Federal Court Cour fédérale

Date: 20131220

Docket: T-8-12

Citation: 2013 FC 1270

Ottawa, Ontario, December 20, 2013

PRESENT: The Honourable Mr. Justice Barnes

BETWEEN:

GILEAD SCIENCES, INC. AND GILEAD SCIENCES CANADA, INC.

Applicants

and

THE MINISTER OF HEALTH AND TEVA CANADA LIMITED

Respondents

PUBLIC REASONS FOR JUDGMENT AND JUDGMENT

[1] This is an application under the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 as amended (NOC Regulations) for an Order prohibiting the Minister of Health (Minister) from issuing a Notice of Compliance (NOC) to Teva Canada Limited (Teva) for a generic version of the Applicants' (collectively Gilead) Truvada® medication.

[2] The patents in issue in this proceeding are Canadian Letters Patent No. 2,261,619 (the 619 Patent) and Canadian Letters Patent No. 2,298,059 (the 059 Patent). Teva asserts that both patents are invalid.

[3] The active pharmaceutical agent (API) that underlies both patents is tenofovir or PMPA. Tenofovir disoproxil or bis(POC)PMPA, a prodrug of tenofovir, is claimed by the 619 Patent and its salt form, tenofovir disoproxil fumarate (TDF), is the subject of the 059 Patent.

[4] TDF is indicated for use on its own and in combination with other pharmaceutical compounds for the treatment of HIV/AIDS. Gilead markets two different drugs containing TDF. These are Truvada® and Viread®. Bristol Myers Squibb (BMS) markets Atripla®, which also contains TDF. Each of these products has a different drug identification number and received its own NOC pursuant to Part C, Division 8 of the *Food and Drug Regulations*, CRC, c 870. Teva served Gilead with a separate Notice of Allegation (NOA) with respect to each of Truvada® and Viread®. Another NOA was served upon BMS with respect to Atripla®. In response, Gilead and BMS commenced three separate applications (Court files T-8-12, T-280-12 and T-1708-12) seeking orders prohibiting the Minister from issuing NOCs to Teva until the expiry of the 619 and 059 Patents.

[5] Although these applications were commenced separately and they remain separate, they raise identical issues and arguments. The parties agreed and the Prothonotary ordered that the Applications would be brought together and the validity issues determined under Court file T-8-12.

The parties further agreed that my decision and reasons with respect to T-8-12 will apply equally to T-280-12 and T-1708-12, although separate orders will be issued for each of those applications.

[6] Most of the relevant evidence in this proceeding was provided by expert witnesses. Drs. Ronald Borchardt, Allan Myerson, Richard Elion and Hans Maag gave evidence on behalf of Gilead. Drs. Robert Zamboni, Lawrence Kruse, Larry Sternson, Michael Parniak and Peter Ford gave evidence on behalf of Teva. Fact evidence on behalf of Gilead was also provided by Drs. William Lee and Reza Oliyai. This fact evidence was primarily directed at the history of the development of tenofovir disoproxil. All of the expert witnesses were qualified to opine on the subjects they addressed and no significant credibility issues were raised.

[7] Among other arguments raised, Teva contends that the claimed discoveries of tenofovir disoproxil and TDF would have been obvious to the person skilled in the art and that the patents in suit amount to the "evergreening" of the now expired patent over tenofovir. Teva also argues that the 619 Patent is invalid on the basis that the claimed discovery of tenofovir disoproxil was anticipated by an earlier patent application. Gilead argues that the discovery of a suitable prodrug and a prodrug salt form of tenofovir were delicate, complicated and unpredictable and therefore inventive.

Medicinal Background

[8] Tenofovir was known to be an effective antiviral agent useful to treat HIV/AIDS. It falls within the class of compounds known as acyclic phosphonate nucleotides and its antiviral efficacy arises from its disruption of the process of viral replication (reverse transcriptase) in human cells. In

that capacity tenofovir acts as a nucleoside reserve transcriptase inhibitor or NRTI. Although tenofovir had been shown to be a very promising compound for the treatment of HIV/AIDS, it did not receive regulatory approval for medicinal use until it was converted firstly to a prodrug or intermediate form (tenofovir disoproxil) and then to a salt form (TDF).

[9] It is undisputed that the discovery of tenofovir in the 1990's responded to a critical unmet need in the treatment of HIV/AIDS. This point is described in the affidavit of Gilead's expert, Dr. Elion.

[10] Dr. Elion is a Board Certified Physician who has provided clinical care to HIV/AIDS patients since 1984. Since 2007 Dr. Elion has held the position of Director of Clinical Research at Whitman Walker Health in Washington, D.C. Between 1984 and 2007, he held several positions relevant to his understanding of the historical treatment of HIV/AIDS, including as medical advisor to the New York Department of Public Health (1990-1991) and a member of the protocol development team for the National Institute of Health's Community Research Program on AIDS (1993-1994). Dr. Elion was also principal and co-investigator on several clinical trials involving the treatment of HIV (1998-2007).

[11] According to Dr. Elion, the first commercial test for HIV was approved in 1985, but there was no means of treating the primary cause of AIDS and clinicians were left to treat only the underlying symptoms (Elion Affidavit at paragraph graphs 33-34). Through research, it was learned that:

> 38. …HIV is a retrovirus whose genetic material is encoded in RNA rather than the customary DNA as for most cells. Upon

> entering the cell, HIV's RNA is converted by the viral enzyme reverse transcriptase to DNA. The newly transcribed viral DNA integrates into the genetic code of the host cell. The viral DNA uses the host cell's replication machinery to produce copies of the virus. The infected cell then multiplies, creating an incurable and deadly infection.

[12] Researchers sought to develop drugs that would stop the replication process at various points along the replication chain, including reverse transcriptase.

[13] In 1987, the first HIV treatment drug, zidovudine (AZT), received approval from the Food and Drug Administration (the "FDA"). By 1996, the FDA had approved nine drugs for the treatment of HIV. Unfortunately, all of these therapies were associated with toxicity issues that caused unpleasant, and sometimes life-threatening, side effects. Patient adherence to drug regimes was also an issue, as patients were often reluctant to take medication that made them feel sick to treat a virus that was not presently making them feel sick (Elion Affidavit at paragraphs 42-51). Another concern with the available therapies was the ability of the virus to build up resistance to these antiviral agents (Elion Affidavit at paragraphs 52-56).

[14] The regulatory approval of TDF in 2001 represented a significant improvement over previous treatment options as it was dosed once daily, had a better toxicity/side effect profile and was less prone to viral resistance (Elion Affidavit at paragraphs 76-78). Based on his clinical experiences, Dr. Elion believed TDF to be more effective than the previous alternatives (Elion Affidavit at paragraphs 81-82). TDF in combination with other therapies has since become the "gold standard" in HIV treatment (Elion Affidavit at paragraph 85).

[15] The primary medicinal problem presented by tenofovir was its limited bioavailability (the ability to get to the target cell) when taken orally. For long-term treatment of HIV/AIDS, effective oral administration of any drug was considered to be essential and IV administration impractical.

[16] The poor bioavailability of tenofovir is described by Dr. Borchardt at paragraph 65 of his affidavit:

> 62. PMPA [tenofovir] poorly passes through these cellular membranes because all cell membranes in animals and humans are made up of lipids, which are oily in nature. Charged compounds, like the ionized form of PMPA, associate with water rather than with oily lipids. This causes them to poorly partition into cell membranes and cell interiors. The oral bioavailability of PMPA is low in animals and humans. For this reason, PMPA is of limited use as an orally administered pharmaceutical antiviral agent.
>
> [Footnotes omitted]

[17] Dr. Kruse also confirmed that drugs like tenofovir that contain phosphonates "are very polar, and therefore are unable to cross cell membranes" (Kruse affidavit at paragraph 37).

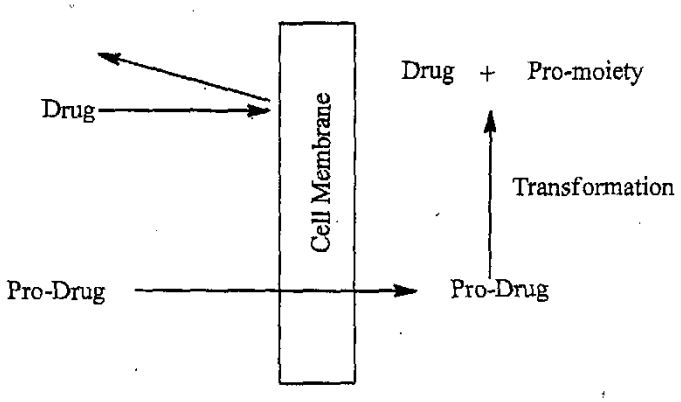
[18] One well-known means by which the bioavailability of an API can be improved is the development of a prodrug. A prodrug is described by Dr. Borchardt in the following passage from his affidavit:

> 43. A prodrug is generally defined as a modified drug made by attaching a promoiety to a parent compound. A prodrug is generally pharmacologically inactive. After oral administration, a prodrug is metabolized by a series of enzymes to produce the pharmacologically active parent compound in the body. This was well known prior to July 26, 1996 and is discussed in many references.

