Federal Court  Cour fédérale

Date: 20160115

Docket: T-366-14

Citation: 2016 FC 47

Ottawa, Ontario, January 15, 2016

PRESENT: The Honourable Mr. Justice Barnes

BETWEEN:

ELI LILLY CANADA INC.

Applicant

and

HOSPIRA HEALTHCARE CORPORATION AND THE MINISTER OF HEALTH

Respondents

and

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Respondent Patentee

PUBLIC JUDGMENT AND REASONS

[1] This is an application by Eli Lilly Canada Inc. [Lilly] made under *the Patented Medicines (Notice of Compliance) Regulations*, SOR 93-133 as amended, [Regulations]. Lilly seeks an

Order prohibiting the Minister of Health from issuing a Notice of Compliance [NOC] to Hospira Healthcare Corporation [Hospira] for its proposed generic version of pemetrexed disodium [pemetrexed] sold in Canada by Lilly under the brand name ALIMTA®. Pemetrexed is an anti-folate drug useful in the treatment of some cancers.

[2] The Respondent Patentee, Takeda Pharmaceutical Company Limited [Takeda], is the owner of Canadian Letters Patent 1,340,794 [the 794 Patent] covering pemetrexed. Lilly holds a license from Takeda to sell pemetrexed in Canada.

[3] The 794 Patent was filed in Canada on March 23, 1989 and issued more than a decade later on October 19, 1999. As an "Old Act" patent, it will expire on October 19, 2016.

[4] It is of some interest that Lilly had previously obtained a license to sell pemetrexed covered under a different patent, namely the Canadian Letters Patent 2,031,890 Patent [890 Patent]. The 890 Patent was issued to Princeton University on July 25, 2000 on the strength of work done by, among others, Lilly employees. As a "New Act" patent, Lilly benefited from the 890 Patent monopoly on pemetrexed until it expired on December 10, 2010. Hospira asserts that Lilly is effectively gaming the system by this attempt to extend the monopoly over pemetrexed by a further six years. It is not entirely clear on the evidence presented why these two patents were not subjected to a conflict proceeding; but for the reasons that follow, it is unnecessary to determine which of them takes priority.

[5] The parties and their witnesses joined issue on a significant number of evidentiary and legal issues and they filed voluminous records in support of their respective positions. As much as the Court would like to address every issue advanced, it does not enjoy the luxury of sufficient time to do so. For reasons of judicial economy and having regard to the summary and non-binding nature of the NOC proceedings, I intend to deal only with the single, determinative issue of sound prediction of utility.

[6] It is sufficient to resolve this application to determine whether the person of skill in 1989 could have soundly predicted the promised utility of the untested compounds falling within Claims 7 and 9 from the test data reported in the Patent and from what was known in the art.

[7] It is common ground that the asserted claims relate to a class of compounds that includes pemetrexed. The vast majority of the compounds covered by Claims 7 and 9 (including pemetrexed) were not specifically disclosed nor were they made or tested by Takeda before the filing date. To fulfil the utility requirement Lilly must, therefore, establish that the promised utility of the untested compounds would have been soundly predicted by the person of skill from the results Takeda obtained from its testing of some of the compounds falling within those claims. On my view of the evidence, Lilly has failed to meet its burden of proof on a balance of probabilities on this issue.

I. The 794 Patent

[8] The Patent opens with the assertion that the "invention relates to the novel Pyrrolopyrimidine derivatives which are useful as antitumor agents, the production and

utilization thereof". What follows is a brief summary of what was known in the prior art about antifolate compounds and an assertion of the advantages of the claimed compounds as antitumor drugs of "major" clinical importance.

[9] At page 25, the effects of the compounds of the invention are described in the following way:

> The compounds (I) of this invention show excellent antitumor effects and mouse tumor cell strains (P388, L1210, L5178Y, B16 melanoma, MethA, Lewis Lung Carcinoma, S180 sarcoma, Ehrlich Carcinoma, Colon38) and human tumor cell strains (HL60, KB, Lu65), decreased the tumor carried by warm-blooded animals [e.g. melanoma, sarcoma, mastocytoma, carcinoma, neoplasia, etc.] and prolong the life-span of tumor-carrying warm-blooded animals.

[10] Subsequent passages from the disclosure refer to the "remarkable" antitumor effects of the compounds making them suitable for the treatment of tumors in warm-blooded animals.

[11] The Patent concludes with 36 claims, with Claim 1 incorporating all of the compounds claimed in Claims 1 to 29. Claim 30 concerns a method for making the compounds and Claims 32 to 36 relate to intermediates used in the synthesis of the compounds. Claim 31 relates to antitumor agents containing the compounds covered by Claims 1 to 29.

[12] Lilly asserts in argument only a subset of the compound claims[1], namely Claim 7 when read with Claims 4, 2 and 1 (Claim 7/4/2/1); Claim 9 when read with Claims 3, 2, and 1 (Claim 9/3/2/1); and Claim 11 when read with Claims 4, 2 and 1 (Claim 11/4/2/1). It also relies on Claim 31 as an aid to interpretation of the promised utility of the asserted compound claims.

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[1] See paragraph 18 of Lilly's Memorandum of Fact and Law.

There appears to be no evidence in the record to support Lilly's case for Claim 11/4/2/1 but, in the end, that is not a matter of any consequence.

[13] There does not appear to be any disagreement about the construction of the above-noted claims. There is also general agreement as to the attributes of the person of skill. I accept the following description of the person of skill set out at paragraph 16 of Dr. Kalman's affidavit:

> 16. '794 Patent is directed to a person possessing the knowledge of the medicinal chemist having either a Ph.D. or a Master's degree in medicinal or organic chemistry with additional knowledge in the area of folic acid biochemistry and cancer chemotherapy, in particular knowledge of chemistry and biology of antifolate and their different enzyme targets. This person would be part of a team that includes pharmacologists with experience in conducting and interpreting the *in vitro* assays referenced in the '794 Patent and also *in vivo* animal models; other pharmaceutical professionals involved in the drug formulation and metabolism; and clinical oncologists.

[14] Hospira and its expert witnesses also do not take issue with Lilly's characterization of the inventive concept of the Patent which is said to lie in the unexpected discovery that classical antifolates bearing a 6/5 bicyclic pyrrolopyrimidine ring system had antifolate activity. I accept Dr. Jones' evidence on this point at paragraph 123 to 129 of his affidavit including the observation that the previous limited efforts to explore 6/5 ring systems for antifolate activity had been unproductive. I also accept that for each of the compounds actually tested by Takeda before the filing date (to the extent that that was established) some measurable level of antifolate activity was obtained vis-à-vis at least one tumor cell line. The question that remains is whether those test data are sufficient to support a sound prediction of utility for the thousands of compounds left untested by Takeda.

II. Utility – The Expert Witnesses

[15] Hospira's case for a lack of sound prediction rests primarily on the evidence of Dr. Thomas Kalman and Dr. Roger Phillips supported, in part, by Dr. Michael Chong.

[16] Dr. Kalman is a Senior Professor in the Department of Chemistry and in the Department of Pharmacology and Toxicology (School of Medicine) at the State University of New York, Buffalo. He has considerable research and teaching experience dealing with the medicinal chemistry and pharmacology of anticancer drugs including antifolates.

[17] Dr. Phillips is a Professor of Cancer Pharmacology at the University of Huddersfield, England. He has extensive experience in the evaluation of potential and anti-cancer compounds with a particular focus on agents that target tumor metabolism. He has special expertise in assessing the predictive value of *in vitro* testing of anti-cancer drugs. He is widely published. He frequently acts as a referee assessing articles submitted for publication to several medical journals and he reviews grant proposals for, among others, Cancer Research UK.

[18] Both Dr. Kalman and Dr. Phillips are well qualified to speak to the issue addressed in their affidavits.

[19] Dr. Chong is a Professor in the Department of Chemistry at the University of Waterloo, Ontario. He is an organic chemist with research interests in synthetic organic chemistry and the preparation, identification and separation of compounds. Dr. Chong's mandate included a comparative structural assessment of the compounds ostensibly tested by Takeda relative to the

class of compounds claimed by the Patent. Dr. Chong was well qualified to address this issue and, for the most part, his opinions were not directly challenged by Lilly.

[20] Lilly's case for sound prediction primarily rests on the opinion of Dr. Terrence Jones. Dr. Jones is a medicinal and synthetic organic chemist with experience in the design and synthesis of novel antifolates for cancer treatment. Between 1996 and 2004, he was the Chief Scientific Officer at Angstrom Pharmaceuticals and since 2004 he has worked part-time as a pharmaceutical consultant. He has published a number of scientific papers and served as a reviewer for the Journal of Medicinal Chemistry. Although Hospira challenged Dr. Jones' objectivity, I am satisfied that he is qualified to speak to the issues addressed in his affidavits. Based on the answers he gave under cross-examination, I also have no reason to doubt his objectivity.

[21] Dr. Wuest's evidence focused mainly on questions of sufficiency. As a synthetic organic chemist, he was well-qualified to address those matters: see his affidavit at paras 1-6. However, his ability to provide an opinion about the utility of the claimed compounds was very much in doubt. He has no experience in working with folic acids or with antifolates and only became acquainted with the area after being retained by Lilly (see pp 5062-5064 Application Record). Because of that lack of relevant experience, I am not prepared to ascribe weight to Dr. Wuest's evidence where it conflicts with that of Dr. Kalman and Dr. Phillips on matters pertaining to utility.

