-O-methylerythromycin A was prepared from erythromycin A by oximation of the C-9 carbonyl, protection of the C-2’ and C-4”*

> *hydroxyl groups, methylation of the C-6 hydroxy group, deoxinmation and removal of the protecting groups, and recrystallization from ethanol according to the method of the U.S. Pat. No. 4.990.602 to give 6-O-methylerythromycin A Form I.*

[85] The Form I that is spoken of is the same Form I as disclosed in the ’527 patent under consideration here since, at page 2 of the ’732 patent reference is made to the United States patent from which priority is claimed in the ’527 patent. At page 2 of the ’732 patent lines 9 and 10 it is written:

> *“Form I is disclosed in the co-pending U.S. Patent 5,858,986, filed even-date on July 29, 1996.”*

[86] Thus Abbott itself has acknowledged that the unidentified crystalline form of the ’602 patent is indeed Form I as identified by the relevant 2 θ values.

[87] Therefore, the ’602 patent constitutes a disclosure of the use of clarithromycin in crystal form in the treatment of bacterial infections. While mammals are not specifically mentioned as the recipients of such treatment in the ’602 patent the use of the words “by oral administration” in the passage at column I previously quoted clearly implies that a mammal, probably a human is being treated.

[88] It is not material that the crystal form in the ’602 patent was not disclosed by use of the very term “Form I” since that is simply a name of convenience given at a later time. We know that it was what we now call Form I since Abbott itself has acknowledged it.

[89] The ’602 patent is enabling. It describes clarithromycin, its use and how to make it in a crystalline form that is Form I. To practice what is taught by the ‘602 patent would be to infringe claim 5 of the ‘527 patent.

[90] The evidence also shows that the experts for both Abbott and Sandoz agree that at least some of the crystalline forms produced using the ’602 as well as other prior art references would be Form I. Abbott’s experts Byrn (paragraphs 124 and 134 of his Affidavit) and Atwood (paragraphs 225 of his Affidavit) opine that under the probable drying conditions used, a mixture of Form 0 and Form I crystals would result. The fact that it is not entirely Form I does not matter since the parties have agreed that a proper construction of claim 5 contemplates a mixture of crystalline forms of clarithromycin which includes Form I. Sandoz’s experts were more certain that Form I would be the resultant crystal (Rohani Affidavit paragraph 604, Lee-Ruff Affidavit paragraphs 136 to 138, Eckhardt Affidavit paragraphs 195 and 196). It does not matter whether the crystals were entirely Form I or a mixture of Form I and something else, the agreed upon construction of claim 5 has been met.

[91] Other prior art cited by Sandoz could likewise be analyzed with similar results. I have not gone into detail since that art, though mentioned as references in the Notice of Allegation were not the subject of specific discussion in the text of the Notice. It is not necessary to do so since the ’602 patent is sufficient to invalidate claim 5 of the ’527 patent for anticipation.

[92] The allegation that claim 5 of the ’527 patent is invalid for anticipation is therefore justified.

c) Obviousness

i) The Finding of Anticipation

[93] It is unnecessary to consider whether claim 5 of the ’527 patent is also invalid for obviousness since it is invalid for anticipation. As Lord Hoffman said in *Synthon, supra,* at paragraphs 20 to 22 what if any “room” was left. In the present case the leading of the ’602 patent leaves no “room”, it covers all that claim 5 covers.

ii) Abbot’s Assertion of Room

[94] In the event that higher Courts are required to consider this matter, I will consider Abbott’s assertions.

[95] Abbott acknowledges that clarithromycin was a known molecule and known to be used to treat humans as an antibiotic, it also acknowledged that it was known that clarithromycin was crystalline. Abbott argues that it was not known that clarithromycin could exist in several crystalline forms, that is, it was polymorphic. Abbott says that if a person skilled in the art produces or come across a crystalline form hitherto unknown or unidentified that person would not know if that form could be used to treat infection and, in particular, whether it would be sufficiently soluble for such use. Abbott points to cross-examination of Sandoz experts (Eckhardt Q 192, Lee-Ruff Q 351) where it is said that if a particular form was insoluble, it could not be used as an antibiotic and

its own exert (Atwood Affidavit paragraph 181) who says that an insoluble the material would pass through the body when ingested like a child swallowing a penny.