> 44. To treat an infection, after oral administration a prodrug must remain stable through acidic and enzyme-laden environments as it passes through the gut, crosses the intestinal mucosa into the blood, and penetrates the infected cells. Inside the infected cells, the prodrug must be processed by several enzymes within the infected cell to produce the pharmacologically active drug.
>
> [Footnotes omitted]

[19] Dr. Kruse offered the following description of a prodrug in his affidavit:

> 24. A prodrug is a drug which is inactive *per se* but is transformed in the body into the active compound (the "parent compound"). The term "prodrug" was coined by Dr. Adrien Albert in 1958. This transformation may be due to enzymatic activation or may be simply caused by a chemical reaction (for instance, the cleavage of a chemical bond as the prodrug moves into a more chemically reactive environment).



> 25. A prodrug is used for one or more of the following reasons:
>
> a. to improve the stability and/or solubility characteristics of the parent compound;
>
> b. to improve the bioavailability of the parent compound;
>
> c, to increase the duration of the pharmacological effects;
>
> d. to increase the ability of the compound to target a specific site; and

e. to decrease toxicity and adverse effects associated with the parent compound.

26. A prodrug should have a number of properties, including:

a. adequate chemical stability from a formulation perspective;

b. chemical stability in the pH environment of the gastrointestinal tract;

c. adequate solubility in the gastrointestinal tract;

d. the ability to withstand cleavage by enzymes in the gastrointestinal tract;

e. good cell permeability;

f. the ability to easily revert to the parent compound once absorbed into the blood stream or when it reaches its cellular target; and

g. non-toxic degradation byproducts.

The 619 Patent - Validity

[20] I accept that Teva's evidence concerning the 619 Patent and the 059 Patent is sufficient to fulfill its obligation to overcome the presumption of validity created by subsection 43(2) of the *Patent Act*, RSC 1985, c P-4, and the ultimate burden of proof on a balance of probabilities thus falls upon Gilead.

[21] The person of skill to whom the 619 Patent is directed is someone with an advanced degree in biochemistry, pharmaceutical chemistry, medicinal chemistry, organic chemistry or chemical engineering with practical experience in drug development including general knowledge of the design of prodrugs.

[22] Only Claim 32 of the 619 Patent is in issue. It is not disputed that Claim 32 is directed to tenofovir disoproxil and its salts. The inventive concept of Claim 32 is the use of the carbonate promoiety disoproxil with the antiviral compound tenofovir. Teva has acknowledged that it is seeking a Notice of Compliance for a pharmaceutical product containing tenofovir disoproxil and it is common ground that the Teva product will infringe if Claim 32 is valid.

Is Claim 32 of the 619 Patent anticipated by the 214 Application?

[23] In *Free Word Trust v Electro Santé Inc.*, 2000 SCC 66, [2000] 2 SCR 1024 at para 26, the Court applied Hugessen's J.A.'s classic statement of the disclosure element for anticipation by prior publication from *Beloit Canada Ltd. v Valmet OY*:

> The test for anticipation is difficult to meet:
>
> > 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.
>
> (*Beloit Canada Ltd. v. Valmet OY* (1986), 8 CPR (3d) 289 (FCA), per Hugessen JA, at p. 297)

[24] The above statement continues to be the legal standard on this issue (see *Bell Helicopter v Eurocopter*, 2013 FCA 219 at paras 109-110, [2013] FCJ No 1043).

[25] The prior art reference relied upon by Teva to establish anticipation is the 214 Application. The 214 Application was filed by Bristol-Myers Squibb Co. (BMSC) on September 10, 1991. It described the invention of "novel orally active prodrugs of phosphonate nucleotide analogs" and their salts suitable to overcome the bioavailability problems associated "with nucleotides and other ionic organophosphate esters". Teva's NOA asserted that the 214 Application "discloses prodrug forms of, inter alia, PMPA and, in particular, prodrugs in which the phosphate functionality had been esterified to improve oral bioavailability" (Applicants' Record, Volume 1, Tab 1 at p 32).

[26] All of the witnesses agree that tenofovir disoproxil is not expressly identified in the 214 Application - a point that is acknowledged at page 18 of Teva's NOA. Dr. Kruse also acknowledged under cross-examination that the 214 Application does not exemplify a carbonate prodrug (see Applicants' Record, Volume 28, Tab 238 at p 8249). Nevertheless, according to Dr. Kruse the person of skill would read the 214 Application to include tenofovir disoproxil on the strength of the following approach:

> 56. R^4 is defined as a physiologically hydrolyzable ester group and although it gives examples of these groups, a medicinal chemist would understand that R^4 is not limited to those groups since the language at page 5, line 1 is "such as". Further, a medicinal chemist would understand that the exemplified groups are not all traditional esters (i.e., $CH_2C(O)NR^5_2$, which is an ester substituted with an amide). Accordingly, a medicinal chemist would understand that the term is broader and <u>includes all functional groups that will act like an ester</u>. It follows that a skilled person would understand that all of these groups are within the definition of R^4 as defined on page 5 of the 214 Application.
>
> [Emphasis added]

According to this view tenofovir disoproxil falls within the class of "functional groups" that act like an ester and is, therefore, disclosed to the skilled reader. Also see Dr. Zamboni's affidavit at paragraph 58.

[27] Dr. Borchardt answered this evidence in the following way:

> 96. The definition of R^4 in the EP '214 Application recites a "physiologically hydrolyzable ester". A carbonate is not a physiologically hydrolyzable ester as defined in the EP '214 Application and would not be understood to be such by a POSITA.
>
> 97. In paragraph 56 of his affidavit, Dr. Kruse relies upon the phrase "such as" to read into the definition of R^4 of the EP '214 Application to expand the definition of "physiologically hydrolyzable ester" beyond the groups it exemplifies to include "all functional groups that will act like an ester". He then draws on this expanded definition to import compounds that are not specifically disclosed by the EP '214 Application. Teva's interpretation of the definition of R^4 would include thousands or millions of compounds.
>
> 98. Dr. Kruse provides a table of promoieties that he considers to be "readily hydrolysable esters" following paragraph 56 of his affidavit. Carbonate esters of nucleotide phospohonates [sic] were not known to be "readily hydrolysable esters" in the context of the EP '214 Application (i.e., useful as prodrugs). In paragraph 59, Dr. Kruse states that the EP '214 Application specifically exemplified 47 compounds, which he set out in Exhibit 2 of his affidavit. Tenofovir disoproxil is <u>not</u> exemplified in the EP '214 Application.
>
> 99. This same, misunderstanding forms the basis for Dr. Zamboni's statements in paragraphs 58(c) and 71 of his affidavit that the definition of "hydrolyzable ester group" in the EP '214 Application includes carbonates. In fact, Dr. Zamboni later corrects his earlier misunderstanding in paragraph 97, where he distinguishes between an ester and a carbonate on the basis of chemical stability. In his own words, "I have always considered a carbonate to be more stable than an ester."
>
> 100. Tenofovir disoproxil is not anticipated by the EP '214 Application. As noted above, the definition of R^4 in the EP '214 Application does not include a carbonate.

> 101. "Carbonate" is a clear and unambiguous chemical term, because it represents a unique structure, -OC(O)O-, that was known to POSITAs at the relevant time. If the inventors of the EP '214 Application intended to include carbonates, they would have done so explicitly by disclosing that structure and providing an example of a compound containing it (i.e., enabling a carbonate prodrug of a nucleotide phosphonate).
>
> 102. Without such a disclosure, a POSITA would not have understood the EP '214 Application to disclose carbonates.

[28] Dr. Maag also disagreed with Teva's witnesses for the reasons set out below:

> 79. The Kruse and Zamboni analysis of the '214 Application and their allegations in respect of novelty hinge on the definition of the R4 group defined at page 5 of the '214 Application.
>
> 80. Drs. Kruse and Zamboni have misinterpreted the definition of R4 in the '214 Application in an attempt to include all functional groups that will act like an ester (including the carbonates disclosed in the '619 Patent).
>
> 81. This is incorrect. The ester groups defined in R4 of the '214 Application do not cover carbonates. Drs. Kruse and Zamboni attempt to extend the definition of R4 because of the phrase "such as" (see for example Kruse affidavit at para. 56). This extended definition would allow the ester groups to include <u>anything</u>, including compounds that are not described. A person skilled in the art would not understand the definition of R4 to include carbonates.
>
> 82. Drs. Kruse and Zamboni concede to this fact in their affidavits by relying on "such as" to extend the very specific limited defined ester groups in R4.
>
> 83. Clearly, if the inventors had intended to include carbonates, they would have included an appropriate chemical definition for such groups and disclosed and enabled such groups, which they did not.

[29] Teva's evidence rests heavily on the significance of the words "such as" found in the 214 Application. Drs. Kruse and Zamboni say that the person of skill would interpret the 214 Application expansively in light of that open-ended language and readily conclude that tenofovir disoproxil was included.

