Federal Court  Cour fédérale

Date: 20151102

Docket: T-1156-12

Citation: 2015 FC 1156

Ottawa, Ontario, November 2, 2015

PRESENT: The Honourable Mr. Justice Annis

BETWEEN:

GILEAD SCIENCES, INC AND GILEAD SCIENCES CANADA, INC

Plaintiffs
(Defendants to the Counterclaim)

and

IDENIX PHARMACEUTICALS, INC, UNIVERSITA DEGLI STUDI DI CAGLIARI, L'UNIVERSITÉ MONTPELLIER II AND CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Defendants

AND BETWEEN:

IDENIX PHARMACEUTICALS, INC,

Plaintiff to the Counterclaim

and

GILEAD PHARMASSET LLC, GILEAD SCIENCES, INC, AND GILEAD SCIENCES CANADA, INC

Defendants to the Counterclaim

AND

**UNIVERSITA DEGLI STUDI DI CAGLIARI,
L'UNIVERSITE MONTPELLIER II AND
CENTRE NATIONAL DE LA RECHERCHE
SCIENTIFIQUE**

Third Parties to the Counterclaim

PUBLIC JUDGMENT AND REASONS
(Confidential Judgment and Reasons issued October 9, 2015)

I. Introduction

[1] Gilead Sciences, Inc and Gilead Sciences Canada, Inc, (together with the Defendant by counterclaim Gilead Pharmasset LLC, hereinafter referred to collectively as [Gilead], seek a declaration that Canadian Patent No 2,490,191 [the '191 Patent] is invalid. They initiated the claim as interested persons under section 60 (1) of the *Patent Act*, RSC 1985, c P-4, as amended, s 27 [the *Act*].

[2] The Defendant, Idenix Pharmaceuticals Inc [Idenix] and the other defendants in the main action are the owners of the '191 Patent.

[3] Gilead Sciences, Inc through its subsidiary, Gilead Pharmasset LLC, is the owner of Canadian Patent 2,527,657 [the '657 Patent] filed on April 21, 2004 and issued June 14, 2011.

The ‘657 Patent includes claims to a novel compound, “sofosbuvir”, for the treatment of Hepatitis C viral infections.

[4] Gilead claims to be an interested person as having a reasonable basis to believe that the manufacture, use or sale of sofosbuvir would be impugned by the Defendants as an infringement of the ‘191 Patent. This has proved an accurate assumption, as evidenced in this matter by the counterclaim of Idenix.

[5] Gilead Sciences Canada, Inc filed a New Drug Submission for sofosbuvir on or about May 21, 2013. Sofosbuvir was approved for sale in Canada through the issuance of a Notice of Compliance on December 13, 2013. Gilead Sciences Canada, Inc now sells sofosbuvir in Canada under the brand name SOVALDI.

[6] SOVALDI is a “revolutionary” drug. It represents a significant breakthrough in the treatment of the Hepatitis C virus [HCV], which is said to infect more than 2.2% of the world’s population. It is an oral treatment that is highly effective with few side effects when compared with other treatments.

[7] Gilead seeks to invalidate the ‘191 Patent on the grounds of insufficient disclosure, lack of demonstrated utility/sound prediction and overbreadth. It does so on the basis that Idenix has claimed a huge number of compounds and their use which lack sufficient disclosure, utility on any basis in the specification of the’ 191 Patent, or in light of the common general knowledge at

the relevant date. Idenix filed its patent application before it had made or tested any compound within the '191 Patent's scope, despite more than 18 months of effort to do so.

[8] Conversely, Idenix claims to be the inventor of the novel nucleoside inhibitor that provides the anti-viral activity in sofosbuvir. It advances the claim, in part, on the basis that the novel nucleoside was an analogue of one of its earlier inventions.

[9] It denies the claim that its inventors did not soundly predict the utility of the novel nucleoside in sofosbuvir. It notes that the novel nucleoside is differentiated by only one substituent with similar stereochemical characteristics to that disclosed in Idenix's earlier invention, which has demonstrated antiviral activity.

[10] Idenix also denies that the '191 Patent does not disclose how to make the novel nucleoside. It claims that the synthesis of the compound was not novel. Based upon the disclosure in the '191 Patent, it could be made by the chemist of ordinary skill in the art, having recourse to the common general knowledge and routine experimentation. It claims the named inventor of the '657 Patent synthesized the novel compound with little difficulty, whereas the Idenix chemist assigned the task, similarly made the compound, but without knowing so because he was not acting like a skilled discovery chemist, but rather a process chemist.

[11] Idenix counterclaims that the novel nucleoside in sofosbuvir was anticipated by the '191 Patent. It seeks a declaration that the '657 Patent is invalid and that Gilead has infringed certain claims of their patent, along with other remedies of a permanent injunction, damages etc. Idenix

has no product, either on the market or pending authorisation by Health Canada, which is covered by the '191 Patent.

[12] Idenix argues in the alternative, that to the extent that it does not have priority of a valid invention, the '657 Patent is invalid under section 53 of the *Act* for knowingly omitting naming Lieven Stuyver as an inventor; a misrepresentation that it claims was made willfully for the purpose of misleading.

[13] After careful consideration of the evidence and submissions of the parties, for the reasons that follow, I allow Gilead's claim. I declare the '191 Patent to be invalid and dismiss Idenix's counterclaim in its entirety.

II. Background Facts

A. *Idenix and its Patents*

[14] Idenix is a pharmaceutical company founded in the late 1990s. It was interested in discovering, developing and commercializing innovative therapeutics in areas of unmet medical needs.

[15] Idenix had collaboration agreements with the Universita Degli Studi Di Cagliari [Cagliari], L'Université Montpellier II [Montpellier], and Centre National de la Recherche Scientifique [CNRS]. In particular, Idenix established with Montpellier and CNRS a

collaborative chemistry laboratory located in Montpellier, France that was overseen by Dr Gilles Gosselin (an employee of CNRS) and by Dr Richard Storer, Idenix's Executive Director of Chemistry.

[16] Idenix also established with Cagliari a collaborative biological testing laboratory located in Cagliari, Italy that was overseen by Professor Paolo La Colla of Cagliari.

[17] On November 29, 2001, WO 01/90121 [US '121] was published disclosing the D-ribose 2'-Methyl (up), 2'-Hydroyl (down) [hereinafter referred to as "2'-C-Me/OH"] nucleoside structures and derivatives for antiviral activity against HCV. On December 6, 2001, WO 01/92282 [US '282] was published similarly disclosing the 2'-C-Me/OH structures for antiviral activity against flaviviruses and pestiviruses. These compounds were the precursors that led to the development of the claimed novel invention, which claims coverage for D-ribose 2'-Methyl (up), 2'- Fluorine (down) [hereinafter referred to as "2'-C-Me/F"] nucleoside structures and their derivatives.

[18] On June 28, 2002, Idenix filed US application 60/392,350 [US '350] and US Patent Application 60/392351 [US '351], both of which are referred to in the '191 Patent. US '350 contained, among its extensive claimed compounds, 2'-C-Me/F compounds. Conversely, the US '351 omitted reference to any 2'-C-Me/F compounds. US '351 is no longer relied upon by Idenix as a priority application for the '191 Patent.

[19] On 31 March 2003, it was announced that Novartis was to acquire a majority stake in Idenix, together including the right to jointly develop its 2'-C-Me/OH nucleoside candidate NM283 to treat HCV.

[20] On April 28, 2003, Idenix filed the US application 60/466,194 [US '194]. On May 14, 2003, Idenix filed US application 60/470,949 [US '949]. Both are priority applications for the '191 Patent.

[21] On June 27, 2003, Idenix filed a Patent Cooperation Treaty [PCT] Patent Application for its Canadian Patent '191, naming the academic institutions as co-proprietors of the Patent. They claimed several broad genera of nucleoside alleged analogues of the 2'-C-Me/OH nucleoside. However, of its 49 claims, 32 of the claimed analogues were for 2'-C-Me/F compounds. The application was based on priority documents: US '350, US '351 (no longer relied upon) US '194 and US '949.

[22] On or about September 22, 2008, the Canadian Intellectual Property Office [CIPO] issued a Requisition objecting to the '191 Patent Application because of; *inter alia*, a lack of unity of invention. Regarding the various genera claimed by Idenix, the examiner identified 15 different classes of compounds. The examiner requested that Idenix restrict the claims of the patent application to one class of compounds.

[23] On March 23, 2009, Idenix submitted amended claims to the CIPO deleting 17 of the claims and narrowing the scope to one class of "Formula IX" compounds, consisting of 32

claims of the 2'-C-Me/F genus. These became the claims to the '191 Patent as finally issued on August 3, 2010 and which are similar to the claims of compounds covered by the '657 Patent of Gilead.

[24] In amending its claims, Idenix did not remove the extensive information relevant to the 2'-C-Me/OH nucleosides that are no longer relevant to the 2'-C-Me/F nucleosides. As a result, the '191 Patent as issued on its face is a highly confusing document. In addition, the '191 Patent discloses no information with respect to the fluorination step to create the 2'-C-Me/F nucleoside, as Idenix never succeeded in synthesizing the compound, to its knowledge at least, prior to filing its application.

[25] During this litigation, Idenix amended its statement of defence "solely for Canada and for the purpose of simplifying the issues to be determined at trial in this proceeding in Canada, without making any admission", to state that "Idenix will not be defending nor asserting a claim of infringement in respect of Claim 1 of the '191 Patent." The effect of this amendment is a matter of contention in this dispute.

B. *Initial Development of the 2'-C-Me/OH Compounds by Idenix*

[26] Up to late 2004, the Montpellier site conducted all of Idenix's discovery chemistry efforts, while the Cagliari site carried out most of the biological testing (viral screening). Starting in 2004, Idenix's facilities in Cambridge, Massachusetts also conducted process chemistry and development biology work.

[27] In the late 1960's scientists developed a class of 2'-C-Me/OH nucleosides. In the early 2000s, Idenix discovered that some known nucleoside analogues, which have a 2'-C-Me/OH structure, had activity in *in vitro* [performed in the laboratory] assays of certain Flaviviridae viruses. Idenix filed patent applications US '121 and US '282 in respect of these compounds. One of these compounds (known as NM283) was a prodrug of a nucleoside analog having a 2'-C-Me/OH sugar ring and cytosine base.

[28] Idenix (then Novirio) held a chemistry retreat in Maui in December 2001. Dr Gosselin, Professor La Colla, Dr Sommadossi, Dr Standring and Dr Storer attended, along with the members of its chemistry discovery team. Among other subjects discussed at that meeting, the Idenix chemists identified several nucleoside analogues of the 2'-C-Me/OH compounds that they would attempt to synthesize, one of which was the 2'-C-Me/F nucleoside.

[29] On March 28, 2002, Idenix assigned the synthesis of the 2'-C-Me/F nucleosides to Dr Jean François Griffon, a chemist located in Montpellier who had previous experience with fluorination of nucleosides. Dr Griffon and his team, which included Ms Audrey Chappe and Ms Elodie Pecheux, attempted to make 2'-C-Me/F nucleosides for two years without success.

[30] Dr Alistair Stewart and Jingyang Wang, Idenix chemists located in Cambridge Massachusetts, continued to work on the synthesis of the 2'-C-Me/F compounds in late 2004-early 2005. They claim to have succeeded in or around January 2005 at a time when Idenix had received information from a former Pharmasset employee about its successful synthesis of the 2'-C-Me/F compound. Idenix clearly successfully synthesized the 2'-C-Me/F nucleoside in March

2005. Idenix did not test a 2'-C-Me/F nucleoside until March 2005, after the publication date of the Gilead '657 Patent.

[31] Idenix contends that Dr Griffon was responsible for its inability to demonstrate that it had successfully synthesized the 2'-C-Me/F compound. It argues that he did not meet the standards of a skilled discovery chemist in many respects.

[32] Idenix contends that he succeeded in synthesizing a 2'-C-Me/F nucleoside without knowing it. It argues that Albany Molecular Research Inc. [AMRI] synthesized the molecule in tests it carried out in 2014 using the same intermediate compound, fluorination reagent, Deoxo-Fluor®, and conditions followed by Dr Griffon during his February 2003 experiments.

[33] Idenix argues that because Dr Griffon did not characterize the products of the reaction he failed to realize his success. It adds that because Dr Griffon misrepresented to his superiors that only one new compound was formed during the experiment, which was not the target compound, it then failed to pursue the most obvious and only known methodology that could successfully synthesize the 2'-C-Me/F nucleoside.

C. *Gilead Parties and their Patents*

[34] Gilead Sciences Inc is an American biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need.

[35] Gilead Sciences Canada, Inc [Gilead Canada] is a wholly owned subsidiary of Gilead Sciences Inc Gilead Canada sells pharmaceuticals in Canada for use in the treatment of diseases such as HIV, cystic fibrosis and Hepatitis.

[36] Pharmasset Inc, under different changing names and country of origin, was a small biopharmaceutical company formed in the late 1990s. Its mandate was to discover and develop new compounds for the treatment of HIV, Hepatitis B virus [HBV] and HCV.

[37] On 30 May 2003, Pharmasset filed US Provisional Patent Application 60/474,368 [US '368] for a 2'-C-Me/F compound, supported by replicon testing data showing anti-viral activity.

[38] On 21 April 2004, Pharmasset filed the Pharmasset PCT application W0 2005/003147 claiming priority from US '368. It was subsequently published on January 13, 2005 [W0 Clark]. The US '368 application and the Pharmasset PCT disclose, *inter alia*, the synthesis of a 2'-C-Me/F cytosine compound and the activity of this compound against HCV in a replicon assay. This synthesis was subject matter of a paper by Clark et al, *Design, Synthesis and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication*, J. Med. Chem., 48, 5504-5508 (2005) [the Clark Paper].

[39] On June 14, 2011, after extensive testing and trials, the Canadian '657 Patent was issued.

[40] In November 2011, Gilead Sciences Inc purchased Pharmasset. Following the acquisition, Pharmasset became known as Gilead Pharmasset LLC. As noted, Gilead Pharmasset LLC is the current owner of the '657 Patent.

[41] Gilead filed its statement of claim on June 15, 2012, with Idenix filing its defence and counterclaim on November 19, 2012. The parties have since amended their pleadings on several occasions.

D. *Pharmasset Synthesizes the 2'-C-Me/F Nucleoside*

[42] During the 2003 period when Idenix was attempting to synthesize the 2'-C-Me/F compound, Pharmasset was engaged in a similar endeavor. According to Dr Patterson, one of the chemists working with Pharmasset at the time, he believed that Pharmasset set about synthesizing 2'-C-Me/F compounds after Jeremy Clark, a recently hired chemist, discovered that either Idenix's US '121 or US '282 Patent omitted them from their coverage. Pharmasset chemists thereafter identified the patent with the omission in coverage as the "Idenix" Patent. Dr Stuyver claims that he found the omission of coverage for the 2'-C-Me/F compound in an Idenix patent which partly qualifies him a co-inventor.

[43] Dr Patterson testified that, Mr Clark, having found the coverage omission in the Idenix patent, was assigned the task of attempting to synthesize the 2'-C-Me/F compound. After a few months of effort, in or around May 2003, Mr Clark succeeded in making the 2'-C-Me/F

nucleoside with a cytidine base (identified as PSI-6130). Pharmasset biologists, overseen by Lieven Stuyver, tested PSI-6130 and found it to have anti-HCV activity.

[44] On or about May 30, 2003, following the testing of PSI-6130, Pharmasset filed the US '368 Application in respect of 2'-C-Me/F nucleosides. The US '368 application included no claims. It named Jeremy Clark and Lieven Stuyver as the inventors.

E. *Dr Stuyver Contests his Removal from the Pharmasset Patent*

[45] On April 21, 2004, Pharmasset filed the PCT application for the '657 Patent naming only Jeremy Clark as the inventor. [REDACTED]

[46] Dr Stuyver contends that he found the omission in the Idenix patent and that he gave Mr Clark the idea of synthesizing the 2'-C-Me/F compound based on his work in other patents involving fluorine at the 2' (down) position. He claims that Pharmasset removed his name out of spite because he left to move back to Europe and that he signed the declaration under duress, applied by Dr Otto.

III. The Witnesses

A. *Expert Witnesses*

(1) Gilead's Experts

[47] Gilead called three experts to testify at trial: a nucleoside chemist (Dr Wnuk), a virologist (Dr Seeger) and a pharmaceutical scientist (Dr Krise).

(a) *Dr Stanislaw Wnuk*

[48] Dr Wnuk is a Professor of Chemistry at Florida International University, a position he has held since 2002. Dr Wnuk obtained a PhD in organic chemistry from Mickiewicz University in Poznan, Poland. From 1985 until 1986, he completed postdoctoral research at the University of Alberta, specializing in the synthesis of modified nucleoside analogues and novel fluorination reactions. Dr Wnuk has worked in the area of nucleoside chemistry, including fluorination of nucleosides, for thirty years. Dr Wnuk is an author of over 180 publications, 80% of which relate to nucleosides or nucleotides, and 30% of which relate to fluorination.

[49] Dr Wnuk is qualified by the Court to provide expert opinion evidence in the following areas: organic chemistry, medicinal chemistry and nucleoside chemistry; synthesis of nucleosides, nucleotides, fluorothioethers, and analogues thereof; fluorination methodologies to synthesize fluorinated nucleosides; developing methods for the fluorination of thioethers, alcohols, sugars, nucleosides and nucleotides, including methods for the introduction of fluorine

at the 5' and 2' positions of purine and pyrimidine nucleosides; and analytical and purification methods used in the synthesis of organic compounds.

(b) *Dr Christoph Seeger*

[50] Dr Seeger has been a Professor of Virology in the Department of Microbiology at the Fox Chase Cancer Center since 1990. Dr Seeger obtained a PhD in Microbiology from the University of Basel in 1982, focusing on the study of retroviruses. Dr Seeger's laboratory has produced cell lines that are used to study the lifecycle of Hepatitis B and Hepatitis C viruses and screen for antiviral compounds. Dr Seeger's laboratory was the second in the United States and the third worldwide to publish on the HCV replicon assay and its use to evaluate and screen antiviral compounds. Dr Seeger's work has been funded for over thirty years by the National Institues of Health and his publications have been cited over 3500 times. Dr Seeger has more than thirty years' experience in research in the field of virology, including extensive experience studying the HCV.

[51] Dr Seeger was qualified to provide expert opinion evidence in the following areas: molecular biology and virology with an emphasis on human pathogenic viruses including Hepatitis viruses (Hepatitis B virus, Hepatitus C virus) and relevant animal model systems belonging to the Hepadnaviridae and Flaviviridae family of viruses, assessment of usefulness of nucleosides and nucleotides for the treatment of infections caused by these viruses, model systems and cell lines for screening antiviral compounds, including enzyme assays, plaque assays, cell-based assays, replicon assays, and high-throughput screens for the discovery and

development of antiviral compounds, interpretation of results from *in vitro* assays and animal studies to assess the activity and toxicity of antiviral compounds.

(c) *Dr Jeffrey Krise*

[52] Dr Krise is an Associate Professor of Pharmaceutical Chemistry at the University of Kansas. His research focus is on the optimization of drug properties in order to maximize the drug's therapeutic usefulness. Dr Krise completed his undergraduate degree in Pharmacy in 1993 and obtained his PhD in Pharmaceutical Chemistry with Honours in 1998 at the University of Kansas under the tutelage of Valentino Stella, a foremost expert in prodrugs. Dr Krise synthesized, evaluated, and wrote papers on a novel prodrug approach that employed phosphates for improving water solubility barriers of drugs. Dr Krise was qualified to provide expert opinion evidence in the following areas: pharmaceutical sciences; pharmacokinetics (absorption, distribution, metabolism and elimination); drug formulation; prodrugs, including nucleoside and nucleotide prodrugs; metabolism of sofosbuvir; and drug discovery and development. Dr Krise was the only prodrug expert to testify in this case.

(2) Idenix's Experts

[53] Idenix called three experts to testify at trial: a chemist (Dr Damha); a second chemist (Dr Barrett); and a virologist (Dr Lamarre).

(a) *Dr Masad Damha*

[54] Dr Damha is Chair of the Chemistry Department and James McGill Professor of Chemistry at McGill University, previously serving as Professor of Chemistry and other positions in the Chemistry Department at McGill since 1992. He has been Director, Graduate Program, Department of Chemistry, 2000-2004, 2006-2008, and 2010. He holds senior positions in various societies including President, Oligonucleotide Therapeutics Society, Board of the International Society of Nucleosides, Nucleotides & Nucleic Acids; sits on editorial advisory boards; and is the recipient of various scientific awards and honours. He has published approximately 155 papers in peer-reviewed journals and book chapters, many of which include the synthesis of nucleoside analogues. He has made more than 80 invited presentations at national and international meetings in the area of bio-organic chemistry, including the synthesis of nucleosides, nucleotides and oligonucleotides. He was an organizer of the 2012 International Roundtable on Nucleosides, Nucleotides and Nucleic Acids in Montreal.

[55] Dr Damha was qualified to provide expert opinion evidence in the following areas: medicinal chemistry and bio-organic chemistry, including the design, synthesis and analysis of nucleosides and nucleoside analogues for use as antiviral agents including via prodrug strategies.

(b) *Dr Anthony Barrett*

[56] Dr Barrett is the Glaxo Professor of Organic Chemistry and the Director of the Wolfson Centre for Organic Chemistry in Medical Science in the Department of Chemistry at Imperial College of Science, Technology and Medicine [IC] in London, England. He is also the Sir

Derek Barton Professor of Synthetic Chemistry and Head of the Synthesis Section in the Department of Chemistry at IC. He is a Fellow of the Royal Society and a fellow of the Academy of Medical Sciences. He trained 127 PhD graduate students and 192 postdoctoral research associates in connection with a variety of research topics in the organic chemistry field, including synthetic organic chemistry and medicinal chemistry. He has published 408 peer-reviewed articles relating to various aspects of organic chemistry. These include 29 publications on the synthesis of carbohydrates and nucleosides, which appear relevant to these proceedings. He is the recipient of prizes from various organizations such as the Royal Society of Chemistry and the American Chemical Society for his contributions to organic chemistry.

[57] Dr Barrett was qualified to provide expert opinion evidence in the following areas: organic and medicinal chemistry, including the synthesis in nucleosides and carbohydrates, analytical chemistry techniques and procedures as used in synthetic chemistry, including the techniques used in the interpretation of the results received and the standard laboratory practices of synthetic chemists.

(c) *Dr Daniel Lamarre*

[58] Dr Lamarre is Professor of Biochemistry and a director of the Molecular Research Laboratory lmmunovirology at Université dé Montreal. He previously held a number of senior research-based positions at Boehringer Ingelheim, in Laval Québec, with a focus on HCV and the discovery of antiviral compounds. He has held numerous fellowships, awards, and research chairs. He supervised three separate teams of approximately 25 scientists in a screening for biological activity of molecules against HCV via inhibition of the NS3 protease, NS3 helicase,

and NS5B polymerase. He has been involved in several important discoveries, including the antiviral drug, ciluprevir and the discovery and development of other significant HCV/HIV drug candidates.

[59] Dr Lamarre was qualified to provide expert opinion evidence in the following areas: in biochemistry with a particular expertise in virology, industrial drug discovery and development, and structure-based rational drug design. His expertise includes a specific focus in HCV and the Flaviviridae family of viruses.

(3) Comments on the Witnesses

[60] As between the nucleoside synthesis witnesses, Gilead submitted that Dr Wnuk is the only expert in this case who is qualified to give opinion evidence in the area of fluorine chemistry. Conversely, they argued that neither Dr Damha nor Dr Barrett is qualified by the Court to provide expert opinion evidence in relation to fluorine chemistry or the fluorination of nucleosides.

[61] I would disagree that neither Dr Damha nor Dr Barrett is qualified to speak to the topic of chemical fluorination of nucleosides. It is apparent however, that Dr Wnuk focused his career on the synthesis of nucleosides, including an extensive amount of time dealing with the fluorination of nucleosides. I weigh this as a factor in the evidence of the contending experts that favours Gilead with respect to the fluorination issues.

[62] Gilead further submits that Dr Wnuk is the only expert who had personal experience with fluorination during the relevant period and is therefore qualified to express an opinion on this topic from first-hand experience in the 2003-4 period. This appears to be an accurate assessment. Dr Barrett acknowledged that the chemistry at issue in this case was not of interest to him at the relevant time. Similarly, Dr Damha did not have experience with the fluorination of nucleosides in the 2003-4 period.

[63] This is a fair submission, as there is an advantage to having an expertise in fluorination of nucleosides at the relevant time. This is particularly germane in being able to describe the limits of common general knowledge on the subject matter and the nature of experimentation at the time, as opposed to providing opinions based on *ex post facto* reviews of written materials provided to the witnesses or obtained through searches conducted a decade after the events.

[64] Gilead was also critical of both Dr Damha and Dr Barrett concerning the superior qualities they attributed to the skilled chemist. Dr Damha testified that the skilled person had problem-solving and reasoning skills that would not be uncreative. He attributed this to the fact that by the time they graduate these persons would have made a contribution to some aspect of the knowledge in the field.

[65] I agree with Gilead's submission that this view could lead to a greater attribution of knowledge and skills than the imaginary skilled chemist would possess. This requires restraint in some areas when relying on Dr Damha's opinions about the skilled chemist's achievements in the synthesis of new compounds.

[66] I find that Dr Barrett similarly overreaches in describing the basic skills of the person skilled in drug discovery, testifying that he or she was "brilliant at reactions, but not inventive". The superior laboratory skills attributed to the person of ordinary skill in the art [POSITA/ skilled chemist] by Dr Barrett diminishes somewhat the weight I attribute to his opinion of the skilled person's ability to synthesize compounds by trial and error experimentation. I also take this into account in tempering the high degree of obviousness that Dr Barrett portrays in synthesizing the 2'-C-Me/F compound and the contrasting harsh criticisms he has of Dr Griffon's work in his failed attempts to synthesize the target compound.

[67] I make a few comments where I find that the witnesses are overreaching. Overall, I did not find that their cross-examination played much of a role in the trial. I preferred different witnesses on different issues, based on the content and depth of support for their opinions, rather than how they testified. I also tended to give more weight to the evidence of the witnesses who were involved in the events in 2003-4, when in conflict with the opinions of the experts.

B. *Fact Witnesses*

(1) Gilead's Fact Witnesses

[68] Gilead did not lead evidence from any fact witnesses in respect of the main claim, but relied on admissions and read-ins from the discovery process. I also gave leave to Gilead to file foreign testimony from a former Idenix chemist, Dr Alistair Stewart. Gilead called one fact witness (Dr Otto) in respect of Idenix's counterclaim contesting inventorship.

(a) *Dr Alistair Stewart*

[69] Dr Stewart was the Director of Chemistry, Manufacturing and Controls at Idenix in Cambridge, Massachusetts. Dr Stewart received a PhD in Organic Chemistry from the University of Oxford in 2003, having studied under Professor George Fleet. Dr Stewart joined Idenix in September 2003 as a Research Scientist 1 in the Process Chemistry group. Dr Stewart worked on a project to make 2'-C-Me/F nucleosides from mid-2004 to early 2005, and oversaw the work of Ms Jingyang Wang. Dr Stewart was not called to testify at trial. However, after hearing parties on a motion in writing, I gave leave to Gilead to file Dr Stewart's witness statement and related cross-examination transcript from the U.K. Proceeding as evidence in this trial. I provide my reasons for doing so when considering Idenix's efforts to synthesize the 2'-C-Me/F compounds and the related evidence of Ms Wang from the UK proceedings, which was admitted on consent.

(b) *Dr Michael J. Otto*

[70] Dr Otto was the Chief Scientific Officer at Pharmasset Inc from 1998 to 2012. His role was to direct the chemistry and biology program, coordinate research efforts, and run the development program for an HIV drug. He holds a PhD in Microbiology from the Medical College of Wisconsin. Dr Otto testified as to the discovery of PSI-6130, the filing of patent applications for PSI-6130, and his recollection of events in respect to allegations made by Dr Lieven Stuyver concerning Dr Stuyver's alleged role in the discovery of PSI-6130 as one of its inventors.

(2) Idenix's Fact Witnesses

[71] Idenix called six fact witnesses to testify at trial (Drs Standring, Griffon, Patterson, Clemens, Stuyver, and Professor La Colla). The parties agreed to the admission of foreign testimony from a seventh witness, Ms Wang in lieu of *viva voce* evidence at trial.

(a) *Dr David Standring*

[72] Dr Standring holds a PhD in Bio-organic Chemistry from Harvard University. He was employed by Idenix Pharmaceuticals Inc. in Cambridge, MA in a variety of senior management positions from 2000 until his departure from the company in 2013. Dr Standring is not a listed inventor on the '191 Patent. He was not involved in the chemistry in respect of the compounds at issue.

(b) *Professor Paolo La Colla*

[73] Professor La Colla is a Professor of Microbiology at Cagliari. Professor La Colla acted as the Director of the Department of Biomedical Science and Technology at the University of Cagliari from 2002 to 2008. He oversaw the collaborative work done at the University of Cagliari between the University of Cagliari and Idenix Pharmaceuticals Inc in respect of testing anti-HIV, anti-HBV and anti-HCV compounds. Professor La Colla did not make any decisions in respect of which compounds to test and had no involvement with the synthesis of the compounds. Professor La Colla was the only named inventor of the '191 Patent (out of four named inventors) called as a witness at this trial.

(c) *Dr Steven Patterson*

[74] Dr Patterson has a PhD in Organic Chemistry with a minor in Biochemistry from Georgia State University. He was employed at Pharmasset between February 2000 and June/July 2004. He became the head of the analytical chemistry group in or around February 2003. Dr Patterson was called to testify by Idenix and spoke about the idea to make 2'-fluoro (down)- 2'-methyl(up) compounds at Pharmasset and how Jeremy Clark was the first person to make such a compound.

(d) *Dr Jean François Griffon*

[75] Dr Griffon is a Senior Research Scientist at Idenix in Montpellier in the nucleoside analogues group. Dr Griffon obtained a PhD in Organic Chemistry in 1998 from Montpellier in the laboratory of Professor Jean-Louis Imbach under the supervision of Dr Gilles Gosselin. Dr Griffon synthesized a number of 2'- and 3'-fluoro substituted nucleosides during the course of his PhD Dr Griffon joined Idenix in 2001. He was assigned the synthesis of 2'-fluoro (down)-2'-methyl (up) nucleosides on March 28, 2002 and he worked on this project until mid-2004.

(e) *Dr Lieven Stuyver*

[76] Dr Stuyver received a PhD in Human Genetics in 1992. He was the head of the biology group at Pharmasset from 1998 to 2004. Dr Stuyver was named as an inventor on provisional US '368, which is cited as the priority application to the '657 Patent, but was not named as an inventor on the PCT patent application that led to the Canadian '657 Patent, or the '657 Patent itself.

(f) *Ms Jingyang Wang*

[77] Ms Jingyang Wang is a Principal Research Scientist at Idenix in Cambridge, Massachusetts. Ms Wang received a Bachelor of Science degree in chemistry in 1989 from Nankai University, Tianjin, China; a Master's of Science in Organic Chemistry in 1995 from University of Manchester, United Kingdom; and a Master's of Science degree in Organic Chemistry in 1998 from the University of Maine. Ms Wang joined Idenix Pharmaceuticals, Inc in 2002 as Process Chemist and was promoted to the position of Research Scientist in May 2004. Ms Wang worked on a project to make 2'-fluoro(down)-2'-methyl(up) nucleosides from late 2004 until early 2005 under the direction of Dr Alistair Stewart. The parties agreed to have Ms Wang's witness statement and related cross-examination from the U.K. proceeding entered into evidence in this trial in lieu of *viva voce* testimony.

(g) *Dr Alexander Clemens*

[78] Dr Clemens is a process chemist who works for AMRI. Dr Clemens performed experiments requested by Idenix in June-July 2014, as well as a repeat of those experiments in August 2014 intended to demonstrate that Dr Griffon had synthesized a 2'-C-Me/F nucleoside, without realizing it. Dr Clemens was not involved in the development of the protocols for the experiments.

C. *The Failure of Jeremy Clark to Testify*

[79] Neither party called Mr Clark to testify. Idenix submitted at one point that the Court should draw an inference against Gilead by its failure to call him. Dr Otto provided evidence of a strained relationship between Mr Clark and Pharmasset (now Gilead). He felt that he had not been appropriately compensated for his invention He sent letters to the company, communicated with the company's lawyers and filed lawsuits against the company and against Dr Schinazi. While he is a former employee, he is not under Gilead's control. He did not testify in the United Kingdom case. It is not a surprise that he did not testify in this matter.

[80] Gilead for its part, suggests that Idenix should have called Mr Clark. Idenix conducted a discovery of Mr Clark and asked a full day of questions relating to his work. It also points out that Idenix made allegations in respect of Clark's work, and therefore, Idenix assumed the burden of proof on such facts. Gilead asks the Court to infer that Mr Clark's evidence would not have assisted Idenix. I do not see why Gilead would want to or needed to call Mr Clark because of these facts. Idenix had his evidence from the discovery of Mr Clark and could have called him. In addition, Dr Patterson described Mr Clark as someone with a somewhat idiosyncratic temperament. I attribute no adverse inference to either party for the failure to call Mr Clark.

IV. Scientific Principles and their Relation to the Issues

[81] The following is a brief introduction to the requisite chemistry and biology principles that inform this decision along with some discussion of their relation to the issues under

consideration. The scientific background information is excerpted from the expert reports and parties' submissions.

A. *Chemical Notation*

[82] The majority of the chemistry at issue is organic chemistry. Organic chemistry is carbon-based chemistry. Each carbon atom in an organic molecule is most commonly capable of forming four bonds to other atoms. Carbon atoms can be characterized according to the number of other carbons they are attached to. A "primary carbon" is a carbon bonded to a single carbon atom. Carbons that are bonded to two or three carbon atoms can be described as secondary or tertiary carbons. When attached to alcohols, they denote a secondary or tertiary alcohol.

B. *Sugar Rings, Nucleosides, Nucleotides and Nucleic Acids*

[83] The '191 and '657 Patents both relate primarily to nucleosides and nucleotides that are modified at what is described as the 2' carbon position of their sugar ring (also referred to as a carbohydrate ring or in this matter ribose). Nucleosides and nucleotides are compounds to which a heterocyclic base (also referred to as a "Base" or "Nucleobase" discussed below) is attached to a sugar ring.

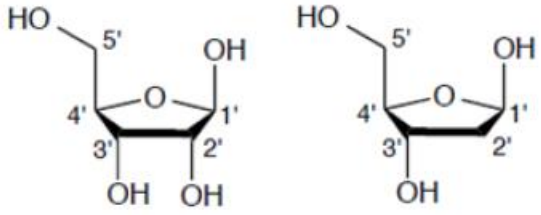
[84] Nucleosides and nucleotides are the building blocks of nucleic acids. Nucleic acid is a general term used to describe a polymer (a large molecule composed of many repeated subunits) of nucleotides linked together by bonds. Deoxyribonucleic acid [DNA] and ribonucleic acid

［RNA］are the primary nucleic acids in cells that serve to encode and carry out genetic information in living organisms.

[85] The HCV genome consists of a single strand of positive-sense RNA. The modified nucleosides or nucleotides are designed to mimic the natural nucleosides that are incorporated by the Hepatitis C virus to form RNA. When this occurs, analogues nucleotides are useful in the treatment of HCV by their disruption of the replication process that is required for new viruses to be formed.

(1) The Sugar Ring

[86] The Sugar Ring can take the structure of a five membered ring containing an oxygen atom. The sugar rings found in RNA and DNA are “ribose” and “deoxyribose” respectively. They are identical except at the 2’ “down” position. The RNA Ribose contains a hydroxyl group at the 2’-C (down) position, while DNA Deoxyribose contains a hydrogen atom at that position. They may be depicted using a “Haworth projection” as follows:

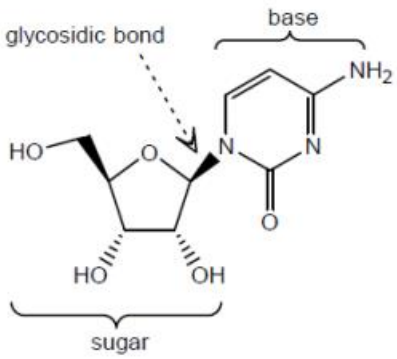


Ribose Deoxyribose

[87] A Haworth projection is a common way of representing the three-dimensional perspective of sugar rings, nucleosides, nucleotides and prodrugs. The Haworth projection provides information about whether substituents are attached above [(up)] or below [(down)] the plane of the sugar ring. Hydrogen atoms on the sugar ring are not depicted. Carbon atoms are represented by either a vertex (a point where two or more straight lines meet), or a line without a carbon symbol. The relative positions of the carbons around the sugar ring are denoted using the prime (‘) symbol along with the number of the carbon.

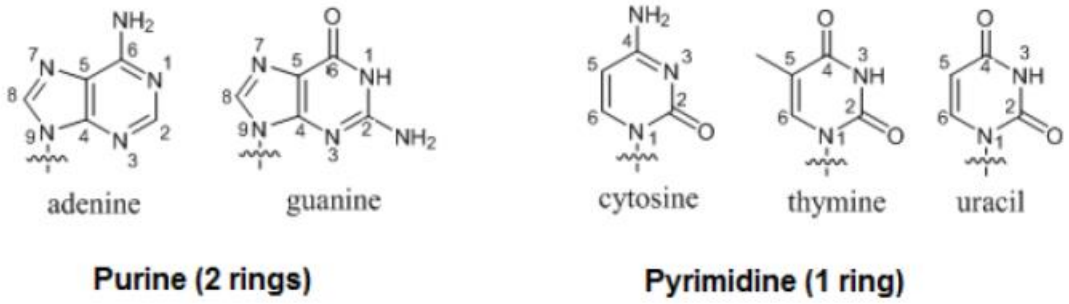
(2) Nucleosides

[88] A “nucleoside” is a chemical compound that consists of a base and a sugar ring. The sugar ring and the base are connected to each other by a chemical bond, known as a “glycosidic bond.” “Glycosylation”, or sugar-base condensation, is the process of coupling the sugar and base. An example of a nucleoside is depicted below. The spatial arrangement of the components on the drawing is illustrated using a wedge and dash drawing with the following bonds: a straight line is a bond in the plane of the paper; a bold wedge is a bond coming out of the page (in the (up) position); a hatched line is a bond coming into the paper (in the (down) position).



[89] Both DNA and RNA use combinations of bases to perform their coding function. In DNA, these bases are thymine, adenine, cytosine and guanine. In RNA, thymine is replaced by uracil. Adenine and guanine are classified as "purines" and contain a double-fused ring. Cytosine, thymine, and uracil only contain one ring and are classified as "pyrimidines". These bases are often represented by a single letter (A, C, G, T or U).

[90] The numbering on the atoms in the bases follows standard convention as illustrated below:



C. *Stereochemistry*

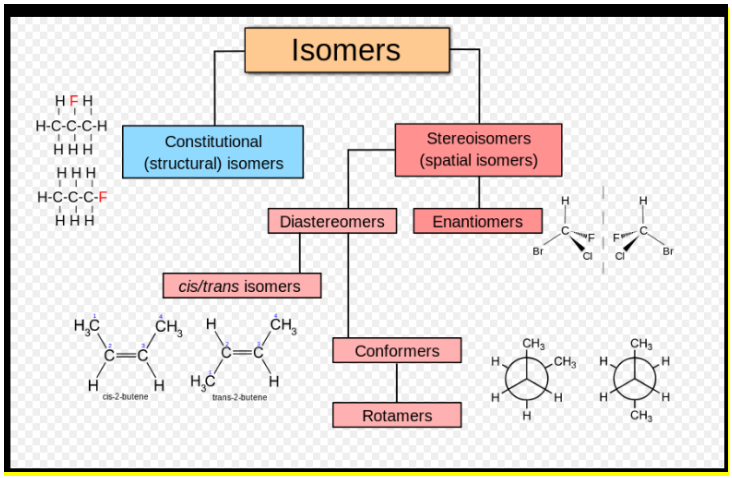
[91] "Stereochemistry" involves the study of the relative three-dimensional spatial arrangement of atoms that form the structure of molecules and their manipulation. Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. An important branch of stereochemistry is the study of chiral molecules. A chiral molecule exists in two different forms, which are mirror images of each other.