[22] Dr. Rick Van Etten is both a cancer clinician and researcher. He is the Director of the Chao Family Comprehensive Cancer Center at the University of California (Irvine) where he is also a Professor of Medicine in the Division of Hematology/Oncology. He has considerable experience conducting animal and human clinical trials in the area of cancer treatment.

[23] The scope of Dr. Van Etten's mandate concerning utility was stated to be limited to Claim 31 (see p 738 Application Record at para 9). Nevertheless, he went on to address utility more generally with reference to a "subset" of Formula I compounds. His opinions on this issue lack analysis and detail and for that reason, they are largely unhelpful.

III. The Promise of the Patent

[24] The parties and their expert witnesses disagree about the scope of the promise of the Patent. There are no material differences concerning the construction of the claim language *per se*.

[25] Hospira argues for a heightened promise of utility and Lilly seeks to effectively read the promise down to a "scintilla" of utility. This is potentially relevant to the determination of whether a person of skill could have made a sound prediction of utility for the untested compounds, including Pemetrexed, on the strength of the data obtained for the tested compounds.

[26] This is a case where the opinions of the expert witnesses bearing on the construction of the promise of the Patent were largely unhelpful. Dr. Jones approached this issue on the basis of

advice that a mere scintilla of utility would suffice and he concluded that the promise of the compound claims was only that some antifolate activity *in vitro* was either shown or could be soundly predicted from Takeda's *in vitro* data. It appears that he made little effort to examine the claims on the basis of all of the language of the specification and relied primarily on the advice of counsel (see his evidence of pp 5762A-5773 of the Application Record and para 156 of his affidavit).

[27] Dr. Kalman's evidence was unhelpful because he relied too heavily on language in the specification that could only be interpreted as a goal or aspiration and he conceded that he had not been instructed to attempt to distinguish between goals and promises. Under cross-examination, he also retreated in some measure from the opinion set out in his affidavit (see, for example his answers at pp 7560-7561 of the Application Record). Dr. Phillips was not extensively cross-examined on this issue but, he too, appears not to have understood the distinction between aspirational language and explicit promises.

[28] In my view, the person of skill would construe the promise of the Patent as falling between the positions advanced by the parties and their experts.

[29] Lilly's case for a truncated promise of utility with respect to the claimed compounds is based, in part, on the absence of any asserted utility in the claim language. Only Claim 31 speaks to utility as antitumor agents containing an antitumor effective amount of the compounds defined in Claims 1 to 29.

[30] I do not give much weight to the absence of an explicit promise of utility in the compound claims. The discovery of a new molecule without disclosing how it might be put to some useful purpose will not support a patent. Accordingly, when a compound claim is silent as to use, the person of skill must resort to the specification to determine the utility promise of the claim. Once there, the person of skill must consider all of the language of the specification with a view to forming a purposive construction: see *Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] 2 SCR 1067, and *Shire Biochem Inc v Canada*, 2008 FC 538 at paras 21-23, 328 FTR 123.

[31] Lilly's argument that the promise of the Patent is limited to the bare requirement of measurable *in vitro* cytotoxic activity is untenable because it ignores clear and unambiguous language in the specification bearing on utility and, in particular, the opening sentence:

> This invention relates to the novel pyrrolopyrimidine derivatives which are useful as anti-tumor agents, the production and utilization thereof. [Emphasis added]

[32] There are several other similar references found throughout the specification to the use or employment of the claimed compounds as antitumor agents often in conjunction with descriptors like "excellent" or "remarkable".

[33] On the strength of this language the person of skill would include within the promise of the Patent the use of the compounds as antitumor agents. On this point, I agree with Dr. Phillips that the promise of antitumor activity would be understood by the person of skill to mean *in vivo* activity in relation to abnormal tissue (see paras 141-142 of his affidavit and p 7349 of his cross-examination). That was also the view of Dr. Van Etten when he equated the reference to "an

anti-tumor agent" in Claim 31 to something that affects a tumor mass. This could be established by disclosed evidence of activity *in vivo* or by evidence of *in vitro* activity from which an extrapolation of *in vivo* activity could be drawn. I do not accept Dr. Jones' evidence that antitumor activity means only that the claimed compounds would exhibit some degree of antifolate activity *in vitro* or that *in vivo* data are merely "icing on the cake" (see p 5766, Application Record). *In vitro* testing does not, absent a sound prediction, establish efficacy against a tumor mass.

[34] The person of skill would not, however, include within the promise of the Patent the highly subjective and qualitative references to "excellent" or "remarkable" nor would she consider that every one of the claimed compounds would be useful to treat tumors in warm-blooded animals. There is also nothing in the Patent establishing that the compounds enjoyed some relative advantage over methatrexate (see the evidence of Dr. Kalman at pp 7510 and 7561, Application Record) or that all of the claimed compounds had toxicities specific to tumor cells. Those references in the specification seem to me to be more in the nature of hopes or aspirations for some of the compounds and not promises for all of them.

[35] I also do not agree that any level of promised efficacy as an antitumor agent would be inferred by the person of skill from the activity data points expressed in the Patent. At the same time, I do not accept Lilly's point that any measurable *in vitro* antifolate activity would satisfy the promise of the Patent. It strikes me that the person of skill would have an activity threshold in mind below which a compound would not be considered to be an antifolate agent with

antitumor effects. Dr. Jones seemed to accept this point albeit not without some equivocation as to what the threshold would be.

[36] When Dr. Jones was questioned about an efficacy threshold, he expressed the view that a "scintilla" of antifolate activity was all the Patent promised. According to Dr. Jones a 10% reduction in tumor size met the required threshold (pp 2687-2688 Application Record) and antitumor activity as low as 0.5% might also have been seen by the person of skill to satisfy the utility requirement (p 5690 Application Record). At paragraph 264 of Dr. Jones' affidavit he stated that "an antitumor agent is something that demonstrates an antitumor effect" but on cross-examination he qualified this evidence by saying "[a] reasonable IC50, for instance, of a compound against tumor cells and tissue culture would constitute an antitumor effect". He went on to acknowledge that the person of skill would expect a level of activity that "might" render the compound useful for treatment (pp 5701-5702 Application Record). Ultimately Dr. Jones conceded in the following exchange that a compound IC50 value greater than 20.0 microgram per millilitre had no cytotoxic activity:

> 629 Q. So if you go to paragraph 215 of your affidavit, you state in the second sentence:
>
> > "Working Example 14 was found to have an IC50 value > 20.0 microgram per ml, a very high value, showing that it had no cytotoxic activity against this cell line."
>
> Do you see that?
>
> A. Yes, I see that. Yes.
>
> 630 Q. Didn't you just tell me that activity of 427 micrograms per ml was cytotoxic, and in your affidavit you're saying greater than 20 micrograms per ml is not cytotoxic?
>
> A. Yes, I see the disparity.

631 Q. So what number would you prefer to go with, the greater than 20 micrograms per ml IC50 value of being not cytotoxic, or the greater than the 427?

A. I have to stand by what I wrote in 215.

632 Q. Greater than 20 microgram per ml, IC50 value?

A. Greater than 20, yes.

Also see p 5773 Application Record.

[37] Needless to say, Dr. Jones' evidence on this point was not entirely consistent. What the experts did seem to agree upon, however, was that the promise of efficacy had a qualitative aspect. In the absence of other evidence on point, I can only conclude that a compound with an IC50 value greater than 20.0 micrograms per millilitre would not be seen by the person of skill to be an antitumor agent.

IV. Utility – Legal Principles

[38] Section 2 of the *Patent Act*, RSC 1985, c P -4, [Act] defines an invention as "any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter". Subsection 34(1) of the Act requires a patentee to "correctly and fully describe the invention and its operation or use" and to "set forth clearly the various steps in a process, or the method of constructing, making or compounding a machine, manufacture or composition of matter". Thus a patentee was required to explain how the invention could be made and effectively used.

[39] Subsection 34(1), however, did not impose on the patentee an obligation to extol the advantages of the invention or to make any particular promises concerning its usefulness. The decision by the Supreme Court of Canada in *Consolboard Inc v MacMillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504, 1981 CanLII 15 (SCC), holds that a patentee is not bound to promise anything about the practical or commercial usefulness of an invention: also see *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 54, [2002] 4 SCR 153. The inventor need not even be aware of the advantages of the invention or the reasons why it works. However, to the extent the patentee makes a clear promise of utility, he will be held to it.

[40] A recent decision about the promise doctrine and utility can be found in *Apotex Inc v Pfizer Canada Inc and G.D. Searle & Co*, 2014 FCA 250 at para 64-67 and 71, [2014] FCJ No 1090, where the Chief Justice Noël stated:

> 64 Under the *Act*, an invention must be useful in order to deserve protection (s. 2). The courts, however, have long held that the minimum requirements for utility under the *Act* are fairly forgiving. First, the inventor need not expressly set out the utility of the invention in the patent (*Consolboard Inc. v. MacMillan Bloedel (Saskatchewan) Ltd.*, [1981] 1 S.C.R. 504 at 525 and 526 [*Consolboard*]. It is merely required that, where the inventor is called upon to prove the utility of the invention, utility can be shown to be demonstrated or soundly predicted as of the patent's filing date (*AZT*). Second, the threshold that must be proven to establish utility is generally quite low, described as being no more than a "scintilla of utility" (*Olanzapine*).
>
> 65 The promise doctrine represents an exception to the above minimum statutory requirements. Though an inventor need not describe any particular utility for the invention, an inventor who explicitly promises a specific result will be held to that promise when called upon to prove utility (*Plavix FCA* at paras. 48 and 49). That the invention may well have satisfied the scintilla threshold is of no assistance in establishing utility where a promise, if it be made, cannot be met (*Plavix FCA* at para. 54).