[30] The person of skill is "trying to understand what the author of the description [in the prior patent] meant" (see *Apotex v Sanofi*, 2008 SCC 61, [2008] 3 SCR 265 at para 25). If there is doubt about what the prior art reference includes, it cannot be taken to meet the definition of anticipation. Faced with uncertainty, the person of skill would not be inclined to read up the prior art language or to draw grammatical inferences of the sort made by Teva's witnesses. Here the uncertainty would be magnified by the absence of any extant prior art describing a carbonate prodrug of a phosphonate nucleotide. I reject the suggestion by Teva's witnesses and, in particular, by Dr. Kruse at paragraph 56 of his affidavit, that by listing a few compounds preceded by the words "such as" a person of skill would conclude that the reference to "physiologically hydrolyzable ester group" means "all functional groups that act like an ester". It seems to me that, in the absence of any evidence of bad faith or misrepresentation and in the face of a stark disagreement among the expert witnesses about whether the 214 Application would be read by the person of skill to include tenofovir disoproxil, what is left is uncertainty and not anticipation. Essentially the same point was made by Justice Judith Snider in *Merck & Co. Inc. v Apotex Inc.*, 2010 FC 1265 at para 602, [2010] FCJ No 1646, where she said that "where the existence of the compound alleged to be anticipatory cannot be reasonably or consistently predicted from a large universe of possibilities, I cannot see how this could possibly meet the test for disclosure." I do not agree that the 214 Application would be read by a person of skill to include tenofovir disoproxil. It teaches nothing about a carbonate

prodrug solution to overcome the bioavailability limitations of tenofovir. Gilead has met its burden of proof on this issue.

[31] It necessarily follows from this finding that Claim 32 of the 619 Patent is not a selection of tenofovir disoproxil from the 214 Application and Teva's selection–related invalidity assertions also fail.

The 619 Patent - Obviousness

[32] The principles of obviousness are set out in section 28.3 of the *Patent Act*. The parties agree that the relevant date for assessing whether Claim 32 of the 619 Patent was obvious is the claim date of July 26, 1996.

[33] In *Sanofi*, above, the Supreme Court of Canada set out the following four-part test for determining if a patent claim is obvious:

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

The fourth step of an obviousness inquiry may require an "obvious to try" analysis which the Court in *Sanofi* described in the following way:

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

An obviousness challenge will not succeed if the prior art only establishes that something might work. It also cannot be built upon a selective analysis of the prior art.

[34] As with Justice Roger Hughes in *Novartis Pharmaceuticals Canada Inc. v Teva Canada Limited.*, 2013 FC 283 at para 161, 2013 FCJ No 303 , I endorse the view of obviousness and obvious to try expressed in the following passage from by Kitchin L. J. in *MedImmune Ltd. v Novartis Pharmaceuticals UK*, [2012] EWCA Civ 1234:

> 90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of

patent protection in all such cases would act as a significant deterrent to research.

91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in *Conor* at [42]:

> "In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation would be needed depended on the particular facts of the case."

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. *In Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

> 93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim…

Also see *Eli Lilly and Company v Janssen Alzheimer Immotherapy*, [2013] EWHC 1737 at para 232.

[35] The strength of the ability to predict success is the lynchpin to an obvious to try analysis and not necessarily whether the means or methods employed to arrive at the result were well-known. This point was recently emphasized by Pelletier J. A. in the following passage from *Apotex Inc. v Sanofi-Aventis*, 2013 FCA 186, [2013] FCJ No 856:

> 78 As a result, the Trial Judge found himself in exactly the same position as did the Supreme Court when it decided *Plavix*, cited above. The focus of the obviousness analysis in *Plavix* was not the difficulty in seperating [sic] the racemates covered by the '875 genus Patent - which included PCR 4099 - but the unknown properties of the resulting enantiomers. :
>
> > The method to obtain the invention of the '777 patent were common general knowledge. It can be assumed that there was a motive to find a non-toxic efficacious product to inhibit platelet aggregation in the blood. <u>However, it was not self-evident from the '875 patent or common general knowledge what the properties would be and therefore that what was being tried ought to work.</u>
> >
> > *Plavix*, cited above, at paragraph 92
>
> 79 The reasons of the Trial Judge make it clear that, as was the case in *Plavix*, it was not possible to predict the properties of the separated enantiomers: Reasons, at paragraphs 673 and 676. The lack of knowledge as to these properties is precisely what led the Supreme Court in *Plavix*, cited above, to hold that it was not self-evident that what was being tried ought to work (*Plavx [sic]*, at paragraph 92,

> quoted above). Simply put, the person skilled in the art would not think of separating PCR 4099 and testing its enantiomers in order to obtain the benefit of its properties when the existence and nature of those properties were unknown.
>
> 80 It follows that although the resolution of PCR 4099 was part of the common general knowledge, nothing turns on this as it is the unknown nature of the properties of the enantiomers which explains why the invention was not "obvious to try".
>
> 81 Given that the Trial Judge applied the test for obviousness set out in *Plavix*, and given that he applied it to the same material facts as the Supreme Court, he ought to have come to the same conclusion. His error lay in failing to recognize that the unknown nature of the properties of the enantiomers of PCR 4099, or of any of the other compounds of the '875 Patent, was fatal to the "obvious to try" analysis. Put another way, the distance between the common general knowledge and the inventive concept of the '777 Patent could not be bridged by routine experimentation since the results to be obtained were unknown. On the facts, this was confirmed by the fact that the inventors, who had more knowledge that the person of ordinary skill in the art, attempted to resolve a number of other compounds before finally trying PCR 4099: see Reasons, at paragraphs 752-759.
>
> 82 As a result, the Trial Judge erred in finding that the invention of the '777 Patent was obvious.
>
> [Emphasis in the original]

[36] Tenofovir disoproxil was the first example of a carbonate prodrug on a phosphonate nucleotide. Because there were no direct comparators, Teva's case is built primarily around the person of skill drawing several inferences from the prior art dealing with prodrugs of other parent compounds where some success had been achieved.

[37] In their application of the prior art to the discovery of tenofovir disoproxil, Drs. Kruse and Zamboni essentially isolated each choice that the person of skill would face and, in doing so, they failed to view the problem in context. By proceeding in this way they fail to recognize that if at the

junction of each investigatory pathway or choice an element of uncertainty arises, the cumulative level of uncertainty must be taken into account. In considerable measure, the Teva witnesses made untenable extrapolations by glossing over or ignoring the degree of scientific uncertainty that would have confronted the person of skill and the inventors at several points along the pathway to tenofovir disoproxil. I do not agree that the prior art illuminates that pathway as clearly as the Teva witnesses suggest. In my view, the evidence from these witnesses is selective and reflects a classic hindsight analysis.

[38] I am satisfied from the evidence that a person of skill would have considered tenofovir to be a worthy candidate for development as a prodrug and in the search for promoiety options that person would have looked, at some point, at the carbonates. However, I do not agree with Teva that the carbonates or the carbomates would be considered by the person of skill to be the only reasonable or viable options. I also do not agree that a person of skill would have predicted directly and without difficulty that any of the potential promoiety options would work. Indeed, the history of prodrug development described in the prior art included many failures and unpredictable outcomes.

[39] Dr. Kruse was questioned during cross examination (Applicants' Record, Volume 28, Tab 238) about the properties that were required for the development of a successful prodrug and, in particular about paragraph 26 of his affidavit. His responses reflect the general complexity of the problem facing the person of skill:

> 199 Q. I think you start that around paragraph 24. You have some pictorials there, and you set out in paragraph 25 some of the kinds of things where a prodrug might have an implication, but I am

looking at 26, and you say that a prodrug should have a number of properties. I think you have seven of them there. Do you see that?

A. Yes.

200 Q. Am I correct in my understanding that what you are saying here is that for a prodrug to be practically successful, it would have to, for example, have adequate chemical stability when you make the thing?

A. For a prodrug to be successful, it would have to have enough of the properties on the list that it actually gets into the target in the body.

201 Q. Right. You put them, I think, kind of in this order, so the first step would be that, chemically, it has to be stable enough that you can make it into a formulation that will remain in the chemical state you want it to remain in?

A. Yes.

202 Q. If you have achieved that, now it goes into the body if we are dealing with an oral, and now it goes into the stomach and the lumen, and now it is exposed to the gastric juices and whatnot. I think the second one is it needs to be stable in that environment?

A. It is going to vary from compound to compound, depending upon where the drug is absorbed, but presumably, it would need to navigate the acid pH of the stomach,

203 Q. Right, because if it got into the stomach, and at that pH it lost its stability and broke up at that point, you wouldn't have the prodrug anymore.

A. That's right.

204 Q. You would now be back to the active - -

A. That's right.

205 Q. Am I correct in my understanding that when we speak of prodrugs, we generally have a component which I am going to call the "active moiety"?

A. Yes.

206 Q. That active moiety, scientists know will have some desirable properties if it got to a cell and did something. Is that generally what happens?

A. Yes.

207 Q. For some reason, that active moiety chemically can't be made adequately or won't go through the body or won't stay in the plasma but ultimately can't get to the cell for some reason?

A. For some reason; correct.

208 Q. Some of these reasons are what may lead a scientist to say, "Maybe we can use a prodrug approach to bring this thing which itself isn't going to get into where we want it, but somehow we will get it in."

A. Yes.

209 Q. We were, say, at (b), so we needed this prodrug that you made to be at least stable enough to survive the pH environment of the stomach and the GI, otherwise it would be broken down right there. You would be back to your active moiety, which the scientist knows isn't getting in somehow?