[92] A chiral molecule and its mirror image are called "enantiomers" of each other.

[93] Enantiomers have identical chemical and physical properties such as boiling point, melting point, density and refractive index. However, they differ in how they interact with polarized light, and may have different biological properties. A mixture of enantiomers in equal proportions is referred to as a "racemic mixture."

[94] Diastereoisomers (diastereomers) are stereoisomers of a compound having two or more chiral centers that are not a mirror image of another stereoisomer of the same compound

[95] The distinction between these terms may be seen from the following drawing



[96] The process of applying a Grignard reagent in the schemes in the '191 Patent describing how to synthesize the 2'-C-Me/OH compounds would result in a racemic mixture of diastereomers of both the 2'-C-Me/OH and 2'-C-OH/Me compounds. These can be separated to obtain the desired 2'-C-OH/Me enantiomer as the intermediate used to synthesize the 2'-C-Me/F target compound.

D. *Fluorination*

[97] The term "fluorination" refers to the addition of at least one fluorine atom to a compound. By January 2004, fluorination reactions were understood to generally proceed via two different mechanisms: "electrophilic fluorination" and "nucleophilic fluorination". Different starting materials and fluorinating reagents were required for electrophilic fluorination reactions as compared to nucleophilic fluorination reactions.

[98] Electrophilic fluorinating agents that were known as of January 8, 2004 include: F_2; SelectFluor; N-flurobenzenesulfonimide; and ClO_3F. Nucleophilic fluorinating agents that were known as of January 8, 2004 include: HF and HF-based reagents (e.g. HF-pyridine, HF-pyridine/ AlF_3 , anydrous HF, HF/Fe $(AcAc)_3$; AgF and AgF-based reagents (AgF/NH_4F); $Et_3N\bullet 3HF$; KF and KF-based reagents (e.g. KHF_2); DAST; Deoxo-Fluor®; tetrabutylammonium fluoride (TBAF); tris(dimethylamino)sulfonium difluorotrymethylsilicate (TASF); $Bu_4NH_2F_3$; $Bu_4NHF_2/Fe(AcAc)_3$; and perfluoro-1-butanesulfonyl fluoride (PBSF).

[99] The 2'-C-Me/F compounds were first synthesized using the nucleophilic fluorination agent of DAST, and thereafter using a more stable version of it sold under the trademark of Deoxo-Fluor®.

E. *Nucleophilic substitution reactions*

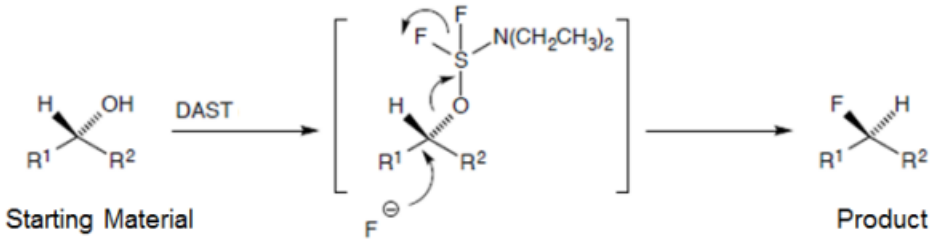
[100] A "nucleophile" (nucleophilic fluorinating agents such as DAST) is an electron rich species that reacts with electron deficient species, termed "electrophiles," to generate new

molecule. A reaction between a nucleophile and an electrophile is called a "nucleophilic substitution reaction." In such reactions, the nucleophile reacts with the electrophile, while another moiety, termed a leaving group, is released.

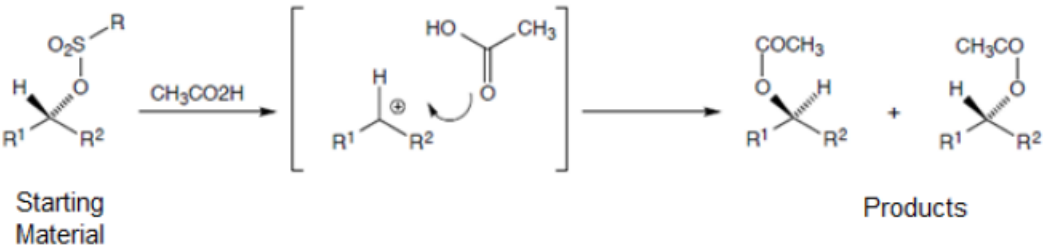
(1) Mechanisms of nucleophilic substitution reactions

[101] Nucleophilic substitution reactions can proceed by two different reaction mechanisms. These are called S_N1 and S_N2 mechanisms, and have different stereochemical consequences.

[102] A "SN2 mechanism" proceeds with complete inversion of stereochemistry and gives rise to a single product. This is illustrated in the scheme below. The starting material with a hydrogen atom above the plane and a hydroxyl group below the plane; the product has a hydrogen atom below the plane and a fluorine atom above the plane: an inversion.



[103] In contrast, a "S_N1 mechanism" gives a mixture of stereoisomers. This is illustrated in the scheme below:



[104] Whether a nucleophilic substitution reaction will occur via a S_N1 or S_N2 mechanism depends on a number of factors, such as the degree and type of substitution, the steric hindrance of the substrate, the strength of the nucleophile, the stability of the leaving group, and the solvent used, among others.

[105] The synthesis of the 2'-C-Me/F nucleoside by Gilead was carried out on the 2'-C-OH/Me compound by a S_N2 fluorination of the tertiary alcohol in that compound with inversion of the stereochemistry resulting to synthesize the 2'-C-Me/F compound.

F. *Protecting Groups*

[106] A nucleoside (and sugar) has multiple potential reaction sites. During a synthetic sequence, some of these reaction sites may need to be blocked from chemical reactions so that a selective chemical transformation can occur at the targeted reaction site. A "protecting group" is a functional group that is temporarily placed on a potentially reactive site of the nucleoside to block it from undergoing unwanted reactions. A protecting group can be removed once the desired transformation is achieved. Certain protecting groups are more compatible with certain reaction conditions than others.

G. *Isolating Molecules*

[107] After performing reactions, chemists must isolate and purify the products of their reaction for analysis and identification. Most commonly, chemists use chromatography to separate and purify reactions.

[108] Chromatography involves the separation of compounds based on different partitions between the mobile phase and the stationary phase. The mobile phase is usually a solvent or mixture of solvents and the stationary phase is usually an inorganic solid like silica or alumina. Chromatography generally proceeds by allowing a solution containing the mixture of products to flow through the stationary phase. Due to the differences in partition, the products of the mixture progress (elute) at different rates through the stationary phase and are collected separately and evaporated.

[109] Three main forms of chromatography bear consideration for the purposes of this case: thin layer chromatography [TLC], column chromatography, and high-performance liquid chromatography [HPLC].

(1) Thin Layer Chromatography

[110] TLC is commonly used to monitor progress of a reaction. TLC provides a chemist with a simple, inexpensive, efficient and relatively fast determination to analyze a reaction mixture and to monitor the progress of a reaction and the extent of conversion of starting material into

product. It also provides an empirical and approximate measure of the purity of the product or products.

[111] In TLC, usually a glass or alumina plate is covered with a stationary phase, usually silica or alumina. The solutions of interest are spotted on the plate at a set distance from the bottom. The reaction mixture is spotted on the plate, and the bottom of the plate is placed in a small amount of solvent or solvent mixture which migrates up the plate by capillary action. The compounds in the reaction mixture are dragged along with the mobile phase at different speeds depending on how avidly they interact with the silica or alumina. The compounds in the reaction mixture are separated based on differences in solubility, polarity and absorption of compounds.

[112] While monitoring an organic synthesis, a chemist can place the starting material in the left-hand lane on a TLC plate, and the reaction mixture in the right hand lane. If both lanes show exactly the same spots on the TLC plate, then the chemist would usually assume that no reaction has occurred. If there was a different spot on the TLC, when compared to the original lane, this would imply that there is one reaction product. If there were multiple additional spots on the new lane, the inference would be that multiple reaction products were formed in the reaction.

[113] A TLC plate may be employed after the separation of the reaction products to assist in determining whether it contains a sugar, such as a 2'-C-Me/F nucleoside. The TLC plate is stained with sulphuric acid, which preferentially charcoals carbohydrates, such as sugars. Spots containing sugars char darkly under UV light. Compounds that do not contain carbohydrates (such as a base that was not successfully coupled to a sugar) will not char as darkly.

(2) Purification by Chromatography

[114] Various forms of chromatography are used to separate mixtures of different compounds for analytical purposes. These include: column chromatography, HPLC and reverse phase HPLC.

[115] In column chromatography, the mobile phase – the reaction mixture – is poured on top of a stationary phase – a column that is typically made of silica gel. Additional solvent is continuously added and fractions are eluted from the base of the column. Different compounds from the reaction mixture flow through the stationary phase at different speeds. The reaction product is collected manually in vails that are combined into similar reaction products, which can be further analyzed.

[116] HPLC is similar to column chromatography. It is a more sophisticated chromatographic technique in which the solution mobile phase is pumped under pressure through a finely divided stationary phase and the eluted solution monitored for composition change by a detector. HPLC is usually much more efficient in separations than column chromatography.

H. *Characterizing Molecules*

[117] Chromatography is used to separate reaction products, but not characterize them. Many methods of characterization of molecules exist. The two relevant methods in this matter are mass spectrometry [MS] and nuclear magnetic resonance [NMR].

(1) Mass Spectrometry [MS]

[118] MS analysis provides a mass spectrum that may provide the molecular composition of the compound as well as providing some information on its structural features. MS can also be coupled with HPLC allowing for separation and characterization using one procedure.

(2) Nuclear Magnetic Resonance [NMR]

[119] NMR spectroscopy is a frequently employed technique that is used for the structural characterization of compounds. It determines either completely or partially, the structure of a compound by giving information on the types of groups of atoms present and their connectivities.

[120] NMR can also be used to authenticate a sample of a compound by comparisons of the NMR spectra with those from an authentic sample. NMR spectroscopy is the primary method used by chemists to characterize unknown compounds and to authenticate other samples.

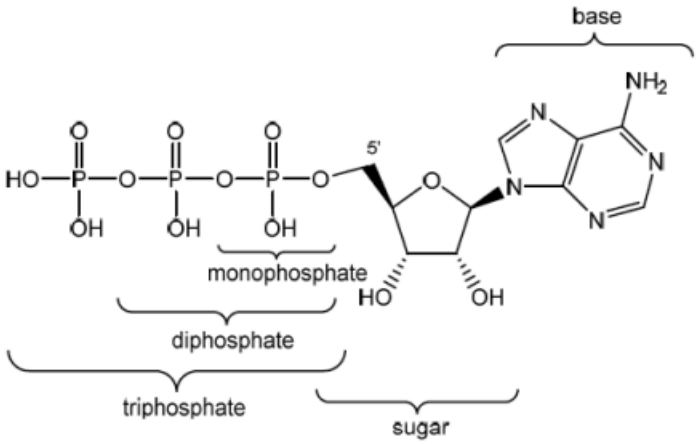
(3) High-pressure Liquid Chromatography Attached to a Mass Spectrometer [LC/MS]

[121] HPLC attached to a mass spectrometer is a more recent technology to separate and characterize reaction compounds. It operates by a small amount of reaction mixture being introduced into to an HPLC column. After leaving the column, the eleunt immediately passes into a mass spectrometer, allowing the chemist to monitor, in real time on an on-going basis, the molecular weights of the compounds leaving the column.

I. *Nucleotides and the Formation of Ribonucleic acid [RNA] and Deoxyribonucleic acid [DNA]*

[122] Nucleosides are precursors of nucleotides. Nucleotides are nucleosides that contain a phosphate bonded to the oxygen atom of the alcohol (hydroxy) unit of the sugar. A nucleotide is defined as a nucleoside having a mono-, di-, or triphosphate group attached to the sugar ring at the 2', 3' and/or 5' position, with the 5-carbon site the most common as is the situation in this matter. The nucleotide in sofosbuvir, i.e. a prodrug of a 2'-C-Me/F is a nucleotide with a monophosphate at the 5' position.

[123] An example of the three forms of a nucleotide is depicted below.



[124] The conversion of a nucleoside into a nucleotide by the attachment of the phosphate (for example PO_3^{5-}) to the C-5 alcohol unit is a chemical process that can occur naturally *in vivo* (inside the cell). Their formation starts after the nucleoside or monophosphate nucleotide enters the cell. The entry into the cell is facilitated by the use of "prodrugs," which are discussed below.

[125] Once inside the cell, the nucleoside, or a mono or di-phosphate nucleotide, undergo up to three consecutive phosphorylation steps at the hydroxyl group attached to the 5'-carbon to form 5'-nucleotide mono-, di and triphosphates respectively. "Phosphorylation" is a metabolization process that may occur *in vivo* whereby a phosphate group is naturally added to a nucleoside or to a mono or di-phosphate nucleotide to become a nucleotide. It is catalyzed by enzymes called "kinases".

[126] A polymerase is an enzyme which can take the nucleotide building blocks and couple them together to make strands of DNA or RNA. For a polymerase to link one nucleotide to the next, it is necessary for the nucleotide to be in a triphosphate form (having three phosphate groups at the 5' position of the sugar ring). For ribonucleosides, a hydroxyl group at the 3' position (the 3' OH group) of one nucleotide will be coupled with a 5' phosphate group at the next nucleotide to result in the phosphate bridge. By this process the triphosphate is converted back to a monophosphate, which forms the phosphate bridge to the next nucleotide.

[127] In summary, as part of the DNA and RNA replication machinery of cells, a nucleoside triphosphate is the required starting material for forming a phosphate bridge to an adjoining nucleotide to form a growing strand of RNA or DNA. Kinase enzymes are responsible for phosphorylating nucleosides and mono and diphosphate nucleotides. Polymerases are enzymes that are responsible for synthesizing the growing strands of RNA or DNA.

J. *Viruses*

[128] "Viruses" are the smallest of all self-replicating organisms. While self-replicating, they have no metabolism of their own, but rather are obliged to invade cells and direct subcellular machinery to produce more viruses. All viruses carry a genome composed of viral nucleic acid (either RNA or DNA) enveloped in a protein coat, called a capsid. Viruses infect living things and make use of their host's cellular reproduction mechanisms to reproduce themselves. Like normal cells, nucleic acids are the genetic material of viruses. Viruses carry their own polymerase called viral polymerase. Viruses can be classified based upon whether they contain RNA or DNA as their genetic material.

[129] Viruses are categorized into families. A family of viruses can include 10, 20 or 30 viruses. The Flaviviridae family encompasses numerous viruses of significant global concern that affect both humans and animals.

[130] The Flaviviridae virus family includes three types: flavivirus, hepacivirus and pestivirus. Some examples of these types include:

***Flaviviridae* Family**

Pestiviruses	**flaviviruses**	**hepacivirus**
Bovine viral diarrhea virus (BVDV)	Dengue fever virus (DENV)	Hepatitis C virus (HCV)
Classical Swine fever virus (CSFV)	Yellow fever virus (YFV)	
Border disease virus	West Nile virus (WNV)	
	Japanese encephalitis virus (JEV)	

[131] Flaviviridae show similarity in their genome (their genetic code, which provides the blueprint for the proteins required to replicate the virus), which includes the viral RNA polymerase. All Flaviviridae viruses have viral RNA polymerase enzymes (flavivirus - NS5, pestivirus - NS5B, hepacivirus - NS5B) that replicate RNA in the same way by building RNA using nucleoside triphosphates.

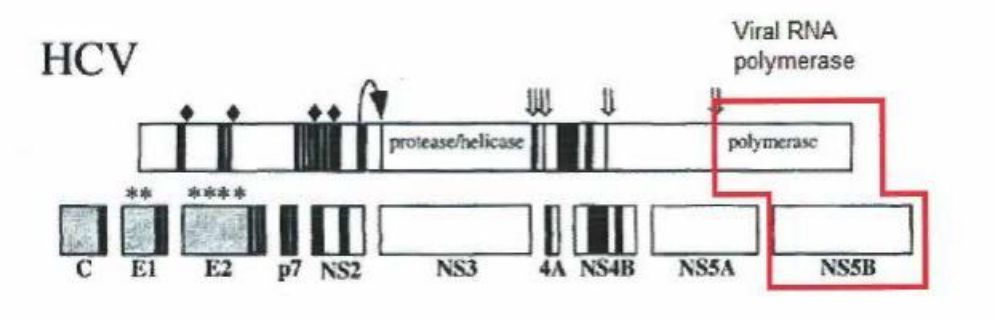
(1) Hepatitis C

[132] HCV is one of the most important viruses of the Flaviviridae family because of its significant impact on human health. HCV is a disease of the liver. It is transmitted by blood-to-blood contact, including through contaminated blood and blood products. Once an individual is infected, HCV continuously replicates and spreads within hepatocytes (liver cells). About 185 million people, roughly 2.2% of the human population, are infected with HCV, and virus transmission remains a significant public health concern.

[133] The most notable feature of HCV infections is that they typically persist, often for decades, with more than 70% of cases with acute Hepatitis C progressing to chronic Hepatitis. Patients with chronic Hepatitis are predisposed to developing chronic active Hepatitis, cirrhosis of the liver, and hepatocellular carcinoma, all of which are responsible for hundreds of thousands of deaths each year. The death rate from HCV will continue to climb for at least 10 years, because of the decades-long lag time between acute infection and liver failure.

(2) The HCV genome

[134] The HCV genome consists of a single strand of positive-sense RNA. The organization of the HCV genome is illustrated below:



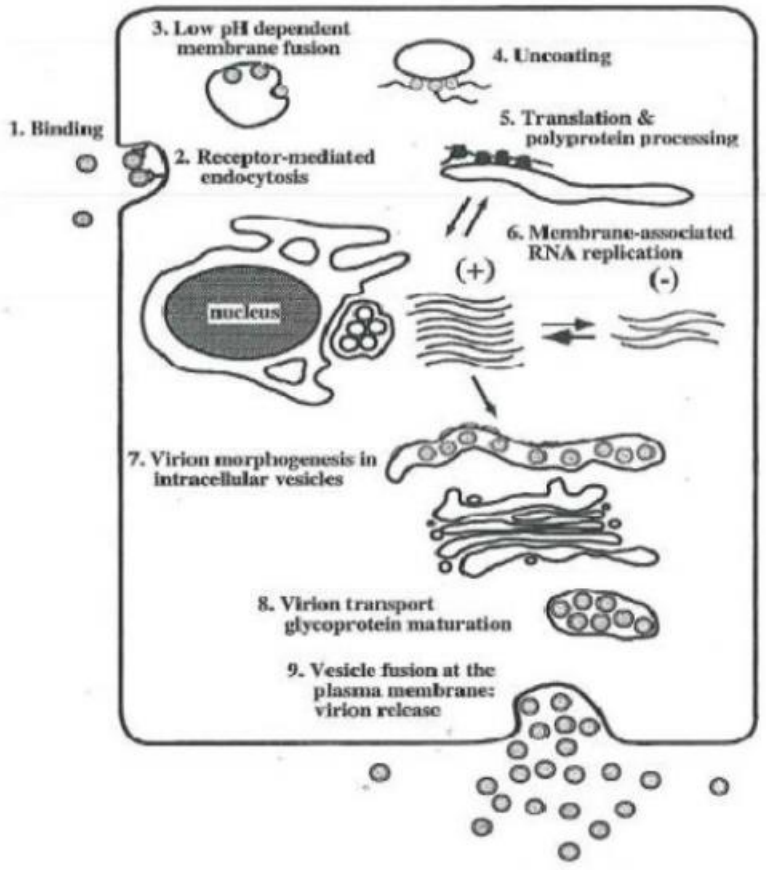
[135] The non-structural [NS] proteins that are encoded by this genome are involved in viral replication and protein synthesis. For example:

(a) NS3 - a protease which helps process the polyprotein to generate mature proteins by cleaving it at specific target sequences; and

(b) NS5B - a polymerase that is responsible for the multiplication of the viral genome. It is the enzyme that connects the nucleotides together to make a chain of viral RNA.

(3) HCV replication

[136] An understanding of the HCV lifecycle is an important aspect of antiviral drug discovery since antiviral drugs often inhibit virus-specific functions that are essential for replication. The HCV lifecycle includes the following steps, as illustrated in the figure below:



[137] The steps are as follows:

(a) The HCV particle attaches itself to (Step 1), and enters, the host liver cell (i.e. hepatocyte) (Step 2);

(b) Once inside the cell, the outer shell of the HCV particle falls apart (uncoating) to expose the RNA strand that the virus carries and will use to make copies of itself (Steps 3 and 4);

(c) The virus uses the host cell's components to read the information present on the RNA strand and produce proteins such as NS5B (the viral protein responsible for making new copies of the HCV RNA strand, also called the HCV polymerase) (Step 5);

(d) NS5B recognizes and binds to specific nucleotide triphosphates that are found in the cell, and incorporates them into the new strand of RNA (RNA replication) (Step 6).

[138] To synthesize RNA (either the replicative negative strand or the positive strand viral RNA), nucleotides triphosphates are specifically required, which are used by the NS5/NS5B polymerase to incorporate ribonucleotides to a growing nascent chain based on the template RNA.

K. *Nucleoside analogues to treat viral infections*

[139] When developing nucleoside analogues to treat viral infections, cytotoxic effects must be avoided. The aim is to kill the virus, not the host cell. Thus, the requirements known in 2003 for direct acting nucleoside and nucleotide analogues for HCV infections should have the following properties:

- be able to enter infected cells without harming them;
- be able to convert into nucleotide triphosphates;
- be recognized in their triphosphate form by the HCV NS5B polymerase protein;
- be incorporated into the new growing HCV RNA strand in place of a naturally-occurring nucleotide; and
- possess some property that, once incorporated into the new RNA strand, inhibits the complete replication of the growing HCV RNA strand.

L. *Evaluating HCV Treatments*

[140] The study of HCV and the development of anti-HCV therapies have been hindered by difficulties in developing appropriate model systems. This is because HCV is a species-selective virus that infects only humans and chimpanzees. Instead, various *in vitro* model systems were used in 2003. These are discussed below.

(1) Phosphorylation assay

[141] The phosphorylation assay is not used to measure direct antiviral activity. As set out above, nucleoside analogue inhibitors need to be converted to their triphosphate form *in vivo* to be recognized by a polymerase. The phosphorylation assay simply determines whether a nucleoside analogue inhibitor can be phosphorylated *in vitro*. This assay uses normal cells that

are not infected with a virus, and therefore, this assay must be done in conjunction with additional assays to fully test antiviral activity.

(2) Polymerase assay

[142] As discussed above, a nucleoside analogue used in the treatment of HCV should inhibit the activity of NS5B. The HCV polymerase assay may be used by the skilled virologist to assess anti-HCV activity (i.e. it can be used to determine the ability of different test compounds to inhibit the HCV polymerase's activity).

[143] However, like the phosphorylation assay, the polymerase assay is not ideal. First, it involves the large-scale production of soluble viral polymerase in bacteria or insect cells. Second, it can only be used if the test compound is in its tri-phosphorylated form. Third, it does not provide data about cytotoxicity. In 2003, a skilled virologist would have been aware of the drawbacks of the polymerase assay.

(3) BVDV, (Bovine Viral Diarrhea Virus) surrogate model

[144] In 2003, there was no HCV cell culture system or a convenient small animal model in which to screen potential anti-HCV compounds. Therefore, prior to the development and adoption of the HCV replicon assay, some scientists used an *in vitro* assay system based on the pestivirus BVDV as a surrogate model for testing nucleoside analogues for anti-HCV activity.

[145] Madin-Darby bovine kidney [MDBK] cells are first seeded onto a monolayer of cultured cells and then infected with BVDV, followed by the addition of serial dilutions of test compounds. After several rounds of viral replication, the initial infection gives rise to visible structures called plaques through the diffusion of the virus from the original site of infection to new sites. The number of plaques on each plate is compared to a control plate that was not tested with any test compound. If a compound inhibits BVDV RNA replication, it will reduce the number of plaques formed as compared to the control.

(4) The replicon assay

[146] The replicon assay was first reported in 1999 by Lohmann et al in the preeminent "Science" journal. A replicon is a portion of the HCV genome that is able to mimic HCV RNA replication in human hepatocytes. A replicon cell culture system can be used to directly measure the ability of a compound to prevent successful replication of the HSV RNA. After adding a test compound to the cell culture, the cells are incubated for a given period of time to allow for viral replication, and then the amount of replicon RNA in the cells is measured. By comparing the amount of replicon RNA in the cells that received the test compound to the amount of replicon RNA in control cells, it is possible to quantify the anti-HCV effect of the test compound.

(5) Measures of antiviral activity and toxicity

[147] In order to be an effective antiviral compound for HCV treatment, a nucleoside analogue must act selectively against the HCV virus, but also be non-toxic to HCV-infected or uninfected cells. A compound's antiviral activity is expressed in the following ways.

[148] The "Effective Concentration 50%" [EC50] is a measure of a compound's antiviral activity, i.e. the amount of a given compound required to reduce virus titer or RNA or protein in virus infected cells by 50%. EC50 is often used interchangeably with a measure of Inhibition Concentration 50% [IC50], which refers to the concentration of a drug that is required for 50% inhibition of the RNA polymerase activity *in vitro*. By determining the amount of test compound required to reduce viral replication (i.e. plaque number) by 50%, the test compound's EC50 can be determined. The lower the EC 50 value, the more potent the compound.

[149] The "Cytotoxic Concentration 50%" [CC 50] on the other hand, is a measure of a compound's cellular toxicity, and refers to the concentration of the compound required to reduce the number of cells by 50%. The larger the CC 50 value, the less toxic the compound.

[150] The "Therapeutic index" is used to assess EC 50 values in relation to their CC 50 values through a ratio [CC 50:EC 50]. Since a high CC 50 value indicates low toxicity, and a low EC 50 value indicates high anti-viral activity, a preferred compound would have a significantly higher CC 50 value than an EC 50 value. A higher therapeutic index is preferable over a lower one.

[151] In order to assess a therapeutic index, the EC and CC values must be obtained for the same cell line as that in which the virus is tested. This is because different cell lines show different sensitivities to different nucleoside analogues.

M. *Prodrugs*

[152] A "prodrug" is a biologically inactive derivative of a drug that upon administration to the human body is converted into its active form by some chemical or enzymatic pathway. Generally, a prodrug is a compound that metabolizes to the active compound at some point *in vivo*.

[153] The negative charge of an unmasked nucleoside mono, di, or triphosphate, i.e. a nucleotide, presents a barrier to cellular uptake, thus preventing drugs from reaching their desired target. The negatively charged mono-, di, or triphosphate has difficulties passing through the cell membrane because the lipid bilayer of the cell membrane resists charged molecules. To overcome this issue, nucleotide prodrugs can be prepared to mask the negative charge on the phosphate groups to increase the passage through a cell's membrane.

[154] Once inside a cell, the prodrug components of the nucleoside/nucleotide are removed. This may involve the cleaving of the leaving group in one, or a number of steps, in the metabolization process. In the case of a nucleotide monophosphate prodrug, the nucleotide monophosphate is then inside the cell and, as it is already monophosphorylated, it is in an excellent position to be converted to its di and triphosphate forms.

V. The Person Skilled in the Art and Common General Knowledge

A. *The Skilled Person*

[155] Patent specifications are addressed to a hypothetical person possessing the ordinary skill and knowledge to which the patent relates and a mind willing to understand the specification (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 para 25).

[156] The Federal Court of Appeal has compared the notional person of ordinary skill in the art to the "reasonable person" in the context of negligence law. This "man in the Clapham omnibus of patent law" has been described in *Beloit Canada Ltd v Valmet OY* (1986), 8 CPR (3d) 289 at 294 (FCA) as:

> The technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right.

[157] I also find apt the description of the skilled person set out in *Valensi v British Radio Corporation* [1973] RPC 337 at 377, as follows:

> The hypothetical addressee is not a person of exceptional skill and knowledge, that he is not to be expected to exercise any invention, nor any prolonged research, inquiry or experiment. He must, however be prepared to display a reasonable degree of skill in common knowledge of the art in making trials and correcting obvious errors in the specification as a means of correcting them can readily be found.

[158] The skilled person has the same capabilities whether the issue is construction of the patent, utility and sound prediction, sufficiency of disclosure, or overbreadth.

[159] The '191 Patent is to be construed as of its publication date (January 8, 2004) from the perspective of the skilled person.

[160] The parties are in agreement that the skilled person would comprise a team of persons having at least a PhD with about three years of practical work experience, or a Master's degree with a corresponding increase in work experience.

[161] There is also agreement for the most part, that the skilled team members would comprise:

(a) a chemist with knowledge or experience in the chemical aspects of drug discovery including the synthesis of nucleosides and standard laboratory techniques for synthesising and characterising nucleoside compounds;

(b) a biologist or virologist familiar with the biological aspects of drug discovery particularly as it relates to Flaviviridae infections and particularly HCV with experience conducting relevant *in vitro* assays, cell culture systems, and interpreting data from *in vitro* assays, cell culture systems and animal models, and in assessing the activity and toxicity of other models for biological activity and toxicity.

[162] Idenix's experts contend that the patent does not address a skilled person with a background in pharmacology with knowledge and experience relevant to bioavailability, pharmacokinetics, drug delivery and metabolism. Their opinion is that the patent is addressed to skilled persons in the art of novel drug discovery comprised in the two groups described above, as opposed to those who work on the after-development of the drug, once invented, which is the field of the pharmacologist.

[163] I agree with this submission and as a result, I give less weight to some of Dr Krise's evidence, particularly concerning the meaning of "a leaving group" in the '191 Patent. I address this issue below.

[164] I further accept Dr Wnuk's opinion that the notional person skilled in the art may still need direction and would only be starting to get into independent work. This is corroborated by Dr Krise's evidence that while recent graduates may have an in-depth knowledge of a very narrow field of study, their knowledge across the remainder of their field remains basic.

[165] I also accept Dr Wnuk's opinion that the skilled person would have little experience in fluorination synthesis. His opinion was that in 2004 only a small percentage of chemists were trained in this art. Dr Wnuk had the advantage of being the only expert to testify with personal experience in fluorination in 2004.

[166] I also agree with Idenix's experts that skilled persons performing the tasks of a discovery chemist must have an awareness of the requirement to characterize compounds resulting from

their synthesis experiments. This would require the skilled discovery chemist to employ reasonable means at his or her disposal to characterize the compounds synthesized. To the extent that there may be constraints on access to technology, these limitations are attributable to the organization responsible for drug discovery and not the competence of the skilled person.

B. *Common General Knowledge*

[167] Common general knowledge is "knowledge generally known by persons skilled in the relevant art at the relevant time", *Apotex v Sanofi Synthelabo Canada Inc*, [2008] 3 SCR 265, 2008 SCC 61 at para 37 (2) [Plavix (SCC)].

[168] In *Eli Lilly and Company v Apotex Inc*, 2009 FC 991 at para 97 [*Cefaclor*], Madam Justice Gauthier, adopted with approval the comprehensive description of common general knowledge from *General Tire & Rubber Co v Firestone Tyre & Rubber Co Ltd* (1971), [1972] RPC 457 at 480 to 481 (UKCA) which I have summarized without citations as follows:

> The common general knowledge imputed to such an addressee must be carefully distinguished from what in patent law is regarded as public knowledge.
>
> Common general knowledge is derived from a common sense approach to the practical question of what would in fact be known to an appropriately skilled addressee - the sort of man, good at his job, that could be found in real life.
>
> Individual patent specifications and their contents do not normally form part of the relevant common general knowledge, though there may be some exceptions.
>
> As regards scientific papers generally,

> • it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates.
>
> • A piece of particular knowledge as disclosed in a scientific paper does not become common general knowledge merely because it is widely read, and still less because it is widely circulated.
>
> • Such a piece of knowledge only becomes general knowledge when it is generally regarded as a good basis for further action [as opposed to generally known and accepted without question] by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art.
>
> • It is difficult to appreciate how the use of something which has in fact never been used in a particular art can ever be held to be common general knowledge in the art.

[169] A party that asserts that a particular piece of information was part of the common general knowledge at the relevant time must prove this fact with evidence.

[170] Idenix relies on the ability of the skilled person to locate the common general knowledge by the use of search engines commonly available in the chemical discovery and education world. It makes reference to Justice Gauthier's decision in *Cefaclor* from para 104 as follows:

> The distinction between common general knowledge and prior art which is part of the state of the art for the purpose of assessing anticipation and obviousness tends to diminish in modern times because of the sophistication of search engines and the availability of electronic publications and databases.

[171] This does not mean however, that scientific papers found by searches or otherwise produced at trial can be used to buttress disclosure deficiencies in the ‘191 Patent unless established as meeting the requirements of common general knowledge.

[172] In addition to expert evidence, the Court has heard from several individuals who were actually working on the synthesis of 2’-C-Me/F compounds during the relevant period. I agree with Gilead’s submission that where the experience of individuals actually working on the problem differs from the theoretical opinions of experts, the contemporaneous factual information should be preferred.

VI. Construction of the ‘191 Patent

A. *Principles of Construction*

[173] The claims of the patent are to be construed prior to any assessment of validity or infringement. It is a fundamental rule that “the claims receive one and the same interpretation for all purposes” *Whirlpool Corp v Camco Inc*, 2000 SCC 67, [2000] 2 SCR 1067 at para 49 [*Whirlpool*].

[174] The modern principles of claim construction were developed by the Supreme Court of Canada in the companion cases of *FreeWorld Trust v Électro Santé Inc*, [2000] 2 SCR 1024 at para 13, 2000 SCC 66 [*Freeworld*] and *Whirlpool*. These principles of claim construction were

later summarized by the Federal Court in *Biovail Pharmaceuticals Inc v Canada (Minister of National Health & Welfare)*, 2005 FC 9 at para 15 as follows:

> 1. A patent is construed as a bargain between the inventor and the public. In consideration of disclosing the invention, the inventor is given a temporary monopoly to exploit it.
>
> 2. It is a statutory requirement that the patent contain a specification and end with a claim or claims "defining distinctly and in explicit terms the subject-matter of the invention for which an exclusive privilege or property is claimed". The specification must be sufficiently full, clear, concise and exact "as to enable any person skilled in the art or science to which it pertains, or to which it is most closely connected, to make, construct, compound or use it". (*Patent Act*, R.S.C. 1985, c. P-4, as amended, s. 27)
>
> 3. The patent is notionally addressed to a person skilled in the art or science of the subject-matter and is to be read as such a person would have read it when it first became public…
>
> 4. The claims are to be read in an informed and purposive way to permit fairness and predictability and to define the limits of the monopoly "[I]ngenuity of the patent lies not in the identification of the desired result but in teaching one particular means to achieve it. The claims cannot be stretched to allow the patentee to monopolize anything that achieves the desired result" (*Free World Trust*, paras 31, 32).
>
> 5. The claim portion of the patent specification takes precedence over the disclosure portion in the sense that the disclosure is read to understand what was meant by a word in the claims "but not to enlarge or contract the scope of the claim as written and thus understood" (*Whirlpool*, para 52).
>
> 6. It is only such novel features that the inventor claims to be essential that constitute the "pith and marrow" of the claim. "The key to purposive construction is therefore the identification by the Court with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention" (*Whirlpool*, para 45).
>
> 7. Some elements of the claimed invention are essential and others are not, based either on common knowledge when the patent

> was published or according to the intent of the inventor, expressed or inferred from the claims…
>
> 8. To overclaim is to lose everything. If the inventor underclaims, the court will not broaden the monopoly in the interests of the "spirit" thereof. This often, as in this case, results in layers of claims, each limitation serving as a potential safety net so that if the broadest claims fall, the monopoly may be saved in part by the more modest claims.
>
> 9. Yet a patent is not an ordinary writing. It meets the definition of a "regulation" in the *Interpretation Act*, and must be read to assure the attainment of its objects. "Claims construction is a matter of law for the judge, and he was quite entitled to adopt a construction of the claims that differed from that put forward by the parties." (*Whirlpool*, para 52)

[175] Claims are to be interpreted in a purposive manner in order to "achieve fairness and predictability and to define the limits of the monopoly" (*Dimplex North America Ltd v CFM Corp*, 2006 FC 586, 54 CPR (4th) 435 at para 49, aff'd 2007 FCA 278, 60 CPR (4th) 277 [*Dimplex*]).

[176] A patent is to be given a "purposive construction", not a technical or literal construction, taking into account the entire context of the specification, including the disclosure and the claims, as they would be understood by the skilled person reading the patent with the object of understanding what the inventor claims to have invented and the scope of the monopoly the inventor wishes to claim (*Freeworld* paras 39-40, 44, 50).

[177] Although a patent is to be given a purposive construction, the Supreme Court has held that competitors and the public are entitled to clear and definite rules as to the extent of the monopoly conferred. The discretionary elements of claims interpretation (e.g. the "spirit of the

invention") must be kept to a minimum, consistent with giving the inventor protection for that which he has actually in good faith invented. Predictability is achieved by tying the patentee to its claims; fairness is achieved by interpreting those claims in an informed and purposive way (*Freeworld* para 43).

B. *Construction of Claims of the '191 Patent*

(1) Claim 1

[178] Idenix is not defending or asserting a claim of infringement in respect of Claim 1. On that basis it only refers to Claim 1 for the purpose of defining the substituents of the other claims that are relevant to those claims.

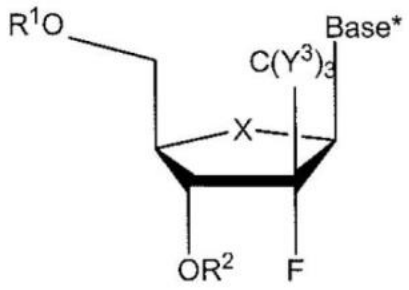
[179] Gilead argues that Idenix cannot resile from its representation to the CIPO that Claims 1-3 are one invention. Gilead claims that this was the implied representation made by Idenix when it was required to narrow its claims to describe a Patent Application for only one invention wherein Claims 1-3 represent the genus claims of the Patent. Gilead submits that the invention therefore, is described by Claims 1-3 and the derivatives thereof.

[180] Gilead wishes to include Claim 1 as describing the invention particularly because the 2' (up) position of Claim 1 includes 45 different substituents. Claims 2 and 3 have this substituent as a methyl group, CH_3. All but the methyl substituent have never been made, tested or their synthesis disclosed. At every turn in the case therefore, Gilead claims that the invention cannot be predicted, its synthesis has not been disclosed, or is overly broad.

[181] I reject Gilead's submission, which is unsupported by any jurisprudence of similar facts. Nor do I understand that Idenix is prevented from abandoning the defence of a too broadly stated claim. The Supreme Court in *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60, [2012] 3 SCR 625 [*Viagra*] at para 80 sanctioned this practice as being acceptable:

> [80] I would not make too much of the fact that Claim 1 included over 260 quintillion compounds. The practice of cascading claims — although it may, as in this case, result in claims that are overly broad — is a common one that does not necessarily interfere in every case with the public's right to disclosure. The skilled reader knows that, when a patent contains cascading claims, the useful claim will usually be the one at the end concerning an individual compound. The compounds that do not work are simply deemed invalid. In accordance with s. 58, any valid claim — in this case, Claim 7 — survives despite the existence of invalid claims.
>
> [Emphasis added]

[182] Therefore, Claim 1 in the '191 Patent is considered only for the purpose of the descriptions of its substituents as they apply to Claims 2 and 3. Claim 1 covers a large number of nucleoside analogues (or their pharmaceutically acceptable salts thereof) which are compounds of Formula (IX). It is depicted as follows:



(a) *Substituents of Claim 1*

(i) Substituent "X" in the sugar ring component

[183] This substituent can be oxygen (O), sulfur (S), SO_2, or CH_2. This encompasses both naturally occurring sugar rings (X = O or CH_2) and modified sugar rings (X = S or SO_2). However, in Claims 2 and 3, it is defined only as an oxygen atom.