66 The promise doctrine will hold an inventor to an elevated standard only where a clear and unambiguous promise has been made. Where the validity of a patent is challenged on the basis of an alleged unfulfilled promise, the patent will be construed in favour of the patentee where it can reasonably be read by the skilled person as excluding this promise. This approach can be traced back to the earliest mentions of the promise doctrine. In *Consolboard*, the source of the promise doctrine in Canadian law, the Supreme Court of Canada reiterated the longstanding principle that (*Consolboard* at 521, citing *Western Electric Company, Incorporated, and Northern Electric Company v. Baldwin International Radio of Canada*, [1934] S.C.R. 570 at 574):

> ...where the language of the specification, upon a reasonable view of it, can be so read as to afford the inventor protection for that which he has actually in good faith invented, the court, as a rule, will endeavour to give effect to that construction.

67 This rule in favour of saving an invention rather than invalidating it in case of ambiguity has been consistently applied by this Court. While the principle is sometimes invoked by reference to the original language found in *Consolboard* (*Anastrozole* at paras. 17 and 19) affirming *AstraZeneca Canada Inc. v. Mylan Pharmaceuticals ULC*, 2011 FC 1023, [2011] F.C.J. No. 1262 at para. 88), it is at other times given effect through the requirement that promises be "explicit" (see *Olanzapine* at para. 76, *Eli Lilly and Company v. Teva Canada Limited*, 2011 FCA 220, [2011] F.C.J. No. 1028 at paras. 18 to 21 [*Atomexetine*], *Plavix FCA* at para. 49). Drawing an analogy with the threshold test applicable to selection patents, the Court in *Plavix FCA* expressed the need for explicitness by saying that a promise must be supported by language "... at least as clear and unambiguous as that used to establish the advantages of the selection over the compounds of a genus patent" (*Plavix FCA* at para. 66). It follows that it is not enough to merely label a promise as "explicit" if it can only be supported on the basis of equivocal inferences and ambiguous indications (*Plavix FCA* at paras. 64-66).

…

71 This passage does not support the broad proposition advanced by Apotex. In my view, Gauthier J. (as she then was) was merely stating that, when a result or advantage is asserted in a patent's claims, it will generally be seen as a promise of utility. This is entirely consistent with Zinn J.'s warning in *Fournier* at paragraph 126 that statements going to utility are particularly

> vulnerable to being read as promises when they are expressed in a patent's claims. Apotex has failed to establish how any of the '576 Patent's claims can be shown to describe use in humans as a particular advantage of the claimed compounds.

[41] I accept Lilly's view that a promise of utility is not to be inferred from the language of the specification. Instead it must be clearly and unequivocally found in the express language of the specification: see *Sanofi-Aventis v Apotex*, 2013 FCA 186 at para 64-65, [2013] FCJ No 856.

[42] Inutility must be assessed on a claim by claim basis although some promises will be construed as over-arching, applying across a subset of all of the claims: see *AstraZeneca v Apotex*, 2015 FCA 158 at paras 4-5, [2015] FCJ No 802. Utility must be proven with respect to the entirety of any particular claim. I do not agree with Lilly that the decisions in *Fournier Pharma v Canada*, 2012 FC 740, 413 FTR 239 and *Searle v Novopharm*, 2007 FC 81, [2007] FCJ No 120, stand for some different proposition. Both of those decisions turned on unique points of claim construction where alternatives were given. In *Searle*, Justice Roger Hughes recognized at paragraph 31 that, where a patent claim includes a class of compounds, proof of the utility of each will generally be required.

[43] Utility is to be assessed as of the date a patent is applied for and it cannot be supported by evidence arising after the filing date: see *Bell Helicopter v Eurocopter*, 2013 FCA 219 at para 131, [2013] FCJ No 1043.

[44] Utility must either be demonstrated or soundly predicted. Demonstrated utility is established with evidence showing that the embodiment in issue works as described in the patent.

Where utility is predicted, there must be a factual basis for the prediction and an articulate and sound line of reasoning from which the desired result can be inferred. The requirements for sound prediction were described in *Apotex v Wellcome*, above, at para 70:

> 70 The doctrine of sound prediction has three components. Firstly, as here, there must be a factual basis for the prediction. In Monsanto and Burton Parsons, the factual basis was supplied by the tested compounds, but other factual underpinnings, depending on the nature of the invention, may suffice. Secondly, the inventor must have at the date of the patent application an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis. In Monsanto and Burton Parsons, the line of reasoning was grounded in the known "architecture of chemical compounds" (Monsanto, at p. 1119), but other lines of reasoning, again depending on the subject matter, may be legitimate. Thirdly, there must be proper disclosure. Normally, it is sufficient if the specification provides a full, clear and exact description of the nature of the invention and the manner in which it can be practised: H. G. Fox, The Canadian Law and Practice Relating to Letters Patent for Inventions (4th ed. 1969), at p. 167. It is generally not necessary for an inventor to provide a theory of why the invention works. Practical readers merely want to know that it does work and how to work it. In this sort of case, however, the sound prediction is to some extent the quid pro quo the applicant offers in exchange for the patent monopoly. Precise disclosure requirements in this regard do not arise for decision in this case because both the underlying facts (the test data) and the line of reasoning (the chain terminator effect) were in fact disclosed, and disclosure in this respect did not become an issue between the parties. I therefore say no more about it.

[45] A sound prediction must be based on “a solid teaching” or a *prima facie* reasonable inference of utility: see *Eli Lilly v Novopharm*, 2010 FCA 197 at para 85, [2010] FCJ No 951. It is not established by speculation or lucky guesses: see *Bayer Inc v Cobalt Pharmaceuticals*, 2013 FC 1061 at paras 52-58, [2013] FCJ No 1152.

[46] Notwithstanding Justice Binnie's remarks in *Apotex Inc v Wellcome Foundation Ltd*, quoted above, the issue of what the patentee must disclose to the public where utility is predicted remains somewhat controversial. In *AstraZeneca v Apotex*, 2014 FC 638, [2014] FCJ No 671, Justice Donald Rennie (as he then was), distinguished *Apotex Inc v Wellcome Foundation Ltd*, above, by limiting Justice Binnie's remarks concerning disclosure to new use patents.

[47] Justice Rennie also drew support from Justice Johanne Gauthier's concurring, separate reasons in *Sanofi-Aventis v Apotex*, 2013 FCA 186, [2013] FCJ No 856, where she questioned the general requirement for a heightened level of disclosure in sound prediction cases. Justice Rennie dealt with *Eurocopter*, 2013 FCA 261, 116 C.P.R. (4th) 161, by describing the contrary view there expressed as both obiter and a less than robust endorsement of the need for heightened disclosure in sound prediction cases: see para 157.

[48] While I have some sympathy for Justice Rennie's and Justice Gauthier's views, I am not persuaded that the state of the law on this issue has changed. In particular, it would take something more than Justice LeBel's apparent reservations expressed in *Pfizer v Novopharm*, 2012 SCC 60 at paras 38-40, [2012] SCJ No 60, to displace the requirement for disclosure described by Justice Binnie in *Apotex Inc v Wellcome Foundation Ltd*, above, and, later, as clearly endorsed by the Federal Court of Appeal in *Eli Lilly v Apotex*, 2009 FCA 97 at paras 14-15, 78 CPR (4th) 388, in *Eli Lilly v Novopharm*, 2010 FCA 197 at para 83, [2012] 1 FCR 349 and in many decisions of this Court.

[49] In my view where utility is based on a sound prediction, there remains an obligation to disclose in the patent specification the factual basis and a sound line of reasoning supporting the prediction. That said, there is no requirement to disclose that which forms a part of the common general knowledge of the person of skill. Such knowledge may be relied upon by a patentee to strengthen its assertion of predicted utility: see *Bell Helicopter v Eurocopter*, above, at para 154.

V. Utility – The Evidence

[50] I need not address the question of whether the testing of the compounds within the asserted claims demonstrated their promised utility. Pemetrexed and most of the other compounds covered by those claims were never tested. The utility of the untested compounds to fulfil the promise of the Patent necessarily rests on a sound prediction.

[51] As indicated above, I do not agree with Lilly that it is entitled to rely upon in-house test data or upon a sound line of reasoning that cannot be found in the Patent. The Patent discloses *in vitro* test results for a small number of compounds and it provides no line of reasoning from which the person of skill could draw a *prima facia* reasonable inference that the thousands of untested claimed compounds would be useful as antitumor agents *in vivo* or even *in vitro*.

[52] There is also no line of reasoning disclosed in the Patent from which the person of skill could extrapolate an *in vivo* antitumor effect from the reported *in vitro* data.

[53] Dr. Jones based his opinion of a sound prediction of utility substantially on data that was not disclosed in the Patent. He also relied, in part, on data that Lilly failed to prove was obtained before the filing date.