A. Yes.

210 Q. In (c), for instance, when you say, "Adequate Solubility," I guess that is a sine qua non because it has no solubility. I think the expression is it is "brick dust," and it just goes through the GI?

A. You have been hanging with scientists too long. That's the exact slang, exactly; yes.

211 Q. It has to be sufficiently soluble so that it can somehow at least have a shot at getting through into the intestine?

A. Yes.

212 Q. Then, of course, when you say, (e), by "Permeability" - - I just want to make sure I understand - - you mean permeability through the intestinal wall which, I guess, would be the endothelium?

A. Yes. I mean it could be any cell permeability. It could be the intestinal wall; it could be the target cell; it could be the nucleus of the target cell. If it is the central nervous system, it could be the blood-brain barrier. So this is kind of a wish list, and a successful prodrug should have a number of these properties. It is almost like a menu that several are probably going to be necessary for any particular drug, but they may differ depending upon the target and so on and so forth.

213 Q. Just on the permeability, I think you are right because to get in through the endothelium into the intestine, it has to get into the cells that are in the intestine. So it has to be permeable at that level, right?

A. Yes.

214 Q. Then, as you mentioned, if it ultimately gets into circulation and is exposed to the target cell that you are interested in, it is now facing another membrane.

A. There are plenty of cases where cleavage of the prodrug occurs in the plasma or even fairly fast in the intestine, and it is still a pretty good prodrug. Enough of it gets into the plasma, or sometimes, the parent that the prodrug is cleaved - - parent in plasma, and it still gets to the target cell.

215 Q. I think, just going back to your original point, that when you get to the target cell, you have another membrane that has to be crossed, generally. Right?

A. That's correct.

216 Q. Then, you mentioned the nucleus, and it too has a - - am I correct calling it a membrane - - around the nucleus?

A. Correct.

> 217 Q. So if this particular drug needs to intervene in the nucleus for whatever reason, it would have another barrier to cross?
> A. Yes.
> 218 Q. So when you say "permeability" in (e), it could be permeability at a number of levels - -
> A. - - or only one.
> 219 Q. Right; depending on the drug and where it needs to be active in the body?
> A. Yes.

[40] When he was later asked about the ability to predict efficacy with phosphonates by extrapolation from prodrug strategies utilized with carboxylic acids, he responded that he would not be able to do so without experimentation (see Applicants' Record, Volume 28, Tab 238 at p 8225 and pp 8252-8253). This evidence does not differ materially from that of Dr. Borchardt at paragraph 148 of his affidavit:

> Needless to say, this complex interplay of opposing chemical and metabolic properties makes for a process that defies rational drug design in that it is entirely unpredictable and completely empirical.

Also see the Maag affidavit at paragraph 100.

[41] Notwithstanding the above evidence, Dr. Kruse makes several material extrapolations in concluding that the discovery of tenofovir disoproxil was obvious (see paragraph 124 of his affidavit). For instance, Dr. Kruse surmises that the person of skill would understand from the 214 Application that a prodrug strategy for phosphonate nucleotide analogs would include "a carbonate". Dr. Kruse also assumes that prodrug strategies used with adefovir would be interchangeable with tenofovir. Because carbonate promoieties had been successfully used to mask the hydroxyl group of carboxylic acids, Dr. Kruse similarly surmises that they could be successfully

employed with phosphonic acids. Despite acknowledging the structural differences between the POM and POC prodrug moieties, Dr. Kruse maintains that the skilled person would expect them to behave in the same way. These assumptions are summarized at paragraph 138 of Dr. Kruse's affidavit:

> 138. The skilled person would anticipate, based on the prior art, that the [(alkoxycarbony1)oxy]alkyl prodrug moiety would break down in a similar manner as the acyloxyalkyl prodrug moieties and at about the same rate of hydrolysis. In addition, the skilled person would expect that an [(alkoxycarbonyl)oxy]alkyl prodrug would work with a phosphonate by reference to the antibiotic prior art. Specifically, considering that (1) both acyloxyalkyl and [(alkoxycarbonyl)oxy]alkyl prodrug groups were successfully used with antiobiotics, and (2) the acyloxyalkyl prodrug group was known to work successfully with adefovir and tenofovir (phosphonates), it follows that the [(alkoxycarbonyl)oxy]alkyl group should also work with tenofovir.

[42] It is unnecessary to deal with all of the points of disagreement among the expert witnesses in this case because there are sufficient material elements of predictive uncertainty in the evidence to dispel Teva's assertion of obviousness.

Carboxylic Acid Experience

[43] Dr. Kruse states at paragraph 77 of his affidavit that the person of skill would look to prodrug moieties found to be useful with carboxylic acids in searching for a prodrug for tenofovir. Dr. Kruse asserts that the prior art taught that prodrug moieties used for carboxylic acids could be used with phosphonic acids. Since carbonates had been used with some success with carboxylic acids, he postulates they could be used with tenofovir.

[44] It seems to me that this evidence over-simplifies the comparative similarities between phosphonates and carboxylic acids. At paragraph 40 of his affidavit, Dr. Kruse vaguely asserts that the two classes are "quite similar". He jumps from that to the conclusion that in looking for a prodrug for a phosphonate the person of skill would look to strategies that had been successfully used with carboxylic acids. This generalization is repeated at paragraphs 138 and 139 of his affidavit followed by the assertion that the testing methods required to prove the expectation of efficacy were well-known and routine. At paragraph 157 Dr. Kruse makes the point again:

> 157. *A priori* there is no reason why a prodrug moiety that works for a drug containing a carboxylic acid would not work for drugs containing a phosphonate. This is especially true considering that the pivaloyloxyinethyl prodrug moiety (POM) was successfully used on multiple antibiotics containing carboxylic groups (such as pivampicillin), as well as on antivirals containing phosphonate groups (such as adefovir and PMPA). Accordingly, the [(alkoxycarbonyl)oxy]alkyl groups, successfully used on antibiotics, should also work on the phosphonate containing antivirals.
>
> [Emphasis added]

This is rather an odd way to express the problem. The sole fact that something is known to work in one context does not logically support an inference that it ought to work in another. The absence of reasons to dispel an inference do not support the drawing of that inference.

[45] Gilead's witnesses contend that even if one was to look in the direction of carboxylic acids very little would emerge that would point to a carbonate solution let alone to the selection of tenofovir disoproxil. Gilead contends that the prodrug experiences with carboxylic acids offered no predictive value in the search for prodrugs either within that class of compounds or outside of it

(ie. the phosphonate class). This point is made by Dr. Borchardt at paragraph s 218-220 of his affidavit:

> 218. Teva raises this allegation in an attempt to rationalize the application of prior art related to carboxylic acids (e.g., antibiotics) to the phosphonate groups at issue in the instant proceeding. Rather, the prior art (Ferres (1983)) warns about generalizing across different structural classes: "[o]bviously, an attempt to generalize to the extent implied in Fig. 27 is fraught with difficulties. . . . Certainly, attempts to transfer penicillin pro-drug ideas to cephalosporins have only met with partial success." Ferres (1983) makes this statement in regards to two different carboxylic acid prodrugs, which are far more similar to each other than carboxylic acid prodrugs are to phosphonate prodrugs.
>
> 219. Teva's allegation that properties of carboxylic acid prodrugs are predictive of the properties of phosphonate prodrugs are unsound for the following reasons:
>
> a. Carboxylic acids and phosphonates are not chemically and biochemically quite similar:
>
> (i) Carboxylic acids contain a carbon atom, whereas phosphonates contain a phosphorus atom. Carbon and phosphorus are different atoms with different chemical and physical properties, and their presence in structures naturally leads to different effects and activities;
>
> (ii) Regardless of the fact that both carboxylic acids and phosphonates have double-bonded oxygens as well as hydroxyl groups, a POSITA would not assume that the chemistry of these two groups will be the same, and indeed it is not the same;
>
> (iii) The phosphonate group contains two hydroxyls (-OH), and thus requires two chemical modifications to mask the negative charge. In contrast the carboxylic acid group only contains one hydroxyl, and thus only one chemical modification is required;
>
> (iv) Different enzymes would participate in the removal of the promoieties from carboxylic acid prodrugs versus phosphonate prodrugs to release the parent drug into the body; and

(v) There was great skepticism that it was even possible to make these compounds, especially since there were no carbonate derivatives of nucleotide phosphates know at the relevant time.

b. There was nothing in the literature that would motivate a POSITA to look at carboxylic acid prodrugs with any expectation that the promoieties could be applied successfully to phosphonate prodrugs, or predict their properties:

(i) For example, PMPA is a bisphosphonate, and thus as described above requires two promoieties to mask the negative charges. Hence, its chemistry is completely unrelated to carboxylic acids. In my opinion, the carboxylic acid esterification literature does not provide a POSITA with any expectation of success regarding phosphonate prodrugs; and

(ii) There was no literature that would support a reasonable expectation of success of taking the promoiety of a carboxylic acid and applying it to a phosphonate to make a chemically stable and orally bioavailable antiviral drug.

c. Notably, the examples and/or literature cited by Teva and its experts contradicts the very proposition being advanced by Teva. The teaching of carboxylic acid prodrugs is not transferable to phosphonate prodrugs as alleged by Teva.