(ii) Substituent "$C(Y^3)_3$ " at the 2'-up position in the sugar ring component

[184] This substituent is a carbon [C] bonded to three atoms [Y^3]. Each Y^3 atom is either a hydrogen [H] or a halogen (F, Cl, Br, or I). The three Y^3 atoms can be the same or different (e.g. CF_3 , CF_2Cl, etc.). The evidence of Dr Wnuk is that forty-four different $C(Y^3)_3$ groups are encompassed by this substituent in Claim 1, in addition to the methyl group $C(H^3)_3$. This substituent is a methyl group (CH_3) in both Claims 2 and 3.

(iii) Substituents for the "Base" at the 1' position

[185] The Base substituent is repeated in Claims 2 and 3 and therefore, is relevant to this litigation. It is one of a large number of different natural and non-natural purine and pyrimidine bases, that includes at least all of the bases listed in the definition of purine and pyrimidine set out on p. 104 of the '191 Patent, as follow:

[186] The term "purine" or "pyrimidine" base includes, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-alkylaminopurine, N^6-thioalkyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-iodopyrimidine, C^6-iodo-pyrimidine, C^5-Br-vinyl pyrimidine, C^6-Br-vinyl pyrimidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups were well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

[187] Idenix experts acknowledged that the bases covered by this definition may be linked to the sugar ring by either a nitrogen atom (N-linked) or a carbon atom (C-linked). Throughout the patent there are also references to schemes and compounds with non-natural and C-linked bases, none of which would work with the invention, and indeed would most likely be harmful if ingested by a human or other host.

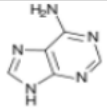
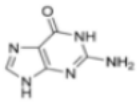
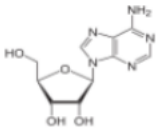
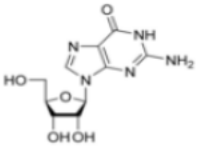
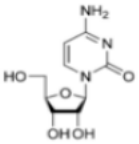
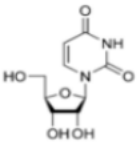
[188] Dr Wnuk was of the opinion that the skilled person would have understood the Formulae of the ‘191 Patent to include a vast number of non-natural bases, thereby referring to an enormous number of nucleosides.

[189] Dr Barrett stated his opinion that in the context of the ‘191 Patent, the POSITA would understand the term “Base” to encompass purine or pyrimidine bases that could be used in the treatment of Flaviviridae (viral) infections. The claimed class of compounds and their use as antiviral agents is the focus of the ‘191 Patent. He similarly opined that the skilled person reading the ‘191 Patent would understand that the novel modifications to the claimed compounds do not occur on the base, but rather occur at the 2’ position of the sugar ring. Thus, the person skilled in the art would read the term “Base” narrowly to refer to the natural bases.

[190] This opinion is consistent with the conclusions of the Supreme Court in *Burton Parsons Chemicals v Hewlett-Packard*, [1976] 1 SCR 555 at page 563 [*Burton*]. It stands for the proposition that where it is obvious to the skilled person that within the specification there are substituents that are incompatible with the use of the invention, those compounds will not be selected.

[191] Dr Damha testified to the same effect as Dr Barrett. He indicated that a nucleoside with a C-linked base would be unnatural. The person skilled in the art would understand N-linked bases to be the normal reference for natural nucleosides. Therefore to a skilled person, if one simply refers to a “base” or a “purine or pyrimidine base” this refers to the N-linked base. Unless specified, the normal understanding is that bases are N-linked bases.

[192] The terms "purine" and "pyrimidine" bases are specifically defined on page 104 of the '191 Patent to include the four commonly known naturally-occurring bases used to make RNA: Adenine (A), Guanine (G), Cytosine (C), and Uracil (U)

Natural RNA Bases	 Adenine	 Guanine	 Cytosine	 Uracil
Natural RNA Nucleosides	 Adenosine (A)	 Guanosine (G)	 Cytidine (C)	 Uridine (U)

[193] While I understand that the definition of Base found in the Patent refers to a large number of natural and unnatural bases, I prefer the evidence of doctors Drs Barrett and Damha that the skilled person would understand that bases refer to those used in the treatment of Flaviviridae that are N-linked, thereby specifying the four commonly known naturally-occurring bases used to make RNA.

(iv) Substituents "R^1" and "R^2" at the 5' (up) and 3' (down) position in the sugar ring component:

[194] These substituents are one of a large number of different substituents that are specifically listed beneath Claim 1 of the '191 Patent. The large number of possible substituents can be broadly categorised as either an atom (e.g. H), a chemical group (e.g. a phosphate), or groups of substituents (e.g. CO-alkyl and lipid). This description of the R^1 and R^2 substituents also applies

to Claim 2. It does not apply to Claim 3 where the R^1 and R^2 substituents are narrowed to a hydroxyl.

(2) "Phosphate" and "Pharmaceutically Acceptable Leaving Group"

[195] There is a construction issue for Claim 2 in respect of the terms "phosphate" and "pharmaceutically acceptable leaving group". The construction of these terms is determinative of portions of issues agreed upon by the parties regarding Idenix's infringement claim. The relevant portion of the description of these substituents, in particular as they apply to the 5' position on the sugar ring, is as follows:

> phosphate … or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R1 is … phosphate

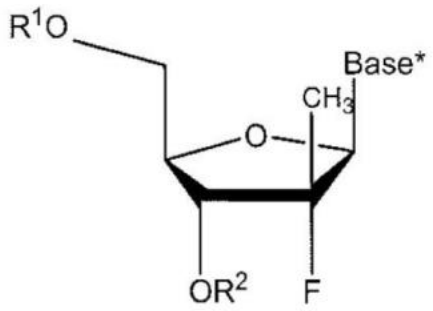
[196] Gilead is seeking a narrow interpretation of this wording such that the prodrug sofosbuvir, which is a phosphoramidate at the 5 position, is not captured by this wording because it is neither a "phosphate" nor a "leaving group". Gilead submits that "phosphate" can only be construed as a monophosphate $-PO_4$. It further argues that a "leaving group" is interpreted by the skilled person as one that is cleaved off <u>in its entirety</u>, whereas the prodrug used in sofosbuvir and Sovaldi is cleaved off in stages.

[197] I find that the construction of these terms is best left to the section on infringement where they have a practical application. I may state here however, that I interpret "phosphate" to include di- and tri-phosphates, while, "a pharmaceutically acceptable leaving group which when

administered in vivo is capable of providing a compound wherein R^1 is … phosphate," I conclude refers to prodrugs generally, without regard to how they are metabolized *in vivo*.

(3) Claim 2

[198] I have already pointed out that Claim 1 in the '191 Patent is relevant for the purpose of the descriptions of its substituents which apply to Claims 2 and 3. Claim 2 has the following structure:



[199] Claim 2 is the compound of Claim 1, wherein hydrogen is the substituent in the 2' (up) position on the sugar ring making it a methyl, while oxygen is the sole "X" substituent on the sugar ring making it a furanose. The other substituents remain the same. The Court's conclusions on the construction of the terms "Base", "phosphate" and "leaving group" made with respect to Claim 1, apply to Claim 2.

(4) Claim 3

[200] Claim 3 is the same compound as Claim 2, except that R^1 and R^2 are H, meaning that the 3' and 5' groups are hydroxyl (OH). The issues concerning the interpretation of "phosphate" and "leaving group" do not arise in this Claim. The Court's conclusions on the construction of the term "Base" made with respect to Claim 1, apply to Claim 3.

(5) Claims 4 to 32

[201] Claims 4 to 32 incorporate "the compounds of claims 1 to 3". It is understood that these Claims incorporate within their scope all of the compounds claimed in each of Claims 1-3. Idenix however is not defending any claims, or claiming infringement of claims based on Claim 1.

(6) Claims 4 to 5 and Claims 17 to 18

[202] Claims 4 to 5 cover the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) in the treatment of a host infected with a Flaviviridae virus (Claim 4), or more specifically, a host infected with HCV (Claim 5). To the extent that these and other Claims are based on Claim 1, they are not valid.

(7) Claims 6 to 9

[203] Claims 6 to 9 (which depend on Claim 4) cover the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) in combination or alternation with a second anti-

viral agent in the treatment of a host infected with a Flaviviridae virus. Claim 7 provides a list of groups of the second anti-virals and Claims 8 and 9 narrow the second anti-viral to types of interferons.

(8) Claims 10 to 12

[204] Claims 10 to 12 (which depend on Claim 4) cover the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) in the treatment of a Flaviviridae infection wherein the compound or pharmaceutically acceptable salt is in the form of a "dosage unit".

[205] The term "dosage unit" refers to a defined amount of compound that is administered to a whole organism (e.g. a human or animal). Such amounts can be provided in the form of a tablet, capsule, injection, suspension, syrup, patch, or the like.

(9) Claims 11 and 12

[206] Claim 11 limits the amount of active ingredient in the dosage unit (50 to 1000 mg). Claim 12 specifies that the dosage unit should be a tablet or capsule.

(10) Claim 13

[207] Claim 13 (which depends on Claim 4) covers the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) in the treatment of a human infected with the Flaviviridae virus.

(11) Claims 14 to 16

[208] Claims 14 to 16 (which depend on Claim 4) cover the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) in the treatment of a host infected with a Flaviviridae virus, wherein the compound of Claim 1 to 3 (or a pharmaceutically acceptable salt thereof) is in its "substantially pure form". The term "substantially" means that, on a weight basis, the β-D-isomer is at least 85-90% of the product (or a pharmaceutically acceptable salt thereof), the remainder of which could comprise other chemical species or enantiomers.

(12) Claims 15 and 16

[209] Claims 15 and 16 relate to such uses wherein the compound is at least 90% (Claim 15) or 95% (Claim 16) by weight of the β-D-isomer.

[210] To be "at least 90%" or "at least 95%" "by weight of the β-D-isomer" means that on a weight basis, at least 90% or 95% of the compound (or its pharmaceutically acceptable salt) is present in the β-D-isomeric form, the remainder of which could comprise some impurities or other compounds.

(13) Claims 19 to 32

[211] Claims 19 to 32 cover the use of the compounds of Claims 1 to 3 (or a pharmaceutically acceptable salt thereof) for the preparation of a medicament for the treatment of a host infected with a Flaviviridae virus.

[212] The term "medicament" means a medicine or drug in a specified formula with an acceptable therapeutic index.

(14) Claims 20 to 32

[213] Claims 20 to 23 cover the manufacture of medicaments which contain a claimed compound with one or more additional anti-viral agents.

[214] Claim 21 provides a particular list of groups of second anti-virals and Claims 22 and 23 narrow the second anti-viral to types of interferon.

[215] Claims 24 to 26 cover the manufacture of medicaments which contain a claimed compound in the form of a dosage unit.

[216] Claim 25 limits the amount of the active ingredient in the dosage unit (50 to 1000 mg).

[217] Claim 26 specifies that the dosage unit should be a tablet or capsule.

[218] Claim 27 covers the manufacture of a medicament wherein the compound of Claim 1 to 3 (or a pharmaceutically acceptable salt thereof) is in substantially pure form.

[219] Claims 28 and 29 cover the manufacture of a medicament wherein the compound is at least 90% by weight of the β-D-isomer (Claim 28) or at least 95% by weight of the β-D-isomer (Claim 29).

[220] Claim 32 covers the use of the compounds of Claims 1 to 3 in the manufacture of a medicament for the treatment of a host infected with HCV.

VII. Utility

A. *General Principles*

(1) Requirement for Utility

[221] It is common ground that there was no demonstrated utility as a June 27, 2003. Idenix has admitted that it did not test any compound falling within the scope of the claims of the '191 Patent until March 2005. Therefore, the only argument for establishing utility in the 2'-C-Me/F compounds is based on sound prediction from its testing of the 2'-C-Me/OH compounds.

[222] Gilead alleges that the '191 Patent is invalid because at the filing date of June 27, 2003, Idenix failed to soundly predict the promised utility.

[223] Section 2 of the *Patent Act* defines "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."

[224] The Supreme Court of Canada [SCC] in *Viagra*, at paras 37 to 40, has recently summarized many of the requirements needed to establish that the invention is "useful" or has "utility":

- All that is required to meet the utility requirement in s 2 is that the invention described in the patent do what the patent says it will do, that is, that the promise of the invention be fulfilled.

- When an invention's utility cannot actually be demonstrated by way of tests or experiments, its utility can nevertheless be established by means of a sound prediction.

- The failure to disclose information on testing compounds goes to the issue of disclosure of the invention, not to that of disclosure of the invention's utility.

- The invention must be useful as of the date of the claim (June 27, 2013) based on the information and expertise then available.

- If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if the prediction at the date of application was not sound, or, irrespective of the soundness of the prediction, there is evidence of lack of utility in respect of some of the area covered.

[225] Where the specification does not promise a specific result, no particular level of utility is required; a "mere scintilla" of utility will suffice. However, where the specification sets out an explicit "promise", utility will be measured against that promise: *Consolboard Inc v MacMilan Bloedel (Saskatchewan Limited)*, [1981] 1 SCR 504 at 525 [*Consolboard*] ; *Pfizer Canada Inc v Canada (Minister of Health*), 2008 FCA 108, [2009] 1 F.C.R. 53. The question is whether the invention does what the patent promises it will do.

[226] Before considering whether the inventors had demonstrated utility, the Court must consider what the specification says the invention will do. The claims at issue are to be read and considered in light of the specification through the eyes and understanding of the person skilled in the art, in relation to the science and information available at the time of filing: *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77, [2002] 4 SCR 153 [*Wellcome/AZT*] at para 51; *Consolboard*, supra at 521; *Freeworld*, supra at para 44; *Eli Lilly Canada Inc v Novopharm Ltd*, 2010 FCA 197 at para 80 [*Eli Lilly/Zyprexa*].

[227] Whether the patent contains a promise of utility is to be ascertained as a first step in the utility analysis. Because the promise doctrine holds an inventor to an elevated standard, it will only apply 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: *Apotex Inc v Pfizer Canada Inc*, 2014 FCA 250 at para 66.

(2) The Promise of the '191 Patent

(a) *The Compounds for which Utility is Claimed*

[228] Gilead asserts that the stated utility of the '191 Patent is for all of the claimed compounds, which it argues includes those covered under Claim 1 of the Patent. On this basis, it has led evidence from its experts that the description of the '191 Patent would be invalid, as it does not identify which compound has activity and in which Flaviviridae virus.

[229] As indicated above, I find that the compounds under Claim 1 are not at issue. The relevant compounds therefore are the 2'-C-Me/F nucleosides in Claims 2 and 3 and their nucleotides and other derivatives thereof. In my view, these compounds are sufficiently identified for the purposes of utility. It is the 2'-C-Me/F sugar ring that is the foundation of the '191 Patent and recognized by both parties as the basis for its antiviral effect, as well as that of the '657 Patent.

[230] If the utility is demonstrated or soundly predicted in a nucleoside of the '191 Patent, that is sufficient for the purposes of meeting the requirements of the *Act*.

(b) *Stated Utility*

[231] Once the compounds are narrowed to the genus of those described in Claims 2 and 3, the promise of the '191 Patent is not an issue of undue contention. Utility is only to be considered for the claims in issue in light of the specification. Gilead and Idenix agree that the Patent contains a promise that the compounds are useful in the treatment of Flaviviridae infections, including HCV infections, in humans and other hosts.

[232] Dr Seeger, who testified on behalf of Gilead on this issue, excerpted numerous references from the '191 patent, opining that the claimed compounds were all stated to be useful in the treatment of Flaviviridae infections, including HCV infections, in humans and other hosts.

[233] The primary reference was to the objects clause at p. 12, stating as follows:

> Further, given the rising threat of other flaviviridae infections, there remains a strong need to provide new effective pharmaceutical agents that have low toxicity to the host.
>
> Therefore, it is an object of the present invention to provide a compound, method and composition for the treatment of a host infected with hepatitis C virus.
>
> It is another object of the present invention to provide a method and composition generally for the treatment of patients infected with pestiviruses, flaviviruses, or hepaciviruses.

[234] These promises are supported by similar references elsewhere in the specification and claims repeating the promise including: The "Field of Invention" at p. 1; the "Summary of Invention" at p. 12; the "Detailed Description of the Invention" section at pp.21-22; the "Features of the invention" at pp. 23-28; the "Active Compounds" section at p. 100; the "Pharmaceutical Composition" section at p. 117; and repeated again in the claims of the '191 Patent, for example at Claim 4 for the "Use of a therapeutically effective amount of a compound as claimed in anyone of Claims 1 to 3 (now considered as Claims 2 and 3), or a pharmaceutically acceptable salt thereof in the treatment of a host infected with a Flaviviridae virus" and related Claims.

[235] Dr Seeger was not contradicted by Idenix. Dr Lamarre, who was Idenix's only witness speaking to utility. He stated in his report at para 69 as follows:

> [69] With respect to what the claimed invention is useful for, both Dr Seeger and I agree that the claimed compounds, or pharmaceutically acceptable salts or prodrugs thereof, "are useful in the treatment of Flaviviridae infections, including HCV infections, in humans and other hosts".

(c) *Toxicity*

[236] Idenix appears to make an overly broad submission with respect to the '191 Patent not containing any promise of being free of toxicity. I cite para 188 of its written submissions to this effect:

> [188] Finally, there is nothing in the '191 Patent's claims or disclosure (or for that matter the expert reports of either party) to suggest a promise that the claimed compounds are: free of toxicity, have reduced side effects, or would necessarily satisfy clinically or regulatory approval standards.
>
> [Emphasis added]

[237] I would agree with this submission with respect to any promise regarding reduced side effects or necessarily satisfying clinically or regulatory approval standards. For example in *Eli Lilly Canada Inc v Mylan*, 2015 FC 17 at paras 87-92 the Court concluded that references to toxicity would not include side effects arising from clinical trials.

[238] Where I disagree with Idenix, if this is the position it takes, is that the Patent, in its demonstration of antiviral activity, makes no promise of demonstrating a satisfactory therapeutic index. It is to be noted that this index is used to assess a compound's antiviral activity in relation to its cellular toxicity. The evidence of Dr Lamarre on cross-examination was that antiviral activity that is toxic is not useful (p. 3264), while Professor La Colla stated that "for an antiviral compound, you want to inhibit the viral multiplication without killing the cell."

[239] Similarly, Dr Seeger testified as follows:

> An effective antiviral compound must act selectively against the virus and be non-toxic to the same virus-infected or uninfected cells. A compound is not useful for treating of viral infection if it is also toxic to the host more specially, a skilled virologist would not consider a compound to be useful for treating a Flaviviridae if it had high cytotoxicity.

[240] I am of the view that the skilled chemist would interpret treatment for a host infected with Hepatitis C virus as requiring effectiveness in combination with low toxicity as measured in accordance with the therapeutic index.

(d) *The Level of Utility and How Utility is Demonstrated or Predicted*

[241] I find that the '191 Patent makes no promise of any specific result or level of treatment. I conclude that Gilead must therefore, prove that Idenix has not demonstrated or soundly predicted a scintilla of utility in the 2'-C-Me/F compounds for the treatment of Flaviviridae to succeed in its argument.

[242] However, I disagree with one of Idenix's submissions of how the skilled person determines a scintilla of utility is demonstrated or predicted. It advances an argument based on Dr Lamarre's opinion in his November report under the title "How a skilled person can measure the utility of the invention?" which concludes at para 86 with the following statement:

> In summary, from reading the '191 Patent, the skilled biochemist would understand that a compound is useful against Flaviviridae if it can exhibit a positive antiviral result in at least one assay in respect of at least one virus from the Flaviviridae family.
>
> [Emphasis added]

[243] There are number of issues that appear to be addressed by Dr Lamarre in the foregoing statement. First, he appears to be saying that the wording of a patent determines how utility is to be demonstrated, apparently as part of its promise. Second, he states that one assay of one virus in one type (e.g. HBV) of the Flaviviridae family is sufficient to demonstrate utility in all the other viruses of that type, as well as all of the other viruses in the other two types (e.g. HAV and HCV) making up the family of Flaviviridae.

[244] I will leave the issue of one assay demonstrating utility across the spectrum of Flaviviridae until Idenix's claims of sound prediction are considered. Idenix needs to be able to establish this as part of its factual basis to be able to soundly predict the utility of the 2'-C-Me/F compounds based on assays of the 2'-C-Me/OH compound.

[245] Returning to the issue of the promise of the Patent determining what constitutes sufficient evidence to demonstrate a scintilla of utility, it would appear that Dr Lamarre is attempting to make up for the dearth of assaying data found in the '191 Patent. By his measure, claiming that testing data available from only one assay is sufficient to demonstrate utility based on the skilled person's reading of the Patent.

[246] I agree with Gilead that no such interpretation can be made from the '191 Patent. More to the point however, the sufficiency of evidence to support a finding of utility is not a conclusion that will be dictated to by the claims or promises of the patent. It is determined as a function of the soundness of the factual basis, in this case for the prediction and the reasonableness of the line of reasoning for the prediction.

[247] Moreover, I understand this position is intended to confront the shortage of testing data for the 2'-C-Me/OH compounds in the Patent. This is only relevant if Idenix is required to disclose the basis for the sound prediction in the Patent. Idenix's position is that it is not required to do so. Otherwise, Idenix possesses abundant evidence of extensive testing by Idenix of its 2'-C-Me/OH nucleosides in different forms of assays to argue that these results should apply across the full spectrum of the Flaviviridae family.

(3) Sound Prediction

(a) *General Principles*

[248] The doctrine of sound prediction can be relied upon by an inventor to justify patent claims whose utility has not actually been demonstrated, most often because the invention has not been made, but can be soundly predicted based upon the information and expertise available. If a patent sought to be supported on the basis of sound prediction is subsequently challenged, the challenge will succeed if, per Justice Pigeon in *Monsanto Co v Commissioner of Patents*, 1979 CanLII 244 (SCC), [1979] 2 SCR 1108, at p. 1117, the prediction at the date of application was not sound, or, irrespective of the soundness of the prediction, "[t]here is evidence of lack of utility in respect of some of the area covered," (*Wellcome/AZT* at para 56).

[249] In order to establish that a sound prediction has been made by the inventor, the Supreme Court of Canada set out a three-part test in *Wellcome/AZT* at para 70, as follows with my underlining:

1. There must be a <u>factual basis</u> for the prediction;

2. The inventor must have an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and

3. There must be proper disclosure (contested by Idenix).

[250] The party challenging the patent for lack of utility has the legal burden of proof. However, since the relevant documents and information are usually or often in the possession or control of the patent owner, the challenger can meet its evidentiary burden by offering expert evidence on the relevant issues. *Bell Helicopter Textron Canada Limitée v Euorcopter*, 2013 FCA 219 at paras 154 & 161-162.

(b) *The Standard for a Sound Prediction*

[251] Idenix cites the decisions of the Federal Court of Appeal *in Eli Lilly Zyprexa* supra at 76 and in this Court *Astrazeneca Canada Inc v Apotex Inc*, 2014 FC 638 at para 182 [*AstraZeneca/Pregabalin*] with respect to the appropriate standard for a sound prediction being a "*prima facie* reasonable inference". In the latter case, the Court states that "[t]he situating of a prima facie reasonable inference between mere speculation and certainty provides the clearest guidance to the proper approach to be taken in this case."

(c) *The Sound Prediction is an Inferred Fact Not Proven in This Matter*

[252] As noted, the Supreme Court has stated in paras 70 and 71 of *Wellcome/AZT* that a sound prediction is an inferred ("sound" line of reasoning from which the desired result can be inferred

from the factual basis) fact ("It bears repetition that the soundness (or otherwise) of the prediction is a question of fact").

[253] The predicted inferred fact that Idenix says arises from its primary facts based on the antiviral activity demonstrated in the 2'-C-Me/OH compounds and sound line of reasoning is that in 2003, the skilled person could soundly predict that, when synthesized, the 2'-C-Me/F nucleoside will demonstrate therapeutic antiviral activity such as is found in its 2'-C-Me/OH compound.

[254] It is common ground that to prove a fact, the evidence must establish the fact on a level of proof on a balance of probabilities, usually described as a likelihood or probability. Anything below that evidentiary standard is not an established fact. Anything found not to be a fact on the balance of probabilities from the evidence is a mere possibility, or if dealing with inferences, mere speculation.

[255] By the Court's analysis that follows, I find that Idenix has not established on the balance of probabilities from the relevant evidence presented to the Court that the skilled chemists on the date of filing of the '191 patent application could soundly predict any antiviral activity in a 2'-C-Me/F nucleoside prior to its synthesis. Accordingly, the '191 Patent is invalid for lack of utility, demonstrated or soundly predicted, as a finding of fact.

B. *Idenix's Claim of Sound Prediction*

(1) Overview

[256] In broad strokes, Idenix claims that the inventors' sound prediction was based on the following three items:

1. a vast body of knowledge regarding antiviral activity of 2'-C-Me/OH nucleoside analogues;

2. an expectation of activity of 2'-C-Me/OH nucleoside analogues against the family of Flaviviridae viruses because they have

    a. similar genomic organization,

    b. conserved sequence/structure motifs and

    c. conserved mechanism of action; in respect of their (NS5/NS5B) viral RNA polymerase enzymes; and because

    d. predictive surrogate and representative Flaviviridae virus models were known; and

3. wide acceptance in the nucleoside field that fluorine is an isostere for a hydroxyl group.

[257] Items 1 and 2 represent the first factual basis for establishing that the 2'-C-Me/OH nucleosides exhibit antiviral activity against HCV. This conclusion is also somewhat a form of a

prediction, inasmuch as Idenix's testing data for its 2'-C-Me/OH compounds, apart from tests on chimpanzees, was on flaviviruses and pestiviruses, but not the Hepatitis C virus using the Replicon assays then available. Idenix's argument is that its tests for antiviral activity in flaviviruses and pestiviruses are nevertheless surrogates to predict the antiviral effectiveness for HCV. Idenix relies on the literature to support its conclusion that the 2'-C-Me/OH compound was tested across the spectrum of Flaviviridae, including using Replicon assays. It also relies on its chimp data, which is an equivalent of the human cell line.

[258] Idenix claims that Item 3 provides the factual basis for the sound of the line of reasoning to predict antiviral activity in the 2'-C-Me/F nucleosides based upon that demonstrated in the 2'-C-Me/OH nucleosides. It submits that the similarity of the stereochemical structures of the fluorine and hydroxyl group as isosteres means that replacing the hydroxyl group in the 2'-C-Me/OH nucleoside with a fluorine would result in a likelihood of some activity in the 2'-C-Me/F nucleoside, because the fluorine "mimics" the hydroxyl.

[259] My analysis that follows will first consider the factual basis relating to the 2'-C-Me/OH nucleoside as described in Idenix' a submissions in Items 1 and 2 above. I find that there is a satisfactory factual basis to conclude that in 2003 the 2'-C-Me/OH nucleosides demonstrated therapeutic antiviral activity against the HCV.

[260] The more detailed analysis concerns Item 3 pertaining to the factual basis and line of reasoning to soundly predict antiviral activity in the 2'-C-Me/F nucleosides based on that in the

2'-C-Me/OH nucleosides . I find that Gilead has met its onus of demonstrating that the sound prediction of utility in the 2'-C-Me/F nucleoside is a mere possibility and is speculative.

[261] For the purpose of making factual findings that could become relevant on appeal of this matter should that occur, I complete my analysis by considering whether Gilead has demonstrated that Idenix is required to sufficiently disclose the sound prediction of utility in the 2'-C-Me/F compounds in the '191 patent, and if so being assumed, whether it has demonstrated that it failed to do so. I conclude that Idenix is not required to disclose the basis for its sound prediction, but had that been the requirement, the '191 Patent fails to do so

(2) Analysis of Idenix's Prediction of Activity across the Flaviviridae Family (Items 1 and 2)

(a) *A Vast Body of Knowledge regarding Antiviral Activity*

[262] As indicated, I am prepared to accept Items 1 and 2 of Idenix's submissions above that there was a factual foundation to predict antiviral activity in the 2'-C-Me/OH nucleosides across the Flaviviridae family. With respect to Item 1, I conclude that Idenix, as the inventor of the use of the 2'-C-Me/OH nucleoside as an antiviral compound, had been working on the invention for approximately 4 years at the time of the application. It had acquired considerable knowledge about the compound's antiviral activity. I do not believe that this proposition is seriously contested by Gilead.

[263] Professor La Colla began testing an adenine compound in July 1999. Thereafter, between October, 2000 and May, 2001, he tested a number of 2'-C-Me/OH nucleosides using different bases, including the other three naturally occurring bases (cytosine, guanine, and uracil).

[264] On November 29, 2001, WO 01/90121 application [Novirio 121] was published disclosing claims of the 2'-C-Me/OH structures for antiviral activity against HCV with the four natural bases (adenine, cytosine, guanine, and uracil). On December 6, 2001, WO 01/92282 [Novirio 282] published the disclosure of the 2'-C-Me/OH structures for antiviral activity against flaviviruses and pestiviruses.

(b) *An Expectation of Activity of the 2'-C-Me/OH Nucleoside Analogues against the Family of Flaviviridae Viruses*

[265] With respect to Item 2 above, I also do not believe that the Items 2(a), (b) and (c) are controversial in stating that the family of Flaviviridae viruses have similar genomic organization with conserved sequence/structure motifs and conserved mechanisms of action in respect of their (NS5/NS5B) viral RNA polymerase enzymes. The evidence of Dr Damha on this point was not seriously challenged.

[266] Only Item 2(d) claiming that there were known predictive surrogate and representative flaviviridae virus models is challenged. This relates mostly to Idenix's failures to test the 2'-C-Me/OH nucleosides using the Replicon assays. This assay tests directly on HCV cell line.

[267] Instead, Idenix's tests were conducted in what were described as "HCV mimic" or surrogate models. The surrogate tests used by Idenix include those for: BVDV, Yellow Fever Virus, West Nile Virus, and Dengue Virus. They are described as a surrogate models because they do not test HCV cell lines, which are limited to humans or chimpanzees.

[268] I am satisfied that the assays conducted by Idenix and reported by other in the documentation known to Idenix supports a conclusion that the inventors had reasonable expectation of antiviral activity from the 2'-C-Me/OH nucleoside across the spectrum of Flaviviridae viruses.

(i) Chimp Data

[269] Idenix conducted tests on Chimpanzees on its NM283 - 2'-C-Me/OH adenosine nucleoside, being the most analogous surrogate to human hosts. Idenix pointed out that the Federal Drug Administration [FDA] authorized Idenix to conduct Investigational New Drug [IND] human clinical trials using the 2'-C-Me/OH nucleoside (NM107/NM283 -adenosine) in December 2002, which it argues it would not have occurred if it were not satisfied with Idenix's testing data. No HCV Replicon data was required before these trials were allowed. Dr Seeger acknowledged that this authorization was likely based on the Chimp testing data.

(ii) *Carroll et al* Article

[270] In addition, Idenix relies upon a study in *The Journal of Biological Chemistry* published in January, 2003 by Steven Carroll and other scientists from Merck describing data from tests

conducted independently using Idenix's 2'-C-Me/OH adenine compound. I accept Idenix's claim that this paper is significant because it is said to confirm the therapeutic activity of the Idenix compounds and its prodrug forms, including its mechanism of action of chain termination activity across the Flaviviridae family based on the conserved critical sequences of their RNA-dependent RNA polymerase.

[271] The Merck conclusions used comparative testing, including HCV replicon assays. The tests confirmed antiviral activity at concentrations resembling those that Professor La Colla obtained in his cell-based surrogate assays. I find that these results largely nullify Gilead's complaint about the lack of replicon assays to support Idenix's sound prediction.

[272] Gilead objected to Professor La Colla testifying about this article. It was not mentioned in the '191 Patent and it argued that this was the first time Gilead was aware that Professor La Colla was relying on it. Professor La Colla claims to have learned of the article by way of an email circulated amongst Idenix discovery personnel. The email was never introduced into evidence. Professor La Colla acknowledges that no one requested his documents and therefore, none were produced.

[273] After hearing argument on this issue, I indicated that I would allow the document to be reviewed, but would have to consider the weight attributed to Dr La Colla's claim to having recollected receiving the article and being "happy" because it confirmed his prediction that the 2'-C-Me/OH compounds would prove to have antiviral activity.

[274] It is difficult to understand how an article of such singular importance could not have been referenced in the '191 Patent. This suggests that none of the inventors would have been aware of its existence. The absence of the production of documents in Professor La Colla's possession is a further concern.

[275] Nevertheless, it may well be that documents known to the inventors did not make it into the Patent. I do not believe that Professor La Colla would intentionally mislead the Court. The article, which was peer-reviewed and published in a well-known scientific journal, should have been of high interest to Idenix. It is the sort of document that would be circulated to all members of the discovery team given its relevance and corroboration of their work. Moreover, Professor La Colla should have been a priority recipient in such circumstances, given the important role he played in testing Idenix's compounds, the validation of which was the focus of the *Carroll* article.

(iii) *Eldrup et al*, *Bhat et al* and *Olsen et al Studies*

[276] The '191 Patent referenced three studies that were discussed in oral sessions on Hepatitis C Virus Flaviviridae at the 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.). These include studies by (1) Eldrup et al describing the structure activity relationship of 2'-modified nucleosides for inhibition of HCV, (2) by Bhat et al describing the synthesis and pharmacokinetic properties of nucleoside analogues as possible inhibitors of HCV RNA replication, and (3) Olsen et al. describing the effects of the 2'-modified nucleosides on HCV RNA replication. The authors reported that 2'-modified nucleosides demonstrated inhibitory activity in cell-based replicon assays. These are references only to the published

abstracts of the presentations at the Savannah conference. However, Dr Storer and others from Idenix attended and reported on the presentations and were definitely within the knowledge of the inventors.

(c) *Gilead Submissions*

[277] I accept Dr Seeger's evidence that normally without the Replicon assay data, there would not have been a sufficient basis for a sound prediction of antiviral activity across the Flaviviridae family based on the 2'-C-Me/OH nucleoside testing data. The evidence on the development of assaying technology is convincing that the advent of the replicon assay commencing in 1999 was immediately recognized as a significant breakthrough in the common general knowledge of the skilled virologist to test for HCV.

[278] Inventors of patent applications filed in relation to Flaviviridae antivirals at the beginning of the 20th century invariably adopted it to validate their conclusions. This includes those of Dr Damha filed in that period and most of the patents referred to by witnesses in the relevant time period throughout the trial. Replicon assays were clearly a requirement for validating HCV utility by the filing date of the '191 Patent.

[279] Regarding other criticisms by Gilead, I would also accept Dr Seeger's statement that Idenix had concentrated its efforts on certain nucleosides querying to some extent these limitations. However, I do not see this impacting on the reliability or validation of its data set underlying its prediction of utility, in so far as the sound prediction is based upon the antiviral activity of the 2'-C-Me/OH nucleosides. I also find that Idenix's testing responds to Dr Seeger's

contention that the literature recognized that all nucleoside analogues are not necessarily active, or are active with different potency across the family of Flaviviridae viruses.

[280] The sound prediction of Idenix focuses on the similarity of the antiviral activity at the 2' position on the core sugar ring of the 2'-C-Me/OH and 2'-C-Me/F nucleosides. Gilead has only patented two nucleosides, which confirms the essential issue for the sound prediction is with respect to the substituents at the 2' position on the ring.

[281] Gilead also argues that the testing conducted by Idenix was too limited to establish the therapeutic antiviral activity across the breadth of Idenix's claims. This complaint refers once again to the particularly large number of compounds covered by Claim 1, mostly in reference to the 2'(up) position or the number of nucleosides bases in Claims 2 and 3. I have already discussed and dismissed this form of overbreadth argument, based upon the skilled person's more selective interpretation of the '191 Patent. With respect to the large number of bases claimed, it was pointed out to Dr Seeger in cross examination that bases were similarly described in Gilead's '657 Patent.

[282] In summary therefore, apart from issue of the soundness of the prediction based on steric mimicry which is addressed below, I find that Idenix's reliance on the activity demonstrated in the 2'-C-Me/OH cytidine nucleoside to establish therapeutic antiviral activity against the Flaviviridae family, including HCV is sufficient as one aspect of its factual basis for its sound prediction of antiviral activity of HCV by a similar 2'-C-Me/F nucleoside compound.

(3) Sound Prediction of Utility Based on Isosteric Mimicry of Fluorine for a Hydroxyl Group

[283] I find that Gilead has demonstrated that Idenix had no sound line of reasoning to predict the antiviral activity of the 2'-C-ME/F compound based on its hypothesis of "steric mimicry." Professor La Colla, as the only one of four inventors that testified, did not demonstrate that the inventors considered that their prediction based on steric mimicry was anything more than a possibility. The contemporaneous documentation also demonstrates that the inventors believed that the hydroxyl group at the 2' (down) position on the sugar ring was essential. The Court similarly finds Dr Lamarre's opinion of sufficient steric mimicry such as to predict the antiviral activity of the 2'-C-Me/OH compound in the 2'-C-Me/F nucleoside at best, to be an educated guess, not supported by the common general knowledge.

[284] Rather, the Court accepts the testimony of Dr Seeger and others that the 2' down position on the D-Ribose sugar ring was recognized as a highly conserved and selective a position and that fluoride is too unpredictable a substituent regarding potential toxicity to provide a sound basis to conclude that the prediction of antiviral activity from the substitution of a fluorine for the hydroxyl was anything but mere speculation.

(a) *The Inventors' Factual Foundation for the Sound Prediction of Utility*

[285] The '191 Patent lists four inventors, two of whom are chemists (Drs Storer and Gosselin), and two of whom are pharmacologists (Dr Sommadossi and Professor La Colla). Dr Storer and Dr Gosselin were both highly experienced research chemists. Neither was called to testify at trial,

even though Dr Gosselin is still affiliated with Idenix and Dr Storer was a key witness in the affairs of Idenix at the time. Idenix called one inventor to testify, Professor La Colla.

[286] Gilead argues that Professor La Colla had been rehearsed significantly for his testimony at trial and was led extensively during his direct examination. Gilead submits that it is not clear whether Professor La Colla's testimony at trial is truly reflective of what he believed and knew at the relevant time. I agree to some extent with this submission, but conclude its effect is somewhat attenuated by the fact that Professor La Colla was testifying in his second language, aided only from time to time by an interpreter.

[287] Nevertheless, the Court is required to give somewhat diminished weight to Professor La Colla's testimony upon being advised of the singular lack of confidence that Idenix displayed towards him by denying him the opportunity to answer fundamental questions relevant to his role in the invention during the discoveries. In a portion of the discovery transcripts running over several pages, the Court noted that every single question that Gilead asked in an attempt to understand what Professor La Colla considered was his contribution to the invention was refused. Idenix eventually provided answers to these questions; some during the trial and further discovery was contemplated but avoided by answering a "stack" of written questions. When the Court learns from references to a discovery transcript that a party's witness has been kept on a very short leash, it cannot but conclude that it should not have more confidence in the witness's testimony than the party does.

[288] More importantly however, the Court has a number of substantive concerns with Professor La Colla's testimony regarding his sound prediction of antiviral activity in the 2'-C-Me/F nucleosides. Overall, I find that he expressed his sound prediction in terms of a possibility, as opposed to a likelihood or probability. He also seem to confuse the strength of his personal belief that his prediction would be sound, with the necessity of demonstrating by objective evidence that it was a probability.