[54] Notwithstanding these fundamental flaws in Lilly's case, I will address the evidence relied upon by Lilly in support of its argument for a sound prediction of utility.

[55] Lilly's theory of sound prediction is based on the drawing of an inference of a scintilla of antitumor activity for the untested compounds from the fact that some structural changes to similar molecules had been shown to be tolerated and, in some measure, active as antifolates.

[56] The evidence Lilly presented in support of this theory was not compelling. Indeed, much of that evidence was surprisingly unresponsive to the very specific scientific points advanced by Hospira's experts as to why the person of skill could not soundly predict antitumor activity either from the test data disclosed in the Patent or otherwise. I would add that Takeda's evidence about whether it obtained all of the data it now relies upon before the Canadian filing date was highly dubious and unreliable. Insofar as Lilly's experts relied upon that information, their evidence is substantially undermined.

[57] All of the witnesses agree that variations to the molecular structures of certain analogues to MTX and other antifolate compounds had been explored before 1989 and found to be tolerated. Both Dr. Kalman and Dr. Phillips accepted that antifolate activity had been observed in the face of a number of modifications to the structures of classical antifolates (see

Dr. Kalman's evidence at pp 7466-7467 Application Record and Dr. Phillips' evidence at pp 7364-7365 Application Record). What Dr. Kalman and Dr. Phillips did not accept was that a person of skill could soundly predict from that evidence and from Takeda's testing that similar or any activity would be expected for the claimed untested compounds.

VI. Lilly's Case for Sound Prediction

[58] Dr. Jones' affidavit states at paragraph 63 that "by the late 1980s a great deal was known regarding the relationship between the structure of classical antifolates and their antitumor activity". This knowledge was said to have enabled medicinal chemists to understand how variations to the three structural elements of classical antifolates (the bicyclic heterocyclic, the bridge element and the benzoyl glutamate residue) would likely affect their antifolate activity. Dr. Jones broadly characterized the prior knowledge in the following way:

> (a) It was known that the bridge "part" of classical antifolates could be varied significantly (made somewhat longer, or shorter, or with some added elements, etc.) without losing antifolate activity;
>
> (b) It was also known that both di- and mono-antifolate esters (in the glutamate "part" of classical antifolates) could have antifolate activity;
>
> (c) It was also known that different types of 6/6 fused ring structures in antifolates could be used without losing antifolate activity. However, it was not known that 6/5 fused ring structures might have any such activity as the only tested 6/5 classical structures had been shown to have no activity.

[59] Dr. Jones provided several prior art examples where variations to the bridge structures of classical antifolates were tolerated. This research indicated that one could vary the length of the

bridge structure or its branches to create compounds that retained antifolate activity. He concluded the prior art review concerning bridge structure variations in the following way:

> 95. It was known prior to March 23, 1989 that compounds having a classical antifolate structure with bridges two, three or four atoms in length; and bridges with a variety of branches on different bridge atoms retained antifolate activity. In other words, the POSA of the '794 Patent would have understood that the bridge moiety of classical antifolates can be varied significantly.

[60] Dr. Jones dealt with the prior art knowledge concerning the glutamate element of classical antifolates, including ester forms, in a similar way. He pointed to evidence showing that "some antifolate esters have been found to be biologically active per se" and that "other antifolate esters may act as prodrugs" that convert to active forms after administration. He concluded with the observation that "by March 23, 1989, it was known that both di- and mono-antifolate esters showed activity both in vitro and in vivo".

[61] Dr. Jones also considered what was known about variations to the bicyclic heterocycle element of classical antifolates bearing 6/6 and 6/5 fused ring systems. From that research he stated:

> Generally speaking, variations [to 6/6 ring structures] was tolerated with retention of activity, although the only 6/5 ring system tested was shown not to be active.

[62] According to Dr. Jones, this research would have suggested to the person of skill that 6/5 ring systems "might be of questionable value" (see para 125 of Jones' affidavit).

[63] Dr. Jones was asked by Lilly to examine different subsets of the Patent claims specifically Claim 7/4/2/1 and Claim 9/3/2/1. He stated that Claim 7/4/2/1 encompasses only 12

compounds… "and their esters, stereoisomers and salts". He effectively excluded esters, stereoisomers and salts on the following basis:

> 168. In my view the inclusion of esters, stereoisomers and salts has little impact on the question of predictability of these compounds. As I have stated above, some antifolate esters have been found to be biologically active *per se* because they directly bind to and inhibit a folate enzyme. Other antifolate esters likely act, at least in part, as prodrugs, which are converted within or without the cancer cell by an esterase enzyme to compounds with a free glutamate residue. Thus to simplify discussion of claims 7/4/2/1 (and later claim 9/3/2/1) I have chosen to limit the glutamate moiety to the diacid form. This form is also specifically claimed and where it is not and is an ester instead, that ester is likely to be active *per se* or likely to be a prodrug convertible *in vivo* to the diacid. Moreover, even if the esters did not have biological activity *per se*, the '794 patent teaches that these esters are useful as intermediates in the synthesis of the diacids, for example, synthesis of Working Example 4 from Working Example 3.
>
> 169. In my review of Dr. Phillips' and Kalman's reports, they do not correctly discuss the state of the art with respect to the significant amount of work that showed that esters of MTX and its analogs also had activity. As I discussed earlier, esters of MTX had been identified as active against cells in culture and L1210 leukemia *in vivo*.
>
> 170. Insofar as salts, these are limited to "pharmaceutical acceptable salts" and therefore would be equivalent to the diacid form.
>
> 171. As for the stereoisomers of these 12 compounds, there are 2 potential chiral centres: the C5 carbon of the pyrroline ring and C1 of the methyl-propyl bridge. As I have discussed earlier, the two stereoisomers of tetrahydrohomofolate both showed antifolate activity. Thus, the chiral centre at the point of attachment of the bridge to the bicyclic ring was known not to be critical. Furthermore, both of the diastereoisomers of the antifolate DDATHF were shown to be equally cytotoxic. Stereoisomers on the bridge had also been investigated and it was known that both stereoisomers of 10-EdAM showed activity.
>
> 172. Thus, I will focus on the 12 diacids (not the esters, salts or diastereomers). [Footnotes omitted]

[64] For Claim 9/3/2/1 Dr. Jones identified 76 diacid forms and again excluded from consideration the esters, salts and stereoisomers.

[65] Dr. Jones went on to examine test results obtained by Takeda, whether reported in the Patent or not. He also considered Takeda's comparative test results for the known compounds MTX and DDATHF which, he said, were consistent with what was known about those compounds. Takeda was also testing various compounds bearing 6/6 fused rings where antifolate activity was also observed.

[66] On the basis of the above-noted research data and prior knowledge available to the person of skill, Dr. Jones addressed the question of whether a *prima facia* reasonable inference could be drawn that the untested compounds within Claims 7/4/2/1 and/or 9/3/2/1 would have the promised "scintilla" of antifolate activity. Concerning Claim 7/4/2/1, Dr. Jones concluded that only a small extrapolation was required to make the necessary predictions. According to Dr. Jones, the person of skill would be influenced by the representative configurations of the seven working example tested compounds and by their structural similarity to the untested compounds[2]. He identified further support for a prediction of utility as follows:

> 252. Second, as discussed in the background section of my affidavit, those of us working in the antifolate field in the 1980s would have known that activity was retained even with significant variation in the structure of classical antifolates. It was known that compounds with two atom and three atom unbranched bridges were active, and that branched three atom bridges were also active. Further, antifolates where X is amino (—NH_2) were known to have activity, and those where X is hydroxyl (—OH) were also known to have activity.

[2] Only three of these are reported in the Patent but Dr. Jones maintained at para 280 of his affidavit that this was sufficient.

> 253. Third, with respect to the esters, I would expect that these would have had activity, as classical antifolates bearing the same or similar ester groups as those included in claim 7/4/2/1 showed activity. I also note that the ester compounds are also useful in that they are intermediates in the '794 Patent's process to make the diacids falling within claim 7/4/2/1.
>
> 254. In light of the above analysis, it is my opinion that it certainly was not a speculation on part of the inventors to claim that the compounds covered in claim 7 would have activity. The inventors had a significant amount of knowledge, whether it be from their own testing or from the common general knowledge, for each data point in the general structure of the compound to be able to make a *prima facie* reasonable inference that the compounds that they had not specifically tested would have an anti-tumour effect.
>
> 255. Further it would have also been my expectation that they would have an anti-tumour effect.

[67] In considering Claim 9/3/2/1, Dr. Jones essentially adopted the analysis he applied to Claim 7/4/2/1 to support the following conclusion:

> 258. In light of the above analysis, it is my opinion that it certainly was not speculation on part of the inventors to claim that the compounds covered in claim 9/3/2/1 would have activity. The inventors had a significant amount of knowledge, whether it be from their own testing or from the common general knowledge, for each data point in the general structure of the compound to be able to make a *prima facie* reasonable inference that the compounds that they had not specifically tested would have an anti-tumour effect.