d. In fact, and as set out below, the prior art taught that it is not predictable to generalize application of a given prodrug strategy from:

(i) One carboxylic acid prodrug to another carboxylic acid prodrug;

(ii) One carboxylic acid prodrug to a phosphonate prodrug; and even

(iii) One phosphonate prodrug to another phosphonate prodrug;

with any expectation that the first prodrug would result in the same properties for the second prodrug, including for

> example, chemical stability and/or improved oral bioavailability.
>
> 220. In summary, Teva fails to appreciate that properties of prodrugs of one type (e.g., phosphonate nucleotides) are not interchangeable or predictable on the basis of previous known prodrugs (e.g., carboxylic acids); rather the properties of prodrugs must be empirically determined.
>
> [Footnotes omitted]

[46] Dr. Maag also challenged Teva's evidence by identifying the "significant" chemical and biological differences between phosphonates and carboxylic acids:

> 170. Paragraph 40: Dr. Kruse states "A phosphonate is chemically and biochemically quite similar to a carboxylic acid." This is misleading and incorrect. There are significant chemical and biological differences between a phosphonate and carboxylic acid. For example, carboxylic acids have one oxygen available for modification by a prodrug moiety, while a phosphonate has two oxygens, which must be modified to eliminate the double negative charge of a phosphonate under physiological conditions. Metabolism of ester prodrugs of carboxylic acids is typically carried out by esterases, while the metabolism of phosphonate esters requires the action of a phosphodiesterase or a phosphotriesterase. Thus, the enzymes involved with the metabolism of carboxylic acid esters are distinct from the enzymes involved with the metabolism of phosphonate esters. As such a person skilled in the art could not predict the behaviour of phosphonate esters prodrugs from carboxylic acid ester prodrugs. Therefore a medicinal chemist would not look to promoieties of drugs containing carboxylic acids to design prodrug moieties for phosphonate groups.
>
> 171. Paragraph 42: Dr. Kruse states that the person skilled in the art would look at prodrug moieties which have been successfully employed with carboxylic acids to arrive at prodrug moieties for phosphonic acid groups. In particular, he states that ".... given the similarities between a carboxylic acid groups and a phosphonic acid group, the skilled person would look at prodrug moieties that had been successfully used with carboxylic acids and apply those to phosphonic

> acids". I do not agree with this statement. A person skilled in the art understood that the metabolic enzymes are different in the two cases (esterases vs. phosphodiesterases for instance) and would endeavor to look for prodrug moieties which are preferentially metabolized by phosphodiesterases. A person skilled in the art would not expect such prodrug moieties to be the same as those identical with groups metabolized by esterases.

Also see the evidence of Dr. Borchardt at paragraph s 121-122 of his affidavit and the evidence of Dr. Maag at paragraph s 158-165 and 174 of his affidavit.

[47] Dr. Borchardt also pointed to failures that arose when carboxylic acid prodrugs were attempted with PMEA (see paragraph s 28 to 30 of his affidavit). This concern is borne out in a 1983 paper by Ferres who cautioned against generalizing about prodrug strategies even within the carboxylic acid group of compounds:

> Obviously, an attempt to generalise to the extent implied in Fig. 27 is fraught with difficulties. The scheme at least provides a useful starting point. There are probably a number of newer penicillins, with complicated side-chains which will defy over- simplified attempts to make predictions on oral absorption along the lines suggested in Fig. 27. Certainly, attempts to transfer penicillin pro-drug ideas to cephalosporine have only met with partial success.

[48] Carbonate esters also did not work in animal studies with the anti-inflammatory carboxylic acid drugs ibuprofen and naproxen. This was the conclusion reached by Samara and others in a 1995 paper "Pharmacokinetic Analysis of Diethylcarbonate Prodrugs of Ibuprofen and Naproxen" *Biopharmaceutics and Drugs Disposition*, Volume 16, 201-210 at p 209 (Applicants' Record, Volume 9, Tab 107 at p 2615):

> The diethylcarbonate esters of ibuprofen and naproxen investigated in this study, ibudice and napdice, did not offer any pharmacokinetic or pharmacodynamic advantages over the parent compounds. They were found to be unstable in the GI tract and therefore underwent rapid conversion to the parent compounds. Thus, neither ibudice nor napdice exhibited any sustained release characteristics following oral dosing to dogs.

[49] Although the expert witnesses disagree about the significance of some of the prior art references (ie. *Samara*, above, and *Safadi* 1993 (Applicants' Record, Volume 15, Tab 55)) my reading of them indicates that the person of skill would at least be cognizant of the issues they raised and, unlike Dr. Kruse, would not dismiss them out of hand as irrelevant.

[50] Under cross-examination Dr. Kruse acknowledged a number of structural differences between phosphonates and carboxylic acids (see Application Record at pp 8221-8222). More importantly, the evidence of the Teva witnesses failed to address, let alone challenge, most of the specific points raised by Drs. Borchardt and Maag and which discounted the comparative value of carboxylic prodrug strategies. In the result, I accept the evidence from the Gilead witnesses to the extent that it discounts the significance of carboxylic acid prodrug models in the search for a promoiety for tenofovir.

Comparing Adefovir/Tenofovir and POM/POC

[51] It is common ground that adefovir and tenofovir were known phosphonate antiviral drugs. They are structurally similar but not identical. Unlike adefovir, tenofovir contains a methyl group on its side chain. Both compounds were understood to have poor bioavailability profiles. BMS had attempted to overcome the bioavailability problems with adefovir and racemic tenofovir by

experimenting with a number of promoieties including (pivaloyloxy) methyl or POM. There was, however, a toxicity problem associated with POM in that it produces pivalic acid and depletes the natural stores of carnitine in the human body. Although carnitine depletion could be addressed with dietary supplements, it was preferable to identify a promoiety that avoided the problem entirely.

[52] Teva's witnesses say that the prior art references concerning the search for prodrugs for adefovir would lead the person of skill directly and without difficulty to the choice of tenofovir disoproxil. I do not agree.

[53] The supposed simplicity of extrapolating from the prior art concerning adefovir as expressed by Drs. Kruse and Zamboni is belied in no small measure by the high number of assumptions that are required (see for example paragraph 124 of the Kruse affidavit). To the extent that the Teva witnesses draw support from the ostensible teachings of the 214 Application and the carboxylic acid experiences noted in the prior art their positions are, as discussed above, untenable. Indeed the 214 Application exemplifies 47 compounds not one of which is a carbonate. The supposed simplicity of the exercise described by Teva's witnesses is further belied by the numerous prodrug options that had been attempted with phosphonate nucleotides not one of which identified a useful carbonate promoiety (see, for example, Starrett 1994 (Applicants' Record, Volume 15, Tab 66) and Krise and Stella 1996 (Applicants' Record, Volume 28, Tab 246)). If the exercise was as simple and uninventive as suggested by Teva, one is left to wonder why the carbonate solution to the bioavailability problem associated with phosphonate nucleotides was not unequivocally expressed in the prior art.

[54] Although Dr. Kruse is undoubtedly correct that adefovir and tenofovir are structurally very similar, his evidence under cross-examination left room for some uncertainty. For instance, he could only state that "small structural changes don't greatly perturb a big, complicated molecule" and the additional methyl group with tenofovir is "at a point where it doesn't affect things very much".[1] This evidence is not sufficiently compelling to displace Dr. Maag's opinion that a person of skill would not assume "that the prodrug experience with adefovir could be applied to tenofovir" (see paragraph 109 of the Maag Affidavit and paragraph s 235-236 of the Borchardt Affidavit). Although Teva argues that Gilead's own research with tenofovir began by examining prodrug moieties that had worked with adefovir, the results, according to Dr. Lee, did not establish a helpful correlation (see Lee Affidavit at paragraph 39).

[55] The Teva witnesses also contend that the POM and POC promoieties would be understood at the time to be effectively interchangeable and that the person of skill would assume them to behave the same way in improving oral bioavailability of their parent compounds. To the extent that they rely upon the 214 Application and the prior art concerning carboxylic acids, these opinions are unsustainable. Dr. Kruse's evidence on this point is further undermined by a material misstatement in his affidavit where he deposed that there were examples in the prior art of prodrugs of tenofovir known to improve oral bioavailability. Under examination he retreated from this statement and conceded the following:

> 667 Q. Dr. Kruse, can you go to "(b) Inventive Concept," paragraph 125. I will read this to you:
>
> "The active parent compound tenofovir was already known, as were prodrugs of phosphonate nucleotide

[1] Also see his testimony at p 8262 where he stated that, even in the absence of oral bioavailability data for bis POM PMPA, he would expect oral bioavailability to be similar or identical.

derivatives, including adefovir and PMPA, that had improved oral bioavailability." (As read)

Would you please identify for me, Dr. Kruse, where in the prior art that you cite at the end of your affidavit, you find examples of prodrugs of PMPA that have improved oral bioavailability?

A. I could certainly cite the patent in suit.

668 Q. The only example that you can refer us to that demonstrates improved oral bioavailability is what is referred to as the 619 patent? Is there anything in the prior art?