[96] To say that if something is insoluble, then it will not work is simply stating the obvious. But that is not the question when considering obviousness. The question for obviousness purposes is that as stated by the Supreme Court of Canada in *Sanofi* at paragraph 66, was it more or less self-evident to a person skilled in the art to try the solubility of the crystal form to see if it would work.

[97] There is no need to recite the *Windsurfing* questions restated by the Supreme Court in *Sanofi* at paragraph 67. Everything in the prior art: molecule, use and a crystal form, is present in the prior art that is what the parties have already agreed. The only outstanding issue, as postulated by Abbott, is whether this particular crystal form is sufficiently soluble so as to provide therapeutic use.

[98] Sandoz's experts (Lee-Ruff Affidavit paragraph 204 to 219, Rohani Affidavit paragraphs 324 to 343 and 648) point out that it would be recognised that some solubility is required. The rate of solubility does not appear to be critical since the rate of solubility of Form II is apparently three times less than that of Form I, Form II is quite adequate for a commercial product. Solubility would be in the mind of any person skilled in the art. There is no evidence to suggest that testing for solubility would be anything other than routine.

[99] In considering the evidence on a balance of probabilities, it is self-evident that a person skilled in the art would test the solubility of any newly identified crystal to determine if it was soluble at a rate sufficient to give therapeutic utility.

[100] If it were necessary to do so, I would find that claim 5 of the ’527 patent was obvious. Sandoz’s allegation that this claim was invalid for obviousness is justified.

INFRINGEMENT

i) Sandoz’s Allegation of Non-Infringement

[101] Sandoz’s Notice of Allegation states that certain claims of ’527 patent, including claim 5, would not be infringed. Certain allegation are made in paragraphs 282 and 283 of the Notice and an undertaking is given by Sandoz to produce “relevant portions” of Sandoz submissions made to the Minister once a protective order is in place. Paragraphs 282 and 283 state:

> *282. Sandoz alleges that Claims 3-5, 9-11, 13-38 will not be infringed by the making, constructing, using or selling by Sandoz of the Sandoz Products.*
>
> *283. The Sandoz Product will not infringe Claims 4, 5, 10, 11, 26-38 because the Sandoz Product will not contain Form I and will not be a composition of Form I for use in the treatment of bacterial infections or as an antibiotic. If Form I were to form in Sandoz process it will not infringe Claims 4-5, 10-11, 26-38 because Form I would not be used in the treatment of bacterial infections or an antibiotic.*

ii) Evidence

[102] After this application was commenced a protective order was issued and Sandoz produced portions of the material that it filed with the Minister. This contained portions of what is called a

Drug Master File (DMF) which included some manufacturing process data and analysis from a third party who is to supply the clarithromycin to Sandoz. No actual samples were provided since Sandoz had not provided any samples to the Minister. No actual data other than what was in the portions of the DMF as to the clarithromycin that Sandoz intends to use in its product is of record. No samples were produced obtained or tested by any party. The only evidence is what is in the portions of the DMF as produced by Sandoz and the opinions of experts retained by Abbott and Sandoz as to what that documentation demonstrates.