[68] It is of some significance that Dr. Jones deliberately avoided addressing Dr. Kalman's and Dr. Phillips' evidence discussing the complexity and difficulty of extrapolating efficacy from one antifolate compound to another. Dr. Jones' explanation at paragraph 277 of his affidavit was that he did not agree with their definition of promised utility and saw no need to address their analysis in more detail. Dr. Jones' criticisms of Dr. Kalman's and Dr. Phillips' opinions were accordingly limited to specific points of disagreement or interpretation concerning

Takeda's reported testing or to differences about the scope of the promise of the Patent. An inference arises from Dr. Jones' refusal to fully engage with Dr. Kalman's and Dr. Phillips' evidence that Dr. Jones' opinion about sound prediction was relevant only to the truncated promise of utility that was suggested to him by Lilly's counsel.

[69] Dr. Jones' affidavit evidence must be read in light of the evidence he gave under cross-examination. That testimony indicated that there was considerably more nuance to his opinions than had been expressed in his affidavits.

[70] Dr. Jones did acknowledge that the mechanisms behind folate metabolism *in vivo* were known to be "fairly complex" involving about 10 to 12 enzymes (p 5606 Application Record). He also accepted that the mechanisms affecting drug delivery *in vivo* are complex.

[71] According to Dr. Jones any uncertainty about the mechanism of action is "irrelevant" once activity has been observed. He said that in such a case a prediction of activity can be made for untested compounds that have similar key structures to tested compounds (see para 10 of his supplementary affidavit at p 5607 Application Record).

[72] Dr. Jones was closely questioned about examples in the prior art that ran counter to the examples he had relied upon for his opinion. For example, he had excluded from his consideration the diastereoisomers on the strength of research showing activity for both diastereoisomers of certain antifolate compounds. He was asked on cross-examination about compounds that exist as diastereoisomers, where one was active and the other not. With some

reluctance, he conceded that possibility (see pp 5631-5636 Application Record). Later in the cross-examination he again conceded the same point in the following exchange:

> l255 Q. So do you agree with me, Dr. Jones, for a compound covered by claim 7 of the '794 patent with a three-carbon bridge or a two-carbon bridge or a three carbon substituted bridge, that, if there was a diastereomer at the C6 position, an ordinary skilled worker would understand that the diastereomers may be equiactive, one may be more active than the other, and one may have no activity and the other one may be active?
>
> A. That's possible.
>
> 1256 Q. Is that reasonable?
>
> A. Is that what a POSA would think?
>
> 1257 Q. Yes.
>
> A. Without doing further experimentation, those are the possibilities.

[73] Even though Dr. Jones was willing to predict efficacy where the evidence supported his opinion, he was considerably more reluctant to do so when evidence was unsupportive (see for example the lengthy exchange at pp 5647-5651).

[74] In another exchange Dr. Jones was asked about the significance of evidence of enzyme binding in the folic acid pathway and whether that would be important to the characterization of a compound as an antifolate. In response he expressed uncertainty about whether the Patent claimed the compounds as antifolates (pp 5814-5815, Application Record). This answer was inconsistent with his affidavit at paragraph 159 and it is inconsistent with Lilly's case.

[75] Dr. Jones acknowledged that the claimed compounds included many ester forms (see p 5816). Nevertheless, he discounted their significance to the issue of sound prediction because

some antifolate esters were known to directly inhibit folate enzymes and others were known to act as effective prodrugs. Under further cross-examination he retreated from the more categorical view expressed in his affidavit:

> 983 Q. On the top right-hand corner it should say number 5. You will agree, at the bottom it appears that he tested some diethyl esters of some 6/6 compounds?
>
> A. Yes, pyridyl pyrimidine.
>
> 984 Q. And they did not show activity?
>
> A. Well, the IC50 was greater than 5. So I don't know what the IC50 is or would be, but it's greater than 5.
>
> 985 Q. But he determined, for those --
>
> A. But that's µg/mL.
>
> 986 Q. He was not able to --
>
> A. Reach an IC50 in the experiment conducted.
>
> 987 Q. Right. For the diethyl esters?
>
> A. For the diethyl esters, yes. These compounds are not compounds of the invention, you will note.
>
> 988 Q. No, they are not. You are correct on that assumption. But you will agree --
>
> A. It's not an assumption. It's a fact.
>
> 989 Q. Well, you are correct on that fact. I stand corrected.
>
> You will agree that a person skilled in the art cannot infer, just because you have made a compound to a diethyl ester, that it will have activity in vivo, can you? You have to do the test to determine?
>
> A. You have to do the test, yes. But esters are frequently used in pharmacological research as prodrug forms. There is no doubt about that. Many review articles have been written upon it.
>
> 990 Q. Right. Esters in general. But as we --

A. Esters in general, yes.

991 Q. As we have seen in the antifolate field, diethyl esters may work or they may not work. You can't predict. You would have to do the test to determine that. Is that fair?

A. Yes, I would say so. But, clearly, from the work of Rosowsky and his colleagues, many esters are active either per se or upon hydrolysis.

992 Q. Let's go back to the Miwa, those diethyl esters. You indicated that they are not covered by the '794 patent, and correctly so. But that doesn't prevent you from drawing inferences with respect to 6/5 structures, does it? 6/5 fused rings in terms of what their activity would be, does it?

A. I guess not. It would not prevent me from making a guess.

[Emphasis added]

[76] Dr. Jones also qualified his evidence about what was known about the activity of classical antifolate compounds with variations in the bridge structures. Under cross-examination he clarified the evidence with the following answers:

1057 Q. So, again, I'm showing you a list of three-atom bridges from Dr. Miwa's affidavit. And you will agree with me that these three-atom bridges were not shown to be active?

A. Okay:

> "As set out below, it had also been shown by the late 1980s that compounds possessing a three-atom bridge also were active antifolates." (As read)

I did not say that all compounds possessing a three-atom bridge were active antifolates. Some were; and some would not be because there were other changes apart from the three-atom bridge. [p 5857, Application Record]

…

1071 Q. So, going from a two-atom bridge to a three-atom bridge?

A. In the case of this ring system, did not result in an active compound.

1072 Q. Right.

A. Because the enzyme inhibitions are not impressive.

1073 Q. Right. So when --

A. But when I made the statement about tetrahydryl homofolate, I was merely exemplifying that three-atom bridges had activity, but they were embedded in a different ring system to the 8-deazafolic acid system studied by DeGraw.

So my review of the literature here was not comprehensive, looking for three-atom bridges. I was exemplifying that three-atom bridges could confer activity in a compound, in an antifolate.

1074 Q. And a person skilled in the art would understand they may not confer activity in an antifolate?

A. This was published in 1988 so yes.

[p 5861, Application Record] [Emphasis added]

[77] This evidence supports Hospira's position that the fact that some antifolates in ester form will sometimes act as prodrugs or as active compounds *per se* does not on its own support a prediction that the thousands of ester forms claimed in the Patent could reasonably be inferred by the person of skill to be similarly active or active at all. The same reasoning applies to the activity profiles for diastereoisomers and compounds with varying bridge structures – not all of them would be predicted to have activity.

[78] I also cannot understand how Dr. Jones can reconcile his admission that test data from one cell line cannot be applied to another cell line with his statement that "similar" results could be predicted from one cell line to another. To my eye, the evidence provided below is inconsistent:

A. I wouldn't compare a result from one cell line to another cell line. They are different cell lines.

1051 Q. So why wouldn't you compare the results?

A. You have to -- you cannot make a judgment about whether one compound is more active than the other if you are jumping across cell lines. You have to test it in the same cell line --

1052 Q. Okay. So --

A. -- before you can make a judgment.

…

1054 Q. No, we have gone through that, and I understand that. We have looked at the numbers and we agree. So Takeda inventors looking at that data could not reach the conclusion that moving the bridge attachment from the C6 position to the C5 would result in a more active compound, could they?

A. Within the KB cell system, they knew that it could not.

Q. Okay.

A. But in another system, they knew nothing until they did the experiment.

…

681 Q. If you go to paragraph 157 of your affidavit, the last sentence you say:

> "...it is my opinion that it would be a reasonable extrapolation or inference that the compounds that have not yet been made and tested would show a similar activity."
>
> Do you see that?

A. Yes.

682 Q. And when you're referring to "a similar activity", can you explain to me what you mean by "a similar activity"?

A. Similar to the activities that had been found for the compounds made and tested, either in vitro or in vivo, you would

reasonably infer that the unmade and untested compounds would have similar activities.

…

686 Q. And a person of ordinary skill in the art reading the '794 Patent, what would they reasonably extrapolate or infer would be its activity in KB cells?

A. When I wrote paragraph 157, I was referring to an anti-tumour effect in vitro and/or in vivo.

I was not particularly thinking of the particular test.

I was thinking of all of the activity data that had been accumulated for that compound, which may involve more than one test.

And for those compounds not yet made and tested, would show similar activity, I mean activity in the round.

687 Q. Okay, so ---

A. It need not necessarily have to replicate on a KB cell if other cells like the Meth A or the L12 tumour they were good IC50's, then you would say that the compounds, the activity of the unmade compounds was similar.

688 Q. So what you're saying is as long as the compound has activity in some cell line or in some test has an IC5O value, you would consider that to be similar to the values in Table 1, page 26?