[289] Specifically, Professor La Colla repeatedly relied on the patent application of Emory University, PCT Publication No. WO 99/43691, entitled "2'-Fluoronucleosides" ["the Emory Patent application"], as did Idenix, as its rationale to support his conclusions of the soundness of his predictions based on steric mimicry. However, the Emory Patent application was speculative in its statements, and more importantly, did not contain any data upon which a prediction of utility for a fluoride substitution of the 2' (down) hydroxyl on the sugar ring could be based.

[290] Professor La Colla summarized his reasoning for his sound prediction of utility of the 2'-C-Me/F compound in the passage as follows:

> THE WITNESS: … And my position was that the compound to be synthesized with the high priority was 2'-methyl (up) and 2'-fluoro (down). The reasons that I had to propose this priority were based on the knowledge of the Emory patent --
>
> …
>
> Emory, Emory University, the Emory patent.
>
> …
>
> THE WITNESS: Where a huge number of 2'-fluoro derivatives were described.

I had two reasons for my personal choice of making 2'-methyl (up), fluoro (down). The first was that in this same patent, it was recognized that fluorine could be the best substituent for an hydroxy group based on the fact that the CO bond is totally similar to the CF bond, that OH and F are acceptor, are hydrogen acceptor groups, and also based on my more general knowledge working with so many chemists, during which we often had the problem of trying the synthesis of new compounds by changing an OH with the fluorine or vice versa. And what was remembered by me was that in most of those cases, the choice was successful because OH and fluoro are so-called bioisosteres, so changing one for the other doesn't change the biological activity of the compound.

The third reason was that in the Emory patent, the antiviral activities claimed for 2'-fluoro compounds were the following: HIV, HBV, HCV, and also they were claimed to have all anti-tumor activity.

So the reason I was interested in this spectrum of activity and in the difference that the 2'-fluoro compounds had in spectrum of activity with respect to our 2'-methyl compounds was the simple question, will substitution of OH (down) with a fluorine give 2'-methyl (up) compounds an additional or a totally new spectrum of activity, that was the question.

But, of course, I had a privileged answer, this was just a scientific curiosity and could be solved only by making that compound.

But the prediction that I could be able to make was that according to my knowledge and reasoning, 2'-methyl (up), 2'-fluoro (down) were going to show the same activity and thus the same spectrum of activity of 2'-methyl (up), 2'-OH (down). This because of said reasons of the bioisostere. So I could not believe that the bioisostere could lead to a total change in the behaviour of the molecule as an inhibitor becoming inhibitor not only of RNA-dependent RNA polymerase but also of reverse transcriptases, also, which are the enzymes HIV and HBV. I couldn't believe that. And I preferred to stick to the hypothesis that due to the bioisosteres and due to the strong, strong conviction that the methyl group could be prevalent in dictating the broad spectrum activity, I could make the *predizione,* the prediction -- .

[Emphasis added]

[291] Professor La Colla indicates that it was a "scientific curiosity that could just be solved by making the compound." The term "just" in this sense I interpret to mean "only." The contingent character of a successful outcome is furthermore consistent with the speculative nature of the language he employs to describe his prediction, i.e. a belief, a question to be answered, a preference or a hypothesis.

[292] Later in direct examination, when attempting to explain his prediction of utility in the face of doubts expressed by others on the Idenix discovery team of chemists at the Maui meeting, he stated:

> And I stood for the fluorine, the fluorine substitution of OH because of the Emory patent that was extremely clear in that respect and also guided other inventors in doing the 2' substitution of an OH with a fluorine.
>
> [Emphasis added]

[293] In fact, the passage in the Emory Patent application with respect to the ability to substitute a fluorine for a hydroxyl, which Idenix argues provides the rationale for its sound prediction, is expressed as a possibility, at best. It reads follows:

> In designing new biologically active nucleosides, there have been a number of attempts to incorporate a fluoro substituent into the carbohydrate ring of the nucleoside. Fluorine has been suggested as a substituent because it might serve as an isopolar and isosteric mimic of a hydroxyl group as the C-F bond length (1.35 A) is so similar to the c-o bond length (1.43 A) and because fluorine is a hydrogen bond acceptor. Fluorine is capable of producing significant electronic changes in a molecule with minimal steric perturbation The substitution of fluorine for another group in a molecule can cause changes in substrate metabolism because of the

> high strength of the C-F bond (116 kcal/mol vs. C-H = 100 kcaUmol).
>
> [Emphasis added]

[294] Later, when confronted with the proof that the Emory Patent application contains no claims of antiviral activity, and indeed no data on anti-HCV or Flaviviridae viruses, Professor La Colla resiled from his "extremely clear" reliance on the Patent, indicating that the Emory Patent application was only useful to establish "a simple chemical fact" that the hydroxyl group and fluorine were isosteres.

[295] He also describes his conclusion as a "guess". The following excerpt is taken from the transcript of his cross-examination:

> Q. Okay. And so this Emory patent has no data on anti HCV or Flaviviridae viruses; correct?
>
> A. Yes. But, the reason I …
>
> Q. Professor
>
> A. The reason I mention this patent
>
> Q. Professor, it was a simple question, you answered it, there is no data in this patent; correct?
>
> A. Yes, but it is not because of data that I mentioned this patent. It is because it is very clearly said that the CO bond is bioisostere to the CF bond, that is enough. I mention this Emory patent <u>just to say</u> that other people already established <u>a simple chemical fact</u>, the bioisostere between OH and fluoro, I didn't apply that. I started from the knowledge of this patent <u>to make any guess</u> on any new and good anti HCV compounds. [pp. 1893-4]
>
> [Emphasis added]

[296] I also note that in reference to his own work as a foundation for his prediction, no examples or description of his involvement in fluorine substitutions or compounds containing a fluorine was provided. This contrasts with the very specific evidence of Dr Stuyver, who claims to have played an important role in Gilead's synthesis of the 2'-C-Me/F compound. Dr Stuyver supports his claim however, by reference to his own work with fluorines, including his role in a patent application by Gilead with a fluorine substitution in the 2' (down) position on the sugar ring. Despite this, his view is that he could not predict antiviral activity in the 2'-C-Me/F compound, which could only be determined by testing.

(b) *Contemporaneous Evidence Relevant to the Prediction of Utility of the 2'-C-Me/F Compound*

[297] The parties presented evidence about a number of events or documents which were relevant to the soundness of the prediction of utility in a 2'-C-Me/F compound, were it synthesized. The Court's analysis will follow these events as they were presented in the arguments of Idenix.

(i) The Discussion at the December 18, 2001 Maui Chemistry Meeting to Synthesize the 2'-C-Me/F Compound

[298] The evidence regarding the Maui chemistry meeting is relevant both to Professor La Colla's prediction and that of the Idenix chemistry group concerning the utility of the 2'-C-Me/F compounds. It was attended by the '191 Patent inventors (Dr Gosselin, Professor La Colla, Dr Sommadossi, Dr Storer), along with Dr Standring and other Idenix discovery chemistry

personnel. A preparatory canvassing the issues and providing some thoughts on them was apparently prepared by either Dr Storer or Dr Gosselin, neither of whom was called to testify.

[299] Idenix refers to passages in the meeting notes that confirm that "[t] he 2'Me substituent is clearly important and appears to make an essential contribution to activity." Dr Lamarre states that the importance of this finding cannot be stressed enough. Dr Seeger disputes this point, indicating antiviral activity is not necessarily an addition of A and B molecules. On the other hand, Idenix does not really dispute that changes of a substituent of any compound can radically change its characteristics. The more relevant evidence on this issue is how the steric similarities of fluorine and the hydroxyl group can form the basis for a sound prediction that the substitution of the fluorine will likely demonstrate antiviral activity.

[300] On this item, the meeting note contains predictions of the likely success of other 2'-C-Me/OH analogues that Idenix was planning to synthesize by replacing the 2' hydroxyl with a range of other substituents. The note clearly reflects a negative prediction of utility for any of the suggested nucleosides to be synthesized with various substituents replacing the 2 hydroxyl group on the sugar ring.

> The 2'-Hydroxyl
>
> For a RNA virus we anticipate that this would be essential but it is worth checking with a few key compounds in the 2'beta-Me C and G series what the exact requirements are particularly since the compounds of interest have a tertiary rather than the usual secondary OH. Analogs lacking the OH will likely confirm its essential nature but should be done. Can the OH be replaced by other groups which will allow H-bond acceptance or donation. A wide range of groups could be of interest including NH3, NHAc, CN, F (although often toxic), CO2H,CONH2, OMe. A priority

> should be to investigate whether the OH can be moved by making CH2OH. If this were possible, it would open up a wide variety of other 5m sugar rings such as those with additional heteroatoms. It is also worth seeing if the hydroxyl position could be accessed from 1' or 3' by CH2OH.
>
> [Emphasis added]

[301] The note presents a pessimistic prediction of any compounds substituting a fluoride for the hydroxyl group, anticipating (1) that hydroxyl "would be essential" and (2) that analogs fabricated "will likely confirm its essential nature". It also described (3) a number of substituents to be considered as replacements for the 2' hydroxyl, of which the fluoride was not the primary compound. The fluoride was however, singled out (4) by being described as "often toxic."

[302] The views expressed in the note appear to be consistent with Gilead's position that in June 2003, the likelihood of utility could not be expected from the 2'-C-Me/F compound, if synthesized.

[303] Professor La Colla testified about the 2 hydroxyl position being "essential" as follows:

> Q. "For a RNA virus, we anticipate that this would be essential."[as read]
>
> What is this referring to?
>
> A. So as the methyl (up) was recognized as fundamental for the anti RNA plus activity, also the 2' hydroxy (down) position was believed to be important by definition because that position makes the nucleoside, the physiologic nucleoside or the ribo analogues, usable for RNA synthesis, the nucleoside, the physiologic nucleosides and the inhibitory nucleoside analogues, in particular those with 2' methyl (up).

> So, perhaps in a short sentence, the point was there will be some possibility to substitute OH with another group allowing hydrogen bonds. And the answer was widely discussed, and everyone came out with its own proposal or way of viewing this problem on the basis of the literature that all of us knew.
>
> So if I may, I can give you which was my position.
>
> And my position was that the compound to be synthesized with the high priority was 2' methyl (up) and 2' fluoro (down).
>
> The reasons that I had to propose this priority were based on the knowledge of the Emory patent.
>
> [Emphasis added]

[304] Professor La Colla's evidence confirms that other Idenix chemists thought that the hydroxyl group would likely prove essential because of its selective role in the RNA. Professor La Colla again cites the Emory Patent application as the basis for his sound prediction. Moreover, in his areas of specialty, Professor La Colla appears to support the conclusions of Dr Seeger that the 2'(down) position in the DNA/RNA ring is unique because of the profound role it plays in physiological biology.

> And there are two types of nucleosides, one with the OH in this position [2' down], physiological nucleosides, and another kind of physiological nucleosides with an H in this position. Because of the lack of the oxygen, these later compounds are called deoxy. The ribo are used to build up RNAs, the deoxy ribo are used to build up DNAs. So between the two compounds, there is a profound difference in terms of what they are useful for. La Colla p. 1460.
>
> [Emphasis added]

(ii) Toxicity - March 7, 2002 – Gemcitabine - Roche Patent Publication - WO 02/18404 [404 Patent]

[305] With respect to the comment that fluoride was often toxic, Professor La Colla understandably could not recall the specific discussions at the Maui meeting. He testified nevertheless, to his disagreement with the comment based on the conclusions he drew from the Emory application described above.

[306] On the matter of toxicity, the Roche 404 Patent, which was referred to in the '191 Patent, was the subject of comment by Dr Lamarre in his reply report. The 404 Patent includes a claim for a di-fluoro nucleoside analogue with the structure of a 2'-F(up), 2'-F(down).

[307] These compounds are similar to the drug Gemcitabine, not to be confused with the gemcitabine process as a means of synthesizing the 2'-C-Me/F compound discussed in the disclosure of synthesis section below. Gemcitabine has a long history in treating cancer, i.e. a drug that kills cells. Dr Seeger explained somewhat this background, as follows:

> [...] originally investigated as a potential antiviral drug -- I expanded on that [in my report]
>
> > -- was determined to be too toxic to be a useful antiviral agent at the time and was developed instead as an anti-cancer agent. It used today against pancreatic cancer and other cancers. (p. 856)

[308] Based on the 404 Patent, Idenix argues that "it was known to the skilled person and to the inventors that fluorine substitutions at the 2'-position were not toxic."

[309] I find this overstates Dr Lamarre's evidence. It was only intended to mitigate the contention that fluorides can be toxic, which he openly acknowledges, as follows:

> [229] The inventors contemplated using a fluorine substitutions despite that it was known that some, but not all compounds containing a fluorine may exhibit toxicity in a host.
>
> [230] Indeed, the inventors were aware of, and included on page 10 of the '191 Patent, the International Publications from Roche (WO 02/18404) and Emory (WO 99/43691), which both disclose that 2'-F(down) can be used to provide antiviral activity in the treatment of hepatitis C.
>
> [Emphasis added]

[310] As noted, the Emory Patent application only discusses the possibility of the Fluorine providing activity against HCV. With respect to the 404 gemcitabine patent, Dr Lamarre does not rely upon the patent as a basis for sound prediction, but only in respect of refuting concerns about toxicity always occurring.

[311] Moreover, Dr Seeger refers to gemcitabine and unsuccessful attempts to place a fluorine at the 2' (down) position on the sugar ring, with a hydroxyl in the (up) position. I cite his evidence at page 863 of his examination in chief, where he notes that the sugar ring with the fluorine (down) and hydroxyl (up) and at the 2' position kills cells:

> Q. At paragraph 224(c), you discuss nucleoside analogues and cytotoxicity. Can you share with the Court the Skilled Virologist's understanding?
>
> A. I alluded yesterday to the historical aspect of drug discovery in reference to nucleoside analogues. I tried to point out that, historically, this field started out in the field of cancer therapy. The goal was to kill cancer cells because they would divide rapidly. Only subsequently was it taken up by virologists. The challenge again is to find the ones that are non toxic. I refer here to a cancer drug. It is called gemcitabine. What is interesting about that drug is that it has a fluoro (down), in the (down) position. It also has a fluoro in the (up) position. What is particularly

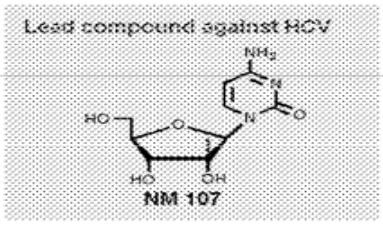
> interesting is, in the 1980s, chemists at Eli Lilly said, "If I have the fluoro(up) and the hydroxyl(down), let's put the fluoro into the (down) position. I might have a great antiviral, a new antiviral." He produced it, and then the virologist told him, "Your drug actually kills cells."
>
> [Emphasis added]

[312] It is not clear that the Roche 404 Patent, even though referenced in the '191 Patent was within the knowledge of Professor La Colla. It was not put to him for comment in an otherwise detailed walk-through of the evidence that supported his prediction of utility of the 2'-C-Me/F compound. Nonetheless, conceding that it is difficult to refute knowledge of the inventors when specifically referenced in the patent, I accept that the inventors were aware of the contents of the 404 patent. This is in addition to considering Dr Seeger's evidence on the toxicological history of modifications at the 2' position described above.

(iii) October 2, 2002, Idenix's Strategy and Progress Meeting

[313] Some 10 months after the Maui meeting, a strategy and progress meeting was held by Idenix. Efforts continued during the intervening period working on analogues of the 2'-C-Me/OH nucleosides without any progress being made in the synthesis of the 2'-C-Me/F compound. The slides prove that not only was the 2'-C fluoride (down) compound not the "lead" or prime target at the time, but experimentation was underway at both the 2' and 3' positions of the sugar ring.

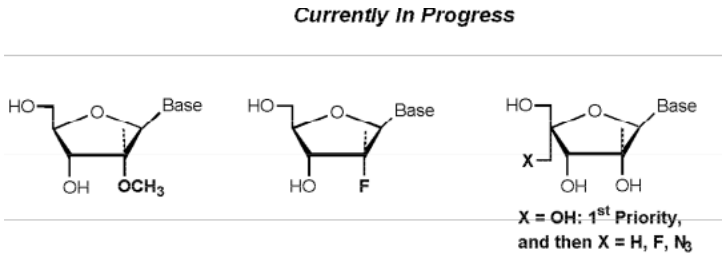
[314] The lack of progress generally being made in synthesizing new 2'-C-Me/OH analogues is evident in the slides used at the meeting, with the slide below showing what little had been accomplished in the interim:



What we know:

- We need a methyl in the 2′ position.
- The methyl should be in the« up » position (NM 272: compound with 2′-C-CH_3 down is inactive).
- We lose activity if we replace 2′-OH down by H (NM 274 is inactive).
- We lose activity if we replace 3′-OH down by H (NM 278 is inactive).

[315] The further portion of the slide at page 10 demonstrates that at this time the 2'-C-Me/F compound was still not the only target composition under development.



[316] Professor La Colla commented on the middle figure [the methyl is inferred at the 2' (up) position of the ribose ring in these figures] which are as follows:

> This compound was my preferred compound at the time, it contains a 2'-methyl (up) and a 2'-fluoro (down). And the fact that the chemists accepted to put it allow the compounds to be synthesized and that they say currently in progress made me very happy but this means that they accepted the whole prediction and the basis for that prediction.

[317] Professor La Colla's statement of a compound being preferred over others is about a triage. In my view, it is not indicative that, if fabricated and tested, the compound would likely demonstrate some utility.

[318] I also do not accept Professor La Colla's conclusion that Idenix's decision to proceed to attempt to synthesize the compound is indicative of it accepting his prediction, or that it is a basis to conclude a likelihood of utility from the compound's possible synthesis.

[319] The evidence in this case suggests strongly that the drug discovery industry adopts a procedure that I would describe as "make-and-test" all candidate compounds that demonstrate some reasonable possibility of success. In other words, drug developers do not require a likely or probable successful outcome for a decision to go forward to synthesize a new compound for testing.

[320] The make-and-test a range of analogue candidates was certainly reflected in the approach outlined in the minutes of the December 2001 Maui meeting. A list of possible substituents at the 2' HO position were targeted for development, even though the minutes evidenced little hope for success.

[321] This methodology was confirmed independently by the evidence of Dr Patterson. He described his reluctance to test for analogues using the Idenix patent application as follows:

> Dr. Schinazi came to us with the news that the compound we called the Idenix compound was active against hepatitis C, he wanted us to consider making analogues. Dr. Watanabe presented some

> analogues of interest, nobody was particularly interested in making that molecule [the fluorine substituent for HO], certainly I wasn't, because we knew that that was made at Idenix and we are certain that Idenix would have covered all the reasonable analogues.
>
> [Emphasis added]

[322] Dr Patterson's description of the certainty of Idenix's predictable behaviour to make and test all reasonable analogues applies to what transpired at the December 2001 meeting in Maui. Fluoride was a reasonable analogue based on a possibility of activity, as were a number of other substituents.

[323] Moreover, if going forward with attempting to synthesize a new drug is evidence of a sound prediction, the test would become circular and tautological. The decision to attempt synthesis would predict utility, as opposed to whether or not the compound can be predicted to be useful, if synthesized.

(iv) November 28, 2002, - Roche Patent Application - No. WO 02/094289 [289]

[324] The further Roche '289 Patent Application describes antiviral activity in a compound described as 2'-deoxy-2'-fluorocytidine with a single fluoro at the 2' (down) position on the sugar ring. The first and only reference to the Roche '289 Patent Application occurred during examination in chief of Dr Stuyver. Dr Stuyver pointed out that the Roche publication predated his unpublished Pharmasset patent application US 60357411. It described a similar Pharmasset compound [PSI-0262], which established antiviral activity for the same compound by testing using the HCV replicon.

[325] Although published in 2002, Patent Application ‘289 was not referenced in the ‘191 Patent. None of the experts or other witnesses made mention of it in their reports or testimony. It was not brought to the attention of Professor La Colla, nor discussed during his testimony. I am not satisfied that the 289 Patent was known to the inventors of the ‘191 Patent on the filing date. Therefore, it is not considered as forming part of their knowledge for the purpose of determining the utility of the ‘191 Patent.

(v) April 1-4, 2003 - Summary of an Idenix internal Scientific Update Course on Fluorination

[326] Idenix claims that it was clear that the prediction for using fluorine in place of the hydroxyl group was well known within Idenix based upon information received from a Scientific Update Course on Fluorination. Dr Griffon and Audrey Chappe attended this course for the purpose of assisting in the synthesis of the 2’-C-Me/F nucleoside. They prepared a report that was later referenced to have been received by email-dated more than two months later on June 9, 2003 from Dr Storer to Moussa Chadhari attaching the Report. According to Dr Lamarre this report shows that the prediction for using fluorine in place of the hydroxyl group was well known within Idenix, when at page 3 of the Summary, it discusses that replacing the hydroxyl group with a fluorine would act similarly with the hydrogen-bond donor.

[327] The report was not referred to by Professor La Colla, concerning information received two weeks prior to the filing of the Patent application, while Dr Storer did not testify. It appears to report on an opinion of one of the instructors at the program regarding synthesis, not the pharmaceutical properties of a 2’-C-Me/F nucleosides. In that regard, it appears to be no more

than the statement in the Emory Patent application, only more generalized to physical properties and of even less certain and authoritative a source. It obviously does not deal with other issues such as toxicity problems associated with fluorine. I cannot attribute much weight to this evidence given its source and the manner by which the evidence has been presented to the Court.

(c) *The Evidence of the Experts*

(i) Dr Lamarre's Opinion on Steric Mimicry

[328] Dr Lamarre was Idenix's expert who it was pointed out was the only expert qualified to opine on both virology and isosteric propreties of atoms and compounds. His expert opinion in this regard was not challenged on cross-examination.

[329] Dr Lamarre's general statement on the predictive outcome of fluorine as a substitute for a hydroxyl group is contained at para 172 of his report as follows:

> By June 27, 2003, the skilled person would also have known that when designing new biologically active nucleosides by a substrate-based Rational Drug Design, <u>often</u> hydroxyl (OH) groups of the nucleoside can be replaced by fluorine (F) atoms.
>
> [Emphasis added]

[330] With respect, the statement is not as strong as was needed to predict a likelihood of antiviral activity in the 2'-C-Me/F nucleosides. The term "often" is not a scalable measure above or below a probability of expectation. It appears to be the type of compromise term sometimes reached where there may be unwillingness to state a proposition in as clear a fashion as is

required, but is as far as the expert is willing to go. In any event, the opinion is at best ambiguous as a backhand sort of support of predictability, which is not what would be expected from an expert supporting a sound prediction of steric mimicry.

[331] The statement is also not specific to the issue of utility, instead being generalized to a situation of "when designing new biologically active nucleosides." This issue here is not about designing new nucleosides. There was no rationale design process followed by Idenix. The evidence demonstrates that Idenix proceeded exactly as Dr Patterson said they would, namely trying to synthesize any number of 2'-C-Me/OH analogues with the view to testing them for antiviral activity, with no likelihood of success as they set off to do so.

[332] The heart of Dr Lamarre's opinion on steric mimicry is contained in his para 173 of his report citing a portion of the introduction of a 1998 article by Professor Jeffrey McAtee and others entitled *A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2'-Fluoronucleosides* in the Journal of Organic Chemistry, volume 63, pp. 2161-2167.

[333] As the Emory Patent application relied on the *McAtee* article for the propositions it cites regarding steric mimicry, the *McAtee* article appears central to Idenix's case on this issue. Apart from this article, no other literature was cited for fluorine substitutions for the hydroxyl group at the 2 position on the sugar ring.

[334] Dr Lamarre cited the following passage from the article, with his emphasis and footnotes in square brackets, in support of his conclusions:

> Fluorine may also serve as an isopolar and isosteric mimic of a hydroxyl group since the C - F bond length (1.35 Å) is so similar to the C - O bond length (1.43 Å) and because fluorine is a hydrogen-bond acceptor. The ability of fluorine to mimic a hydroxyl group makes this atom uniquely suited to nucleoside analogues as a replacement of OH in the sugar portion of a nucleoside. In addition to our long standing interest in the synthesis of novel nucleoside analogues, [3] we were interested in incorporating an R -fluorine substituent at the 2′ position of the sugar ring for several reasons. First, the electronegativity of fluorine should stabilize the anomeric bond and suppress a significant pathway of in vivo decomposition, [4] thereby improving the acid stability of the nucleoside (Scheme 1).
>
> Second, hydroxyl groups often serve as "handles" for the first step in oxidative degradation of biomolecules in vivo. [2c] By replacing OH with F, it is possible to create a ribo-like sugar that has a substituent at the 2′ position sterically and electronically similar to a hydroxyl group, but which cannot undergo oxidative catabolism.
>
> [Emphasis of Dr Lamarre]

[335] While Gilead did not cross examine Dr Lamarre on this evidence, the Court is entitled to make a few observations on some of the obvious aspects of the *McAtee* article. First, the proposition of substituting a fluorine for a hydroxyl in the article is described in terms of possibilities: "Fluorine may also serve as an isopolar and isosteric mimic of a hydroxyl group" and "[b] y replacing OH with F, it is possible to create a ribo-like sugar."

[336] Second, the passage from the introduction to the article cited by Dr Lamarre bears no relation to the purpose of the study. The study was reporting on unsuccessful attempts to

synthesize 2' fluoro (down) nucleosides, because they were lacking in availability, as was described in the passage just after that quoted by Dr Lamarre, as follows:

> Finally, few of the ribo or (down) 2′-fluoro nucleoside derivatives were known. Therefore, we endeavored to find a simple and efficient synthesis of these compounds in order to generate novel analogues for biological evaluation.

[337] The authors' goal was not met in terms of synthesizing fluorinated nucleosides for biological evaluation, inasmuch as only 2 of the 10 compounds synthesized proved active and they turned out to be toxic. ("[u] nfortunately, only compounds 15b and 18b showed any antiviral activity against HIV, but they exhibited toxicity as well, indicating that the compounds are nonselective inhibitors of HIV" p. 2163). This failed experiment would seem to speak to the opposite of any sound prediction of antiviral activity, besides negating the common general knowledge in support of the predictability of either activity or non-toxicity of 2' fluoro (down) nucleosides.

[338] More importantly, there are also no footnotes supporting the portion of the article cited by Dr Lamarre in his report, although other statements in the comment are footnoted. From that point of apparently no supporting literature, one would have thought that between 1998 and 2003 the literature and texts would have included examples of fluorines "mimicking" the 2' (down) hydroxyl. I can find no basis therefore, to consider sufficient evidence was provided to support any the propositions on steric mimicry of fluorine likely being able to replace a hydroxyl as representing the common general knowledge or seriously supported in the literature.

[339] The Court also does not need expert opinions to advise it that if the *McAtee* article is the best that Dr Lamarre could come up with as the basis for his sound prediction, this speaks legions for the hypothetical nature of his proposition. It also would explain why, as a scientist, he appears reluctant to make a stronger statement on the probability of the prediction of utility for the 2'-C-Me/F nucleosides.

[340] Finally, I should comment on Dr Lamarre's testimony that introduced a factor, namely described as the "Structure Activity Relationship" or SAR, which appears relevant to the mimicry argument, but is not discussed in his report. I quote a fairly long passage from the transcript of Dr Lamarre's introduction of this concept into the evidence when discussing steric mimicry:

> Q. So paragraph 171, you talk about "given this foundation", what is your view and, of what the skilled person would gather, starting with the foundation that was known by the inventors?
>
> A. So the inventors were, I guess, quite knowledgeable about this 2' position, the methyl "up" being a major part of the invention, and the OH (down), which is in the natural substrate, they knew that this, the enzyme is quite -- you know, the enzyme is able to make a difference at that position when there is a hydrogen at that position versus OH. The hydrogen being in a deoxyribose nucleotides and being used for DNA, for example.
>
> So clearly, the OH is an important group at that position.
>
> MR. JUSTICE ANNIS: I am not following that, I would like to understand that better. I haven't heard anybody talk about the H and the OH yet -- H is the DNA, right, OH is for the --
>
> THE WITNESS: Correct. We have discussed the ribonucleotides is the OH, at that position. And in the deoxy --
>
> MR. JUSTICE ANNIS: It is H.

THE WITNESS: It is an H, yes. And these substrates are used for DNA synthesis, and now we are talking virus that has an RNA genome. So even if there is in the cell a lot of deoxy nucleotide pull

MR. JUSTICE ANNIS: But would methyl H, did it work, did it have antiviral activity?

THE WITNESS: The H?

MR. JUSTICE ANNIS: Methyl H, yes.

THE WITNESS: No.

MR. JUSTICE ANNIS: It doesn't work at all?

THE WITNESS: No, that is what I was getting at, the enzyme is really able to discriminate in between the OH and hydrogens just because it has an RNA genome, and it will not use the H (down), which is, you know, there is a lot of pull in the cells, so it is able to make that discrimination between the two.

So the 2' position is very, you know, there is what we call limited SAR in that position.

MR. JUSTICE ANNIS: What is SAR?

THE WITNESS: Structure activity relationship. When the chemists are exploring --

MR. JUSTICE ANNIS: Structure?

THE WITNESS: Structure activity relationship. That is a term that we use in medicinal chemistry.

So at that position, the fluorine, that is the importance for this patent, the fluorine is considered as a very good isosteric mimic because of the nature of the fluorine, because of the size of that atom which is close to the, has a similar size than the OH, and to the fact that this fluorine atom, when attached to the carbons at that 2' position, the length of this C-F is similar to the length of a COH or the CO, hydrogens.

So you have an atom of similar size at the proper place, at this place, which is a good mimic for that type of inhibitor.

[Emphasis added]

[341] The analytical concept of the structure activity relationship appears to be relevant to this case, or at least Idenix's argument based on mimicry of the structure so as to produce activity by the analog nucleoside.

[342] It is from this passage that I made the above conclusion that Dr Lamarre agreed with Dr Seeger's general proposition that the 2' (down) position on the RNA nucleoside is highly selective. I believe that this statement was also supported by Dr Lamarre's references to their being "a lot of pull" and that "this is what we call limited SAR in that position."

[343] In other words, his testimony appears to be that the 2' (down) position on the ribose ring is highly selective to structure, which explains why fluorine would have the best chance of replacing the hydroxyl and still showing activity - despite the limited SAR and pull in that position.

[344] I found Dr Lamarre to be a very fair witness. I am satisfied that he did his best in giving his opinion, but was careful not to overreach. He knew he could not go any further and left it at that. That said, I do not find in the circumstances however, based on his own carefully nuanced evidence, that he makes the case of antiviral activity being a probability from a fluorine substitution of the 2' (down) hydroxyl on the ribose ring.

[345] To convince the Court more evidence was needed from the literature and perhaps more evidence regarding the structure activity relationship concept. If it is common ground that the 2' (down) position on the ribose ring has "limited SAR", it suggests that there are comparative

measures of "pull" that may be used to measure activity. In any event, that is speculation, but the lack of probative evidence to support Idenix's claims is not.

[346] In addition, the *McAtee* article appears to support the conclusion that one still has to worry about toxicity, even if the nucleoside analogue proves active, as was the comment to the same effect made at the Idenix Maui meeting. The fact that Idenix had to rely upon what appears frankly to be an unhelpful article in 2009 to make an argument based on predictable steric mimicry in 2003, is indicative of the absence of any solid documentation, and therefore experimental data underpinning a claim that utility would be probable as a result of a fluorine substitution of the hydroxyl in the 2'-C-Me/OH nucleoside.

[347] That is not unexpected for a compound, yet to be invented, that Idenix is predicting can fool a highly selective and essential chemical position in medical science, to achieve therapeutic activity against a most pernicious virus.

(ii) Dr Seeger's Opinion on the Conserved Nature of the 2' (down) Hydroxyl Group on the Sugar Ring

[348] Where I find Dr Lamarre's evidence to fall short of the requirement to establish a sound prediction, (which is not Idenix's legal onus), I find that Dr Seeger's opinions, already presaged by the passages cited from Dr Lamarre's testimony, discharge Gilead's onus in referencing the selectivity of the 2' (down) hydroxyl group in distinguishing between RNA and DNA analogues.

[349] Dr Seeger's evidence basically comes down to predicting any change in the hydroxyl group as "a big change at an important place on the RNA." His evidence is probably best highlighted in the cross-examination conducted challenging some of his views, which I find did not succeed in attaining its objective, but not for lack of trying.

[350] Dr Seeger points out that any change to any compound will change its properties. Starting with a methyl (up) and the hydroxyl (down) that provide the activity in the 2'-C-Me/OH nucleoside does not change that.

> Q. They have advanced their knowledge with respect to that position in a compound that has 2' methyl (up)?
>
> A. No. The hydroxyl is there. They leave the hydroxyl natural. The expectation is in fact, we discussed it this morning a change there will probably be dramatic or it will be profound. Nevertheless, we can try. Why not? Let's figure it out. Really, the methyl is methyl(up). That is the methyl(up), and we are talking about the hydroxyl (down) here. The hydroxyl is still here. It still has the structure of the RNA, if you wish with that methyl(up).
>
> Q. That is ground zero for them. It is not any given compound. You starting with methyl(up) and OH(down). You have a body of knowledge with respect to that?
>
> A. Here it is not a matter of addition. In other words, you are not saying, "Now I am having A here, and then I go from A plus B equals this." Every molecule you make has now its own new property. If you change one atom, it has an influence on the whole molecule; right? That is why everyone is new whether you start with a methyl or with the natural base or whatever you do. You are creating something new.
>
> [Emphasis added]

[351] Dr Damha said much the same thing, including the variability that fluorine can introduce into compounds (page 2026-7):

> THE WITNESS: So when you replace an OH group with fluorine, OH is a polar functional group. Fluorine is less polar, yet is electronegative like oxygens. So for that reason, when you do a replacement of an OH to a fluoro, you are kind of keeping the same type of electronegativity of the group, but you are altering it slightly to endow the molecules with different properties.
>
> And so I give references to the fact that many fluorinated organic compounds exhibit interesting properties, as has been shown the case for many type of molecule, steroids, nucleoside.

[352] Justice Michael Phelan noted in *Alcon Canada Inc v Cobalt Pharmaceuticals Company, 2014 FC 462 [Alcon/moxifloxacin]* at para 160 that even small changes can have profound effects on activity.

> [160] The importance of the stereochemistry of the Claim 12 compounds was discussed by a number of experts. It appears to be common ground that even small changes to a molecule can have profound effects on activity.
>
> [Emphasis added]

[353] Dr Seeger's view is that that the change at the hydroxyl group is a "big change at an important site" [Emphasis added], the point being that you just do not know the nature of its impact:

> A. The polymerase as a family, they have this distinction. There are structural indications of why it is so, and I could expand on it. I won't because it will take some time. That is exactly the point, this distinction. That is why, when you change this residue,

> you don't know whether it works at all, whether it goes into RNA, or whether it goes into DNA. It must have an impact.
>
> …
>
> Q. This is your conclusion reading this cite?
>
> A. No, that is not the conclusion from me. Again, I am not manipulating the building blocks of nature; right? There are just two kinds. The only distinction is that hydroxyl. If you go and change that chemically, this must have an impact.
>
> …
>
> Q. Can we just look at the next paragraph of your affidavit where you say it can have a significant impact. You are saying, "modifications in the 2' position can have a significant impact," not must?
>
> A. I can say "can." I can say "must." I just submit, it is the most conserved region. It is an important distinction. You change it, the expectation is it must have an impact. It can. It must. You name it. This is a big change at the very important site.
>
> [Emphasis added]

[354] Dr Seeger's summary opinion was that the results of a change at the 2 hydroxyl position is unpredictable, the only way to find out is by testing:

> Q. Thank you, Dr Seeger. Given the sensitivity that exists at the sugar ring and in particular, as you have mentioned, at the 2' position, what would the Skilled Virologist's understanding be as to whether a factual basis or a Sound Prediction could be made if a modification is made to the sugar ring?
>
> A. As I said, there is no way you can make any prediction. You have to do the experiment and find out what the activity of that particular compound is.

(iii) Dr Patterson's Opinion on Predictability of Activity

[355] Idenix did not hesitate to seek opinions on the issue of the prediction of activity from Dr Patterson, although not called as an expert and without notice in its witness statement. Gilead objected to this evidence, which I nevertheless allowed. I concluded that Dr Patterson's evidence, like that of Dr Stuyver, objected to later by Idenix, was relevant coming from someone who was an active participant in the historical events, as opposed to experts opining on those events a decade later.

[356] The important passages of Dr Patterson's evidence are, as follows:

> Q. And why were you reasonably optimistic?
>
> A. Well, we have replaced a hydroxyl with the fluorine. They are similar in size, shape, they have similar electronic structure, so it's, you know, if, you know, I think it's reasonable to expect that it would be active.
>
> [...]
>
> Q. And other people substituted hydroxyl for fluoro?
>
> A. Yes. Dr Watanabe was pretty well known for doing that.
>
> Q. And why would that have been done?
>
> MR. MARKWELL: Objection [already ruled upon].
>
> THE WITNESS: Well, we like to talk about isosteres in medicinal chemistry. I prefer the term "bioisosteres", but it's a similar concept. So if you have a biological molecule, let's say a peptide or an amide, we have these structures that are similar, though not necessarily identical, but similar in size, shape, and electronics, and very often, not always but very often, they are accepted by the biological systems. [p. 1780]

[357] Idenix also relies upon Dr Patterson's testimony that fluorine in the 2' (down) position would be his "number one pick" for developing an analogue of the Idenix Compound, which was how Pharmasset described the starting material. I point out that a number one pick of a chemical reaction is not evidence of a sound prediction, but I also consider this aspect of his testimony, which is similar to that of Dr Damha when discussing the sufficiency of disclosure of synthesis.

[358] Dr Patterson's evidence on the prediction of utility was more nuanced than simply argued by Idenix. He presented a long discourse on the problems with predicting outcomes of nucleoside analogues generally.

> THE WITNESS: So in that context, I was optimistic, but I did not share his absolute certainty.
>
> MR. JUSTICE ANNIS: Because there is some problem with nucleosides?
>
> THE WITNESS: Yes, sir, a nucleoside has to be a substrate of multiple enzyme systems, so it's very difficult to predict whether a particular nucleoside is active. They are, in effect, prodrugs, so they have to be transported, usually transported into cell and then, you know, converted to the monophosphate, then the diphosphate, then the triphosphate, with some exceptions. And it is that triphosphate that is the active metabolite. So because of all these enzyme systems, it is not like you just hit a single system where it's much easier to predict, right.
>
> …
>
> THE WITNESS: Right, so one of the ways that we medicinal chemists suspect whether a molecule, an active molecule works against a single target or multiple targets is we ask, <u>does that particular molecule follow a discernible structure activity relationship</u>? Can we, <u>with a few actives</u>, predict the activity of, you know, analogues, <u>will it be more or less active</u>?
>
> …

> THE WITNESS: Nucleosides rarely do that. And that is because they have to act, they have to be activated by no fewer than three enzymes to get the active metabolite, and that active metabolite then has to be a substrate for the viral polymerase. So in that context I was optimistic but I did not share his absolute certainty.
>
> [Emphasis added]

[359] Dr Patterson also makes an admission of sort of the medical chemist's blinkered thinking in his testimony as follows:

> I frequently tell people what organic chemists understand best is structure, and some people say organic chemists only understand structure, and I think that is what we need are some structures on a board or something.

[360] There was very little evidence relating to the 2'-C-Me/OH molecule that one could say with confidence that there was a discernible structure activity relationship, which subject was hardly mentioned in any of the witness's testimony. Nor were there any "actives" to speak of to predict the utility of the 2'-C-Me/F compound.

[361] However, the main difficulty I have with Dr Patterson's opinion evidence was that it misses the point of Dr Seeger's evidence about the selectivity of the 2' (down) position on the RNA and DNA and related issue of the toxicity of fluorines. Dr Patterson spoke of the difficulties of predicting outcomes in respect of nucleosides generally. This fails to take into consideration to what extent his optimism should have been attenuated when applied to a substitution at the most conserved and selective position in chemical biology. It also fails to

consider the issue of fluorine often being toxic. In fairness, he was not called to offer these opinions.