[103] The essential points found in the DMF documentation giving rise to the arguments raised by the parties are subject to a confidentiality order and are:

- A graph produced from PXRD testing conducted on a sample on July 26, 2001;
- A statement that the clarithromycin to be provided will have four peaks observed by PRXD with 2 θ values: 8.5^{o}, 9.5^{o}, 10.9^{o} and 11.5^{o}
- A statement saying: "*Different polymorphs have been described in the literature for clarithromycin. We can confirm that the product identified in this DMF corresponds to the polymorph Form II, which is the same as the UPS standard*". What the "UPS standard" may be is not in evidence;
- A process for preparation of the clarithromycin is provided, the process proceeds to a point to where what is described as a clarithromycin intermediate is produced which is washed with solvent X and optionally

recrystallized and dried under vacuum without the temperature exceeding temperature X. It says:

> *"100 Kg of wet or dry clarithromycin intermediate and solvent X are loaded in the reactor. The mixture is heading to refluxing temperature and stirred until a complete or almost complete solution is achieved. The solution can be optionally filtered and transferred. The equipment is washed with enough solvent X, which is also added to the previous solution. Optionally the solution is concentrated by distillation. The solution is cooled to a temperature below temperature Y in different cooling steps. During each cooling step, stir the reaction mixture for some minutes. If the suspension is transferred to another vessel, the equipment is washed with the required amount of solvent X.*
>
> *The product can be optionally recrystallized again using the same procedure. After the last recrystallization, the solid is filtered and washed with enough solvent X or aqueous solvent X. The product is dried under vacuum without exceeding temperature X.*
>
> *Not less than 50 Kg of clarithromycin are obtained. Several batches can be dried together or dried and afterwards homogenised to obtain one homogeneous final batch.*
>
> *After drying, the product can be sieved and/or micronized to fulfil the requirements of the customer.*

[104] It is this information that provides the basis for the competing opinions of the experts and argument of counsel.

iii) Opinion of Experts

[105] The evidence contains some simple assertions by Sandoz that its product is Form II and has four 2 θ values that correspond with those associated with Form II. These are assertions about which scientific experts cannot disagree except to let the lawyers argue in support of or to be sceptical of those assertions.

[106] The experts disagree as to two things, the PXRD graph and the result of drying clarithromycin out of a solution "without exceeding temperature X".

[107] As to the PXRD graph, Abbott argues that the graph is dated 2001 yet the process description is dated 2003 thus cannot be representative of any production batch. Abbott further argues that the graph is in any event not representative of all batches of clarithromycin that will be produced and that at least some batches will contain some detectible Form I.

[108] As to whether the particular graph shows the presence of Form I, Abbott relies on a portion of the transcript of the cross-examination of its expert, Dr. Atwood, at pages 11 to 23 where he says that at the left side of the graph he can detect two peaks consistent with the presence of Form I. Other peaks may be masked by the other peaks in the graph showing Form II. Sandoz argues that there are no such peaks and that, at pages 17, 18, 22 and 23 of the same transcript, Dr. Atwood estimates that the amount of Form I in the sample is in the order of 1 to 2 percent but also that the level of detection in the test run is also 1 to 2 percent.

[109] In other words, Sandoz argues, it is questionable whether any reliable detection could be made.

[110] I am not persuaded by the evidence that this particular PXRD illustrates the presence of any detectable Form I in the sample analysed.

[111] Abbott argues further that this is only one graph of one sample and cannot be said to be representative of all batches of clarithromycin that have been or will be produced. Abbott argues that the production protocol which stipulates that drying will occur under vacuum "without exceeding temperature X" means that many batches will contain at least some Form I. Abbott points to the evidence of experts who say that if the drying occurs above 80°C, the resulting crystals will be Form II (Atwood affidavit paragraphs 167 and 168) but if the drying occurs at the temperature between 50°C and 80°C, the resulting product will be predominantly Form I (Rohani cross-examination question 207). It argues that the evidence is that the drying step is not required to be carried on at any particular temperature so long as it does not exceed temperature X (Rohani cross-examination questions 1002 to 1011). As discussed previously in these Reasons, the prior art indicates that drying is normally carried out at temperature between ambient (20°C to 25°C) to about 40°C to 50°C. Dr. Byrn at paragraph 136 of his affidavit provides a table illustrating that in order to convert Form I to Form II at various temperatures from 25°C to temperature X it would take from 35,000 years (25°C) to 7.6 hours (temperature X). He concludes at paragraph 137 that one could not, within that range arrive at pure Form II or pure Form 0 or pure Form I in every case or even in most cases. In other words most of the material produced will include at least some Form I.