A. Similar, roughly the same. Not the same, but in the same range.

[Emphasis added]

[79] Dr. Jones maintained that Takeda's inability to understand the mechanism of action for the claimed compounds (i.e. why they were producing antitumor effects) was irrelevant. According to this view, all the person of skill needed to make a sound prediction of efficacy for the untested compounds was knowledge that the similarly-structured tested compounds exhibited some antitumor activity in one or another cell line *in vitro*. Dr. Jones described this as a

prediction of "activity in the round" (see p 5728 Application Record). His evidence at page 5732 of the Application Record reflects this point:

> Okay, you have all of the data that is in front of you, except that you do not have the data for Working Example 14 in KB. Okay?
>
> What would the person of ordinary skill in the art reasonably extrapolate or infer that the IC50 value for Working Example 14?
>
> REF MR. CREBER: Objection, not relevant.
>
> BY MR. SPRIGINGS:
>
> 697 Q. Again, I'm using the words from paragraph 157 of your affidavit where you say:
>
> > "...in my opinion it would be a reasonable extrapolation or inference that the compounds that had not yet been made and tested would show a similar activity."
>
> A. I did not say a similar activity in KB cells.
>
> I have already explained I would be comparing activity found as a whole with the activity yet to be found as a whole.
>
> I find it difficult when you try to limit the statement I made in 157 -- paragraph 157 to a KB cell result.
>
> I did not intend that when I wrote paragraph 157.

[80] This strikes me as a highly dubious line of reasoning, particularly, in the context of Dr. Jones' acknowledgement that there are no universal predictive rules that a person of skill could apply to all of the structural variations to antifolate analogues.

[81] As noted above, Dr. Jones appears to accept that the person of skill could not predict antitumor activity across cell lines. That was also the evidence given by Dr. Kalman and

Dr. Phillips. Nevertheless, according to Dr. Jones, without knowing the mechanism of action, the person of skill could still infer, from highly variable data for a handful of compounds, that some measurable antitumor activity would appear in some cell line from thousands of untested compounds with varying structures. With respect, Dr. Jones' resort to a prediction of "activity in the round" does not represent a sound line of reasoning sufficient to support a prediction of the promised utility, particularly in the face of the specific barriers to a prediction identified by Dr. Kalman and Dr. Phillips. Instead what Dr. Jones offers as a prediction of utility "in the round" is no more than a guess.

[82] Dr. Wuest gave some evidence on the issue of sound prediction but he clearly lacked expertise in that area and his evidence was not compelling. At paragraph 101 of his affidavit, he noted the structural resemblance of the compounds of the Patent to MTX, DDATHF folic acid and derivatives "in at least certain aspects of their biological effects, such as their ability to bind to enzymes in the folic acid pathway". Nevertheless, his opinion was limited to generalizations (see paras 50 and 101 of his affidavit at pp 770 and 784 of the Application Record). Under cross-examination, his lack of conviction was more obvious. When he was directed to a claimed compound with certain structural differences to other known antifolates, he gave the following tepid response:

> So that particular structure contains two of the core structural- features that are found in molecules such as folic acid, MTX and DDATHF. It does not contain the full M benzo lated glutamic acid that you find in folic acid, MTX and DDATHF, but it contains part of that unit. In other words, the structural analogy between Compound 4 and the antifolate class that I'm describing in paragraph 33 is more partial than it is in the case of other compounds, <u>but it is not so far away from the structures as to rule out the possibility of some kind of an antitumor effect based on similar biochemical mechanisms</u>. [Emphasis added]

[83] It is also of significance that when Dr. Wuest was asked about stereochemistry and, in particular, the different chemical and physical properties associated with diastereoisomers, Lilly's counsel refused to let him answer (see pp 5178-5182 Application Record). Dr. Wuest had opened the door to this line of questioning with his affidavit evidence bearing on the issue of sound prediction and these refusals were unjustified; they also support an inference that Dr. Wuest's answers would not have supported Lilly's case.

[84] Dr. Wuest limited the "meaningful" or "effective" scope of Claim 7/4/2/1 to include only 16 compounds. This ignored the esters which he said "can't be converted by hydrolosis into a narrow set of 16 dicarboxylic acids" (see para 38 of his affidavit at p 766 of the Application Record). He adopted the same approach to Claim 9 which he concluded was effectively limited to only four unique compounds (see paras 39 and 40 of his affidavit at p 767 of the Application Record). Dr. Wuest did acknowledge, however, that if the person of skill took the esters and diastereoisomers into account, the size of the claimed classes would be "a very large number".

[85] Dr. Jones' quantitative assessment of the scope of the Claims 7/4/2/1 came to 12 specific diacid compounds and, for Claim 9/3/2/1, to 76 specific diacid compounds. Both counts excluded esters, diastereoisomers and salts. Dr. Jones' substantive explanation for excluding esters, stereoisomers and salts was the following:

> 168. In my view the inclusion of esters, stereoisomers and salts has little impact on the question of predictability of these compounds. As I have stated above, some antifolate esters have been found to be biologically active *per se* because they directly bind to and inhibit a folate enzyme. Other antifolate esters likely act, at least in part, as prodrugs, which are converted within or without the cancer cell by an esterase enzyme to compounds with a free glutamate residue. Thus to simplify discussion of

> claims 7/4/2/1 (and later claim 9/3/2/1) I have chosen to limit the glutamate moiety to the diacid form. This form is also specifically claimed and where it is not and is an ester instead, that ester is likely to be active *per se* or likely to be a prodrug convertible *in vivo* to the diacid. Moreover, even if the esters did not have biological activity *per se*, the '794 patent teaches that these esters are useful as intermediates in the synthesis of the diacids, for example, synthesis of Working Example 4 from Working Example 3.
>
> 169. In my review of Dr. Phillips' and Kalman's reports, they do not correctly discuss the state of the art with respect to the significant amount of work that showed that esters of MTX and its analogs also had activity. As I discussed earlier, esters of MTX had been identified as active against cells in culture and L1210 leukemia *in vivo*.
>
> 170. Insofar as salts, these are limited to "pharmaceutical acceptable salts" and therefore would be equivalent to the diacid form.
>
> 171. As for the stereoisomers of these 12 compounds, there are 2 potential chiral centres: the C5 carbon of the pyrroline ring and Cl of the methyl-propyl bridge. As I have discussed earlier, the two stereoisomers of tetrahydrohomofolate both showed antifolate activity. Thus, the chiral centre at the point of attachment of the bridge to the bicyclic ring was known not to be critical. Furthermore, both of the diastereoisomers of the antifolate DDATHF were shown to be equally cytotoxic. Stereoisomers on the bridge had also been investigated and it was known that both stereoisomers of 10-EdAM showed activity.
>
> 172. Thus, I will focus on the 12 diacids (not the esters, salts or diastereomers). [Footnotes omitted]

[86] Like Dr. Wuest, Dr. Jones expressed the initial view that ester forms could be essentially excluded from consideration because they do not influence the activity of the core element of the molecule. Nevertheless, under cross-examination, this position was considerably qualified with the acknowledgement that, without experimentation, the activity of ester and diastereoisomer forms of antifolate compounds could not be routinely predicted and that inactivity was a possibility (see pp 5833-5834 and p 5929 Application Record). In addition, he was only able to

say that some antifolate esters have been found to be biologically active *per se* and others may act as prodrugs. [Emphasis added]

[87] Dr. Van Etten's affidavit does not support Lilly's case for sound prediction of all of the compounds of Formula I. Neither does his affidavit identify which of those untested compounds (or subset of the compounds) could be soundly predicted to have "anti-tumor efficacy". His opinion on this issue is offered in the following guarded language:

> 68. In my opinion, the anti-tumour efficacy of at least some of the Formula I class compounds would be considered by a person of ordinary skill in the art of cancer biology to be both demonstrated and soundly predicted by the following data presented in the '794 Patent: (1) the demonstration of tumour cell growth-inhibitory properties of several of these compound(s) in vitro at sub-nanomolar concentrations (p. 26 lines 5-13 and p. 27 line 20); (2) the demonstration of>500-fold selectivity of the WE-14 compound to inhibit the growth of leukemic cells (HL-60) versus normal cells (HEL) (p. 27 lines 15-22); and (3) the stated anti-tumour effects of the compound(s) in vivo in warm-blooded animals bearing tumours derived from diverse mouse and human tumour cell lines (p. 25, lines 2-10). [Emphasis added]

[88] When he was asked about this evidence under cross-examination, he gave the following answer:

> Q. And in paragraph 68 you say, in my opinion the anti-tumor efficacy of at least some of the Formula I class compounds; do you see that?
>
> A. Yes.
>
> Q. And again, here when you refer to at least some of the Formula I class compounds, which ones are you referring to?
>
> A. The most obvious ones are the ones for which they provide in vitro data. So, again, the same suspects four, six, 14, 16.
>
> Q. Are there any others?

> A. We could presume that they, as I mentioned for some of the other working examples because they made the effort to prepare larger amounts which is what a working example usually means, that they probably did conduct at least in vitro testing with some of these compounds, but it's not exclusively presented in the patent.

[89] He also expressed the view that the Patent could not plausibly claim antitumor properties for every claimed compound because "in order for them to make that claim, they would have to synthesize each and every single one of them and test them" (see p 4921-4922). This is not an endorsement for a sound prediction and, instead, it appears to line up more closely with the evidence of Dr. Kalman and Dr. Phillips.