(iv) Dr Stuyver on the Unpredictability of Toxicity and Activity of the Fluorine Compound

[362] Dr Stuyver, called by Idenix also provided an opinion in cross-examination on the predictability of antiviral activity of the new compound with the fluorine at the 2' (down) position before its synthesis, as follows:

> Q. Would you agree that if you take the structure that is Structure Number 3 on this page here, when you set off on a synthesis route, who can tell from looking toward this structure that this is going to act as an antimetabolite [that may have a toxic effect on cells]?
>
> A. Let me make sure I understand your question. So you ask me if from looking to this molecule, this structure, whether you can make a prediction whether it is an antimetabolite; is that your question?
>
> Q. Yes.
>
> A. You can't.
>
> Q. Is it your view that in the beginning of 2003, looking at this structure, you can tell that the drug is going to be a candidate direct antiviral?
>
> A. But in the beginning of 2003, this was not a drug, right. And in 2003 you make, and in 2002, you make plans, hypothesis, you synthesis, and you test. But you cannot say this is -- <u>at that moment, you cannot say this is going to be antiviral or antimetabolite</u>. [PP 3998 – 3999]
>
> [Emphasis added]

[363] Idenix quotes Dr Stuyver from an article in 2004, after the 2'-C-Me/F nucleosides had been synthesized, noting that "fluorine is isosteric with a hydroxyl group" and that antiviral activity from the substitution is anticipated as follows:

> Since FdC [the invention] is an analogue of cytidine and fluorine is isosteric with a hydroxyl group, it is anticipated that its 5'triphosphate would inhibit the viral NS5B RNA-dependent RNA polymerase.

[364] If this statement is intended to show that Dr Stuyver has resiled from the inability to predict the antiviral outcome prior to testing on the new 2'-C-Me/F nucleoside, I conclude that it proves the foresight of hindsight when speaking publicly about an invention claimed to have been invented by the speaker, and who also claims to have directed the chemist inventor to make the compound. I prefer to attribute the meaning of "educated guess" to the term "anticipated" from the passage quoted. This article was not put to Dr Stuyver for confirmation purposes, although called as Idenix's witness and having provided the opinion above on the unpredictability of the outcome of the utility of the new compounds without testing.

(d) *The Cytotoxicty of Fluorines*

[365] I also find that there was no distinction in the inability to predict whether a new fluorine compound would be toxic at either the 2' (up) or (down) position on the RNA nucleoside analogue. In this respect, Gilead also points out that the inventors were aware in a companion patent filed also on the same date as the '191 Patent of June 23, 2003 that there had been a recent death in trials of a compound described as FIAU. It was compound with a fluoro in the 2' of

position. This fact was not contained in the '191 Patent. Professor La Colla was aware of toxicity concerns with FIAU and other 2'-fluoro compounds.

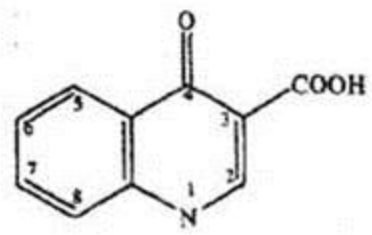
[366] Given the evidence of the unpredictability of fluoro compounds exhibiting toxicity, I conclude that this was another factor making it impossible to predict whether a new fluoro compound will exhibit toxicity without testing.

(e) *Alcon/moxifloxacin*

[367] As a final issue, I am required to consider the recent decision of Justice Phelan in *Alcon/moxifloxacin* which Idenix claims applies to the facts in this case and should be followed. I disagree. The facts in *Alcon/moxifloxacin* are highly distinguishable from the novel circumstances presented in this matter.

[368] The 114 Patent claimed a class of quinolone compounds, which includes moxifloxacin, characterized by a fused pyrrolidine bicycle at the C-7 position of the quinolone ring.

[369] The core structure of the quinolones is:



[370] The Applicant claimed that the utility of a compound substituting a methyl for a fluorine compound at the C-8 position could be soundly predicted, although the compound had not been synthesized at the time of filing.

[371] The Applicant relied on the common general knowledge that compounds with a methoxy group at the C-8 position were active. This included European Patent Application No 0 241 206 [Sankyo] and European Patent 0 230 295 A2 [Kyorin] as examples of prior art teaching that compounds with a methoxy group at the C-8 position had good activity. The Court found that the inventors therefore, had a sound basis to predict that substituting a methoxy group at that position for the fluorine in the example cited in the Patent would either enhance or not hinder the high antibacterial activity demonstrated in the example.

[372] The most obvious distinction between *Alcon/moxifloxacin* and this matter is that compounds with methyl at the C-8 position had previously been synthesized and shown active by testing. Obviously, neither Idenix, nor any other drug discovery organization possessed testing data on the 2'-C-Me/F nucleosides or a comparable compound with activity of a fluorine at the 2' (down) position at the time of filing, except Gilead, which was not otherwise known at the time.

[373] Another important distinction between the two cases is that there is no comparing the predictive outcome from a highly substituted core compound in existence since 1960, with the first ever substitution of an element known for its toxicity as a replacement for the most selective and highly conserved group in a biological compound.

[374] In *Alcon/moxifloxacin* the Court was dealing with a core compound whose usefulness had been demonstrated in administration to humans since 1960. It was not an entirely new compound like the 2'-C-Me/OH nucleoside that was just entering the first level of clinical trials, whose utility remained to be fully established (and which was eventually withdrawn). This case is quite distinguishable from that in *Alcon/moxifloxacin*.

(f) *The Last Word to Wellcome/AZT*

[375] I find Justice Binnie's comments in *Wellcome/AZT* at paras 63 and 64 highly apposite in noting the distinction between the predictability of chemical reactions and the predictability of the pharmacological effects, and thus of the pharmacological utility of new substances:

> 63 Our Federal Court of Appeal subsequently applied the doctrine of "sound prediction" in the context of a patent for a pharmaceutical product in *Ciba-Geigy AG v. Commissioner of Patents* (1982), 65 C.P.R. (2d) 73. In that case, Thurlow C.J. upheld product and process claims in relation to certain "new amines" useful in cardiac treatment, but added the qualification that what is predictable chemically may not be predictable pharmacologically, at p. 77:
>
> > The predictability of a particular result seems to me to be essentially a question of fact, though in some situations it may be a matter of common knowledge. With respect to chemical reactions it is apparent from the foregoing that knowledge in the chemical art as to the predictability of chemical reactions has advanced considerably in the 50 years since *Chipman Chemicals Ltd. v. Fairview Chemical Co. Ltd.*, [1932] Ex. C.R. 107, was decided. <u>The predictability of chemical reactions should not, however, be confused with predictability of the pharmacological effects and thus of the pharmacological utility of new substances.</u>

> [Justice Binnie's emphasis]
>
> 64 Thurlow C.J. was not laying down as a matter of law that pharmacological utility cannot be predicted because, as he said, predictability is "essentially a question of fact". It will depend on the evidence. In *Beecham Group Ltd. v. Bristol Laboratories International S.A.*, [1978] R.P.C. 521 (H.L.), for example, claims in respect of a semi-synthetic penicillin were invalidated as being little more than an announcement of a research project (p. 570). In that case, on the facts, Lord Diplock stated at p. 579:
>
> > The evidence in the instant case is overwhelming that it is not yet possible to predict in advance what, if any, special therapeutic advantages will be possessed by a penicillin made to a particular formula. The only way to find out is to make it and discover what its therapeutic characteristics are by conducting extensive tests upon it *in vitro* and *in vivo*.

[376] I find the evidence bordering on overwhelming that it would not have been possible to soundly predict in advance the therapeutic advantages of substituting a fluoride for the hydroxyl on the 2'-C-Me/OH nucleoside. I agree with Drs Seeger and Stuyver, and implicitly, the Idenix chemists at their Maui meeting that the only way to find the 2'-C-Me/F nucleoside's therapeutic value was to make it and discover what its therapeutic characteristics are by reliable and valid testing. This is what Gilead did, and Idenix did not.

(4) Conclusion on the Sound Prediction of Utility of the 2'-C-Me/F Compound

[377] For all the reasons above, I find that Gilead has demonstrated that Idenix could not demonstrate, nor soundly predict as an inferred fact or *prima facie* reasonable inference, the utility of the 2'-C-Me/F nucleoside on June 27, 2003 as an effective treatment of HCV.

C. *Disclosure of Sound Predictions of Utility in the Patent*

(1) The Requirement to Disclose Utility for New Use Inventions

[378] The parties disagree on the requirement stated in the jurisprudence to disclose the factual basis and line of reasoning for the sound prediction in the patent. Idenix, relying on the analysis of Justice Rennie, as he then was, in *AstraZeneca/Pregabalin* limits the disclosure requirement of soundly predicted utility to "new use" inventions.

[379] Gilead, argues that there remains some wiggle room in *AstraZeneca/Pregabalin* and the subsequent Court of Appeal decision of *Bell Helicopter Textron Canada Limitée v Eurocopter Société*, 2013 FCA 219 [*Bell Helicopter*]. I disagree that Justice Rennies's reasoning leaves much to the imagination on the necessity to disclose the utility for a "new compound" invention. He states at para 158 of *AstraZeneca/Pregabalin* that he was "compelled [my emphasis] to follow the Supreme Court's remarks in Teva sildenafil and the interpretation of *Wellcome/AZT* endorsed by Justice Gauthier in *Apotex Inc v Sanofi-Aventis, 2013 FCA 186 (CanLII), para 42 [Sanofi-Aventis Plavix]).*"

[380] I adopt Justice Rennie's reasoning, which I find properly reflects the binding jurisprudence on our Court. Accordingly, as the '191 Patent relates to a sound prediction of a new composition, there is no utility disclosure requirement. I assume that this exemption from disclosure applies both to the factual basis and the line of reasoning.

[381] Despite my conclusion that Idenix is not required to disclose the factual basis for its sound prediction of utility, I nevertheless, am required to determine whether its disclosure was sufficient should the law on this issue change in the future, which admittedly is contentious: *Pfizer Canada Inc v Pharmascience*, 2013 FC 120 at para 157; *AstraZeneca/Pregabalin* (which is under appeal).

(2) Common General Knowledge in Disclosure of Utility

[382] The jurisprudence has recognized a dispensation from disclosure of all or elements of a sound prediction if it is a matter of common general knowledge. This applies to both disclosure of the factual basis and the line of reasoning. The law was described by Justice Noel, as he then was, in *Bell Helicopter* at paras 153-155, as follows:

> [153] Where the factual basis can be found in scientifically accepted laws or principles or in information forming part of the common general knowledge of the skilled person, then no disclosure of such factual basis may be required in the specification. On the other hand, where the factual basis is reliant on data which does not form part of the common general knowledge, then disclosure in the specification may indeed be required to support a sound prediction.
>
> [154] As noted in the Manual of Patent Office Practice issued by the Canadian Patent Office (at paras 12.08.04b and 12.08.04c), since a sound line of reasoning is directed to a skilled person, those elements of the doctrine of sound prediction that would be self-evident to that person in view of the common general knowledge need not be explicitly disclosed in the specification. The soundness of a line of reasoning can also be effectively assessed by asking whether the skilled person would accept the logic presented in the specification and derive from the sound prediction as a whole an expectation that the invention will provide the promised utility.

> [155] As a result, where the sound prediction is based on knowledge forming part of the common general knowledge and on a line of reasoning which would be apparent to the skilled person (which is often the case in mechanical inventions), the requirements of disclosure may readily be met by simply describing the invention in sufficient detail such that it can be practiced. A contextual approach is thus appropriate in each case.

(3) Is the Disclosure by Idenix Adequate?

[383] Apart from any reliance on the common general knowledge and assuming disclosure is required, the issue here to be considered is whether the '191 Patent describes a factual basis and sound line of reasoning to soundly predict antiviral activity in the 2'-C-Me/F nucleoside. As Gilead concentrated on the disclosure of the factual basis of testing the 2'-C-Me/OH nucleosides being surrogates of HCV, I will limit my comments to this issue as well. It is further narrowed to the question of Idenix disclosing its testing data on the 2'-C-Me/OH nucleoside as part of its factual basis, as well its factual basis to claim that the BVDV and other assays may be used as surrogates for demonstrating antiviral activity against HCV.

(a) *Disclosure of Factual Basis of Idenix's Testing Data on the Me/OH Compound*

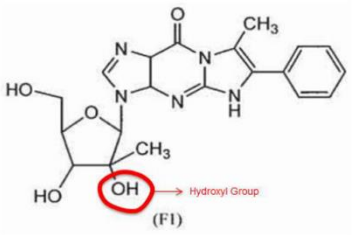
[384] Idenix claims it disclosed testing data in the '191 patent in Examples 25 and 26 and by reference to its prior PCT applications Nos. WO 01/09121 [Application '121] and WO 01/92282 [Application '282].

(i) Examples 25 & 26

[385] Example 25: Example 25, while it describes various tests including those that could be used to assess the antiviral activity of the compound against a specific virus, contains no data.

[386] Example 26: Example 26 discloses experimental data in respect of Compound F. Gilead argues that Compound F is not within the scope of the claims and that the data is flawed.

[387] The structure of Compound F is not disclosed in the '191 Patent. Moreover, Idenix's claims are based upon Compounds NM107, NM283, which were not publicly disclosed. Compound F is also not the same compound used by Idenix as the basis for its claims in the '191 Patent. Compound F has an unnatural and highly modified tricyclic base. The structures of Compound F in comparison with that of Idenix's NM 107 compound are depicted below. The data from Compound F is not properly disclosed and is not relevant therefore to the 2'-C-Me/F nucleoside.



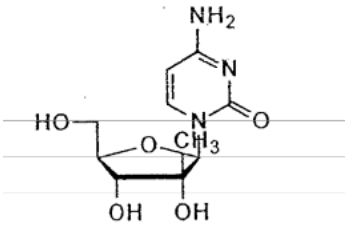


Figure 5: Structure of Compound F

[388] The data in Example 26 on Compound F was displayed in two tables, one above the other, as follows:

CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
F	>100	>100	>100	43	37	49	39	60	2

CC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

	CC_{50}							
Compound		BVDV	YFV	DENV 2	WNV	CVB-2	Sb-1	REO
F	>100	10	2.5	1.3	1	37	43	2

[389] There are obvious problems with the tables. While the chemical formula is provided, there is no structure for the compound necessary to understand it stereochemical properties around which structure activity relationships apply.

[390] The EC50 values in the bottom row of the first table are said to reflect assays done in quadruplicate or triplicate. They are expressed in single numbers when there should be averages or a standard deviation. Moreover, the table does not describe which assay was used. The specification describes two different assays by which a compound's EC 50 could be calculated that measure different aspects of antiviral activity. The skilled virologist would want to know which assay was conducted in order to be able to properly interpret the data presented. Dr Seeger testified that in the absence of experimental details, there was little useful information provided in the first table. I accept his testimony on these points.

[391] The second table contains no headings in the top row. EC 50 values are repeated in the table already referred to in the first table, where the second table is said to relate to CC 50 values on toxicity. Cell line information is absent, which is significant as values differ depending upon cell lines. Dr Seeger concludes that the tables in Example 26 do not clearly show any corresponding cytotoxicity data in respect of the cell lines that were used in the antiviral activity assays. It is therefore, not possible to determine the therapeutic index for Compound F.

[392] Dr Lamarre's opinions expressed in his report on the subject and his brief testimony do not deal with the majority of issues raised by Dr Seeger. Specifically, Dr Lamarre did not challenge Dr Seeger's conclusion that it was not possible to determine the therapeutic index for Compound F.

(ii) Patent Application '949

[393] Dr Lamarre relied on data from Patent Application '949 which disclosed Idenix's testing data to demonstrate activity in its 2'-C-Me/OH compounds. However, Idenix amended its '191 Patent Application, including striking the introductory paragraph at page 1 by which specific reference to Application '949 was removed. As far as the Court may determine by removal of this paragraph, no further reference can be found in Patent '191 to Patent Application '949. This is assumed to be the reason that Idenix did not attempt pursue reliance on the data from this Application during argument.

(iii) Applications ‘121 and ‘282

[394] Idenix claims these applications disclose antiviral activity data for a number of 2’-C-Me/OH nucleosides against both BVDV and YFV. Gilead did not make submissions with respect to the testing data in these applications.

> Idenix Pharmaceuticals discloses the use of branched nucleosides in the treatment of flaviviruses (including HCV) and pestiviruses in International Publication Nos. WO 01/90121 and WO 01/92282. Specifically, a method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active, 1', 2', 3' or 4'-branched ß-D or ß-L nucleosides or a pharmaceutically acceptable salt or derivative thereof, administered either alone or in combination with another antiviral agent, optionally in a pharmaceutically acceptable carrier.

[395] In its argument challenging Idenix’s reliance on Patent Application ‘949, Gilead submitted that Idenix is not entitled to incorporate data by reference because this is explicitly prohibited by the *Regulations* made under the Act. As it turns out, Idenix did not rely on application ‘949.

[396] However, Application ‘282 discloses anti-BVDV in anti-YFV activity for the 2’-C-Me/OH nucleosides. Dr Lamarre describes this testing evidence in his November 2014 report as follows:

> In particular, the 2'-Me(up), 2'-OH(down) compounds were tested using all four natural bases against the flavivirus (yellow fever

> virus) and pestivirus (bovine viral diarrhea virus) prototypes for their genera. A spectrum of antiviral activity is shown on pages 186, 190, and 191 of WO 01/92282. From the data and structures described in WO 01/92282, the skilled person would understand that the key aspect of this nucleoside analogue is the 2'-Me(up) substituent because all other substituents are the same as a naturally occurring ribonucleoside. Further, based on the data provided, the skilled person would expect similar antiviral activity for other Flaviviridae. The antiviral data for the flavivirus and pestivirus prototypes is tabulated below [which is not reproduced], which clearly demonstrates the antiviral activity of 2'-Me(up), 2'-OH(down) compounds:

[397] I find that the '191 Patent, by reference to the '282 Application and its purpose for doing so, has sufficiently disclosed the antiviral testing data of 2'-C-Me/OH nucleosides for the flavivirus (yellow fever virus) and pestivirus (bovine viral diarrhea virus). I do not agree however, with Dr Lamarre's comment that "based on the data provided, the skilled person would expect similar antiviral activity for other Flaviviridae", which is intended to encompass the HCV.

(iv) Disclosure of Factual Basis to Claim that BVDV May Be Used As a Surrogate for Demonstrating Antiviral Activity against HCV

[398] Idenix has not disclosed its testing data on chimpanzees in the '191 Patent. This would have satisfied the requirement to disclose its testing data regarding HCV. It has already been noted that none of Idenix's data was based upon the replicon assay, which the skilled virologist would have expected in 2003 to demonstrate antiviral activity against HCV.

[399] The '191 Patent discloses genetic similarities and protein function similarities amongst members the Flaviviridae family and at page 2 specifically provides that "bovine viral diarrhea virus (BVDV) is often used as a surrogate <u>to study</u> the HCV virus" [my emphasis]. At page 3 of

the ‘191 Patent references are made to the *Koonin* and *Dolja* (1993) article discussed by Professor La Colla in relation to common motifs characteristic of RNA directed RNA polymerases.

[400] I do not find this information sufficient however, to disclose a factual basis to claim that BVDV may be used as a surrogate for demonstrating antiviral activity against HCV.

(v) Common General Knowledge

[401] The question here is whether the failure to disclose the utility in the Patent can be compensated for by the common general knowledge. Idenix advances the following materials as demonstrating that it was common general knowledge in June 2003 that BVDV was an adequate surrogate to test for HCV.

1. Slide Presentations of Bhat et al., Eldrup et al., and Olsen et al. from the 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.)

[402] These documents, which were disclosed on page 10 of the ‘191 Patent and described above, consist of slide presentation decks used as visual backups for the oral presentations. The presentations precede the application date of June 27, 2003 by just over two months.

[403] Dr Seeger states in his December Report that presentation slides from scientific conferences would typically not be published and the skilled virologist would typically not have been provided with copies of them. Based solely on the information provided in the ‘191 Patent,

a skilled virologist would not have known whether the abstracts had been published. A skilled virologist would have had to perform a literature search to find this out. As well, Dr Seeger points out that the published abstracts themselves do not provide any data or structure or information about the nature of the nucleosides tested. Although some presentation abstracts can be published in conference newsletters or conference abstract books, the information that can be gleaned from an abstract is limited and not peer reviewed. In this case the only information mentioned was that "nucleoside analogs modified at the 2'-position" had shown antiviral activity using the replicon HCV assay.

[404] The abstracts attached to the conference program were of no assistance as they only made reference to undisclosed nucleoside analogs modified at the 2'-position being found to inhibit synthesis of viral RNA in a cell-based replicon assay in the absence of cytotoxicity, and nothing else of relevance.

[405] Idenix is unable to provide evidence of any weight as to the availability of the documents in the form of details as to even when or how it received a copy of the presentation slides, or even their general availability at this time a decade later. There is no indication that the abstracts were made available to Idenix, other than that they are now in its possession. The person who attended the conference, Dr Storer, was not called. He sent an email to Dr Standring, but without attachments. I suspect the only person who could have testified on receipt or public availability of these documents was Dr Storer.

[406] Accepting Dr Seeger's evidence that the information orally presented based on the Savannah slide presentations which were not distributed, but referred to in the '191 Patent, I conclude that this information does not meet the requirement of section 81 (2) of the documents being available to the public on June 27, 2003. I also conclude that they do not represent common general knowledge either in content, timeliness or evidence of general acceptance.

[407] Because there are no publicly available documents disclosing the factual basis that BVDV assays may be used as a surrogate for demonstrating antiviral activity against HCV, the '191 Patent does not disclose a key element of its factual basis for a sound prediction of utility. Idenix has made no attempt to claim that BVDV testing as surrogates for testing for HCV is common general knowledge, nor is there any evidence that it is.

2. Carroll et al Article

[408] This article was not mentioned in the '191 Patent. There is also no evidence that the content of the paper by Carroll et al was "generally known and accepted" by a majority of those working in the field. Rather, the *Carroll* Paper was published on April 4, 2003, less than three months before the filing of the '191Patent. Further, the mere fact that something was published is not sufficient to establish that it formed part of the common general knowledge. While I have admitted the document in respect of Professor La Colla having knowledge of it, the fact remains that there is no contemporaneous documents emanating from the inventors to establish that this paper was known and accepted by the person skilled in the art as part of the common general knowledge. I conclude that it was not part of the common general knowledge.

[409] The Court concludes that it was not common general knowledge in June 2003 that BVDV was an adequate surrogate to test for HCV.

(b) *Disclosure of Sound Line of Prediction*

[410] Gilead has not challenged the lack of disclosure of the sound line of reasoning claimed by Idenix based on steric mimicry of the fluorine of the hydroxyl group in a substitution. Accordingly, I will leave it for another occasion whether a reference as brief as that at page 10 of the '191 Patent to the Emory Patent application could constitute sufficient disclosure of a line of reasoning of steric mimicry.

> PCT Publication No. WO 99/43691 to Emory University, entitled "2'-Fluoronucleosides" discloses the use of certain 2' -fluoronucleosides to treat HCV.

[411] The passage referred to in the Emory Patent application is as follows:

> In designing new biologically active nucleosides, there have been a number of attempts to incorporate a fluoro substituent into the carbohydrate rmg of the nucleoside. Fluorine has been suggested as a substituent because it might serve as an isopolar and 15 isosteric mimic of a hydroxyl group as the C-F bond length (1.35 A) is so similar to the c-o bond length (1.43 A) and because fluorine is a hydrogen bond acceptor. Fluorine is capable of producing significant electronic changes in a molecule with minimal steric perturbation The substitution of fluorine for another group in a molecule can cause changes in substrate metabolism because of the high strength of the C-F bond (116 kcal/mol vs. C-H = 100 20 kcaUmol).

(c) *Conclusion*

[412] The Court concludes that Idenix has not disclosed a sound prediction of utility in the 2'-C-Me/F nucleoside as it had not disclosed its factual basis for its position in June 2003 that the 2'-C-Me/OH nucleosides had antiviral activity against HCV.

VIII. Sufficiency of Disclosure of the Synthesis of the Invention

A. *Introduction and Legal Principles*

(1) Introduction

[413] The principal, issue, which takes up almost all of the discussion in this section is whether the '191 Patent sufficiently discloses how to make the 2'-C-Me/F nucleoside. I conclude that Gilead has established that the '191 Patent as supplemented by the common general knowledge does not sufficiently disclose how to synthesize the 2'-C-Me/F compound.

[414] This determination takes all of Idenix's arguments into consideration and is based on my factual findings, including preferring the evidence of Gilead's experts to that of Idenix's. As a result, it is not necessary for the Court to consider Idenix's contention that the enabling disclosure of the synthesis of the 2'-C-Me/OH nucleosides for the test of anticipation under section 28.1 is the same as the disclosure of how to make the compound under section 27(3)b) of the *Act*.

[415] Gilead also raises a preliminary argument that based upon Claim 1 of the '191 Patent, and treating all claims as one invention, there was a failure to disclose the invention as it was impossible to identify any single invention contrary to the requirements set out in the Supreme Court decision of *Viagra*. I reject this argument, concluding that *Viagra* has no application to the facts in this matter.

(2) Legal Principles

(a) *Disclosure Requirements*

[416] Disclosure is an important element of the bargain between the inventor and the public. It is the *quid pro quo* for valuable proprietary rights to exclusivity which are entirely a statutory creature of the *Patent Act*. In return for the grant of the monopoly, the inventor must provide the public with an adequate description of the invention with sufficiently complete and accurate details so as to allow a workman skilled in the art to which the invention relates, to construct or use it *Wellcome/AZT,* at para 37.

[417] The Supreme Court described the essentials of disclosure in *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at p. 1637-38 and 1641, [*Pioneer Hi-Bred*] as follows with citations omitted:

> Canadian courts have stated in a number of cases the test to be applied in determining whether disclosure is complete. The applicant must disclose everything that is essential for the invention to function properly. To be complete, it must meet two conditions: it must describe the invention and define the way it is produced or built. The applicant must define the nature of the invention and describe how it is put into operation. A failure to

> meet the first condition would invalidate the application for ambiguity, while a failure to meet the second invalidates it for insufficiency. The description must be such as to enable a person skilled in the art or the field of the invention to produce it using only the instructions contained in the disclosure…and once the monopoly period is over, to use the invention as successfully as the inventor could at the time of his application.
>
> […]
>
> It is nonetheless clear that apart from steps which appear to be obvious and common knowledge for an experimenter skilled in the art, a person to whom the disclosure is addressed "is not required to exercise or to be possessed of more, and, if the specification contains something that necessitates the working out of a problem, the patent cannot be supported".
>
> [Emphasis added]

[418] In determining whether Idenix complied with s 27(3), the Supreme Court in *Viagra* at paras 50 & 51provides a framework for the analysis of the sufficiency of disclosure in the form of three questions that must be answered:

(a) What is your invention?

(b) How does it work?

(c) Having only the specification, can the person of ordinary skill in the art produce the invention using only the instructions contained in the disclosure?

[419] This framework reflects the language of section 27(3)(a) and (b) of the *Patent Act* which is as follows:

27. (3) The specification of an invention must	**27.** (3) Le mémoire descriptif doit :
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	a) décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
(b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;	b) exposer clairement les diverses phases d'un procédé, ou le mode de construction, de confection, de composition ou d'utilisation d'une machine, d'un objet manufacturé ou d'un composé de matières, dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l'art ou la science dont relève l'invention, ou dans l'art ou la science qui s'en rapproche le plus, de confectionner, construire, composer ou utiliser l'invention;

[420] Neither party has raised any issue about how the invention works. "What" is the invention shall be briefly discussed when considering Gilead's interpretation of the *Viagra* decision. The sufficiency of the disclosure of whether the skilled chemist can make the compound based using only the instructions in the disclosure is obviously the primary concern of this section.

(b) *Common General Knowledge and Routine Experimentation*

[421] I have already addressed some aspects of the law with respect to common general knowledge and routine experimentation. It is common ground that both are permissible to assist

the skilled person's task of making the invention work, (*Pioneer Hi-Bred,* p. 1641 supra; *Teva Canada Limited v Novartis AG*, 2013 FC 141 at para 384.

[422] Idenix's position on recourse to these two principles in this case is perhaps best summed up at para 371 of its submissions as follows:

> [371] … With respect to the '191 Patent, the skilled person is taught how to make the precursor molecule for the fluorination. With respect to the fluorination step, the skilled person would know of various possible fluorinating agents that he or she could try, and would be most drawn to the most widely used reagent for converting an alcohol to a fluoride, namely DAST or an equivalent reagent such as Deoxofluor. While exact reaction conditions were not known (given that the claimed compound was novel), finding appropriate conditions would be exactly within the realm of routine trial and error experimentation expected of a skilled chemist.
>
> [Emphasis added]

[423] I have already commented on the broadening of what constitutes common general knowledge in the age of computers citing Justice Gauthier in *Cefaclor* at para 104, which I repeat here:

> The distinction between common general knowledge and prior art which is part of the state of the art for the purpose of assessing anticipation and obviousness tends to diminish in modern times because of the sophistication of search engines and the availability of electronic publications and databases.

[424] Idenix's position on the limit to common general knowledge found in scientific databases is described as follows from its written final submissions.

> It is not Idenix's position that the common general knowledge encompasses all information contained in the Scifinder or Beilstein Crossfire databases. The skilled person would need to know what to search for before these tools could be of any use. However, if a specific transformation was of interest to a skilled chemist, the results of the proper search for this specific transformation would become of primary importance to the skilled person.

[425] That is not so much the issue in this matter where the circumstances describe a series of searches and the need for experimentation with each one as sub-steps to go forward. This case is about whether what is found from the searches can be said to be generally accepted as common general knowledge, or conversely whether a series of searches requiring experimentation constitutes an onerous burden. It is also about the evidence of the chemists' work at synthesizing the compound in the period of 2002 to 2005.

(c) *No issue of Inventive Steps*

[426] The parties have not attempted to advance any serious issue about an inventive step being a factor in the reliance on common general knowledge or undue experimentation in delimiting common general knowledge or experimentation. It is obvious by definition that something cannot be common knowledge if it incorporates an inventive step. Similarly, the Supreme Court in *Plavix* (SCC) specifically excluded trial and error experimentation in aid of an inventive step. Justice Rothstein, speaking to the role of experimentation involving an inventive step, stated as follows at paragraph 33:

> [33] What amount of trial and error or experimentation is permitted before a prior disclosure will not constitute enabling disclosure? Certainly, if the applications judge finds that an

> inventive step was required to get to the invention of the second patent, the specification of the first patent will not have provided enabling disclosure. But even if no inventive step is required, the skilled person must still be able to perform or make the invention of the second patent without undue burden.
>
> [Emphasis added]

[427] The experts of both parties made general contradictory statements as to the inventiveness, or not, in making the compound, but went no further. Dr Barrett claims that no inventiveness was involved in the fluorination step. His opinion on this issue is found at para128 of his November report:

> [128] I acknowledge that in some cases a combination of known reactions may not be routine, as there may be inventiveness in determining the sequence of steps to follow. This is not such a case. In this case, the '191 Patent explicitly sets out two alternative methods to synthesize appropriate precursor molecules. Only one additional step to what is described in the '191 Patent need be taken, and this step, the substitution of an alcohol to provide a fluoride, would have been straightforward for the person skilled in the art, especially since it was amply described in the contemporaneous art.
>
> [Emphasis added]

[428] Dr Damha is of the same opinion at para 106 of his September report:

> [106] It is my opinion that a PSIA would have been able to prepare compounds within the scope of claims of the '657 Patent using the disclosure of the '191 Patent without inventive ingenuity and without undue experimentation...

[429] Dr Wnuk, at para 198 of his November report disagrees with the statement of Dr Damha that the preparation of the 2'-C-Me/F compound lacked inventive ingenuity, (he did not respond

to Dr Barrett's comment, as the two reports were served on the same day). However, the issue of inventiveness of the 2'-C-Me/F synthesis is not developed in the remainder of the evidence. Dr Wnuk simply disagrees with the broad general statement of the Idenix experts, stating that neither the common general knowledge nor trial and error experimentation was sufficient to advise the skilled person how to make the target compound.

[430] Gilead prefers to argue that the literature and knowledge of the skilled chemist at the time does not establish any common general knowledge with respect to the fluorination step. In addition, it submits that the steps and procedures Idenix outlines to arrive at the synthesis of the 2'-C-Me/F compound would require an undue burden of experimentation. It implicitly relies upon Justice Rothstein's comment in *Plavix* (SCC) at para 33 above that "even if no inventive step is required, the skilled person must still be able to perform or make the invention of the second patent without undue burden". [Emphasis added].

[431] In this regard, it is noted that in *Plavix* (SCC), where inventiveness was an issue, the Supreme Court at para 78 included "methods for obtaining that compound" as an aspect of "the inventive concept", which I equate to an inventive step.

> [78] In the present case, it is apparent that the inventive concept of the claims in the '777 patent is a compound useful in inhibiting platelet aggregation which has greater therapeutic effect and less toxicity than the other compounds of the '875 patent and the methods for obtaining that compound.
>
> [Emphasis added]

[432] Dr Damha was apparently of the same view stating as follows:

> There is no magic. Really, chemistry, if I, and I say this with due respect, is, the inventiveness is the compound, its use, the discovery, making it.
>
> [Emphasis added]

[433] The concept of inventive steps could have been made relevant to the outcome of this decision, if set out as an issue for the Court to decide. It represents a first means to delimit the application of common general knowledge and experimentation. It also could have been raised in infringement issues to fix the essential features under the "Catnic principle" (*Catnic Components Ltd v Hill & Smith Ltd*, [1982] RPC 183 at pages 242-43 [*Catnic*] , as endorsed by the Supreme Court in the *Free World* and *Whirlpool* decisions). Inventive steps similarly are material in deciding who the inventor is or are where there may be two steps of inventiveness in terms of coming up with the idea of the compound and the making of the invention.

[434] Both parties appear to have their own reasons on different issues to avoid raising any consideration of an inventive step, which they have clearly chosen not to do. I agree that it is not necessary here where the case may be decided on alternative findings of fact. But to the Court it seems an unusual strategy, where in most litigation normally one advances all submissions that might contribute to a successful final judgment.

(d) *Gilead's Submission on the Insufficiency of Disclosure based on Viagra*

[435] Gilead advances two novel submissions at two different places in its submissions that unsuccessfully attempt to apply the *Viagra* decision to have the '191 Patent declared invalid. In this part, the issue appears to be about the insufficiency of disclosure in light of *Viagra*, while

further below, under the rubric of "what is the invention", Gilead argues there is no invention because Idenix could not synthesize all the compounds in Claims 1 to 3.

[436] The foundation of both arguments is described at paras 172 to 174 of Gilead's submissions, which I set out below, without footnotes:

> [172] The Court held that while it is possible for different claims in a patent to disclose separate inventions, "individual patents must be considered on a case-by-case basis" and that the Court must look to the whole of the disclosure and the claims to ascertain the nature of the invention and methods of its performance.
>
> [173] The Court looked to the specification as a whole in which the patentee described "the invention" as a class of compounds. The Court held there was nothing to support the view that the use of sildenafil (claim 7) was a separate invention from the use of any of the other claimed compounds. No specific attributes or characteristics were ascribed to sildenafil that would have set it apart from the other compounds.
>
> [174] Finally, the Court considered the statutory requirement that each patent must be in respect of only one invention and the lack of any divisional applications filed by Pfizer. The Court held that: "It would be disingenuous for Pfizer to imply that there is one invention in the patent application for the purpose of complying with s 36(1) and then to submit that each claim concerns a distinct invention for the purposes of this appeal.

[437] Gilead's first raises its argument on the sufficiency of disclosure at paras 175 to 177, citing para 75 of the *Viagra* decision, as follows (without footnotes):

> [175] Sufficient Disclosure – In concluding that the patent did not sufficiently describe the invention, the Supreme Court made the following important comments of more general application:
>
> > [70] As I noted above, this Court made it clear in *Consolboard* that the specification, which includes

> the claims and the disclosure, must define the "precise and exact extent" of the privilege being claimed so as to ensure that the public can, having only the specification, make the same use of the invention as the inventor (p. 520). In my view, the courts below misread *Consolboard* when they stated that the only questions that must be answered are "What is your invention?" and "How does it work?" Dickson J. did not state that those were the only relevant questions. In fact, quoting *Minerals Separation*, he went on to say, at p. 520:
>
> With respect to each question the description must be correct and full in order that, [...]
>
> when the period of monopoly has expired the public will be able, having only the specification, to make the same successful use of the invention as the inventor could at the time of his application.
>
> [Emphasis by Gilead]
>
> [71] The Court reiterated this in *Pioneer Hi-Bred*: "The description must be such as to enable a person skilled in the art or the field of the invention to produce it using only the instructions contained in the disclosure" (p. 1638).
>
> [...]
>
> [74] The disclosure in the specification would not have enabled the public "to make the same successful use of the invention as the inventor could at the time of his application", because even if a skilled reader could have narrowed the effective compound down to the ones in Claim 6 and Claim 7, further testing would have been required to determine which of those two compounds was actually effective in treating ED

[176] The Court specifically rejected Pfizer's argument that the disclosure was sufficient because third parties were eventually given enough information to be able to use the invention:

> The fact that Teva carried out this minor research project is irrelevant to Pfizer's obligation to fully disclose the invention. More importantly, what must

> be considered is whether a skilled reader having only the specification would have been able to put the invention into practice. The trial judge clearly found that the skilled reader would have had to undertake a minor research project to determine what the true invention was.
>
> [Emphasis added by Gilead]
>
> [177] The Supreme Court held that the patent was insufficient because "a skilled reader having only the specification would not be able to put the invention into operation." As a remedy, the Court held that: "the logical consequence of a failure to properly disclose the invention and how it works would be to deem the patent in question invalid. This flows from the quid pro quo principle underpinning the Act. If there is no quid — proper disclosure — then there can be no quo — exclusive monopoly rights."
>
> [My emphasis]

[438] I admit to difficulty in following this argument. The reference to the "failure to properly disclose the invention and how it works" seems in reference to the first two questions posed in *Viagra*. Citing the passage referring to "a skilled reader having only the specification would not be able to put the invention into operation" seems to be about disclosure of the synthesis of compound. Idenix argues that *Viagra* is basically a case about the disclosure of the invention and not about the sufficiency of disclosure of how to make the invention. I am not able to make the distinction between the two lines of argument in *Viagra*, inasmuch as the Supreme Court appeared never to have made reference to which of the subparagraphs of section 27(3)(a) or (b) it was relying on in the decision.

[439] I do not think that this is important in any event. I find that *Viagra* has insufficient parallels to be applied to this matter. *Viagra* is a case about a situation where the invention is known and the inventor is quite able to describe it, but leaves the addressee up in the air as to

which of two claims contains the accurate disclosure, thereby requiring a minor research project to find out.

[440] The facts of this case bear no relation to those in *Viagra* where it is clear from Claims 1-3 and the other dependent claims that the fluorine (down), and a methyl (up) at the 2' position of the carbon ring is the invention, even if Claim 1 consists of millions or more compounds. The issue remains whether disclosure of the synthesis of the nucleoside has been disclosed in the Patent and by the common general knowledge and routine experimentation. Indeed, Idenix argues that a skilled reader having only the specification in hand would be able to synthesize the invention in the Patent and by the common general knowledge supplemented by routine experimentation.

[441] The Supreme Court disagreed with the lower courts in *Viagra* that there were separate inventions in the claims. Gilead argues that Idenix has resiled from its representation to the CIPO that Claims 1-3 are one invention by not defending Claim 1. I cannot understand on what basis this conclusion is founded, or why Idenix is prevented from abandoning the defence of a too broadly stated claim. I have already referred to *Viagra* at paragraph 80 of the decision as authority that this practice is acceptable.