A. That may be the only example of oral bioavailability, but I refer back to the Srinavas paper for bioavailability in general for PMPA.

669 Q. Once again, we are referring to the anti-HIV activity that spoke to the in vitro culture testing that was done?

A. Yes.

670 Q. That is what you are using to say that - -

A. That shows improved - -

671 Q. That prodrugs of PMPA showed improved oral bioavailability over the parent compound?

A. It showed improved bioavailability but not oral bioavailability.

672 Q. So there is no example of oral bioavailability in the prior art?

A. I am unable to recall it.

673 Q. In the next sentence, you say:

"In fact, the bioavailabilities of these known prodrugs of adefovir and PMPA were comparable with the prodrugs of tenofovir disclosed in the 619 patent.

In essence, the only example that you are able to point me to is what is disclosed in the patent, so there is nothing that you are comparing?

A. I believe that's correct.

674 Q. Finally, you say:

"There is no mention in the 619 patent of particular advantages of the disclosed prodrugs over other prior art prodrugs of tenofovir."

However, we just established that you weren't able to identify any examples of prodrugs of tenofovir in which any oral bioavailability testing was done prior to the 619 patent.

A. I believe that's correct with respect to oral, but I don't make the statement "oral" here.

675 Q. Right; but with respect to oral, only oral bioavailability, you would agree with my statement?

A. Yes.

[56] In the absence of reliable data, I do not agree that a person of skill would readily assume that the bioavailability properties associated with POM prodrugs would be associated with POC prodrugs. Instead I prefer the evidence of Dr. Borchardt at paragraph 188 of his affidavit. I also accept Dr. Maag's evidence that the person of skill would be at least concerned about potential stability problems associated with these promoiety classes (see Dr. Maag's Affidavit at paragraph s 112-117 and the 1993 Srinivas paper (Applicants' Record, Volume 15, Tab 65 at p 4424)).

What the Prior Art Did Teach

[57] The overall complexity of the problem confronting a person of skill at the time is accurately reflected in a 1996 review article authored by Jeffrey Krise and Valentino Stella "Prodrugs of phosphates, phosphonates, and phosphinates" in *Advanced Drug Delivery Reviews,* Volume 19, pp 281-310 (Applicants' Record, Volume 28, Tab 246). The paper describes itself as a review of the available literature "on the use of prodrugs to overcome the drug delivery obstacles associated with phosphate, phosphonate and phosphinate functional group containing drugs". It begins with a statement that the "ability to orally deliver these drugs and to target them to desired sites has led to limited success". The authors describe in considerable detail the prodrug strategies that had been utilized for this group of compounds and the mixed results that had been achieved. The issues that needed to be addressed to obtain a viable prodrug were described in the paper in the following way:

> Although alterations in apparent clearance rates may be important, the principal goals of most prodrug modification efforts on phosphate, phosphonate and phosphinate drugs is alteration of membrane permeability to improve oral (GI permeability), brain,

tumor and cellular delivery (mainly to virally infected cells) of these agents.

When these prodrugs are used for improving oral bioavailability, various issues dealing with GI absorption of drugs must be considered. The ability to address these issues will ultimately determine the proper selection of the prodrug system and its likely success. The optimal scenario for enhanced systemic delivery of prodrugs after oral dosing is as follows:

1. The prodrug must display adequate chemical stability for formulation purposes as well as stability in the variable pH environment of the GI tract.
2. The prodrug should have adequate solubility in the GI tract environment to allow for dissolution.
3. Once dissolved, the prodrug should also display enzymatic stability to lumenal contents as well as the enzymes found in the brush border membrane.
4. The prodrug should have properties that allow for good permeability (generally associated with an adequate log *P* value).
5. After permeation of the lumenal membrane, the prodrug could revert to the parent drug either in the enterocyte or once absorbed into systemic circulation. Post-enterocyte reversion is desired because conversion in the enterocyte would also allow for back diffusion into the GI lumen, a problem which is not generally recognized.

When the prodrug is formulated to increase cellular permeability into viral-infected cells, tumor cells or across barriers like the blood brain barrier, the desired characteristics might change. Replacing the desire for complete and rapid post absorption reversion, is a need for balance in lability. The most optimal scenario, however unrealistic, would be for the prodrug to have complete enzymatic and chemical stability during the absorption process and in blood but readily revert to the parent compound once it has permeated the targeted cell, thereby ‘trapping’ the drug in the cell (Scheme 2).

Considering both of these scenarios, prodrugs for improved oral delivery and prodrugs for improved cell targeted delivery, the rate of bioreversion is a very important process that must be considered in detail when designing prodrug systems. For example, if bioreversion is very fast and non-specific, prodrug reversion may take place before the limiting barrier is overcome. On the other hand, if reversion is slow and inefficient at all sites, the prodrug may

> readily reach the site of action but never release enough parent drug to elicit a pharmacological response. With these factors in mind, choosing a suitable bioreversible protective group for phosphates, phosphonates and phosphinates presents a major challenge.
>
> [Applicants' Record at pp 8282-8283]

The paper concludes with an acknowledgement of the advances that had been achieved in this area with a recognition that "more innovative research was still required to overcome the barriers to the delivery of polar drug molecules":

> Great strides have been made toward solving the problems associated with the in vivo delivery and targeting of phosphate, phosphonate and phosphinate functional group-containing drugs using prodrugs. With few exceptions, most efforts have involved technologies applied to alter the polarity of other functional groups like carboxylic acids. Some new chemistry and innovative findings have been presented. Alternative chemistry and more imaginative approaches may be necessary before more complete success is realized. It is our hope that this review will bring its readers reasonably up to date on the current literature in this important area of prodrug research. Additionally, we hope it helps stimulate further and more innovative prodrug research into overcoming the barriers to the delivery of polar drug molecules.
>
> [Applicants' Record at p 8297]

[58] I do not agree with Teva that a person of skill would have discounted the Krise and Stella research paper because the authors were likely motivated by a desire for research funding. This is pure speculation. There is no evidence to suggest that these apparently competent investigators overstated the predictive uncertainty of the prior art. To my thinking the person of skill would approach a timely review article written by respected research scientists with no less confidence than a paper written by someone working in an industrial setting. Indeed, a thorough overview of

current research on a given subject is likely to offer more insight to the person of skill than any single piece of research directed at overcoming one problem among many others.

[59] A 1995 review paper by David Fleisher et al published in the *Advanced Drug Delivery Review* titled "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs" (Fleisher, David et al, "Improved oral drug delivery: solubility limitations overcome by the use of pro drugs" (1996) 19 *Advanced Drug Delivery Reviews* 115 at 128; Applicants' Record, Volume 8, Tab 89(19)) also addressed the problems associated with the development of prodrugs at that time. The authors attributed the relative lack of success in developing oral prodrugs to the selection of "the wrong drug candidate" and to the need to overcome the "formidable challenge" to balance "the properties of prodrug chemical stability and enzymatic lability in concert with prodrug solubility and parent drug or prodrug intestinal permeability".

[60] The state of the prior art was not one of scientific consensus or certainty and carbonate promoieties were apparently not a particular focus of study. The 1994 Starrett, above, reference fairly expresses the state of knowledge at the relevant time and it effectively undermines the opinion evidence relied upon by Teva:

> Relatively few examples of phosphonate prodrugs or prodrugs of closely related analogues of phosphonates have appeared in the literature. Farquhar and co-workers have reported the use of (acyloxy)alkyl prodrugs of organophosphates to phosphates to increase permeation across biological membranes. The acyloxy alkyl ester of phosphonoformate has been prepared, and Krapcho et al. have employed (acyloxy)alkyl prodrugs to improve the bioavailability of phosphinates. A prodrug of PMEA has been synthesized by linking a synthetic polymer bearing mannosylated residues to PMEA.1 In contrast to phosphonates, a much wider range of prodrugs have been successfully employed for preparation of carboxylic acid prodrugs. Acyloxyalkyl esters, as well as

> glycolamide esters, alkyl esters, and amides, have been extensively used. The goal of the present study was to build on the carboxylic acid experience and evaluate a wide array of structural types as potential prodrugs of the phosphonate functionality. Preliminary results describing *in vitro* antiviral activity of the bis[(pivaloyloxy)methyl] prodrug of PMEA (10a) against HIV, HCMV (human cytomegalovirus), HSV-1, and HSV-2 have recently been published in communication form. We herein report on the synthesis, oral bioavailability, and antiviral activity of several different classes of phosphonate-derived prodrugs of PMEA.
>
> [Applicants' Record at p 4434] [Footnotes omitted] [Emphasis added]

The authors then conclude the paper by observing that their data "should provide the impetus for further exploration of this exciting class of compounds" (POM not POC).