[90] It is also noteworthy that Dr. Van Etten acknowledged that the references in the Patent to "anti-tumour effects" and, in Claim 31, to "an anti-tumour agent" inform the person of skill that multiple, efficacious *in vivo* test results for a subset of Formula I compounds had been obtained. The following passages from his affidavit are also instructive:

> 65. These in vivo tests are not described in detail in the '794 Patent, but the language on p. 25 states that Formula I compounds have "anti-tumor effects" against several mouse and human tumour cell lines, "decrease the tumors carried by warm-blooded animals, and prolong the lifespan of tumor-carrying warm-blooded animals." Because the word "tumor" refers to a cancer mass in a living organism, to a person of ordinary skill in the art of cancer biology, the term "anti-tumor effects" as used in the '794 Patent (p. 2 and p. 25) would imply that multiple tests of the ability of a subset of these compounds to inhibit tumour growth in animals had been carried out. It is very likely that such tests would be done in immunodeficient laboratory mice that were inoculated subcutaneously with the various tumour cells lines, as was the general practice in the cancer biology field in the l980s. The Patent goes on (pp. 27-29) to discuss various pharmaceutical preparations for oral and parenteral delivery of the drugs, as well as potential dosing schedules.

> 66. The Claims of the '794 Patent are listed on pp. 58-71. Claims 1-29 again describe compounds of the Formula I class, with 16 members of this class cited explicitly by their formal chemical names. Claim 31 of the Patent cites "an anti-tumor agent containing an anti-tumor effective amount of the compound or salt as defined in any one of the claims 1 to 29, in admixture with a pharmaceutically acceptable carrier".
>
> 67. As discussed above, a person of ordinary skill in the art of cancer biology would likely infer that this refers to an agent or compound with anti-tumour effects, which in turn implies effects against a tumour mass in vivo. This is reinforced by the inclusion of the phrases "...an anti-tumor effective amount..." and "...in admixture with a pharmaceutically acceptable carrier". The term "an anti-tumor effective amount" seems to be used rather than the word "concentration" because the precise in vivo concentration required for an anti-tumour effect usually cannot be determined from in vitro experiments, but rather is dependent on a particular dose or amount of the compound that is administered to an organism. The reference to a "pharmaceutically acceptable carriers" reinforces that in vivo applications are being considered here.

[91] Dr. Van Etten was not asked to construe or consider any of the remaining claims of the patent. Beyond the qualified and generalized opinion noted above, he made no attempt to identify the factual basis or the sound line of reasoning necessary to support a sound prediction for utility for the asserted claims other than Claim 31.

VII. Hospira's Case Concerning Sound Prediction

[92] The better evidence on the issue of sound prediction was provided by Hospira's expert witnesses. The strength of much of that evidence was enhanced by Lilly's failure to directly challenge it. The particulars provided by Hospira's witness also stand in rather stark contrast to the frailties of the Lilly evidence discussed above.

[93] It is not disputed that the folic acid pathway was in 1989 known to be complex involving a number of enzymes with complex three-dimensional structures. Antifolates were known to work by binding to the active site of an enzyme (or enzymes) thereby inhibiting their function. This, in turn, interfered with DNA replication and cell division.

[94] It is not a matter of disagreement that the Patent provides biological test data for only four compounds. In comparison, Claims 7 and 9 covered thousands of compounds, the utility of which had to be established by sound prediction.

[95] Dr. Kalman's opinion on sound prediction was supported by the complexity of the processes that were required to obtain antifolate activity. According to Dr. Kalman, small structural differences to classical antifolates can result in dramatic differences in biological activity including inactivity (see para 162 at p 3188 Application Record). This point is reflected in a history of the co-discovery of Pemetrexed by Dr. Edward Taylor where he described the problems he faced at the relevant time:

> "It seemed highly unlikely that DDATHF (compound D), whose extraordinary activity served to launch this collaborative program, would prove to be the ultimate structure of choice. We therefore embarked on what amounted to a classical SAR, or structure-activity-relationship study, where structural changes are made systematically, and each new compound emerging from this work is then evaluated. Every portion of the structure of DDATHF was probed in the hope that a picture of an optimal structure might emerge. We had to bear in mind that every change in structure can affect solubility, absorption, bioavailability, metabolism, partition. coefficients, toxicity, possible activity against other biological targets, stability (pharmacokinetic and biochemical properties), as well as resonance, inductive effects, electronic distribution, chemical reactivity and stability, shape, size and bond angles, pK_a and hydrogen bonding capacity (chemical properties). Furthermore, the effect of a change in one part of the molecule can

> modify or cancel what might have appeared to be a potentially useful change in another part of the molecule."

[96] Of course Dr. Taylor was looking for an optimal drug candidate and not simply for antifolate activity. Nevertheless, the complexities of the problem of predicting activity from one molecule to another remain the same.

[97] Dr. Kalman identified several hurdles facing the person of skill who was attempting to predict antitumor activities. These included uncertainty arising from the following factors:

(a) Transport of the compound into the tumor cell. Different cell types and tissues vary in their ability to transport antifolates into target cells (see paras 169-173 at pp 3191-3194 Application Record).

(b) The extent of polyglutanylation. This was known to be affected by differences among cell types and by the structure and stereochemistry of the antifolate. This, in turn, can influence antitumor activity.

(c) The ability to bind to enzymes in the folate-dependent pathway. It was known in 1989 that small differences in molecular structure could affect the ability of a compound to bind with an enzyme or could cause a significant difference in activity against different enzymes.

(d) To be effective, ester forms must convert to acids by hydrolosis by an esterase enzyme in a tumor cell. This capacity was known to vary by tumor type, the species of animal and the structure of the ester form.

[98] Dr. Kalman also noted that the Patent disclosed *in vitro* data for only four compounds and yet Claims 1-4, 6, 7, 9, 11, 13 and 31 covered thousands of compounds. The four tested compounds were structurally unrepresentative of the thousands of untested compounds claimed and would not have provided the person of skill with sufficient factual information to predict the

promised utility. This would also be the case if the person of skill had the undisclosed Takeda test data at hand including its *in vivo* data.

[99] Dr. Kalman summed up his opinion on sound prediction in the following way:

> 274. The '794 Patent would not have provided an Ordinary Skilled Worker with a sound line of reasoning in March, 1989, to predict whether or not the compounds covered by claims 1-4, 6, 7, 9, 11, 13 and 31 had the Promised Utilities for the following reasons:
>
> (a) the structures of the compounds tested are not representative of the scope of compounds claimed;
>
> (b) the structures of the Exemplary Compounds are not representative of the scope of compounds claimed;
>
> (c) the claimed compounds include diastereoisomers, and the Ordinary Skilled Worker in March 1989 would have known that stereoisomers can differ in their biological activities;
>
> (d) differences in structures of antifolate compounds will affect: (1) the ability of the compound to be transported into the tumor (and normal) cells; (2) the extent of polyglutamylation once inside the cell; and (3) its ability to inhibit target enzymes in the folate-dependent pathway;
>
> (e) the absence of any information about the mechanism of action of the compounds that had been tested or claimed in the '794 Patent; and
>
> (f) the *in vitro* assays described in the '794 Patent are not soundly predictive of *in vivo* efficacy of all antifolates.
>
> 275. An Ordinary Skilled Worker would not have been able to soundly predict, based upon information provided in the '794 Patent, that all of the compounds falling within the full scope of claims 1-4, 6,7, 9, 11, 13, and 31 would have the Promised Utility.

[100] For the most part, this evidence was left unchallenged in cross-examination. Dr. Kalman acknowledged the potential for observing antitumor activity in the context of differences in the structure of classical antifolates but he did not waiver in his opinion that this potential for activity would not support a sound prediction that all of the compounds falling within the asserted claims would be likely to have antitumor activity *in vitro* or *in vivo*. His evidence at pages 7352 to 7354 reflects his disagreement with Dr. Jones concerning the ability to predict antifolate activity "similar" to the results obtained by Takeda for the compounds it tested:

> 966. Q. Yes, but you never heard of a prima facie reasonable inference. You weren't provided with that legal assumption, were you?
>
> A. I don't know what that is.
>
> 967. Q. Do you know what an inference is?
>
> A. You interpret something or you infer something from something, yes.
>
> 968. Q. Would you agree where you hadn't made a particular compound of a class but you had made compounds around it, one might infer through structural activity relationships that they would have similar, not identical, but similar activity. That would be an inference because you hadn't perhaps actually made nor tested that new compound, fair?
>
> A. That is an inference but that is something that I would not infer.
>
> 969. Q. Because you are not a medicinal chemist?
>
> A. I am not a medicinal chemist but I have worked extensively with medicinal chemists and I know that very minor changes in structure could have quite significant differences in terms of substrate specificity for enzymes and also activity.
>
> 970. Q. And sometimes there is very little difference, that they all show similar types of activity?
>
> A. That is correct but you can't predict based on the structure alone.

> 971. Q. No, but if you have data for a number of compounds within c1ass and you see that you have activity for each of them… granted, there are some changes. Minor structural change may not... would be an inference. It may not be certain but an inference that you would see similar activity.
>
> A. In new compounds or in…
>
> 972. Q. Yes, in something similar, structurally similar to what you had actually made and tested.
>
> A. I wouldn't make that inference.
>
> 973. Q. Okay
>
> A. I know for a fact that compounds would have been very minor structural differences with quite big effects.