[442] I also do not accept that *Viagra* stands for the principle that a "minor research project" properly describes the test for what constitutes an "undue burden" in terms of making the invention based on routine experimentation. The need for the testing in *Viagra* was only to show

that the disclosure of the invention was ambiguous between two possibilities, when the active agent was known and should have been disclosed in the first place.

B. *What is the Invention?*

(1) Quasi-Agreement on the Description of the Invention

[443] In *Viagra,* the Supreme Court states at paragraph 53 that the first step in determining whether disclosure requirements have been met is to define the nature of the invention:

> [53] In determining whether the disclosure requirements have been met in this case, the first step is to define the nature of the invention in Patent '446. This must be done in order to comply with s. 27(3) of the Act, which requires, among other things, that the specification "correctly and fully describe the invention". Therefore, we must ask: What is the invention in Patent '446?

[444] To a point, the parties have generally agreed that the invention in the '191 Patent is a class of 2'-C-Me/F compounds that have anti-Flaviviridae activity. Idenix's written submission on what the invention is, as follows:

> [2] What is the Invention? By the filing date of June 23, 2003, the inventors of the Canadian Patent 2,490,191 had soundly predicted that a novel class of compounds would have anti-Flaviviridae activity. The compounds of the invention belong to a class of nucleoside analogues having a particular modification at the 2' position of the sugar ring, namely a fluorine atom in the (down) position and a methyl in the (up) position.

[445] Gilead's counsel described the invention in its oral submissions as follows: "The invention here would be the group H compounds together with, what I showed you a minute ago from *Christiani v Rice*, [1930] SCR 443 a means of making that which is invented with utility."

[446] Idenix appears to misapprehend Gilead's position when it states that it accepts that there is no requirement for an inventor to have actually made a compound falling within the claims.

> Both parties agree that under Canadian law there is no requirement for an inventor to have actually made a compound falling within the claims. In other words, the requirements of an "invention" and/or inventive concept should not be conflated with an actual physical making of a compound of the invention.
>
> [Emphasis added]

[447] The confusion may arise as to what Gilead intended by "a means of making that which is invented". Gilead does not limit this to being able to disclose how to make the invention.

[448] This is apparent from Gilead's submissions under the heading of the "Nature of the Invention". Gilead again relies on the *Viagra* decision, but this time it is in support of the proposition that the Court may consider extrinsic evidence to ascertain the nature of the invention. Where I find this submission difficult to follow however, is that the failure to make the 2'-C-Me/F compounds despite two years of effort does not appear to be the issue. Rather Gilead's concern is Idenix's abandonment of Claim 1. Gilead's submission is as follows at paragraphs 188-9 of its written argument:

> [188] Applying the reasoning from Viagra, there is no reason to treat the compounds claimed in claims 1-3 as separate inventions. It would be disingenuous for Idenix to say that there is one invention in order to overcome an examiner's office action and then submit that each claim concerns a distinct invention for the purpose of this action. This is a direct application of the reasoning in paragraph 68 in *Viagra*.
>
> [189] In *Viagra*, the Court looked to the actual conduct of the inventors to ascertain what their invention was. In this case, the inventors' conduct clearly demonstrates that they did not have an invention at the time they filed, since they did not have a means of making the compounds claimed. Therefore, the '191 Patent fails for the fundamental reason that the named inventors had not actually made any invention, contrary to the long-standing principles of law articulated by the Supreme Court of Canada in the 1930 decision of *Christiani v. Rice*.
>
> [Emphasis added]

[449] My problem with Gilead's submission is that I do not find that Idenix is arguing that Claims 1-3 are separate inventions. This appears to be Gilead's conclusion, because Idenix subsequently chose not to defend Claim 1. I say this because the reference in paragraph 189 above to Idenix not having had the means to make the compounds claimed, seems to relate back to its submission in paragraph 188. This in turn, appears to relate to the abandoned Claim 1 and Idenix's inability to make all the compounds with the $C(Y^3)_3$ group in the 2' (up) position. I have already referred to paragraph 80 of *Viagra* that acknowledges the propriety of abandoning claims that are too broadly framed. I therefore, reject this submission.

[450] On the other hand, if the submission concerns Idenix's failure to make the 2'-C-Me/F nucleosides by the substitution of the fluorine at the 2' down position, I agree with Idenix that this is not relevant to the definition of the invention. In this matter the invention is the 2'-C-Me/F nucleoside with predictable utility. I understand that "What is the invention" is an independent

consideration of the requirement of being able to describe how to make the invention. In either case, there does not appear to be any requirement to have actually been able to make the invention. Otherwise, there would be no basis to predict utility for inventions that had not been made; or at least, it would add another factor to soundly predicted inventions.

[451] If the related issue for soundly predicted inventions is that the prediction of utility is hypothetical based on the inventor's knowledge, when the inventor's actual knowledge is that the compound cannot be made despite attempts to make it, that issue has not been pleaded, or at least argued, and is not before me.

C. *Does the '191 Patent Disclose how to Synthesize the 2'-C-Me/F Compound?*

[452] In the analysis that follows I first consider whether and to what extent the synthesis of the 2'-C-Me/F nucleoside is expressly disclosed in the '191 Patent, bearing in mind the acknowledgment that the Patent contains no description of the fluorination step that ultimately synthesizes the 2'-C-Me/F nucleoside.

[453] Thereafter, I consider whether common general knowledge and routine experimentation are sufficient to disclose the synthesis of the 2'-C-Me/F compounds. This analysis is based upon the testimony of the experts and the contemporaneous evidence from the Idenix and Gilead chemists involved in efforts to make the compound during the relevant 2002 to 2004 period.

[454] With respect to the Court's analysis of the work of Dr Griffon, it also considers allegations by Idenix that he did not perform to the level of a skilled chemist. This includes allegations that he failed to recognize that he had synthesized the 2'-C-Me/F nucleoside, as was allegedly demonstrated by experiments conducted for Idenix by AMRI in 2014 simulating his February 2003 experiment with Deoxo-Fluor® on a carbohydrate nucleoside.

(1) Is the Synthesis of the 2'-C-Me/F Compound Disclosed in the '191 Patent?

[455] The Court is here considering the express written disclosure contained in the '191 Patent without the added disclosure of synthesis from the common general knowledge.

[456] It is common ground that as of the relevant dates, the synthesis of a 2'-C-Me/F nucleoside was novel, as Dr Barrett implied by it never having been made. It is also common ground that the '191 Patent contains no information with respect to the fluorination step. On this basis alone, the Patent fails to teach how to make the claimed compounds. It relies on common general knowledge and experimentation in order to meet the disclosure requirements to carry out the essential fluorination step.

[457] The best Idenix can achieve therefore, is to demonstrate that the intermediate used to synthesize the 2'-C-Me/F nucleoside, which is a 2'-C-OH/Me sugar ring or nucleoside required for a fluorination by DAST, was disclosed in the '191 Patent. No prior step in the synthesis process is at issue. I find Idenix does not teach how to make the intermediate compounds in the '191 Patent. Essentially, the few relevant pages found in the '191 Patent are directed towards the

synthesis of the 2'-C-Me/OH nucleosides of which Idenix held patents, and not the intermediate to be fluorinated.

[458] The '191 Patent claims 2'-C-Me/F nucleosides without describing any synthetic scheme by which any such compound can be made. As for its precursor the 2'-C-OH/Me sugar ring or nucleoside compounds, the synthetic schemes in the '191 Patent are directed to the 2'-C-Me/OH class of compounds having 2'-OH(down) substituents, with only inferred instruction on how to make the precursor 2'-C-OH/Me compounds necessary for the fluorination step.

(a) *Gilead's General Submission on the Disclosure Due to Idenix's Abandonment of Claims in the Application*

[459] As indicated, Idenix abandoned a number of claims and 22 of its 23 formulae in the Patent Application. These were not contained in the '191 Patent as issued. Both parties directed the Court to the file history of the '191 Patent which contains evidence on this downsizing step by Idenix.

[460] Idenix has stated that the effect of the downsizing of its Patent Application is that,

> … some of the language used in the '191 Patent may relate to some of the formulas disclosed in the '191 Patent but which are not claimed in the '191 Patent as issued. As such, some of the specification that is directed to formulas other than Formula (IX) may not be relevant in construing the claims of the '191 Patent.

[461] Gilead's witnesses, in particular Dr Wnuk, provided an opinion with respect to the irrelevancies in the '191 Patent remaining after the removal of claims and formula, along with

Claim remaining in issue. As an example, I set out a summary of his opinions in this regard from his first report as follows:

> (b) It is my opinion the skilled person would have understood from the title of the '191 Patent and initial pages of the specification that the patent is directed to 2' and 3' prodrugs of 1', 2', 3' or 4' branched nucleosides for use in the treatment of Flaviviridae infections, such as HCV infections. The '191 Patent discusses twenty-three Formulae that each appear to encompass a different broad class of substituted nucleosides. The skilled person would have understood that, depending on the Formulae, different substituents are available at each of the positions on the sugar ring, including changes to the sugar ring itself. The skilled person would have also understood the Formulae of the '191 Patent to include a vast number of non-natural bases. As a whole, the skilled person would have understood that the '191 Patent refers to an enormous number of nucleosides with various substituents possible on the sugar ring as well as on the base. The skilled person would have understood that the '191 Patent provides some synthetic schemes and examples for making some of the nucleosides discussed in the specification or body of the '191 Patent (which I understand is that part of the patent that precedes the claims), but certainly not all. In particular, the skilled person would have understood that the '191 Patent provides no schemes or examples which describe how to make nucleosides with a substituent other than OH or H in the 2' (down) position or the '3 (down) position. The skilled person would have also understood that the '191 Patent provides examples that relate to the preparation of starting materials and intermediates that can be used in the synthesis of particular nucleosides with a substitution at the 4' position. The '191 Patent also provides information regarding some biological assays that it says can be used to assess the compounds referred to in the '191 Patent, as well as biological assay results in respect of a single compound, that the '191 Patent refers to as Compound F. The skilled person would have noted that no chemical structure or drawing for Compound F is provided in the '191 Patent. Further, the skilled person would have noted that the nomenclature provided for Compound F is incomplete and thus the exact structure of the compound would not have been understood by the skilled person.
>
> (c) The skilled person would have understood that the '191 Patent ends with 32 claims. Claims 1 to 3 relate to particular chemical structures. Claims 4 to 32 relate to using the compounds of Claims 1 to 3 in the treatment of flaviviridae infections, including HCV. Rather than being directed to "modified 2' and 3'-

> prodrugs of 1', 2', 3' or 4'-branched nucleosides" or the twenty-three Formulae contained in the specification, Claims 1 to 3 are directed only to one Formula, Formula (IX). Further, Claims 2 and 3, while still very broad, limit the nucleosides covered to those with a methyl in the 2' (up) position and a fluoro in the 2' (down) position. The skilled person would have found the focus on this particular substitution pattern unexpected, as the '191 Patent does not highlight or provide any example or scheme directed to a nucleoside with these two substituents. Further, the skilled person would have been confused by the scope of the claims, as the focus in the Examples was clearly on nucleosides with a methyl group at the 4' position and no such nucleosides appear to be covered by the Claims.

[462] Dr Wnuk's comments on the contents of the '191 Patent taken without interpretation by a skilled chemist seeking to understand the Patent are irrefutable. Some were confirmed by Dr Damha in his cross-examination. This did not, however, extend to the claims' portion of the specification, or to Dr Damha's opinions of the extent of misdirection.

[463] Dr Damha, in his reply report to Dr Wnuk's interpretation of the '191 Patent, as it read without the benefit of the information from the application file, gave a similar explanation as that contained in Idenix's submissions to the Court, as follows:

> Dr Wnuk, however, did not mention that during the prosecution of the '191 Patent, the Canadian Intellectual Property Office issued an office action requiring the '191 Patent be restricted to one invention. As such, the claims of the '191 Patent were restricted to compounds of Formula (IX) and their use. Dr Wnuk's comments about aspects of the disclosure relating to compounds other than Formula (IX) are therefore misplaced.

[464] The true interpretation of the '191 Patent is to be arrived at by consideration of what a competent person skilled in the art reading the specification at its date of issue would have

understood it to have disclosed and claimed, (*Freeworld* at para 52). As such, the '191 Patent must be construed without reliance upon extrinsic evidence, which I conclude includes the information contained in the CIPO's files.

[465] However, it is also my opinion that the skilled chemist would have figured out that there was a disconnect between the Claims and much of the content of the specification. This would have led to identifying the only relevant formula based on Formula (IX) with the fluorine in the '2 (down) position. In this respect I, therefore, agree with Dr Damha's opinion that Dr Wnuk's interpretation of the Patent specification is too literal. While reflecting a first impression of the document, it does not state what the skilled person would have eventually taken from it.

[466] On the other hand, very little can be taken from much of the 170 pages, and often the specification misdirects. This occurs in the schemes and discussions on synthesis that were only stated to be relevant to the disclosure of how to make 2'-C-Me/OH nucleosides, and not to its 2'-C- OH/Me diastereomer used as the intermediate to synthesize the 2'-C-Me/F nucleosides.

[467] On the other hand, I find that the Court was not prevented from construing the Claims, which all were clearly directed at compounds with the methyl (up) and fluorine (down) structure at 2' position on the sugar ring. Claim 1, which was abandoned by the Idenix, was similarly related to the other compounds claimed with the fluorine at the 2' (down) position.

[468] Idenix's expert witnesses provided assistance to the Court in the construction of the Claims, as well as referring the Court to those portions of the '191 Patent that they considered

relevant to the issues at hand, such as the definition section of Bases. Gilead directed the Court's attention to inconsistencies in the specification that affected the interpretation of the claims, for example the various and different references to phosphates. Gilead advanced no general argument that the Claims were unintelligible on these issues because of the contents of the specifications.

[469] However, I do give some weight to Dr Wnuk's opinions that the disclosure of the synthesis of the 2'-C-Me/F nucleoside was adversely affected by the fact that so much of the specification was irrelevant, making the relevant information more difficult to determine. This in addition to the facts that the '191 Patent contained no information on the essential fluorination step to make the invention and that the schemes in the Patent directed the skilled person to the 2'-C-Me/OH as a final product; thereby away from its diastereomer 2'-C-OH/Me compounds as the appropriate intermediate to synthesize the 2'-C-Me/F nucleoside, add to my conclusion that the express disclosure on the synthesis of the intermediate was also lacking.

(b) *Schemes of Synthesizing the Intermediate 2'-C-OH/Me Compound*

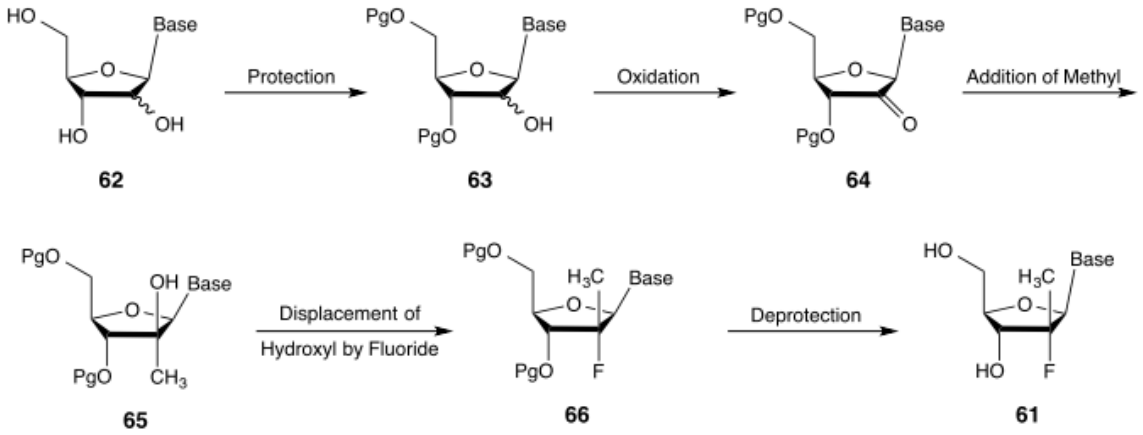
[470] It was acknowledged that there were three approaches to synthesizing the 2'-C-Me/F nucleoside, two of which use the 2'-C-OH/Me compounds as intermediates. Schemes 11 and 5 from Dr Barrett's first report shown below depict the first two approaches. They are the Nucleoside Modification and the N-Glycosidation (sugar ring) approaches. The Nucleoside Modification approach uses a nucleoside starting material, while the N-Glycosidation approach is carried out by modifying a sugar D-ribose ring derivative starting material, which after fluorination of the ring, is coupled with a uracil base by glycosidation. For the purpose of these

discussions on disclosure of the synthesis of the intermediate, only the methylation step (e.g. the step between molecules 64 and 65 in scheme 11 below that adds the CH_3 group) that creates the 2'-C-OH/Me precursors are at issue.

(i) The Nucleoside Modification Approach

The Nucleoside Modification Approach

SCHEME 11



[471] Scheme 11 of Dr Barrett's drawings starts with a uracil nucleoside compound 62, which is protected at the 3'- and 5'-hydroxyl groups on the sugar resulting in compound 63. It in turn is oxidated with a reagent to change the 2'-alcohol (CH_3) to the 2'-ketone (O) resulting in nucleoside 64. These two steps are described in the '191 Patent and are not at issue.

[472] Nucleoside 64 is methylated with methyl lithium in diethyl ether at -78 C following the method of A. Matsuda et al. to create nucleoside 65, being the 2'-C-OH/Me nucleoside. This is the sought-after intermediate nucleoside that will be fluorinated to produce the 2'-C-Me/F

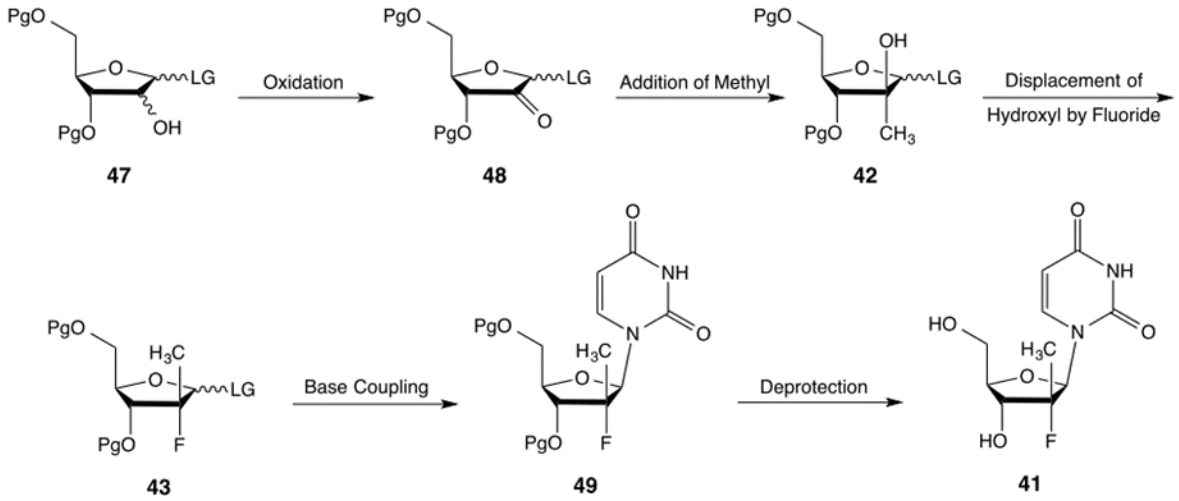
nucleoside. This methlation step (Nuceloside 64 to 65) is to be compared with the schemes found in the ‘191 Patent (further below at Scheme 3 under the title of Synthesis of 2 '-C-Branched Nucleosides) which do not show or make reference to the intermediate, but only Idenix’s compound of the 2’-C-Me/OH nucleoside.

[473] In Dr Barrett’s drawings, Nucleoside 65 after undergoing further deprotection and protection steps is fluorinated with DAST in toluene solution at -20 F resulting in the protected target 2’-C-Me/F nucleoside 66, along with elimination products not shown on the scheme. The ‘191 Patent has no information on this step. Compound 66 is deprotected, resulting in compound 61 being the target 2’-C-Me/F nucleoside. The entire fluorination step is absent from the ‘191 Patent.

(ii) The N-Glycosidation Approach

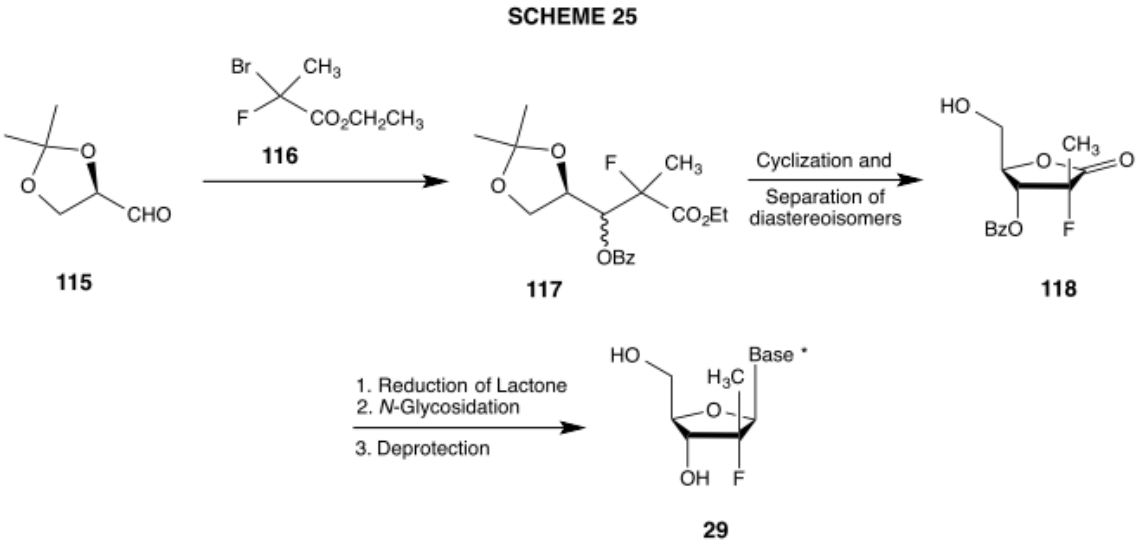
[474] The N-Glycosidation, or sugar ring approach, follows much of that of the Nucleoside approach, except that the starting material is a sugar D-ribose ring and the DAST reagent is not in a toluene solution. After the fluorination step, a Vorbrüggen reaction followed by deprotection is employed to complete the synthesis to add the base. This approach is depicted in scheme 5 below from Dr Barrett’s report.

SCHEME 5



(iii) The Gemcitabine Approach

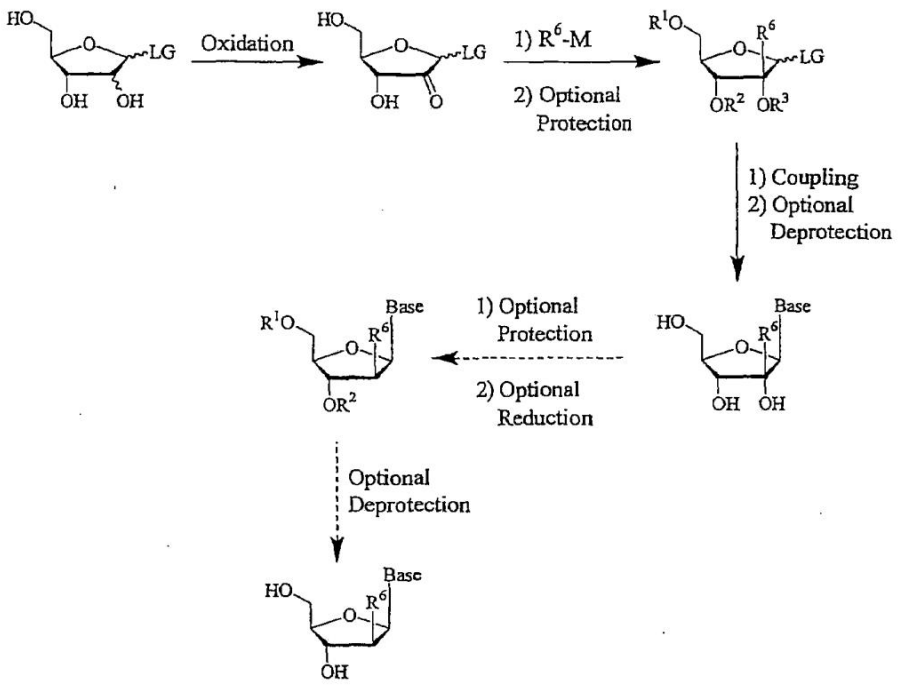
[475] The Gemcitabine "Small Molecule Strategy" approach is so named as it was originally used to produce the anti-cancer drug bearing its name. The procedure described in Scheme 25 below, involves using an aldol or Reformatsky reaction followed by a cyclization to form a sugar with the "2' methyl (up)"- 2' F (down), substituents already established in their correct positions to which a base is coupled. There is no mention or depiction of this scheme in the '191 Patent.



(iv) The Schemes in the '191 Patent

[476] The relevant schemes in the '191 Patent all show the target compound with the hydroxyl remaining in the 2' (down) position, being the Idenix patented 2'-C-Me/OH nucleosides. In other words, they do not depict either the inverted diastereomer intermediate 2'-C-OH/Me or the target 2'-C-Me/F compounds. Typical of these schemes is Scheme 3 from the Patent depicting a N-Glycosidation approach starting from a sugar ring with a 2'-C-Me/OH nucleoside as a product prior to the optional protection and reduction. It is found at page 123 in the Patent in the section entitled "B. General Synthesis of 2 '-C-Branched Nucleosides", *1. Glycosylation of the nucleobase with an appropriately modified sugar*. The scheme reads left to right across the top and then down.

Scheme 3



[477] Compound 1 is the starting material being the D-ribose sugar ring. Compound 2 is the result of the oxidation process of the starting material, while Compound 3 is the result of the methylation process being the 2'-C-Me/OH sugar ring compound (the methyl is the substituent R^6) before coupling with the base. The fourth Compound on the line below shows the coupling of the base to the sugar ring making the target 2'-C-Me/OH nucleoside. The fifth and sixth compounds, being the protection and optional reduction steps on the scheme, are not relevant.

[478] Scheme 4 at page 125 of the '191 Patent depicts the Nucleoside Modification approach, which is similar to Scheme 3, only with the starting material being a nucleoside. Scheme 9, a more generalized version, also shows the target compound with the OH in the 2' (down) position, as well as having a purine base. The 2'-C-Me/F nucleoside is only active with the pyrimidine bases of uracil or cytidine. These drawings all show the synthesis of the 2'-C-Me/OH nucleoside,

while Scheme 9 has a base that would not provide anti-viral activity if the 2'-C-Me/OH diastereomer (i.e. the 2'-C-OH/Me compound) was used to make a 2'-C-Me/F nucleoside.

(c) *Idenix's Experts Evidence on the Disclosure in the '191 Patent*

[479] Despite the schemes directing the skilled person to the synthesis of the 2'-C-Me/OH nucleoside, Idenix's experts insist that the '191 Patent provides the teaching to make the intermediate 2'-C-OH/Me compounds. Dr Barrett summarizes Idenix's case as follows at para 128 of his November report

> [128] In this case, the '191 Patent explicitly sets out two alternative methods to synthesize appropriate precursor molecules. Only one additional step to what is described in the '191 Patent need be taken, and this step, the substitution of an alcohol to provide a fluoride, would have been straightforward for the person skilled in the art, especially since it was amply described in the contemporaneous art.
>
> [Emphasis added]

[480] Dr Barrett's explanation of the explicit description of how to make the two alternative methods starts with a retrosynthetic analysis of the skilled person working backwards from the chemical properties of the 2'-C-Me/F compound. The skilled person, after viewing the target compound, is led to the conclusion that the synthetic route must use the DAST fluorination method to make the molecule. That research also leads the skilled chemist to recognize that the target intermediate molecule must have the methyl (down) and hydroxyl (up) inverted at the 2' position from all the compounds depicted in the schemes in the '191 Patent.

[481] With respect, a retrosynthetic analysis to make a compound that is not described or shown in the Patent is not what the skilled person would consider as an explicit description of how to make the compound.

[482] From this undescribed starting point of a retrosynthetic analysis, being the essential first step in the novel synthesis, the skilled chemist is said to be directed to the intermediate compound via the *O'kuru* article. It is to be found by the skilled chemists among the few relevant passages in the '191 Patent. Dr Barrett states as follows:

> At the least, Harry-O'kuru and Example 2 teaches a person skilled in the art how to use all of the necessary reagents, and perform all of the necessary reactions, for the synthesis of nucleoside 41 other than the step in which the alcohol is converted into the fluoride.

[483] I think it would be better to state that "at the most" a skilled person might find his way to the synthesis of the intermediate in the '191 Patent, except that I would agree with Gilead's argument that the passage in question quoting the *O'kuru* article equally directs the POSITA away from the 2'-C-OH/Me intermediate as follows:

> EXAMPLE2: REPARATION OF2'-C-METHYLRIBO-8-METHYLADENINE
>
> The title compound was prepared according to a published procedure (R.E. Harry O'kuru, J.M. Smith, and M.S. Wolfe, "A short, flexible route toward 2'-C-branched ribonucleosides", J. Org. Chem. 1997, 62 1754-1759) (Scheme 9).
>
> [Emphasis added]

[484] Example 2, refers explicitly to Scheme 9 which is the 2'-C-Me/OH compound, also with the purine rather than the pyrimidine base. The title compound in Scheme 9 is also the 2'-C-Me/OH compound, not the intermediate 2'-C-OH/Me compound.

[485] As was further pointed out by Gilead, the *O'kuru* article does not explicitly explain or point to the methylation step with methyl lithium in diethyl to create the intermediate 2'-C-OH/Me compound. Rather it refers to the *Matsuda* article used by Jeremy Clark, *A. Matsuda et al*, "Alkyl Addition Reaction of Pyrimidinme 2'-Ketonucleosides: Synthesis of 2'-Branched-Chain Sugar Pyrimidine Nucleosides", Chemical Pharamaceutical Bulletin, 1988, 36(3), 945-953. The *Matsuda* article provides the methodology to synthesize the 2'-C-OH/Me precursor compound. The *O'kuru* article only references the *Matsuda* article in a footnote. The passage referring to the footnote is not about antivirals, but cancer compounds. It states:

> In the past 10 years, a number of 2'C- branched nucleosides have displayed promising anticancer (Footnote 1) …

[486] Footnote 1 contains a long list of reference articles, nearly all of which are written by or contributed to by Dr Matsuda, none of which are titled, as follows:

(1) (a) Matsuda, A.; Takenuki, K.; Itoh, H.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1987**, *35*, 3967. (b) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945. (c) Ueda, T.; Matsuda, A.; Yoshimura, Y.; Yakenuki, K. *Nucleosides Nucleotides* **1989**, *8*, 743. (d) Matsuda, A.; Takenuki, K.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 234. (e) Matsuda, A.; Nakajima, Y.; Azuma, A.; Tanaka, M.; Sasaki, T. *J. Med. Chem.* **1991**, *34*, 2917. (f) Yoshimura, Y.; Saitoh, K.; Ashida, N.; Sakata, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 721. (g) Yoshimura, Y.; Satoh, H.; Sakata, S.; Ashida, N.; Miyazaki, S.; Matsuda, A. *Nucleosides Nucleotides* **1995**, *14*, 427. (h) Takenuki, K.; Matsuda, A.; Ueda, T.; Sasaki, T.; Fujii, A.; Yamagami, K. *J. Med. Chem.* **1988**, *31*, 1063. (i) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 812. (j) Yamagami, K.; Fujii, A.; Arita, M.; Okumoto, T.; Sakata, S.; Matsuda, A.; Ueda, T. *Cancer Res.* **1991**, *51*, 2319. (k) Cory, A. H.; Samano, V.; Robins, M. J.; Cory, J. P. *Biochem. Pharmacol.* **1994**, *47*, 365.

[487] The *Matsuda* document, which turns out to be the article at sub-footnote 1(b), is equally imprecise in that the reaction type must first be selected from the various examples it provides. Selecting the one that provides stereo selectivity, in turn leads to 10 different examples from experiments, from which entry 6 is the appropriate one, as follows:

TABLE I. Reaction of Compound 11 with Various Organometallic Reagents

Entry	Reagent	Conditions	R	Isolated yields (%)			
				12	13	14	15
1	MeMgBr	THF, −50 °C	Me	55.3	20.9	19.8	0
2	MeMgBr	Et_2O, −50 °C	Me	51.9	42.6	0	0
3	MeMgBr	Et_2O, −78 °C	Me	53.3	40.0	0	0
4	MeMgBr +MAT	Toluene, Et_2O, −78 °C	Me	77.7	17.4	0	0
5	MeMgBr $+BF_3 \cdot OEt_2$	Et_2O, −78 °C	Me	48.8	36.9	0	0
6	MeLi	Et_2O, −78 °C	Me	88.0	0	0	0
7	Me_3Al	$CHCl_3$, −50 °C	Me	82.2	0	0	0
8	EtMgBr	Et_2O, −50 °C	Et	12.6	43.3	0	24.9
9	Et_3Al	$CHCl_3$, −50 °C	H	0	0	0	94.6
10	PhMgBr	Et_2O, −78 °C	Ph	84.0	0	0	0

[488] I agree with Gilead that this is not express disclosure of how too make the intermediate compounds needed to synthesize the 2'-C-Me/F nucleoside.

[489] Idenix also argues that the discussion on stereochemistry at pages 102-3 of the Patent is sufficient to disclose how to synthesize the 2'-C-Me/OH precursor. Idenix here refers to the useful properties of nucleosides in the methylation process used to form the 2'-C-Me/OH nucleoside. It argues that this "is sufficient to disclose how to synthesize the 2'-C-Me/OH precursor."

[490] In this respect, Dr Wnuk acknowledged that it would be common general knowledge that the process of applying a form of the well-known Grignard reagent referred to in the Patent would result in a racemic mixture of diastereomers of both the 2'-C-Me/OH and 2'-C-OH/Me compounds that could be separated to obtain the desired precursor enantiomer.

[491] However, a general reference to a form of a reagent that results in a by-product compound of the 2'-C-Me/OH compound that is irrelevant to the teaching instructions that focus on the making that compound, cannot be said to sufficiently disclose how to make the intermediate compound. In effect, I find that Idenix is relying on common general knowledge to advise the skilled reader, both that the 2'-C-OH/Me is the intermediate required to make the 2'-C-Me/F nucleosides, as well as how to make that intermediate, with at best snipits of useful information well buried in the '191 Patent.

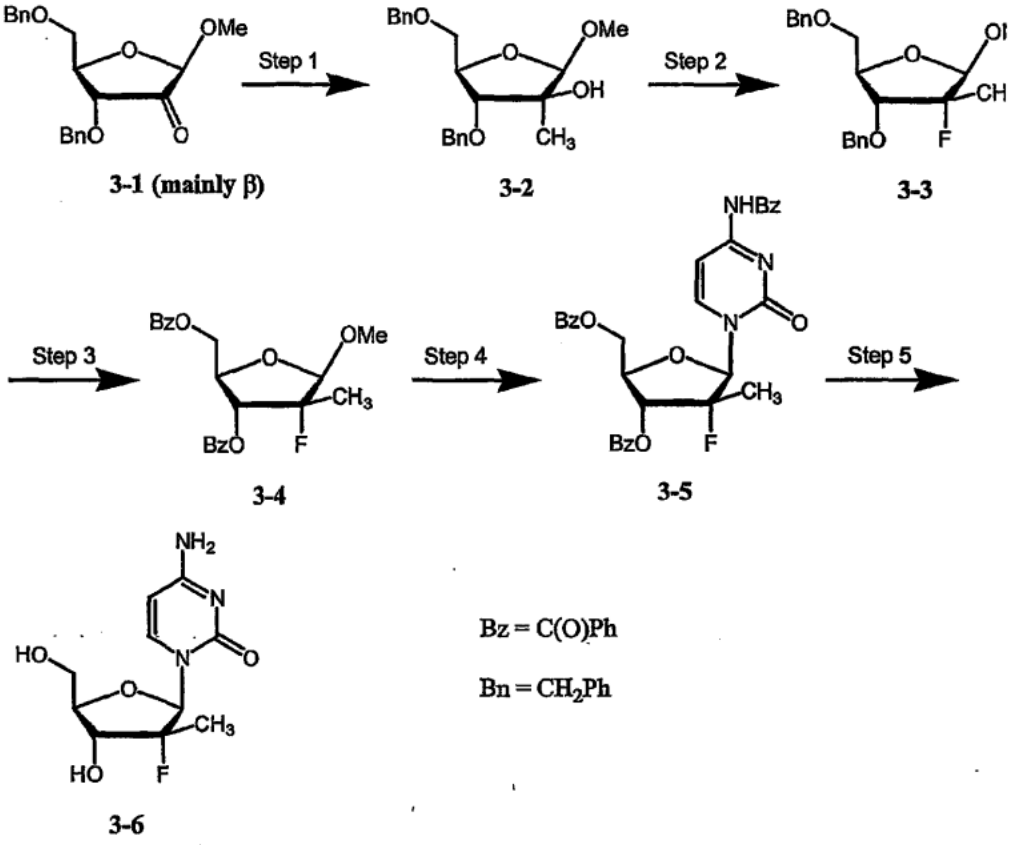
(d) *Comparison with the Description in the '657 Patent*

[492] The '191 Patent can be compared with the '657 Patent which sets out six schemes with all of the details of the steps and the particulars applying to each step to enable synthesis of the 2'-C-Me/F nucleoside. An example follows using the sugar ring approach. The scheme starts after

the oxidation step described earlier whereby ketone was applied to a protected sugar ring to produce compound 3-1. Step 1 is the methylation step to produce the 2'-C-OH/Me sugar ring. Step 2 is the fluorination step to produce the 2'-C-Me/F sugar ring. Steps 3, 4 and 5 are the Glycosidation steps to produce the nucleoside with the uracil base as compound 3-6.

Example 1: Synthesis of (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Starting from a Carbohydrate [sugar ring without the base]

Scheme 3



Step 1: Compound 3-1 (7.7 g, 0.022 mmol) was dissolved in anhydrous diethyl ether and cooled to -78°C. To this solution was added MeLi (30 mL, 1.6 M in diethyl ether). After the reaction was complete, the mixture was treated with ammonium chloride (l M, 65 mL) and the organic phase was separated, dried (Na_2S0_4),

filtered, and concentrated to dryness. Silica gel chromatography followed by crystallization from diethyl ether-hexanes afforded pure compound 3-2 (6.31 g). ^{1}H NMR (400 MH_z, $CDC1_3$): δ 1.40 (s, 3H), 3.41 (s, 3H), 3.49 (dd, 1H, J= 10.3, 6.89 H_z), 3.57 (dd, 1H, *J* = 10.3, 3.88 H_z). 3.84 (d, 1H, *J* = 7.3 H_z), 4.03 (m, 1H), 4.48 (s,lH), 4.58 (m, 3H), 4.83 (d, 1H, *J*= 11.6 Hz), 7.31-7.36 (m, 10H); ^{13}C NMR (100 MH_z, $CDCl_3$): δ18.4, 55.4, 72.2, 73.4, 79.5, 80.2, 84.7, 107.4, 127.7, 127.8, 127.83, 128.5, 138.2, 138.3.