[61] The prior art belies Teva's argument that the creation of an efficacious prodrug for tenofovir was a simple linear exercise devoid of ingenuity. To my thinking Dr. Maag's evidence at paragraph 98 to 100 fairly expresses the problem faced by the person of skill looking for a promoiety for tenofovir and establishes that the discovery of tenofovir disoproxil was inventive:

> 98. For any given parent compound for which a prodrug form is desirable, there are often a large number of possibilities from which to choose. There is no way to predict in advance which prodrug moieties will be both sufficiently stable to allow the drug to pass through gastrointestinal tract and enter the blood stream and at the same time be sufficiently labile to be cleaved and thereby release the parent drug in the cells where it can be effective. As discussed further below, this complexity is naturally compounded when, as is the case with tenofovir, the parent drug requires multiple promoieties to mask multiple negative charges, each of which must be cleaved at the appropriate point by different enzymatic mechanisms. Furthermore, given the impact that structural changes can have on the properties of a parent drug compound, knowledge of prodrug moieties used for a given parent compound is of limited use when searching for a

> prodrug for a different compound. The addition of a prodrug moiety can alter the whole molecule's chemical and biological properties, including its solubility and ability to be recognized by enzymes.
>
> 99. The other level of complexity in designing prodrug moieties is that one has to consider the breakdown products that will be released when the moiety is cleaved from the parent compound as well. Such breakdown products should not be toxic as they will be released into the body.
>
> 100. In summary, prodrug design is a multi-faceted complex problem that has no clear, predictable solution. If the person skilled in the art was seeking to develop a prodrug form of the compounds described in the '619 Patent, there would have been many prodrug approaches to consider and pursue. There was no way to predict in advance which prodrug moieties would work.

The Inventive History

[62] The evidence of the work that Gilead carried out to develop tenofovir disoproxil also tips the evidentiary scales in its favour. Professionals working in the field are not overly prone to devoting time and resources pursuing lines of enquiry that are unpromising. As with the notional person of skill, they tend to be knowledgeable and reasonably up-to-date in their fields of work and in many cases – unlike the person of skill – they bring inventive minds to the workbench. Gilead had such a skilled and motivated team that included researchers who had worked with tenofovir at BMS. At the time Gilead was relatively small with no marketable products. If anyone had a motivation to quickly overcome the bioavailability problems associated with tenofovir, it would be the research scientists at Gilead.

[63] There is no evidence on the record before me to suggest that the Gilead team was intellectually inferior to the person of skill or that the invention narrative set out in the affidavits of

Dr. Lee and Dr. Oliyia is overstated or disingenuous. It is true that NOC proceedings are not the best forum for testing all of the relevant evidence and in this case the record may be incomplete. Nevertheless that record is all I have.

[64] [omitted]

[65] [omitted] In early 1994, Gilead filed an investigational new drug application in the United States to permit the use of adefovir dipivoxil to treat HIV. Although the studies that followed showed that adefovir dipivoxil had antiviral properties, toxicity concerns were present. In 1999, those concerns led the FDA to decline to approve adefovir dipivoxil for the treatment of HIV.

[66] [omitted] Tenofovir had exhibited antiviral activity comparable to adefovir and it was selected as the lead compound for development of a prodrug form. From its experience with adefovir dipivoxil, Gilead knew to avoid the POM prodrug moiety. According to Dr. Lee, Gilead's criteria for developing a prodrug of tenofovir included adequate stability and solubility, metabolic lability and a capacity to break down to yield the parent compound at a place where it would have its desired cellular effect. Dr. Lee's affidavit explains in considerable detail the steps that Gilead then took to develop tenofovir disoproxil:

> 38. [omitted]
>
> 39. This was an empirical process that involved synthesizing the prodrugs, testing in a variety of *in vitro* and *in vivo* models, and analyzing the results. In our efforts to find a prodrug of PMPA we started by synthesizing PMPA prodrugs utilizing prodrug moieties that we had found to work with PMEA, expecting that there may be some correlation between the prodrug moieties that worked for PMEA and those that would work for PMPA. We were surprised to

discover that many prodrug moieties that worked with PMEA did not work with PMPA.

40. [omitted]

41. [omitted]

42. As of early 1996, none of the PMPA prodrugs we had synthesized were showing the necessary balance of chemical stability, solubility, acceptable pharmacokinetics, safety and metabolism that we thought we needed, Looking at all of the screens that we performed (chemical screens, metabolic tissue screens from multiple species and multiple animal bioavailability screens), we were unable to identify a molecule that had the appropriate physical properties and metabolic stability to provide suitable bioavailability in humans.

43. Gilead consulted with an eminent pharmaceutical chemist, Dr. Valentino Stella, of the University of Kansas. Dr. Stella was a nationally recognized expert in pharmaceutics and prodrug design. In February 1996, Dr. Stella came out to Gilead in order to take a fresh look at the PMPA prodrug program. We presented to Dr. Stella an overview of the prodrug work which had been attempted for PMPA and which, to that point, had not yielded a suitable prodrug.

44. [omitted]

45. [omitted]

46. Dr. Murty Arimilli, Dr. Joseph Dougherty and others working together under Dr. Chung Kim (now retired) synthesized a variety of carbonate and carbamate prodrugs of PMPA. Examples of the prodrugs that were invented at this time are represented in Table 1 of Canadian Patent No. 2,261,619.

47. [omitted]

48. Multiple alkyl carbonates were synthesized and found to be stable to chemical hydrolysis, which had been doubted previously. In addition, these compounds performed quite well in metabolic stability screens we conducted. The POC prodrug demonstrated good bioavailability in animals. Since the POC prodrug moiety does not break down to pivalic acid, there were no concerns about carnitine depletion as there had been with POM.

> 49. Bis(POC)PMPA (tenofovir disoproxil) was selected for clinical development as an anti-HIV agent on the basis of its enhanced cellular permeability, solubility, efficacy, low toxicity, stability and improved oral bioavailability over PMPA. A stable crystalline fumarate salt of Bis(POC)PMPA was identified in the fall of 1996 and we moved forward through formulation and clinical development.
>
> 50. Tenofovir disoproxil fumarate received regulatory approval from the FDA on October 26, 2001 for the treatment of HIV and is sold under the brand name Viread®.

[67] The importance of evidence bearing on the history of a discovery has recently been emphazied in *Apotex Inc. v. Sanofi-Aventis*, 2013 FCA 186, [2013] FCJ No 856, where Justice Johanne Gauthier stated at paragraph s. 137-139:

> 137 The Trial Judge believed that the evidence before him with respect to the separation of the enantiomers was significantly different from the evidence before the Supreme Court of Canada in *Plavix* because: i) he found that a line had been drawn in the sand at the time the application was filed, and that as part of the process of developing a racemic drug a sponsor would be motivated to separate the enantiomers to get information to pre-empt expected new regulatory requirements (See Reasons at paragraphs 748-749); and ii) in his view, the separation itself did not involve substantial difficulties and was routine. However, Rothstein J. made it clear in *Plavix* that whether the separation or resolution of the enantiomers was routine or involved arduous work would assume small significance in this case when one considers the whole course of conduct that led to the decision to separate (See *Plavix* at paragraph 89).
>
> 138 It appears to me that the Trial Judge did not really weigh the extent, nature, and amount of efforts required to arrive at a decision to actually develop PCR 4099, as opposed to any other racemic compound covered by the '875 Patent to the point that separation will become relevant. As mentioned by Pelletier J.A. above at paragraph 73, Rothstein J. found in *Plavix* that the '875 Patent did not differentiate between the efficacy and toxicity of any of the compounds it covered. The Trial Judge essentially agreed and held that the '875 Patent did not point either directly or indirectly to PCR

> 4099, even if PCR 4099 itself was known as one of the 21 compounds used in the examples of the '875 Patent.
>
> 139 The Trial Judge did not find that the person skilled in the art would obviously start a development project based on the '875 Patent compound with PCR 4099 as opposed to any other compound, including the 21 compounds expressly used in the examples. In fact, Sanofi's actual course of action militates against such a conclusion.

[68] The lengthy and multi-step process followed by Gilead to develop tenofovir disoproxil belies Teva's assertion that the person of skill would have come to that "self-evident" solution without difficulty. I am satisfied that the discovery of tenofovir disoproxil was inventive and, by definition, non-obvious. Gilead is therefore entitled to an order prohibiting the Minister from issuing a NOC to Teva until the expiry of the 619 Patent.

The 059 Patent - Validity

[69] There is no substantive disagreement about the qualifications of the person of skill with respect to the 059 Patent. The 059 Patent is directed to a pre-formulation scientist with experience in the selection and preparation of salt and solid state forms of pharmaceutical compounds. Such a person could have an advanced degree in physical pharmacy, organic chemistry or a related field and a number of years of academic or industrial experience or both.

[70] The 059 Patent describes the superior qualities of the fumarate salt of tenofovir disoproxil for use in pharmaceutical formulation. The validity of Claim 3 and Claim 4 of the 059 Patent are at issue in this application. The parties substantively agree on the construction of the claims. Claim 3 describes crystalline forms of the fumarate salt of the compounds described in the Claim 1 of the

patent. Claim 4 describes the compounds described in Claim 1 enriched or resolved at a particular chiral center.

[71] Teva says that, as of the priority date of July 25, 1997, the 059 Patent was invalid by reason of obviousness. The parties agree that the inventive concept of the 059 Patent is the choice of the fumarate salt form of tenofovir disoproxil. According to the specification, TDF, had "an unexpectedly superior combination of physico-chemical properties compared to the free base and other salts".

Was the Choice of the Fumarate Salt Form of Tenofovir Disoproxil Inventive?