[112] Sandoz responds in two ways. First it argues that there is no evidence that it will recrystallize product below 80°C and secondly, if it recrystallized at temperature greater than 80°C then Abbott's own expert says that the resulting product will be "isolated Form II" relying on Dr. Atwood affidavit paragraph 168. Abbott counters by saying that when Dr. Atwood used the term "isolated Form II" he was using it in the sense described in paragraph 36 of his affidavit which is that Form II must not be simply a transient form not capable of PXRD, it must be sufficiently existent, that is permanent, so as to be capable of such analysis. Abbott contrasts Dr. Atwood's use of the term "isolated Form II" with the term "pure Form II" which he explains in paragraph 31 of his affidavit to be something that has no detectible Form I. Thus it is argued, Dr. Atwood use of "isolated Form II" does not exclude clarithromycin where detectible Form I is present.

[113] Viewing the evidence as whole, I conclude that it is likely that many batches of clarithromycin that may be produced will be subject at a drying step sufficiently below temperature X and likely within the range of ambient temperature to about 50°C that there will be in the resulting product some detectible amount of Form I. Thus the clarithromycin product that Sandoz would probably distribute in Canada would, at least in several batches, include some detectible amount of Form I this thus fall within the scope of claim 5 as properly construed.

[114] I am aware that the burden of proof in demonstrating that the allegation of non-infringement is not justified (to use a double negative) lies with Abbott. As Layden-Stevenson J. said in *AstraZeneca AB. V. Apotex Inc.*, 2006 FC 7 at paragraph 23, the burden of proof as to infringement rests with Astra (here Abbott) on the balance of probabilities:

> ***23*** *After hearing argument relating to the burden of proof, I articulated my understanding of the law as set out in a plethora of authorities beginning with Merck Frosst Canada Inc. v. Canada (Minister of National Health and Welfare) (1994), 55 C.P.R. (3d) 302 (F.C.A.) and culminating with Genpharm Inc. v. Procter & Gamble Pharmaceuticals Canada, Inc. et al. (2004), 37 C.P.R. (4th) 289 (F.C.A.). Counsel for both parties were satisfied that I had accurately summarized the law. Succinctly stated, the respondent Apotex's allegations of non-infringement are presumed to be true and the applicant Astra bears the legal burden of establishing, on a balance of probabilities, that none of Apotex's allegations are justified. In relation to validity, Astra may rely on the presumption of validity and Apotex must then meet an evidentiary burden to rebut the presumption. The legal burden remains with Astra throughout.*

[115] I am satisfied that the burden has been met. I conclude that sufficient recrystallization will take place at a temperature below temperature X and at or approaching the temperature indicated in the prior art as between 20°C and 50°C so as to produce at least some detectible Form I and in the final product. Thus Sandoz's allegation that its product will not infringe claim 5 of the '527 patent is not justified.

CONCLUSION AND COSTS

[116] I must commend counsel for Abbott and Sandoz for making great efforts in reducing the issues in this application to one claim of one patent. The evidence, in the form of well organized compendia, was clearly presented. The arguments were well focused, including arguments as to the effect of the *Sanofi* case which has just been released a few days before the hearing of this application.

[117] I have concluded that the allegation as to invalidity is justified and the allegation as to non-infringement is not justified. In the result, the application for prohibition will be dismissed.

[118] I invited counsel for the parties to make written submissions as to costs and to indicate what an appropriate amount would be. These submission were made before the release of these Reasons, thus counsel would not have known the result of the application. The parties agreed that costs should be fixed in the amount of $150,000.00. I agree that this is an appropriate amount and award costs to Sandoz the successful party in that amount.

"Roger T. Hughes"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

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