Step 2: Compound 3-2 was dissolved in CH_2C_2 and was treated with DAST (4.0 mL, 30.3 mmol) at room temperature. The solution was stirred at room temp overnight. The so-obtained mixture was poured into sat $NaHC0_3$ (100 mL) and washed with sat $NaHC0_3$ (l x 15 mL). The organic layer was further worked up in the usual manner. Silica gel chromatography (1:5 EtOAc-hexanes) gave crude compound 3-3 (0.671 g) that was sufficiently pure for the next step. ^{1}H NMR (400 MH_z, CDC_3): δ 1.43 (d, 3H, *J*= 22.8 H_z), 3.35 (s, 3H), 3.49 (dd, 1H, *J*= 10.5, 5.4 H_z), 3.55 (dd, 1H, J= 10.5, 4.1 H_z), 3.87 (dd, 1H, J=23.5, 7.5 H_z), 4.26 (m, 1H), 4.56 (d, 2H, *J*= 6.9 H_z), 4.66 (d, 2H, *J*= 8.2 Hz), 4.72 (d, 1H, *J*= 10.8 H_z), 7.29- 7.36 (m, 10H); .^{13}C NMR (100 MH_z, $CDCI_3$): δ 17.0 (d, *J*= 24.4 H_z), 55.2, 77.1, 73.4,73.8,77.3,80.3,81.2 (d, *J*= 16 H_z), 99.7 (d, J= 178.9 Hz), 106.8 (d, *J*= 32.0 Hz), 127.7, 127.8, 128.1, 128.3, 128.5, 128.6, 137.8, 138.3; ^{19}F NMR (100 MHz, $CDC1_3$): δ -8.2 (m, IF).

Step 3: Compound 3-3 (0.39 g, 1.1 mmol) was dissolved in 1:2 EtOH-EtOAc and treated with Pd/C (~0.l g) and cyc10hexene (~1 mL). The mixture was heated to reflux ovemight and then filtered through celite*.·The solvent was removed *in vacuo* and the residue was dissolved in pyridine (~5 mL). To this solution was added benzoyl chloride (0.22 mL, 1.83 mmol) and the mixture was stirred at room temp ovemight. The pyridine was removed in vacuo and the residue was partitioned between CH_2Cl_2 and sat $NaHCO_3$) (10.0 mL). The organic phase was dried (Na_2SO_4), filtered, and the solution was concentrated to dryness. Column chromatography provided 0.350 g of pure compound 3-4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, 3H, *J*= 22.4 H_z), 3.39 (s, 3H), 4.46 (dd, JH, *J*= 11.6, 4.7 H_z), 4.58 (m, lH), 4.65 (dd, lH, *J*= 11.6, 3.9 H_z), 4.87 (d, 1H, *J*= 9.9 Hz), 5.64 (dd, 2H, J= 24.1, 7.8 H_z), 7.29-7.36 (m, 10H); ^{19}F NMR (l00 MHz, CDCl): δ-7.5 (m, IF).

Step 4: A solution of bis(trimethylsilyl)-N-benzoylcytosine (0.28 g, 0.77 mmol) and compound 3-4 (0.20 g, 0.5 mmol) in 1,2 dichloroethane (2 mL) and toluene (2 mL) was treated with TMSOTf (0.I5 mL, 0.77 mmol). After most of the starting material disappeared as judged by TLC, the solution was cooled to room

> temp, washed with water (1 x 5 mL), brine (1 x 5 mL), dried (Na_2S0_4), filtered, and concentrated to dryness. Flash chromatography followed by crystallization from CH_2Cl_2-hexanes afforded compound 3-5 (68 mg). mp 241°C; ^{1}H NMR (400 MH_z, $CDCl_3$): δ 1.49 (d, 3H, *J*= 22.4 H_z), 4.64 (dd, 1H, *J*= 12.9, 3.4 H_z), 4.73 (app d, 1H, *J*= 9.5 H_z), 4.89 (dd, 1H, *J*= 12.7, 2.2 H_z), 5.56 (dd, 1H, *J*= 20.7,8.6 Hz), 6.52 (d, 1H, *J*= 15.9 H_z), 7.38-7.67 (m, 10H), 7.89 (d, 2H, *J*= 6.9 H_z), 8.07-8.11(m, 5H), 8.67 (s, 1H); ^{19} F NMR (100 MH_z, $CDCl_3$): δ 2.85 (m, IF).
>
> Step 5: Compound 3-5 (40 mg, 0.05 mmol) was dissolved in methanolic ammonia and stirred at room temp for 48 h. The solution was concentrated to dryness and chromatographed (SiO_2) eluting with 1:4 EtOH-CH_2Cl_2. The yield was about 12 mg of pure {2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine, 3-6. IH NMR (400 MH_z, DMSO-d_6): δ 1.16 (d, 3H, *J*= 22.0 H_z), 3.61 (dd, 1H, *J*= 11.6, 5.2 H_z), 3.60-3.83 (m, 3H, *J* = 10.5, 5.4 H_z), 5.24 (S, 1H, exchangeable with D_2O), 5.59 (s, 1H, exchangeable with D_2O), 5.71 (d, lH, *J* = 7.3 H_z), 6.08 (d, 1H, *J* = 19.0 H_z), 7.24 (d, 1H, *J*= 17.7 Hz, exchangeable with D20), 7.87 Cd, lH); ^{19}F NMR (100 MH_z, DMSO-d_6): δ 4.13 (m, IF).

[493] In light of the details provided in the ‘657 Patent, which is acknowledged by Dr Damha, I find it incomprehensible that he could testify that the ‘191 Patent provided the same level of specificity of synthesis. This is his evidence from the passage cited below at pages 2517-18 of the transcript:

> And do you agree with me that at pages 70 to 88, the Pharmasset inventor, Mr Clark, provides a very specific synthetic protocol for making 2'-methyl-fluoro nucleosides using both the nucleoside approach and a sugar approach?
>
> A. Yes.
>
> Q. And he specifies the reagents, the concentrations, temperatures, all of the reaction conditions the person reading this patent would need to put these compounds into practice; right?
>
> A. Yes, he provides experimental details to do that.

> Q. And this same level of information is not found in the '191 Patent; will you agree with that?
>
> A. I disagree with that.
>
> …
>
> THE WITNESS: Okay. With the exception, Your Honour, of the DAST reaction, everything else, it is in the '191 Patent, the oxidation --

(e) *Conclusion of Disclosure of the Synthesis of the 2'-C-Me/F nucleosides in the '191 Patent*

[494] Idenix's experts insist that the schemes that are contained in the description of the '191 Patent are directed to precursors of the compounds claimed. I agree with Gilead's submission that a review of these schemes, as well as other patents filed by Idenix, demonstrates that this argument is little more than an attempt by Idenix, with the benefit of hindsight; to read something into the '191 Patent that is simply not there.

[495] Moreover, the very same schemes in the '191 Patent and identical instructions to make the compounds found in the '191 Patent are duplicated in prior Idenix patents that make no claim for any fluorinated compounds [i.e. the predecessor Patent application 351].

[496] More importantly, it is indisputable that none of the synthetic schemes or examples provided in the '191 Patent contain any instructions on the fluorination of nucleosides or sugars rings. I agree with Dr Wnuk's observation, which is indisputable, that the '191 Patent does not

even suggest what starting materials, reagents, or reaction conditions could be used to make such compounds, nor does the ‘191 Patent mention fluorination or fluorination reactions whatsoever.

[497] In my view, the absence of any meaningful disclosure in the ‘191 Patent that both misdirects and confuses the reader as described by Dr Wnuk places the skilled person in generally the same circumstances as Dr Griffon, Mr Jeremy Clark and Dr Stewart and Ms Yang at the beginning of their research projects to make the compound. They would have no teaching apart from the compound formula itself, and some of the generally well known initial and completion steps, like that of protection, oxidation and coupling, with nothing whatsoever on the Gemcitabine approach.

[498] The skilled chemist was starting basically with a blank piece of paper, turning to the search engines with the hard work ahead required to make the novel 2’-C-Me/F compound, and not even aware of all the different unsuccessful attempts by Idenix, when it applied for the ‘657 Patent.

[499] The evidence that follows from Idenix’s experts substantiates this conclusion. They rely on a retrosynthetic analysis to synthesize the target Compound. A disclosure said to start at the end of the process with the synthesized compound is an indication that the significant synthesis steps must be worked out by the skilled reader, with little or no help from the ‘191 Patent.

[500] In conclusion, I find that the ‘191 Patent discloses neither the synthesis of the 2’-C-Me/F compound, nor its precursor 2’-C-OH/Me compounds.

D. *Is the Synthesis of the 2'-C-Me/F Compound a matter of the Application of the Common General Knowledge and Routine Experimentation?*

(1) Retrosynthetic Analysis

[501] It is common ground that Pharmasset's patent application WO 2005/003147, published on January 13, 2005 [WO Clark Publication] was the first disclosure of how to make any 2'-C-Me/F compounds. Anyone endeavoring to make the nucleoside prior to that time would have had to work backwards from the formula, with no published literature on how to make the compound.

[502] The experts also agree that the synthesis of the 2'-C-Me/F nucleoside required a "retrosynthetic" form of analysis working backwards from its formula and structure. After the Court mused at one point whether a retrosynthetic analysis can be employed as enabling disclosure, it disappeared as a description by Idenix of the synthetic process the skilled chemist would follow. Dr Barrett for example, resiled somewhat from the requirement to carry out a retrosynthetic form of analysis, suggesting that the route to follow was clearly marked out for the skilled person simply by looking at the compound, which I think is the same thing. Nevertheless, his analysis in his November report refers to the steps in a retrosynthetic analysis (paras 132, 135, 162, 164 and 181).

[503] Dr Damha provided the Court with the most fulsome description of what was entailed in a retrosynthetic analysis at para 113 of his September 7, 2014 report as follows, with my breakout of salient points in square numbered brackets:

> [113] … In the most general terms, the PSIA will look at a target compound to be synthesized. They will do a retrosynthetic or partial retrosynthetic analysis [1] working backward from the target compound to a known compound. For some target compounds a full retrosynthetic analysis which examines all potential precursors [2] may not be necessary where the successful synthetic pathway is more likely than other less likely routes. This is the case with the Claimed Compound which is really a straight forward synthesis. From this retrosynthetic analysis, a synthetic scheme is outlined which often [3] will require multiple synthetic steps through intermediate compounds including the use of protecting groups to prevent unwanted reactions from occurring on intermediate compounds. A literature search is performed to support the reaction conditions [4] for the individual steps in the synthetic scheme. [5] Experimentation is then done to carry out the synthesis of the target compound. Purification and analytical techniques may be employed on [6] intermediates and [7] the target compound. This routine approach is the common and accepted practice for the PSIA not only in the early 2000s but throughout the history of chemistry

[504] The Court was not presented with any documentation that demonstrated a retrosynthetic analysis could be used to teach how to make a compound made in this fashion. This is surprising given that it is clearly a common tool of the trade. Dr Stuyver mentioned retrosynthetic analysis as a process of discovery of new compounds, not teaching how to make a compound already invented. Dr Patterson provided his definition of a retrosynthetic analysis as follows:

> So you will start with the idea of your target molecule in mind, and you will work backwards step by step until you find some commonly available, commercially available hopefully, starting point.

[505] A retrosynthetic plan is at best a contingent roadmap for a proposed route through a labyrinth of research and trial and error experimentation that, when it confronts a dead end, goes back to the last step, and then again maybe the last step before that, and tries another route. There

is no common general knowledge to any plan, as every plan is different and depends upon context, including the abilities of the person making the plan, which for a skilled chemist, is not someone with much experience in the field. A retrosynthetic analysis is used precisely because the synthesis path is unknown. It represents the chemist's best estimate of how to synthesize the target compound.

[506] Dr Wnuk disagreed that a retrosynthetic analysis could be employed in this fashion to describe common general knowledge of synthesis of a novel compound that would not lead to a wide variety of pathways and sub pathways all involving more research and more experimentation that would not sufficiently disclose how to make the target compound. I accept Dr Wnuk's evidence as reflecting common sense.

(2) Steps in Idenix's Retrosynthetic Analysis

(a) *A Literature Search*

[507] There was no literature on how to make the 2'-C-Me/F compound. As a result, Drs Griffon, Stewart and Jeremy Clark all had to conduct literature searches as the first step undertaken in their approach to synthesizing the 2'-C-Me/F nucleoside. Dr Griffon appeared to have spent two months on a research project before proposing on June 27, 2002 to undertake his first attempted synthesis. His notes show that he was in constant continued research as outcomes proved unsuccessful. Dr Stewart spent on average 2 hours a day over 6 months researching the synthesis of the 2'-C-Me/F compound. Because Jeremy Clark did not keep good notes, it is not clear what research he undertook. It appears that he started with the Gemcitabine approach before

switching to the nucleoside approach, and then finishing off with the sugar ring approach. According to Dr Patterson, he had considerable help from the experienced chemists at Pharmaset, although he apparently rejected advice from the senior chemists to use a nucleoside approach. He successfully synthesized the 2'-C-Me/F nucleoside using the nucleoside approach a few months later.

[508] The resort to literature as a starting point in making the compound to determine which synthetic pathway to follow is very different from Dr Damha's understated description above of a literature search being "performed to support the reaction conditions for the individual steps in the synthetic scheme". Besides demonstrating that there was no common general knowledge supporting the synthesis of the 2'-C-Me/F compound, it is not conceivable that the disclosure of enablement is sufficient if it requires a series of literature searches and experimentation at each step, bearing in mind that the lead-off route offers three pathways.

(b) *Which of the Three Known Initial Pathways for Synthesis?*

[509] Dr Barrett indicated that three choices confronted the skilled person as the opening pathway to follow to synthesize the 2'-C-Me/F compound. Dr Wnuk agreed, describing what was entailed by these choices, which I describe in a somewhat précised form:

> 1. Decide which strategy of three to follow to attempt to make the molecule; *a small molecule strategy* [Gemcitabine approach] by making an open chain carbohydrate with the desired substituents, then formed a sugar ring from that open chain carbohydrate, and then attempted to attach the sugar ring to the desired base; *a sugar strategy* wherein the skilled person could have begun with an available sugar ring, attempted to install the

> desired substituents, then attempted to attach the sugar ring to the desired base; and *a nucleoside strategy* wherein the skilled person could have started with an available nucleoside and attempted to install the desired substituents therein.
>
> 2. In each instance, the skilled person would have had multiple different starting materials to choose from, multiple reagents to choose from, multiple possible routes that could have been tried, multiple protecting groups available, and multiple possible reaction conditions that could have been attempted for each step in the chosen route.

[510] Idenix's experts suggest the appropriate pathway would have been evident to the skilled person, being either the sugar or the nucleoside route. The evidence of Mr Clark's efforts is not consistent with Idenix's theory. Mr Clark apparently synthesised the compound some seven months after he first discussed the idea with Pharmasset management, and then after first trying the Gemcitabine route that proved unsuccessful. Dr Watanabe apparently counselled him to follow the nucleoside approach. This was contrary to Dr Coe's advice, again demonstrating that no one knew the most appropriate starting route. The Gemcitabine route was also tried without success by Dr Griffon, who of course, tried all approaches, without success.

[511] Dr Coe opined as follows:

> In our experience and indeed in that of manner other [sic] particularly the de Clerc group the most viable routes to fluoro nucleosides are by sugar/base condensation methods the anomer problem notwithstanding, for the very reasons you have discovered, in that the leaving groups generated in situ e.g. in DAST reactions are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of blocking groups. Further migrations of groups can readily occur: see our papers in JFC 1993 62 145 and 1993 60 239. Having said this some of the route [sic] you have tried are OK except that I think you are using the wrong reagents, leaving groups and reaction conditions.

[512] It turned out to be a good wrong guess in the sense that eventually all three routes have proved achievable. It appears that Mr Clark first synthesized the compound via the sugar route. But he also did it using the nucleoside route, with better yields, as had been a factor driving Dr Griffon to use that route with Deoxy-Fluor, which is a more stable form of DAST. Dr Stewart and Ms Wang only succeeded after they had heard that Pharmasset had successfully synthesized the compound via the nucleoside route. The point is that until successful, no one had any idea of which route to follow. Idenix was in no position, based on the common general knowledge or otherwise, to disclose any particular synthesis route to follow in 2004.

(c) *Which Fluorination Pathway?*

[513] Dr Wnuk, the only expert with fluorination experience at the relevant time, describes the challenges that faced the discovery chemist in determining which fluorination pathway as follows:

> i) Further, different fluorination reactions, involving multiple distinct fluorinating agents, were available to the skilled person in January 2004, but there was no understanding of how to make a nucleoside with a 2'-fluoro(down) and a 2'-methyl(up). At that time, fluorination reactions were understood to generally proceed via two different mechanisms: electrophilic fluorination and nucleophilic fluorination. Different starting materials and fluorinating reagents were required for electrophilic fluorination reactions as compared to nucleophilic fluorination reactions.

[514] He stated that the different fluorinating agents known as of January 8, 2004, included, but were not limited to:

(a) Electrophilic: F_2; SelectFluor; N-flurobenzenesulfonimide; and ClO_3F; and

(b) Nucleophilic: HF and HF-based reagents (e.g. HF-pyridine, HF-pyridine/ AlF_3, anydrous HF, HF/$Fe(AcAc)_3$); AgF and AgF-based reagents (AgF/NH_4F); $Et_3N \bullet 3HF$; KF and KF

[515] The choice of fluorinating reaction (electrophilic or nucleophilic) and, ultimately, of fluorinating agent would have influenced the kind of starting material used in a particular route. It would add complexity to the particular route chosen, as the skilled person would have had to consider using different protecting groups to address the different interactions between the fluorinating agents, their solutions and conditions of activity, and the various interactions of the precursor compounds.

[516] I find the evidence as of January 8, 2004 supports Dr Wnuk's opinion that there was no teaching as to how to fluorinate a tertiary carbon at a nucleoside's 2' position in a stereoselective manner. I also accept his evidence that it was not common general knowledge that using a nucleophilic fluorination approach, or indeed any fluorination approach, would successfully synthesize a 2'-C-Me/F compound.

[517] There was no statement of common general knowledge from any text-or peer reviewed articles supporting the Idenix experts' opinion that DAST would be the choice to follow in 2004 for this particular form of synthesis. The Idenix opinions are largely based upon the number of articles from searches conducted regarding fluorination processes generally, none of which describe DAST being used to fluorinate a tertiary carbon in a ribose ring or nucleoside.

[518] With respect to the articles found from the searches, Dr Wnuk raises concerns for numerous reasons about the power of searches conducted a decade after the fact: "based on my own experience, [I] know that its search functions are more powerful today than they were even 5 years ago". This seems to be demonstrated by Dr Barrett's testimony about the searches he carried out, as stated at para 236 of his November report:

> For instance, as can be seen from Griffon's initial search, the 3' position in the nucleoside 41, for example, contains a –CH(OH)- group. I have on October 26, 2014 repeated this search in SciFinder with a 2002 or earlier filter and found this gave 426 references but none of these were nucleosides. Of these references, 15 were reactions using DAST (51) or Deoxo-Fluor® (52). Reaxys (Beilstein Crossfire in 2002) is a far better database for searching reactions than SciFinder. I have on October 26, 2014 repeated this search in Reaxys with a 2002 or earlier filter and found this gave 44 references for the use of DAST (51) or Deoxo-Fluor® (52) or a related sulfur reagent for the conversion of a tertiary alcohol into a tertiary fluoride. It is interesting that Griffon only found 48 references rather than the 426 that I found.
>
> [Emphasis added]

[519] Dr Wnuk also challenges the claims of Dr Barrett with the results of his own search. He located 32 reactions using DAST as the fluorinating reagent contained in 7 references (5 papers and 2 patents). His search also located 25 reactions using HF as the fluorinating reagent contained in 10 references (3 papers and 7 patents). Consequently, he concluded that HF appears in more references than DAST.

[520] Dr Griffon used HF as a fluorinating reagent before trying a scheme involving Deoxo-Fluor®. I find that the literature of the time did not sufficiently draw the skilled person to the

DAST family of reagents when embarking on a new synthesis with no teaching and only common general knowledge.

[521] Dr Coe, the expert in the field consulted by Idenix on the very problem at the time in question, proposed four different methods for the synthesis of a 2'-C-Me/F nucleoside, none of which involved the nucleophilic fluorination of a tertiary alcohol on a sugar with DAST or an equivalent reagent. He mentioned DAST in the cover portion of his letter in passing as an example of his advice to adopt the sugar ring approach, as opposed to the nucleoside starting material.

[522] It is significant that he did not recommend a DAST or Deoxo-Fluor® experiment, given that there was no mention of Dr Griffon's February 13, 2003 experiment in Dr Storer's letter of February 9, 2003 in respect of the target compound which was Target 9 as indicated:

> Target 9 is an attempt to replace the tertiary OH of the ribo analogue with fluorine. We've tried a variety of procedures from the exocyclic methylene analogue in attempt to effectively add HF across the double bond. We had no success with that. We're now looking at attempting to take the 2'-α methyl anhydro compound and open that with fluoride. I'm not too hopeful for success with that. Appendix 3 shows a summary of this. Your thoughts on how to introduce the tertiary fluoro substituent in compound 1 would be appreciated.

[523] If Idenix is correct that the most obvious first choice route would have been via DAST or Deoxo-Fluor®, Dr Coe's letter should have laid out the scheme involving the need to invert the substituents at the 2' position on the sugar ring etc. Instead, Dr Coe refers to DAST only in support of using the sugar route approach "for the very reasons you have discovered in that the

leaving groups generated in situ (e.g. in DAST reactions) are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of blocking groups". According to Idenix's experts, DAST was the obvious route of any retrosynthetic analysis, yet it is not even stated as one of the suggested schemes by Dr Coe. This is not to cast aspersions at Dr Coe. It reflects that no one knew how to synthesize the 2'-C-Me/F nucleoside prior to Jeremy Clark finding a route, apparently with lots of advice from the senior chemists he worked with.

[524] I have already stated that I accept the accuracy of Dr Wnuk's statement that he is not aware of any publication prior to 2005 that describes the use of DAST or Deoxo-Fluor® to fluorinate a tertiary alcohol on a nucleoside in a stereoselective manner, particularly at the 2' position on the Deoxy sugar ring. At that time, it was not known nor could it have been predicted with any degree of confidence that DAST or Deoxo-Fluor® could be used to fluorinate a sugar (or sugar moiety) bearing a methyl at the 2' (up) position or at the 2' (down) position.

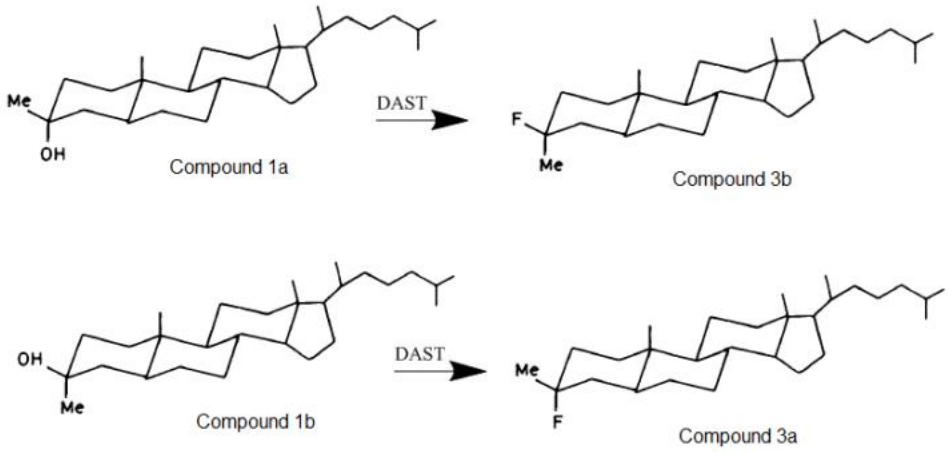
[525] Dr Damha takes issue with this statement, but the examples of the stereospecific structures he provides of fluorinating are largely of a secondary and those for tertiary carbons bear no similarity with those of the sugar ring with the methyl in the (up) placement at the 2' position.

[526] Dr Wnuk states at para 129 et seq. of his first report that the outcome of using DAST type agents depended on the structure, as follows (footnotes omitted):

> Of importance, the behavior of the fluorinating agent DAST/Deoxo-Fluor® had been shown to depend on the structure of compounds on which it is being used. More specifically, the

> ability of DAST/Deoxo-Fluor® to generate a fluorinated compound was known to be dependent on the structure of the starting material (e.g, primary, secondary vs. tertiary alcohol; linear vs. cyclic compound).

[527] An example of the tertiary fluorination relied on by the Idenix experts is found in the article of *Van Robays M. et al*. (1986), *J. Chem. Soc. Perkin Trans 1*: 251-254, which is also cited by Dr Wnuk regarding the unpredictability of fluorination outcomes:



[528] There was also a problem with the unpredictability of DAST reactions. In January 2004, the skilled person would have been aware that fluorination reactions can have unpredictable outcomes. This was especially true when one was trying to synthesize a new nucleoside with a novel substitution pattern on the furanose sugar ring. Such would have been the case for the skilled person, as of January 8, 2004, trying to make a 2'-C-Me/F nucleoside. This was confirmed by Mr Clark and the team of authors from Pharmasset in their 2005 article who wrote as follows:

> The fluorination of tertiary alcohols using DAST has been reported, but the stereochemistry of such trans-formations is substrate-specific and often unpredictable. For instance, Yang et al. reported that the DAST fluorination of a tertiary alcohol in 2-bromomethyl-DL-myo-inositol proceeds with retention of configuration. Wachtmeister et al. obtained a 4-fluoro-1-cyclopentanol containing a tertiary fluorine in 25% yield using DAST as a fluorinating reagent, and this transformation proceeded with inversion of configuration. Further-more, dehydrations or eliminations, rearrangements, and ring contractions are often pervading problems in the DAST fluorination of highly functionalized molecules.

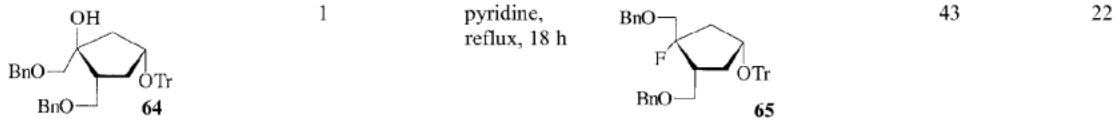
[529] I agree with Idenix that there were articles that discussed the use of DAST or Deoxo-Fluor® in the synthesis of carbohydrates. For example, both parties cited the 2002 Singh article *Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST* [*Singh*] Exhibit 35b. Its purpose was "to summarize the most recent advances in the introduction of fluoro- and fluorinated groups into organic compounds using Deoxo-Fluor® and DAST as nucleophilic fluorinating reagents". When questioned on the comment from the article that "nucleophilic fluorination reactions of organic compounds using fluorinating reagents are one of the most widely used methodologies in the field of fluorine chemistry", Dr Wnuk responded that the same would be said about any article reviewing a specific reagent.

> A. Yes. But I agree with this of how the review articles, review articles is, of course, written on DAST, so if review article would be written on different fluorinating reagent, like HF, most probably the author would start "HF reagent is widely used reagent", that is introductory sentence; yes? Which is very common how we write review article. But that is true in terms of DAST.

[530] In fact, "one of the most widely" means there must have been other widely used methodologies, which was Dr Wnuk's evidence.

[531] I do not find that the cross examination of Dr Wnuk established anything but that the use of DAST type agents to fluorinate was not common general knowledge to produce a 2'-C-Me/F compound in 2004. The cross examination led Dr Wnuk through the process of SN_1 and SN_2 reactions with DAST-type agents. He agreed that it was generally known that they could produce a substitution and a fluorination in one step using the 2'-C-OH/Me intermediate compound that could result in a mixture containing the target compound.

[532] In doing so, he was referred to the *Singh* paper in respect of the *Wachtmeister* paper [Exhibit 222] cited at reference 22 from the Table of 13 examples of Table 2 described as "Fluorination of Hydroxyl Group Located on a Pyranoside Ring", which involved a fluorination of a tertiary alcohol as follows:



[533] Dr Wnuk pointed out that the *Wachtmeister* and related papers are not in respect of a fluorination at the 2' position of the sugar ring or nucleoside. He stated at para 237 of his first report that in contrast, these papers discuss fluorination at the 4' position, which has different reactivity and (in a nucleoside) is not as sterically hindered as the 2' position (due to the proximity of the base to the 2' position of the sugar). In addition, these papers deal with

carbocyclic nucleosides or sugars which have CH 2 and not oxygen (O) in the ribose ring. Presence of oxygen at the adjacent carbon often affects the fluorination.

[534] I also could not help but note that in *Singh*, in the paragraph including the table citing the *Wachtmeister* article, when describing DAST or Deoxo-Fluor® used as the reagent for a carbohydrate ring, the authors pointed out at pages 2565-66 the challenges those reactions pose, as follows:

> There are only a very small number of naturally occurring fluorinated carbohydrate compounds, an example of which is nuc1eocidin (53), an antibiotic isolated from streptomyces clavus. Because of their low natural abundance, but widespread utility and acidity, the syntheses of fluorinated carbohydrates are of great importance. However, because numerous protection and deprotection steps are required to set up the desired hydroxyl group for substitution with fluorine, introduction of fluorine into a carbohydrate moiety is difficult. Deoxofluor (1) and DAST (2) have been utilized for such molecules (Table 2)
>
> [Emphasis added]

[535] During his cross-examination Dr Wnuk, as he was expected to do as an expert assisting the Court, acknowledged that the piecing together of various references pulled from articles treating a wide variety of situations could produce what at the time could only have been a theoretical route to synthesize the 2'-C-Me/F compound. It in no way convinced the Court that Dr Wnuk, the only expert testifying with an expertise in fluorinating these compounds at the time in question, was not correct in concluding that there existed no common general knowledge that a DAST approach should be followed to synthesize the 2'-C-Me/F compound in 2004.

[536] Finally, in the alternative, I conclude that being drawn to a reagent, or it being a first choice, does not constitute common general knowledge or meet the requirements of section 27(3)(b). It cannot be otherwise, because routine experimentation cannot serve the purpose of establishing the correctness of the choice. To be common general knowledge in relation to the synthesis of a compound, the statement must possess some fore-ordained degree of near-certainty, to be confirmed, not proven, by routine experimentation. Nor would a first choice of the key synthesis reagent be a sufficient basis for going forward.

[537] Similarly, section 27(3)(b) requires that the description of how to make the compound be almost certain, with some scope for routine experimentation to make the invention work. Otherwise, this would not be "set(ting) out clearly the various steps in … making … a …composition of matter, in such full, clear, concise and exact terms" as to enable its synthesis. The statement from the common general knowledge cannot be a description of a likelihood, or a sound prediction of a choice of a route, or key reagent to follow to synthesize a compound. That would not be sufficient hard coinage for a monopoly.

(d) *Toluene as the solvent for DAST reactions*

[538] As described in the excerpt above, Dr Damha is of the view that once the choice of DAST is made, the rest is "routine trial and error experimentation expected of a skilled chemist." This view extends to both the choice of toluene as a catalyst and the conditions for its employment.

[539] In my mind, the resort to toluene as a reagent raises an issue of where common general knowledge ends and trial and error experimentation begins. The conditions for use of toluene, if

accepted as the common general knowledge, to be employed with the DAST reactions in the circumstances, would nevertheless require consideration of the issue of whether the experimentation for its use would be undue.

[540] In either event, if resort to toluene is a matter of trial and error experimentation, I find on the evidence of the experts, that its employment in the successful synthesis of the 2'-C-Me/F compound would be undue.

[541] I am in agreement with Dr Wnuk that it was not common general knowledge that the synthesis of the 2'-C-Me/F nucleoside using DAST or Deoxo-Fluor® required the critical steps of the use of toluene as the solvent, or that the temperature of the solution should be -20 degrees as applied in Jeremy Clark's successful synthesis.

[542] The evidence of Idenix on the use of toluene was provided by Dr Damha at para 247 and 48 of his reply report as follows:

> [247] Another thing that Dr Wnuk says is that toluene is not a solvent typically chosen for DAST reactions (para 212 of his report). However, this is contrary to two papers that he cited in his report. In Singh, [supra], the authors discuss the applications of Deoxo-Fluor and DAST as the most widely used methodologies to introduce fluorine in organic compounds. The authors state at page 2576:
>
> > Fluorinations with 1 [Deoxofluor] and 2 [DAST] were most frequently conducted in anhydrous solvents such as CH_2Cl_2, $CHCl_3$, CCl_3F, hexane, isooctane, toluene, H_2O and glyme.
>
> [248] Yang S.S. et al. (1993) Carbohydrate Research 249:259-263 was also cited in Wnuk's report, and also discusses the use of

> DAST in toluene. These references show that toluene was known as a solvent that could be used for DAST fluorinations in the early 2000s.
>
> In any event, other solvents including dichloromethane (DCM; CH_2Cl_2) also work for DAST fluorination. Regardless, the choice of solvent is another distraction, as it is a factor that can be routinely modified by a skilled person, and therefore would not be determinative of whether a skilled person would be able to make a DAST fluorination work in a routine manner.
>
> [Emphasis added]

[543] Dr Wnuk points to the article by *Singh*, reviewing the literature to the effect that all the DAST or Deoxo-Fluor® examples used dichloromethane as the solvent listed, not toluene. The *Singh* article listed toluene as the fifth or sixth option in the review based on papers of many other scientists where DAST or Deoxo-Fluor® was used for the conversion. Dr Wnuk notes that "nobody is talking on (sic) the toluene, and those were the papers of many other scientists which were using DAST for the conversion". The only article cited in the literature where toluene was used with DAST appears to be that of Dr Yang. The *Singh* article provides no other references, which explains perhaps why it is found at the end of the solvents used with DAST type reagents.

[544] Dr Wnuk also points out the critical nature of the selection of toluene as the solution for DAST and the temperature for the reaction. The *Singh* article states on page 2562 that "For most of the compounds, fluorination proceeds below room temperature, sometimes as low as -78°C". This is a range of almost 100°C. The *Yang* article reported that the toluene used with DAST was heated for 10-15 minutes at 70-75°C.

[545] The Court also relies upon Dr Wnuk's observations at paras 190 to 194 of his first report that the use of toluene at a temperature of 20°C, along with the cytosine base (instead of uracil), was critical for the success of Dr Stewart and Ms Wang in ultimately synthesizing the 2'-C-Me/F nucleoside. Idenix appears to make no attempt to contradict this evidence, other than objecting to the introduction of Dr Stewart's evidence, but not that of Ms Wang. I set out Dr Wnuk's evidence in full because Idenix is relying on its employees eventually synthesizing the 2'-C-Me/F compound, even though it refused to admit the transcripts of Dr Stewart's testimony in the United Kingdom case.

> [190] Of importance, the fluorination reaction discussed by Dr Stewart on page 135 of his laboratory notebook 081 was conducted in a toluene solvent. As was known in the art, toluene is not commonly used as a solvent for DAST and would not have been the solvent of choice by a skilled person for conducting fluorination reactions with DAST. It is worth noting that toluene was not even used by Dr Stewart in his previous attempts when using DAST. However, toluene was the solvent used and described by the WO Clark Publication to obtain 2'-fluoro(down)2'-methyl(up) nucleoside compounds using DAST. Although I do not know for certain, given the reaction conditions used by Dr. Stewart, I believe he used the teaching provided in the WO Clark Publication to help him with his attempt to synthesize the 2'-fluoro(down)-2'-methyl(up) nucleoside.
>
> [191] In reviewing Ms Wang's notebook, it appears that during the month of December 2004, Ms Wang attempted to synthesize a fluorinated nucleoside having a 2'-methyl (up) and a 2' fluorine (down) using a nucleoside compound containing uracil as a starting material. Ms Wang attempted to fluorinate the starting nucleoside with DAST (in a DCM solvent) but failed due to reorganization which is, as indicated above, a common occurrence when using this reagent.
>
> [192] In January 2005, Ms Wang started using another nucleoside compound bearing cytosine (instead of uracil) as starting material for the fluorination reaction. I note that, as of January 13, 2005, the WO Clark Publication had been published and suggested to use, as a starting material, nucleoside compounds bearing a protected cytosine as a base. Ms Wang protected the nucleoside compound

> bearing a cytosine (e.g., at the 3' and 5' positions of the sugar moiety as well as the base) using the same protecting groups as those taught by the WO Clark Publication. Ms Wang then made an intermediate containing a ketone at the 2' position of the sugar of the protected nucleoside to introduce a methyl substituent at the 2' (down) position of the sugar moiety using the methodology described in the WO Clark Publication. Following the introduction of the methyl substituent at the 2' (down) position, Ms Wang changed the protecting groups at the 3' and 5' positions of the sugar moiety to those suggested in the WO Clark Publication. Finally, in March 2005, Ms Wang attempted to fluorinate a protected nucleoside compound at the 2' position using DAST under the conditions taught in the WO Clark Publication.
>
> [193] I note that the fluorination reaction discussed by Ms Wang in her lab book entry of March 9, 2005 was conducted in toluene at a temperature of -20 o C. As indicated above, toluene would not have been considered to be the solvent of choice for conducting fluorination reactions with DAST. However, toluene was the solvent used and described by the WO Clark Publication to obtain 2'-fluoro(down)2'-methyl(up) nucleoside compounds.
>
> [194] It is interesting to note that in her laboratory notebook 073, Ms Wang refers to the process of the "patent" or the "Pharmasset patent" without providing a specific reference to identify such document. However, it seems that this reference is likely to the process and methodology described in the WO Clark Publication since Ms Wang appears to have used the experimental conditions provided in the WO Clark Publication.

(3) Excess of Choice

[546] Dr Damha, recognizing the significant amount of choice facing someone setting off to synthesize the 2'-C-Me/F compound, states as follows at para 250 of his reply report:

> [250] Despite the wealth of literature available to the skilled person, Dr Wnuk also provides sweeping comments that many possible routes need to be tried, many different fluorinating agents or other reagents available throughout the process with no expectation of success (paras 112-5). I do not think that excess

> choice would mean that a given transformation would not be routine. Rather, choice provides a safety net to the chemist in the event that one of the choices unexpectedly does not work as planned. More importantly, this ignores the schemes in the '191 Patent relating to 2'nucleosides that can be used as logical starting points. To the extent Wnuk is suggesting that there are other ways to accomplish the conversion of an alcohol on a nucleoside to a fluorine, I agree. Unless he proves, which he has not, that these don't work his point is meaningless.
>
> [Emphasis added]

[547] The evidence does not support Dr Damha's views. A wealth of literature available to the skilled person setting out choices is not any indication of whether the synthesis of the compound was common general knowledge. Certainly, routine trial and error experimentation does not occur where there is an excess of choice, not to mention that an excess of choice entirely excludes the possibility that the disclosure of the 2'-C-Me/F compound could be made by common general knowledge. In addition, I have already pointed out that the minimal inferred information contained in the '191 Patent provides no logical starting point to synthesize the 2'-C-Me/F compound, contrary to Dr Damha's assertions.

[548] I also disagree that Dr Wnuk's evidence can be characterized as demonstrating other ways to accomplish the conversion of an alcohol on a nucleoside to a fluorine. His evidence demonstrated that Idenix did not meet its obligation to disclose how to synthesize the 2'-C-Me/F compound. He concluded that the fact that, in hindsight, individual steps in a chemical synthesis have some precedent in the literature does not mean that the overall sequence of steps for making a new compound was easy to determine. Most new compounds are made using reagents and methods that have been reported previously in the literature. However, determining the proper sequence of reactions to conduct, and the appropriate reagents for carrying out each step, often

requires significant creativity and/or an extensive amount of experimentation. I agree with these views, without making any finding on whether making the 2'-C-Me/F compound was an inventive step.

(4) Reliance on Pharmasset Work

[549] I agree with Gilead, that Idenix cannot rely on what Pharmasset had accomplished, which was not known to them when the Application was published. As there was no literature describing or available information explaining how the 2'-C-Me/F compound should be synthesized, there would be no common general knowledge that there was any synthetic route for its synthesis.