[72] Fumarate is a salt form that had been previously approved in pharmaceutical preparations and would, therefore, be understood to be safe for human use. Both PMPA (tenofovir) and bis(POM)PMPA (tenofovir disoproxil) were known and disclosed in the prior art. The difference between the inventive concept and the state of the art as of July 1997 is the fumarate salt of the compounds described in the Claim 1 of the patent. This includes the fumarate salt of bis(POM)PMPA (tenofovir disoproxil fumarate), which is specifically at issue in this application. These points are not in dispute. The validity of the patent turns on whether using fumaric acid as a salt former with bis(POM)PMPA was "obvious to try" and whether it was more or less self-evident that a suitable pharmaceutical salt would result.

[73] Teva says the methodology for selecting an appropriate salt for pharmaceutical formulation is routine. Teva asserts that fumaric acid was obvious to try as it had already been used in several other drugs approved by the FDA and was listed in the prior art as a salt former along with other

weak acids for closely-related compounds. Moreover, the skilled person would have a high expectation that fumaric acid would form a suitable salt when combined with tenofovir disoproxil; that synthesizing and testing the resulting salt would require a minimal degree of effort; and, that the skilled person would be motivated to select fumaric acid as one of the potential salt formers in light of the prior art.

[74] Gilead argues that although fumarate was known, it was rarely used in FDA approved pharmaceuticals and that any references in the prior art are irrelevant to the 059 Patent. Gilead says that at the relevant time, it would be impossible to predict whether a salt would form by using fumaric acid. Further, if a salt did form, it would be impossible to predict whether it would have suitable properties for pharmaceutical formulation.

[75] Gilead points to the "Rule of 2 or 3" to support the position that fumaric acid was not obvious to try. In his affidavit, Dr. Myerson, Gilead's expert, explains:

> 27. Salts of pharmaceutical drug compounds are formed by reacting the parent or "free" form of the drug with an acid or base. If the parent is basic, the drug is reacted with and acid; if acidic, it is reacted with a base. Acids are defined as compounds that in an aqueous solution can release a solvated proton; bases are compounds that accept a proton.
>
> 28. The dissociation of a monoprotic acid can be described by an equilibrium relation between the acid and the ion of the acid and a hydrogen ion. The equilibrium between the unionized acid and the two ions is characterized by an equilibrium constant Ka. Because the values of equilibrium constants are very small numbers, they are normally expressed in terms of their negative logarithms, and are generally known as pKa.
>
> 29. For a monobasic compound, the dissociation equilibrium is expressed in terns of the protonated base in equilibrium with a hydrogen ion and the neutral base, and thus a pKa is also defined for

> this equilibrium. The pKa is very important in selecting the potential counterions in attempting to form a salt of either an acidic or basic drug.
>
> 30. Salt screening falls under the general category of solid form selection. Solid form selection refers to the decision of what type of crystalline (or amorphous) solid of the active pharmaceutical ingredient ("API") is to be employed in the final drug product.
>
> 31. At the relevant time, in order to find stable salts, a person skilled in the art ("POSA") would undertake a salt screen. A salt screen for a freebase involved picking potential acidic salt formers whose pKa was less than that of the free base by 2-3 units or more. A POSA would also pick solvents or solvent mixtures that would allow dissolution of the free base and the acidic salt former.

[76] Dr. Myerson points out that the pKa difference between the free base tenofovir disoproxil and fumaric acid is 0.73. Taking this into account, the person of skill could not have predicted that a stable salt would form. As a result, the person of skill would not have chosen fumaric acid as a salt former (see the Myerson Affidavit at paragraph 98.

[77] Teva's expert, Dr. Sternson says that the "Rule of 2 and 3" is not a hard and fast rule; rather it is "one of the many factors that may be considered when selecting a potential salt form of a compound" (see the Sternson Reply Affidavit at paragraph 2). Teva notes that, as of July 1997, the papers cited by Dr. Myerson include examples where the rule does not apply. Further, the art taught that weak acids could be used to form salts with structurally related compounds.

[78] I agree with Teva's expert on this point. There are sufficient references in the art to exceptions to the "Rule of 2 or 3" to suggest that it is not a hard and fast rule. Although fumarate salts were not the most commonly used pharmaceutical salts, the FDA had approved formulations

using these salts at the relevant time. Further, fumaric acid was known to form suitable salts with related compounds (see the Sternson Affidavit at paragraph 70). Since a preformulation scientist would likely look to salt formers that have already received approval from the FDA, this is sufficient to establish that fumaric salt would be, at least, one of several obvious salt formers the person of skill would try in attempting to develop a pharmaceutically acceptable salt of tenofovir disoproxil.

[79] This does not end the inventiveness inquiry. I must also assess whether it was more or less self-evident that the inventors would successfully arrive at a pharmaceutically acceptable salt of tenofovir disoproxil.

[80] Teva cites *Ratiopharm Inc v Pfizer Ltd*, 2009 FC 711, [2009] FCJ No 967 aff'd 2010 FCA 204, [2010] FCJ No 968 [*Amlodipine*], for the premise that salt selection is a routine procedure. In *Amlodipine*, Justice Hughes considered the validity of a patent claiming the besylate salt of the compound amlodipine. The Canadian filing date for the patent in that case was April 2, 1987. Therefore, the date to assess the knowledge of the person of skill in that case is approximately a decade earlier than the knowledge of the person of skill in the present application. Justice Hughes found the patent to be invalid by reason of obviousness. He made factual findings with respect to the motivation of the person of skill to try specific salt formers and the predictability of success (at paragraph 170). Most relevant to this application, he described salt screening to be a "well-known" and "routine pre-formulation procedure" for the person of skill (at paragraph s 155 and 167).

[81] As of July 1997, salt selection was no less routine than it was in the *Amlodipine* case. Dr. Sternson, Teva's expert, discusses in his affidavit that tenofovir disoproxil could theoretically form salts with many different acids. He concedes that identifying the "best" salt is important and that this involves testing for various properties to find a suitable formulation (i.e. stability, dissolution rate, solubility, etc.). However, Dr. Sternson goes on to explain that the procedures for selecting potential salt formers and screening any resulting salts for the desired properties is a matter of "using methods that were routine and well-known to persons of skill in the art" (Sternson Affidavit at paragraph 65). Notably, Dr. Myerson conceded in cross-examination that once the salts are formed characterization of the properties of those salts can be undertaken in four to six weeks via a salt screen (Applicants' Record, Volume 23, Tab 190 at p 6903).

[82] Gilead argues that there were multiple choices available to person of skill in developing a suitable salt for tenofovir disoproxil such that there was no clear pathway to fumaric acid. The fact that there were multiple pathways available to the person of skill does not necessarily lead to the result that a claimed invention was non-obvious: see *Hoffman-La Roche Ltd v Apotex Inc*, 2013 FC 718, [2013] FCJ No 844 at paras 316-341. Although a person of skill may not have predicted with a high degree of certainty that fumaric acid could be used to produce an acceptable salt formulation for tenofovir disoproxil, there would still be an expectation that, with routine screening of a handful of acidic salt formers, one or more acceptable compounds would emerge. The idea that fumaric acid was an unlikely candidate is belied, in part, by the fact that Gilead included only one other acid in its screening, that being citric acid. According to Dr. Myerson, the person of skill would have known at that time that citric acid was likely to be unstable (Applicants' Record, Volume 23, Tab 190 at pp 6944-6945).

[83] In this case it is noteworthy that, despite its assertion that the choice of fumaric acid was counterintuitive and that its success as a useful salt former was unpredictable, Gilead presented no evidence of the inventive history behind the 059 Patent. Specifically, Gilead produced no evidence to show that it unsuccessfully screened numerous promising acidic salt formers and only resorted to fumaric acid as a last resort. It seems to me that if historical evidence of the sort produced by Gilead in support of the 619 Patent is to receive meaningful consideration, the absence of such evidence may well lead to an opposite inference (see *AstraZeneca Canada Inc v Teva Canada Ltd*, 2013 FC 245, [2013] FCJ No 241 at para 64).

[84] In the face of an obviousness attack, the absence of evidence uniquely in the possession of Gilead leads me to conclude that the development of TDF was routine and not the end product of an onerous or inventive process of discovery. On the evidence before me, the choice of a salt form for tenofovir disoproxil that met Gilead's needs and that was shown by a routine screen to be better than the free base and one other salt form of questionable value is neither surprising nor inventive.

Conclusion

[85] For the foregoing reasons, this application is allowed in part. A declaration is granted prohibiting the Minister from issuing a Notice of Compliance to Teva in respect of its proposed tenofovir disoproxil fumarate product until the expiry of Canadian Letters Patent 2, 261,619.

[86] At the request of the parties, the issue of costs is reserved. If the parties cannot agree on costs, written submissions not to exceed 10 pages in length will be considered. I will allow Gilead 21 days to file its submission and Teva will be allowed 14 days to respond.

JUDGMENT

THIS COURT'S JUDGMENT is that:

a) The application is allowed in part;

b) The Minister is prohibited from issuing a Notice of Compliance to Teva in respect of its tenofovir disoproxil fumarate product until the expiry of Canadian Letters Patent 2, 261,619; and

c) The issue of costs is reserved pending further written submissions from the parties.

"R.L. Barnes"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

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