[101] I also prefer the evidence of Hospira's witnesses concerning the importance of understanding the mechanism of action to the issue of sound prediction. On this issue, I accept the evidence of Dr. Kalman where he addressed the relevance and importance of understanding the mechanism of action in the following way:

> 271. The '794 Patent does not disclose the "new mechanism" that is responsible for the antitumor activity of the compounds covered by claims 1-4, 6, 7, 9, 11, 13 and 31 and enzymes involved in folic acid metabolism they specifically target (distinct from DHFR). That being the case, one cannot look to the literature for guidance on SAR, since SAR is target-specific (as explained above). For well-characterized drug targets, those structural features important for binding and/or efficacy will have been determined, allowing the medicinal chemist to design compounds to interact with such features. Absent information regarding the target of action, the Ordinary Skilled Worker would not be able to determine which parts of a compound of formula (I) were required for activity and which would be detrimental for activity.
>
> 272. Antifolate compounds having a pyrrolopyrimidine core had never been previously synthesized or tested for antitumor activity; thus, it would have been impossible to develop a meaningful SAR for all of the compounds covered by each of claims 1-4,6,7,9, 11, 13 and 31. Importantly, no tests results of inactive compounds are disclosed in the '794 Patent; thus, an Ordinary Skilled Worker

> would be unable to determine the "limits" of allowable substitutions or replacements encompassed by formula I of the '794 Patent.

[102] Dr. Phillips made the same point at paragraphs 216 and 217:

> 216. The only data reported in the '794 Patent relates to testing done in two human cell lines:
> KB and HL-60. As of March 23, 1989 (or even today), an Ordinary Skilled Worker would have known that different human cancer cell lines will have different sensitivities to the same antifolate because of differences in biochemical functions between the cell lines. As of March 23, 1989, the National Cancer Institute (NCI) had adopted an *in vitro* screen to assess the *in vitro* activity of compounds submitted for testing. The NCI screen used 60 different human cancer cell lines because of the differences in activity seen from one human cancer cell line to another. It was well known to an Ordinary Skilled Worker that a compound's level of activity (or lack of activity) in one human cell line could not be used to soundly predict the compound's level of activity (or lack of activity) in another human cell line.
>
> 217. Furthermore, in the absence of knowledge of the mechanism of action of the compound being tested, an Ordinary Skilled Worker would not have been able to soundly predict a compound's activity (or lack of activity) in HL-60 cells based on the same compound's level of activity (or lack of activity) in KB cells. Similarly, an Ordinary Skilled Worker would not have been able to soundly predict a compound's activity (or lack of activity) in KB based on the same compound's level of activity (or lack of activity) in HL-60 cells. For example, if the compound depends on polyglutamation for activity, it would have been known that different cell lines have different levels of polyglutamation. See for example Pizzorno, G. *et al.*, "Inherent Resistance of Human Squathous Carcinoma Call Lines to methotrexate as a Result of Decreased Polyglutamylation of This Drug", *Cancer Research*, 1989, 49(19), pp. 5275-5280. A copy of this article is attached to my affidavit as **Exhibit "11"**.

[103] Dr. Chong's affidavit provides a detailed analysis of the structural features of the specific compounds referenced in the Patent in comparison to the structural elements of the claimed compounds.

[104] According to Dr. Chong's calculations, the asserted claims include thousands of compounds, including esters and stereoisomers (see paras 24 and 25 of the Chong affidavit). In comparison, the number of compounds referenced in the asserted claims was no more than 44. Dr. Chong described their structural features or variations in his affidavit as follows:

> 45. Of these 44 compounds, i.e., the Formula (I) Examples, there are no 4-carbon bridge compounds. Also, there are only two 2-carbon bridge compounds and the remaining 42 compounds are 3-carbon bridge compounds. Neither of the two 2-carbon bridge compounds have a pyrrole ring; whereas, the 3-carbon bridge compounds include both pyrrole compounds and pyrroline compounds. In addition, the two 2-carbon compounds have the same structures except for the $–COOR^1$ and $-COOR^2$ groups: Working Example 12 is the diethyl ester form ($- COOCH_2CH_3$) of Working Example 15, which is in the diacid form (-COOH). The remaining compounds 45-62 set out in Exhibit "14" are potential intermediate compounds.

[105] At paragraphs 48 to 66, Dr. Chong went on to identify the structural elements of the claimed compounds missing from the Patent's Working Examples (4, 6, 14, and 16) and also missing from all 44 of the compounds specifically identified in the Patent (exemplified, reference, working and the compounds of Claims 14 to 29). This evidence indicates that the compounds Takeda ostensibly tested were structurally distinct from the compounds covered by the asserted claims.

[106] Dr. Chong's analysis was essentially left unchallenged by Lilly's experts but it was relied upon by Dr. Phillips and Dr. Kalman to support their opinions that the compounds presumably tested by Takeda were structurally unrepresentative of the array of untested compounds included within the asserted claims. Given their evidence that the presence of even small structural variations to classical antifolates can result in dramatic differences in biological activity

(including inactivity), there was, according to this view, no sound basis to predict antifolate activity for the untested compounds.

[107] Dr. Phillips agreed with Dr. Kalman that "minor" structural changes to antifolate compounds "can have a dramatic effect on activity; in fact, a single change can render an extremely potent compound inactive". Dr. Kalman noted that Takeda's own test data confirmed this potential (see para 162). This evidence was similarly not directly challenged by Lilly. Instead, Lilly attempted to make its case for a sound prediction based only on an inference of some measurable activity "at large".

[108] Even with Lilly's truncated promise of utility, I do not accept that a case of sound prediction has been established. In the face of Dr. Kalman's and Dr. Phillips' evidence that Takeda's test data were insufficiently representative, I do not agree that the person of skill in 1989 could predict antifolate activity for all of the untested compounds in the asserted claims, including pemetrexed.

[109] A similar problem arises from the failure of Lilly's witnesses to directly address Hospira's evidence concerning the claims covering the myriad of antifolate esters and diastereoisomers.

[110] It is not disputed by anyone that diastereoisomers were known in 1989 to be different compounds that often exhibit significantly different chemical and biological properties from one

another. Nevertheless, before the filing date Takeda had not isolated or tested any of the claimed diastereoisomers (see the evidence of Dr. Tetsuo Miwa at pp 4168-4169).

[111] Similarly, the ability of antifolate esters to hydrologize is subject to a number of variables that cannot be predicted in advance (see paras 185-187 of the Kalman affidavit and paras 209-210 of the Phillips affidavit).

[112] I do not agree with the Lilly experts that the diastereoisomers and ester forms of the claimed compounds would be effectively excluded or ignored by the person of skill from a sound prediction analysis. Those compounds could only be excluded from consideration if the person of skill could safely assume they would not constitute a negating influence over a compound's antitumor activity. Neither Dr. Jones nor Dr. Wuest made a convincing case for such a benign effect. For example, at paragraph 33 of Dr. Wuest's affidavit he only stated that the conversion of esters into the corresponding carboxylic acids is "routine" and "can occur" under various well established conditions such as when ester forms are used as prodrugs. This led him to assert only that "[i]n principle, many different ester forms may be suitable for use in this way" [emphasis added]. This response is no different than the evidence provided by Dr. Kalman and Dr. Phillips. For example, when Dr. Phillips was cross-examined about the issue of stereochemistry, he gave the following response:

> Q. Certainly there were examples in the literature that the stereochemistry did not appear to affect the activity.
>
> A. There are other examples where it does. It is common general knowledge. [p 7225]

[113] He gave a similar answer when asked about the use of antifolate esters as prodrugs:

> Q. And indeed sometimes delivering it as a prodrug would be more effective than the active moiety?
>
> A. Delivery of the prodrug would very much depend on the prodrug activation system.
>
> 938. Q. I am not saying every time it would be better, but sometimes it would be better.
>
> A. Depending on the mechanism, depending on the substrate specificity and a whole raft of different reasons.
>
> 939. Q. And if the compounds, let's say, had poor solubility you might go with a salt form, that might improve it?
>
> A. It might. It might make it worse too.

[114] The evidence of Drs. Kalman, Phillips and Chong was clear and decisive and for the most part it was left unchallenged. I accept their evidence about the significant barriers to predicting antifolate activity for an untested compound based on data for another.

[115] In contrast, the evidence from the Lilly experts was equivocal and vague. This was particularly the case for Dr. Jones' evidence concerning a theory of sound prediction of activity "in the round". This seems to me to be largely meaningless generalization intended to avoid the evidence offered by Dr. Phillips and Dr. Kalman about the inherent difficulties of predicting antifolate activity from one compound to another and across cell lines.

[116] In the result, I do not agree with Lilly that a person of skill would have made a prediction of utility for the thousands of untested compounds included in the asserted claims. This is equally the case if one accepts Lilly's assertion of the promise of the subject claims as being merely some antifolate activity in some cell line *in vitro*. Takeda's attempt to monopolize such a huge class of compounds on the strength of its highly discrete test data is a clear case of over-

reaching and it falls squarely within the concerns expressed in *Wellcome*, above, at paragraph 80, about the stockpiling of stables of chemical compounds before their utility has been demonstrated or predicted.

[117] For the foregoing reasons, this application is dismissed with costs payable to Hospira at the upper level of Column IV.

JUDGMENT

THIS COURT'S JUDGMENT is that this application is dismissed with costs payable to Hospira at the upper level of Column IV.

"R.L. Barnes"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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