E. *Dr Griffon's Work*

[550] Dr Griffon is a central figure in this litigation for a number of reasons. First, he attempted to synthesize the 2'-C-Me/F compound using a wide variety of fluorination agents for a period up towards two years without success. His failures therefore, represent real-time evidence that synthesis of the compound by Idenix could not be completed in reliance upon common general knowledge and routine trial and error experimentation.

[551] Second, it is for this very reason, that, everything else aside, if Idenix cannot provide an explanation for Dr Griffon's lack of success, its claim must fail. Idenix's argument is that Dr

Griffon did not conduct himself as would a skilled chemist, and moreover misstated the results of his experiments, thus preventing his supervisors from correcting his alleged inadequacies.

[552] Third, and a somewhat inconvenient corollary to his alleged incompetence, Idenix is also attempting to demonstrate that Dr Griffon successfully synthesized the compound without knowing it. Idenix attempts to prove this by a simulation said to be carried out by AMRI of Dr Griffon's Deoxo-Fluor® experiment on synthesizing the 2'-C-Me/F nucleoside in February 2003. I will deal with all of these contentions below.

(1) Dr Griffon's Attempts to Synthesize the 2'-C-Me/F Compound

(a) *Dr Griffon and Idenix's Nucleosides Analogues Group*

[553] Dr Griffon is an experienced synthetic chemist who had synthesised hundreds of molecules, most of them nucleosides, over the course of his training and time at Idenix. Between 1994 and 1998, Dr Griffon obtained his PhD in Dr Jean-Louis Imbach's lab at Montpellier where his PhD supervisor was Dr Gilles Gosselin. Both are recognized as highly competent senior chemists in their fields. During the course of his PhD thesis, Dr Griffon made a number of 2' and 3' fluoro substituted nucleosides. Following his PhD, Dr Griffon did a two year postdoctoral fellowship at the Southern Research Institute in Birmingham Alabama in a lab headed by a well-known nucleoside expert named Dr Jack Secrist.

[554] Dr Griffon joined Idenix in February 2001 in Montpellier France, in the Nucleosides Analogues Group. At the time, the same Dr Gosselin who had supervised Dr Griffon's PhD was

the director of research at Idenix. In and around 2004, Dr Griffon's job responsibilities included conducting literature searches, developing novel synthetic strategies, carrying out those strategies, and analyzing reaction products.

[555] Dr Griffon carried out his own TLC analysis and had access to nuclear magnetic resonance NMR and MS at Montpellier. Dr Griffon did not have access to liquid chromatography-mass spectrometry LC/MS (the process that combines the separation and characterization of reaction products in one step) until 2006.

[556] Dr Griffon reported directly to Dr Gosselin and to Dr Storer, the latter being the senior vice president of chemistry at Idenix who split his time between Montpellier, France and Cambridge, Massachusetts.

[557] Drs Gosselin and Storer directed the chemistry efforts at Idenix. Part of Dr Griffon's job was to work with them on novel compounds and to see if new compounds could be synthesized. This involved reviewing literature and, if necessary, adapting literature to new applications.

[558] Dr Griffon was assigned the task of synthesising a 2'-C-Me/F nucleoside in March 2002. Initially, the 2'-C-Me/F compound was not Dr Griffon's priority, but by July 2002, this compound had been designated as a "high priority". Dr Griffon was assisted by Audrey Chappe, a technician in the lab, and Elodie Pecheux, a trainee student.

[559] Dr Griffon and those assisting him, planned and executed a number of different general strategies for synthesizing a 2'-C-Me/F compound between March 2002 and the summer of 2004. In the period of 2002 to 2004, the Nucleoside Analogues Group at Idenix Montpellier, included Drs Griffon, Storer and Gosselin who met every two months or so to review progress and identify target molecules and timelines. These meetings lasted approximately 2-4 hours on average and were summarised in a series of reports that were then circulated to the chemists.

[560] In addition to these group meetings, Dr Griffon had other meetings directly with Dr Storer and often discussed chemistry problems or issues with the other PhD level chemists at Idenix including Drs David Dukhan, Frederic Leroy, and Jean-Christophe Meillon.

[561] Dr Griffon's work was summarized in monthly reports. Copies of these reports were sent to Drs Storer and Gosselin on a monthly basis, with copies sometimes to Dr Imbach. The purpose of these reports was to explain Dr Griffon's synthetic efforts and achievements. Dr Griffon believes that his lab notebooks and monthly reports are an accurate record of his synthetic attempts. On cross-examination, Dr Griffon acknowledged that he does not have clear memories of his work between 2002 and 2004 separate and apart from looking at the documents.

[562] In addition to his monthly reports, Dr Griffon summarised his synthetic efforts and literature searches in a report prepared at the end of the project. In this final report, Dr Griffon reported on his experiments, many of which were tried a number of times, using a number of different reaction conditions and involving a mix of nucleophilic and electrophilic fluorinating agents.

[563] On March 28, 2002, at an Idenix Montpellier Chemistry Meeting attended by Drs Storer, Gosselin and Imbach among others, Dr Griffon was given the task of synthesizing a 2'-C-Me/F nucleoside. At the time, Dr Griffon's priority was to make a 2'-methoxy (also described as OCH_3) (down) nucleoside and he was also asked to make a number of other nucleosides with 2'-methyl (up) and various groups at the 2' (down) position. Between 2002 and 2004, Dr Griffon worked on other projects as well.

(b) *Literature Searches*

[564] Dr Griffon commenced his efforts with literature searches. These appear to have been discussed at the May 2002 Idenix Montpellier Chemistry Meeting. Idenix has criticized the manner in which Dr Griffon carried out the literature searches, indicating that they were too restrictive in the substituents entered into the Scifinder search engine and consequently did not turn up as many relevant articles as could have been found if properly done. This will be discussed below.

[565] The results of Dr Griffon's literature searches were presented in an Idenix report on June 27, 2002. His initial search using a general formula for 2'-methyl-2'-substituted nucleosides (with a methyl group in the 2' (up) position and various groups in the 2' (down) position, including a tertiary fluorine), yielded no results. Consequently, Dr Griffon understood at the time that he was being asked to carry out a novel synthesis.

[566] Dr Griffon also searched using a general formula for a tertiary fluoride structure. Dr Griffon explained that he did so because he could not find any references to a sugar or nucleoside

with a fluoro methyl group (where a methyl group and fluoro atom attached as substituents to the same carbon) so he extended the search to more general structures. This search gave 48 results for a tertiary fluorine.

[567] Dr Griffon refined his search to look for the fluorination of a tertiary alcohol, and this search yielded two results. He carried out another refinement using a search for the transformation of an epoxide to a linear molecule containing tertiary fluorine, and this yielded two results. Dr Griffon conducted these searches in order to explore different potential strategies for introducing a fluorine atom at the 2' position.

[568] Based on all of the searches that he did, Dr Griffon proposed a synthetic route to 2'-C-Me/F nucleosides in his June 2002 report. This route was based on synthetic strategies for installing fluorine at the 4' position. In his report, Dr Griffon set out scientific references relating to 4' fluorinated nucleoside derivatives before setting out his proposal, which was a 2'-ethenyl nucleoside strategy.

[569] By July 2002, the 2'-C-Me/F project was described as a "high priority" in a summary of a presentation given by Dr Griffon at an Idenix Montpellier Chemistry Meeting at that time. Dr Griffon noted in his summary that the proposed synthetic strategy had to be refined in order to be started as soon as possible.

[570] Dr Griffon explained on cross-examination that the "high priority" designation meant that "the main chemistry effort either by me or Audrey [Chappe]" had to be the 2'-C-Me/F

nucleoside. This is reflected in a summary of an Idenix Montpellier Chemistry Meeting held a little later in July 2002 where the 2'-C-Me/F target was described as a "new synthetic priority for Jean-François Griffon" and matched Dr Griffon's recollection of the project at that time.

[571] Starting in September 2002, he proposed a series of strategies using different fluorination agents to synthesize the 2'-C-Me/F compound. Strategies 1 to 6 were nucleoside strategies, while the remaining strategies were sugar ring approaches.

(c) *First Attempts at the Synthesis of the 2'-C-Me/F Nucleoside*

[572] He first proposed a 2'-ethenyl nucleoside strategy with silver fluoride (AgF) as the fluorinating reagent. He determined that only two compounds had been synthesised, neither of which was the desired fluorinated nucleoside.

[573] In light of this, Dr Griffon made two further nucleoside proposals in his September 2002 report. One proposal was another 2'-ethenyl nucleoside strategy, using HF/pyridine AlF_3 as the fluorinating reagent. The other involved the reduction of a protected 2'-iodomethyl (down) anhydro nucleoside (which was an undesired product of the failed first 2'-ethenyl strategy) followed by fluorination of the protected 2'-methyl(down) anhydro nucleoside with HF/pyridine, AlF_3. Neither was successful as reported in the November and December 2002 reports.

[574] Dr Griffon met with Dr Storer, Dr Gosselin and Professor Fleet in December 2002. They discussed Dr Griffon's work on the 2'-anhydro nucleoside strategy, and Professor Fleet proposed a synthetic strategy which involved the use of a positive fluorine source (an electrophilic

fluorinating reagent) reacting with a carbon-carbon double bond in a sugar. Gilead points out that Professor Fleet, recognized as a brilliant carbohydrate chemist, did not propose the fluorination of a tertiary alcohol with DAST or Deoxo-Fluor®.

[575] In January 2003, Dr Griffon continued his work on the synthesis of a 2'-C-Me/F nucleoside. In his Progress Report he noted that "starting from the 2'-ethenyl derivative [i.e. Strategies 1 and 2] … all the attempted experimental conditions failed". Dr Griffon also noted that he was unable to complete the reduction, being the first step of his third Strategy.

[576] In the January report, Dr Griffon indicated that he would be trying an unprotected nucleoside under several experimental conditions. The various attempts involved fluorination with: i) HF-pyridine, AlF_3 at 80° C and 120° C (Strategy 3 above, but without 3' and 5' protection); ii) KF, Kryptofix 2.2.2, pTsOH, DMF, reflux (Strategy 4); and iii) KHF_2 refluxed in either ethylene glycol or 2-methoxyethanol (Strategy 5). The February 2003 Progress report stated that none was successful.

(d) *Letter Seeking Assistance from Dr Coe on the Fluorination Step*

[577] In February 2003, Dr Storer of Idenix wrote Dr Coe, a consultant who the Court recognizes was an expert in fluorine chemistry. In his letter, Dr Storer described a number of targets of interest to Idenix and asked for Dr Coe's suggestions on how they might go about synthesizing them. In the first paragraph of his letter Dr Storer noted that "[w] e are OK with the nucleoside chemistry, it's the fluorine chemistry we are struggling with and where your help will

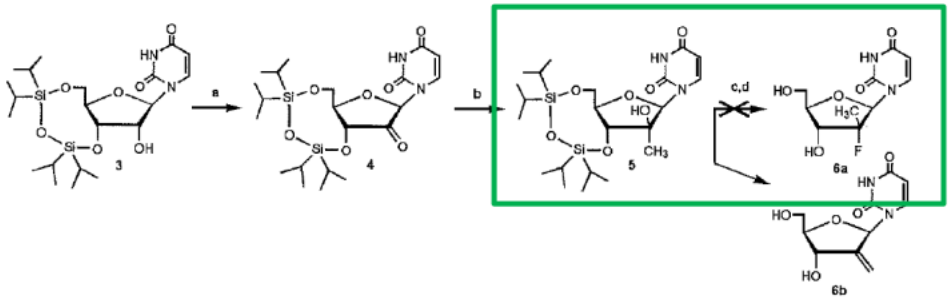
be valuable." In the section of his letter discussing nucleoside analogues, Dr Storer noted that "we have a number of nucleoside targets which contain fluorine most of which we are struggling with. The targets are all ribonucleosides of one sort or another and have an additional substituent, usually a methyl group, at the 2'-position."

[578] Dr Storer went on to discuss the 2'-C-Me/F nucleoside, describing it as "an attempt to replace the tertiary OH of the ribo analogue with fluorine". Dr Storer stated that:

> We've tried a variety of procedures from the exocyclic methylene analogue in attempt to effectively add HF across the double bond. We had no success with that. We're now looking at attempting to take the 2'-α methyl anhydro compound and open that with fluoride. I'm not too hopeful for success with that. Appendix 3 shows a summary of this. Your thoughts on how to introduce the tertiary fluoro substituent in compound 1 would be appreciated.

(e) *The Deoxy-Fluor Fluorination of a D-Ribose Nucleoside with a Uracil Base*

[579] Dr Griffon's February 2003 progress report also sets out a summary of making a 3'-5'-protected 2'-C-OH/Me nucleoside and then fluorinating it using Deoxo-Fluor® (which is also described in the report as bis-(2-methoxyethylamino) sulphur trifluoride). This is the experiment that AMRI attempted to simulate in 2014. Dr Damha testified that Deoxo-Fluor® is very similar to DAST and is thermally more stable over a range of temperatures than DAST. Dr Griffon's proposed synthesis was based upon the *Wachtmeister* article, wherein the substitution was of the tertiary C-4 hydroxyl group with a fluorine using Deoxo-Fluor® on the proper intermediate 2'-C-OH/Me nucleoside (molecule 5). The fluorination step in the strategy is highlighted in the diagram below.



[580] The February 2003 progress report records Dr Griffon's view in relation to the Deoxo-Fluor® experiment that "one new compound was formed during the reaction", and he identified this as a compound with a carbon-carbon double bond at the 2' position (a 2'-ethenyl derivative). His view at the time was that the reaction had failed. Dr Griffon repeated the reaction on 19 February 2003 using slightly different reaction conditions. Idenix argues that the 2'-C-Me/F nucleoside was in fact synthesized during this experiment. Idenix is highly critical of Dr Griffon in respect of his failure to separate and analyze the results, which is considered in detail below.

(f) *March 2003 LiF and TBAF as the fluorinating reagents*

[581] In March 2003, Dr Griffon made two new proposals for the 2'-C-Me/F project. One was a 2'-anhydro unprotected nucleoside strategy using LiF as the fluorinating reagent. The other was a 2'-methyl-arabino nucleoside strategy using $(CF_3SO_2)2O$ to make an intermediate and TBAF as a fluorinating reagent to displace the intermediate on a protected nucleoside.

[582] Dr Griffon's April 2003 progress report indicates that the reaction to fluorinate an unprotected 2'-anhydro nucleoside using LiF which he had proposed in March 2003 had failed.

(g) *Dr Griffon Attends a Fluorination Course*

[583] From April 1-4, 2003, Dr Griffon attended a fluorination course in Stratford-upon-Avon with one of his colleagues from Idenix, Dr Claire Pierra. They summarized what they had learned at the course in a report which they sent to Dr Storer who subsequently forwarded it to other Idenix chemists. Their email states that they "focused on the electrophilic and nucleophilic fluorine sources because we thought it was the most interesting part for our current chemistry." The course was called "Making and Using Fluoroorganic Molecules" and was given by Professor Jonathan Percy and Dr Alison Stuart. The report discussed numerous electrophilic fluorinating reagents and nucleophilic fluorinating reagents, and set out potential applications of some of those reagents for the synthesis of Idenix targets. There does not appear to have been any special consideration of DAST type reagents.

(h) *Dr Coe Replies*

[584] On April 9, 2003, Dr Coe replied to the letter which Dr Storer had sent him in February 2003. Dr Coe discussed the "more interesting nucleoside problems" and stated that:

> [i]n our experience and indeed in that of manner other particularly the de Clerc group the most viable routes to fluoro nucleosides are by base/sugar condensation methods the anomer problem not withstanding, for the very reasons you have discovered, in that the leaving groups generated in situ e.g. in DAST reactions are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of blocking groups. Further migrations of groups can readily occur. See our papers in JFC 1993 62 145 and 1993 60 239. Having said this some of the routes you have tried are OK except that I think you are using the wrong reagents, leaving groups and reaction conditions.

[585] Dr Coe went on to propose four different routes to the 2'-C-Me/F target compound. None of the methods proposed by Dr Coe involved the fluorination of a tertiary alcohol (in particular, a 2'-C-Me/F nucleoside or sugar) with DAST or Deoxo-Fluor®.

a. Method 1 involved the fluorination of a 2'-methyl (down) 2'-hydroxyl (up) sugar via an imidazole sulfonyl intermediate using Et3N●3HFE as the fluorinating reagent.

b. Method 2 involved a similar approach to Method 1, via an imidazole sulfonyl intermediate, but starting with a nucleoside instead of a sugar.

c. Method 3 involved the fluorination of a 2'-anhydro nucleoside with AHF or Bu_4NH_2F.

d. Method 4 involved the reaction of a tertiary alcohol with pyridine/HF.

(i) *Dr Griffon's Work from May 2003 to July 2004*

[586] A summary of the Idenix Montpellier Chemistry Meeting in May 2003 indicates that the 2'-C-Me/F project was "still a high priority" at that time.

[587] Dr Griffon's May 2003 progress report indicates that he had made "attempts for introducing the fluorine atom at the 2'-(down) position following Paul Coe's report".

[588] One of the strategies that Dr Griffon described in his May 2003 progress report is a 2'-methyl-arabino nucleoside strategy using an imidazole sulfonyl intermediate and $Et_3N \bullet 3HF$ as the fluorinating reagent adapted from the recommendation of Dr Coe. Dr Griffon determined that this step was unsuccessful.

[589] Dr Griffon's May 2003 report indicated that when he attempted the fluorination step of this strategy, "no reaction occurred; the starting material was mainly recovered."

[590] The other strategy which Dr Griffon described in his May 2003 progress report in the section referencing Dr Coe's report was a 2'-anhydro nucleoside strategy using $Bu_4\ NH_2F$ as the fluorinating reagent. Dr Coe proposed the reaction of a 2'-anhydro nucleoside with Bu_4NH_2F in his April 2003 letter in Method 3.

[591] In or around July 2003, Dr Griffon prepared a summary of his work on the 2'-C-Me/F project between September 2002 and May 2003. In that report, he also proposed an electrophilic fluorination sugar strategy involving fluorination of a 1,2-double bond with an electrophilic reagent, Selectfluor.

[592] The summary of the July 2003 Idenix Montpellier Chemistry Meeting indicates that the 2'-C-Me/F project was "still a high priority" at that time. The summary also notes that "a strategy starting from the corresponding fluorinated sugar might be the solution" and that "up to now, all procedures starting from a nucleoside were unsuccessful".

[593] Dr Griffon confirmed in his July/August 2003 progress report that the 2'-anhydro nucleoside strategy using Bu_4NH_2F derived from Dr Coe's report was unsuccessful.

[594] Dr Griffon's progress reports for September 2003 – January 2004 do not record him doing any work on the 2'-C-Me/F project. The project was discontinued at the Idenix Montpellier Chemistry Meeting held on 5 November 2003.

[595] In February 2004, Dr Griffon did further work on the 2'-C-Me/F project, attempting a 2'-ethenyl nucleoside strategy involving the fluorination of nucleosides with protected bases. However, Dr Griffon reported that this strategy had failed in February 2004.

[596] In March 2004, Dr Griffon sent Dr Gosselin a report regarding the various strategies which he had attempted and set out proposed sugar strategies. Dr Gosselin then sent the report to other members of the Montpellier team asking for their personal contributions to the project.

[597] In the summary of the April 21, 2004 Chemistry Meeting between Dr Storer, Dr Gosselin and Dr Griffon, it was noted that three different sugar strategies were in progress in order to synthesize a 2'-C-Me/F sugar. The proposed sugar strategies were:

a. Opening of a spiro α-chloroepoxide in a sugar.

b. Addition of an electrophilic fluorinating agent on a sugar 1,2-double bond.

c. Total synthesis of the sugar synthon.

[598] In his April 2004 progress report, Dr Griffon recorded work on these strategies. He discussed the opening of a spiro α-chloroepoxide on a sugar, and described the strategy as having been elaborated in collaboration with David Dukhan, a PhD chemist at Idenix. Dr Griffon reported that at that date they had not been able to synthesize the desired precursor for the fluorination step.

[599] The electrophilic fluorination of a sugar 1,2 double bond strategy using Selectfluor was also in progress in April 2004, and Dr Griffon reported that up to that point the strategy had not been successful.

[600] Finally Dr Griffon's April 2004 progress report also discussed the total synthesis of the sugar synthon strategy. This was the sugar strategy based on the method for making gemcitabine. That strategy was in progress as of April 2004.

[601] By May 2004, the opening of a spiro α-chloroepoxide sugar strategy was on "stand by" which meant that Dr Griffon did not perform any other attempts on that strategy.

[602] Dr Griffon also noted in his May 2004 progress report that the addition of an electrophilic fluorinating reagent on a 1,2-double bond sugar had failed.

[603] Work on the total synthesis of the sugar synthon (gemcitabine) strategy continued in June 2004.

[604] Dr Griffon made a further attempt at the electrophilic fluorination of a 1,2-double bond sugar in July 2004, but this did not produce a compound incorporating fluorine.

[605] Further work was also done on the total synthesis of the sugar synthon (gemcitabine) strategy in July 2004, but the aldol condensation failed.

[606] Dr Griffon's later progress reports suggest that no work was done on the 2'-C-Me/F project after July 2004.

[607] At the end of the project, Dr Griffon prepared a summary report setting out all the work that had been attempted in relation to the synthesis of 2'-C-Me/F nucleosides. After discussing literature searches, the attempted nucleoside routes, and the sugar routes, the conclusion of the report stated that "all the strategies that were attempted to introduce a methyl group at the 2'-'(up)' position and a fluorine atom at the 2'-(down) position failed". Dr Griffon sent his report to the Idenix chemistry team in Cambridge, MA.

(2) Did Dr Griffon Meet the Standards of a Skilled Person?

[608] The major hurdle to Idenix's sufficiency of its enabling disclosure is the inconvenient fact that Dr Griffon failed to make the 2'-C-Me/F compound, which Idenix attempts to prove was not the case, and that he made it but failed to recognize his success. As pointed out, if the Court cannot accept Idenix's arguments challenging the competence of its own employee's work, then any argument based on common general knowledge and normal trial and error experimentation must also fail, given his efforts to synthesize the compound without success.

[609] Idenix's strategy therefore, is to demonstrate that Dr Griffon made the compound supporting the contention that both he and Jeremy Clark succeeded demonstrating it was not difficult to do, at the same time to show he was incompetent, apparently to demonstrate that even incompetent chemists could make this compound with enough experimentation. This argument is then supplemented by the further submissions that he prevented his superiors and fellow chemists of the Idenix discovery chemical team from learning of his incompetence by misinforming them of his results.

[610] Idenix has made a number of allegations against Dr Griffon with the view to demonstrating that he was not a skilled chemist, which I set out below from its written submissions:

> [447] While Griffon's credentials may meet the level of the skilled person (in the Court's view, they exceeded them), his work or his conduct does not meet the level of what would have been expected of the skilled person. In particular, Griffon:
>
> a) Performed a flawed literature search and subsequently was led down a suboptimal path;
>
> b) Did not follow the two most pertinent results from his literature search;
>
> c) Routinely did not bother to analyze the products that he obtained from a reaction;
>
> d) Failed to follow the experimental conditions as described in prior art publications that he attempted to rely upon;
>
> e) Did not follow the explicit instructions from Drs Coe and Fleet and from the fluorination course;
>
> f) Drew incorrect conclusions and misrepresented the outcomes of his experiments in his monthly progress reports;

> g) Did not give his supervisors the opportunity to provide meaningful advice; his supervisors were only shown his incorrect progress reports, rather than his lab notebooks to know what Griffon or his assistant or student was actually doing;
>
> h) Exhibited a poor understanding of basic chemistry principles; and
>
> i) Exhibited poor judgment by allowing undergraduate students to carry out critical reactions.

[611] I do not find all of the allegations to be totally germane, or at least supportive of Idenix's argument. I therefore, take the liberty of restating what I understand its argument is in relation to these allegations, providing some preliminary comments where I think useful.

> (a) *Conducted a flawed search, including not following the two most pertinent results from his flawed literature search, and as a result, failed to immediately adopt a synthesis strategy using DAST (Points a) and b));*

[612] Dr Griffon conducted his search of the literature applying the regularly used search tool SciFinder. Dr Barrett indicates that he found no references to articles or other materials that referred to the 2'-C-Me/F compound. He understood that he was being requested to conduct a novel synthesis without any literature advising how to go about making the target compound.

[613] Dr Damha and Barrett claim that Dr Griffon incorrectly refined his search to exclude nucleosides or sugars by using the "CH 2" groups rather than "C" or "CH". They submit that he should have been aware that the target compound does not have such structural features and that this supposedly excluded many useful references. However, they did not point to any particularly important reference that was overlooked as a result of this refinement of his search. I do not see

this criticism as having any effect on Dr Griffon's decision to not initiate his synthesis using the DAST reagent.

[614] I am also troubled by the fact that it does not appear that Dr Griffon was given an opportunity to comment on this alleged failure on his part. All that Idenix did was confirm the nature of his searches. He should have been presented with the opinions of Drs Damha and Barrett and asked for an explanation of whether he agreed with their criticisms and whether it made any difference in the outcome of his work.

[615] Additionally, Dr Griffon could not recall whether this was a subject that he discussed with his superiors, given that more than a decade has passed since these events occurred. His searches were described in his reports and at least one presentation. This is just one of the topics that his superiors should have been called to speak to, if unsatisfied with Dr Griffon's work in 2002.

[616] Dr Griffon was also criticized for not following the two most pertinent results from his literature search. Dr Griffon admitted that he did not see the reference in the *Olah* article relating to the fluorination of a tertiary alcohol. However, this is not relevant to the use of the DAST reagent, as the article is a discussion concerning the reacting of HF pyridine with a tertiary alcohol. None of the experts commented on it.

[617] The report of his search results extends over 12 pages of various articles and materials. This might explain somewhat his overlooking an apparently irrelevant article.

[618] Dr Griffon was also criticized for not following the *Van Robays* article that turned up in his search, referred to above, in which the authors describe a tertiary alcohol being successfully converted into a tertiary fluoride with inversion of stereochemistry using DAST. Dr Wnuk noted that among the number of experiments described in the article, often the major product was a rearrangement, and not the desired fluorinated product. This is supported by Dr Coe's indication that fluorine reactions were "messy".

[619] In addition, I have already pointed out the very different structure of the starting material used in the article. Dr Wnuk considered it an important distinction that the article did not involve a nucleoside or ribose sugar. I accept his evidence that the *Van Robays* article described a successful substitution of the fluorine for a tertiary alcohol in a structure bearing none of the stereochemical challenges of the nucleoside or the ribo sugar. I also agree that it could not represent the common general knowledge or bear sufficient weight to direct Dr Griffon to use DAST as the reagent to synthesize the target compound.

[620] Moreover, Dr Griffon testified that his own work indicated that DAST gave very low yields, which is why he used Deoxo-Fluor® instead. This appears an accurate conclusion given the yields from Mr Clark's experiments. Idenix also hinted that Dr Griffon ought to have used DAST instead of Deoxo-Fluor® in his experiments. I accept the evidence that that Deoxo-Fluor® is a surrogate of DAST, and Dr Griffon's opinion that it was known at that time to be more stable and safer than DAST, and in some cases, more powerful. In any event, Idenix now claims that Dr Griffon successfully synthesized the 2'-C-Me/F compound using Deoxo-Fluor®, which puts that argument to rest.

[621] In this regard, I also reject any suggestion that the literature pointed to using the sugar approach rather than the nucleoside route, as Dr Damha tries to argue in his reference to the *Wachtmeister* article. Again this appears to be another irrelevant criticism, given that Idenix alleges that Dr Griffon was successful in fluorinating the ribose nucleoside, while Jeremy Clark apparently made the 2'-C-Me/F compound via both pathways.

[622] In addition, Dr Griffon described the technical problems faced at Montpellier in simply obtaining literature found in his searches. He testified that after the set of searches was done, the recovery of all the publications was a long process because at that time, the Idenix chemists had limited online access to materials. For the others, it was a tedious process either to go to the University library to physically make a Xerox copy of the publications, or alternatively with greater delays, to run the bureaucratic gauntlet by ordering the publication through the library department of the University.

[623] I have already found that the common general knowledge does not necessarily point to employing DAST or Deoxo-Fluor®. Moreover, Dr Griffon's supervisors and other experts consulted raised no objections with recommendations of fluorination by both routes. I do not find the evidence of Idenix's experts sufficient to demonstrate a failure on his part to conduct appropriate searches, or otherwise direct him to begin his synthesis using a nucleophilic fluorinating reagent.

[624] I also take stock in Dr Griffon's extensive experience in using different fluorinating agents, including using DAST to fluorinate a 2' or 3' secondary alcohol, with the other hydroxyls

protected with a benzoyl group. The topic of his thesis was to introduce fluorines at the 2' or 3' position of nucleosides. He was considerably more experienced and knowledgeable than the skilled chemist in the fluorination of nucleosides. He could be expected to rely on his own research and experience, particularly where, as Dr Wnuk stated, there was generally little expertise in the field in 2002-3.

[625] There is evidence that Dr Griffon had previously discussed his work with Drs Storer and Gosselin, and likely also his fellow chemists at Idenix. Dr Fleet had also been consulted and had not recommended a route using DAST. This evidence only confirms that there was no common knowledge that would necessarily have led Dr Griffon to start off on the DAST approach. It also confirms that he was attempting to synthesize a novel compound, with little direction. This in turn justifies the efforts of several months before he attempted the Deoxo-Fluor® experiments in February 2003. By that time, Dr Griffon had been working on the 2'-C-Me/F nucleoside project for about 10 months. He had tried a number of strategies and different fluorinating agents. Dr Coe's recommendations only arrived in April 2003 and they did not recommend fluorination of a tertiary alcohol on a sugar with DAST in any of the routes he proposed. Even if Dr Griffon had succeeded in his Deoxo-Fluor® experiment in February 2003, this would have only been after an excessive period of experimentation.

[626] I therefore reject the submissions of Idenix that Dr Griffon did not adhere to the approaches of the skilled chemist in not commencing his synthesis project by using DAST to fluorinate the 2'-C-OH/Me nucleoside, or that his literature search played any significant role in his choice of synthetic pathways.

[627] I also adopt Dr Wnuk's opinion that the routes selected by Dr Griffon were reasonable in the circumstances and required excessive experimentation if he was to succeed in inventing the 2'-C-Me/F compound

(b) *Routinely did not bother to analyze the products that he obtained from a reaction (Point c); and drew incorrect conclusions (Point f);*

[628] Idenix alleges that Dr Griffon was successful in synthesizing the 2'-C-Me/F compound when he employed fluorination approach using Deoxo-Fluor®, but due to inadequate analysis of the products failed to realize this.

[629] Two attempts were made by Dr Griffon to make the compound using Deoxo-Fluor® in February 2003. The first was on February 13, 2003 and the second on February 19, 2003. Only the first attempt appears to be the subject of comment by the parties. The experiment involves a number of steps, including the preparation or use of the intermediate 2'-C-OH/Me compound. None of his work in these tests appears to be the subject of criticism.

[630] Idenix argues that Dr Griffon's failure was in not analyzing the product of his synthesis, as the skilled drug discovery chemists would have done to determine all the compounds in the reaction mixture. Had he done so it argues, he would have realized that he had synthesized the 2'-C-Me/F compound. It supports these claims by the successful synthesis in the alleged simulation of Dr Griffon's Deoxo-Fluor® experiments that AMRI carried out in 2014.

[631] I do not accept these arguments for three reasons. First, I conclude that Dr Griffon exercised appropriate skill in conducting his experiments and in his decision not to analyze all of the reaction mixtures of his Deoxo-Fluor® experiment.

[632] Second, I am not satisfied that the Deoxo-Fluor® experiments conducted by Dr Griffon succeeded in synthesizing the 2'-C-Me/F compound, as claimed by Idenix.

[633] Third, Dr Griffon was constrained by his working environment at the University of Montpellier, which I find was a contributing factor to his not having employed mass spectra or NMR to analyze the reaction mixture claimed by Idenix to contain the target compound.

(i) Dr Griffon's Decision Not to Characterize a Reaction Product Because of its Lack of "Charring"

[634] After completing the Deoxo-Fluor® experiment, Dr Griffon carried out an HPLC analysis. This enabled him to determine that there were six or seven different compounds in the reaction mixture. He could not identify the compounds using this technology. The detection of compounds required an analysis using a Mass Spectra or NMR testing apparatus. It is a significant fact that Montpellier owned these testing apparatuses. It imposed restrictions on Idenix's capability to analyze compounds synthesized from its chemists' experiments.

[635] Dr Griffon purified and separated the crude reaction mixture using silica gel column chromatography. He eventually combined the separated product into three fractions intended to concentrate the compounds from the reaction. He identified the vials from the initial separation,

which he combined to make fractions. Fraction 1 of 27 mg was composed of vials 5-7, Fraction 2 of 20 mg was the combination of vials 8-9, and Fraction 3 of 72 mg was vials 10-14 (the starting material).

[636] Dr Griffon placed a drop from each fraction on the bottom of the TLC slide and drew a line above the three spots as a starting line. He placed the slide into a solvent which moves the products up the slide based on differences in solubility, polarity and absorption of compounds. The location of the compounds on the TLC plate can be determined by holding it under UV light.

[637] Additionally, he stained the plate with sulphuric acid. This causes the "spots" of the compound to become visible. This type of stain preferentially charcoals carbohydrates such as sugars.

[638] Spots containing sugars would be expected to char darkly when using a sulphuric acid stain. Compounds that do not contain carbohydrates (such as a base that was not successfully coupled to a sugar) will not char as darkly, whereas the 2'-C-Me/F nucleoside is a sugar that would char. TLC does not identify which compounds have been made, but gives an idea of whether a reaction occurred and can give some information about the nature of any products by the effect of the charring of stain carbohydrate spots.

[639] The final TLC plate from the experiment using the Deoxo-Fluor® as the reagent is set out below. It is important to note that it is depicted as taken from Idenix's written submissions along

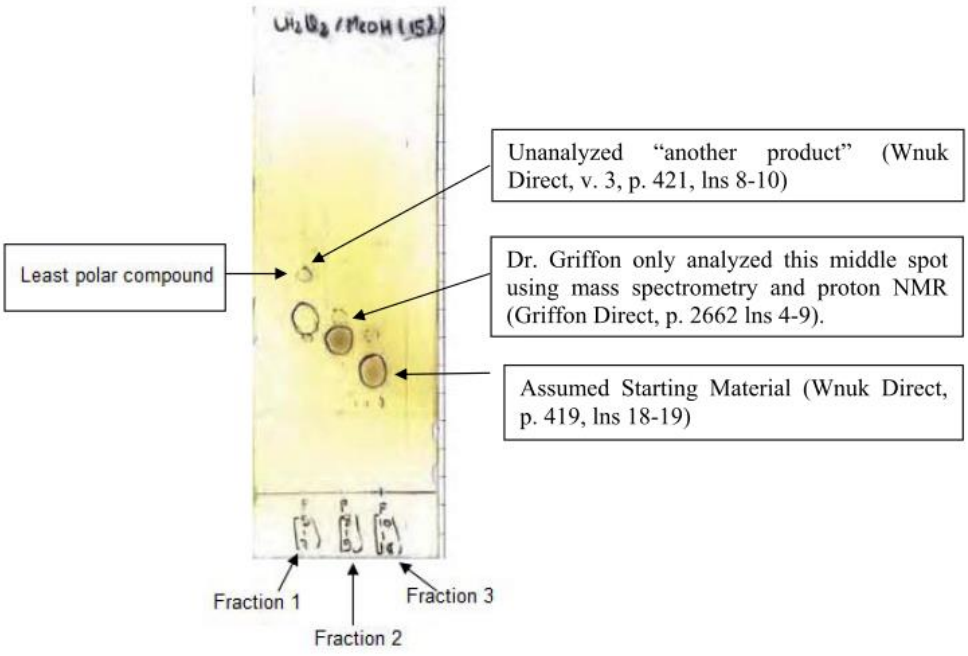
with its explanatory labels, about which more will be said below. The compounds contained in three fractions are in the vertical lanes with the visible compounds being circled in pencil.

[640] The evidence indicates that the compounds in the right-hand (starting material) and middle lane charred being indicative of sugar carbohydrates. There is no evidence of charring of the compound on the left lane.

[641] Dr Griffon acknowledged that he was not able to identify the compounds in the fractions from his experiment using the final TLC plate. To do so required analysis of the reaction fractions using the mass spectra or NMR testing apparatus.

[642] Idenix's comments identify the uncharred left-hand column as containing the product which it argues that the skilled chemist would have analyzed using mass spectra or NMR. Dr Griffon identified the product of Fraction 2 in the middle lane as a carbohydrate that could be a ribose nucleoside. It was analyzed using the University's mass spectra and NMR equipment and found not to contain the target compound.

[643] The right hand lane, although apparently a carbohydrate mixture by its charring, was not analyzed. Dr Griffon assumed it to be starting material. This does not appear to be in dispute.



[644] Dr Griffon was asked why he did not analyze all the compounds using mass spectra and NMR. His explanation was as follows:

> Q. Now why like, if you had three fractions separated, why didn't you run mass spec or NMR on all three fractions?
>
> A. Because, okay, because on this one I assumed that it was the starting material based on the TLC analysis.
>
> MR. JUSTICE ANNIS: Now just help me there, did you light something up on the screen?
>
> THE WITNESS: This one.
>
> MR. JUSTICE ANNIS: The bottom one, yes, okay.
>
> THE WITNESS: This one was identified
>
> MR. JUSTICE ANNIS: That is what you thought was the starting material, the one on the right hand lane?
>
> THE WITNESS: Yes, yes.
>
> MR. JUSTICE ANNIS: All right.

> THE WITNESS: And this one
>
> MR. JUSTICE ANNIS: You are looking at the one in the left lane now?
>
> THE WITNESS: Yes, was assumed as the base alone without the sugar, this one. And the reason why it is because it is not charring, so definitely there is no sugar attached on the base here.
>
> [Emphasis added]

[645] I find Dr Griffon's testimony to be clear on this issue. He concluded that the target 2'-C-Me/F nucleoside was not the product in the left lane of his experiment. His statement "definitely there is no sugar attached on the base here" was an expression of a strongly held opinion: there was no charring, therefore, it was not a carbohydrate, thereby eliminating the possibility of it being a 2'-C-Me/F nucleoside.

[646] Dr Wnuk agreed this was a reasonable assumption for Dr Griffon to make. The relevant portions of his opinion are found at para 15 of his Sur-Reply as follows:

> [...] In my opinion, these were reasonable assumptions for Dr Griffon to make. In particular, it would have been reasonable to assume that fractions 5 to 7 contain the uracil base as the corresponding TLC spot does not appeared to have charred darkly.
>
> [...] Spots containing sugars would be expected to char darkly when using a sulfuric acid stain. As the spots corresponding to fractions 5 to7 does not appear to be very dark, it suggest that sugars are not present in large quantities in the spots.

[647] Idenix's counsel did not attempt to pursue any discussion of Dr Griffon's assumption that the third lane product did not contain a nucleoside based on his comparative charring analysis.

Admittedly, he was called as Idenix's witness, which might have drawn objections had his evidence been pursued. However, the issue of the charring of carbohydrates was not considered in any of Idenix's experts' reports or testimony of its witnesses, nor was Dr Wnuk cross-examined on the subject. It should be noted that the issue also arose in the United Kingdom Sovaldi decision, so it is not as though Idenix would have been surprised by Dr Griffon's testimony.

[648] Instead, Idenix appears to have adopted a novel strategy in its final submissions. It distinguishes between the two-circled compounds in the left-hand lane. For the first time that the Court is aware of, it claims that Dr Griffon ought to have analyzed the upper spot or spots from the Fraction 1 mixture in the left lane.

[649] As far as the Court is able to determine, previous references in this case, and that in the United Kingdom, contained no distinction between the spots in the left-hand lane. Rather, the compounds in the left-hand lane were considered together for assessing the reasonableness of Dr Griffon's assumption that there was no sign of charring in the reaction mixture.

[650] However, from the labeling of the Idenix slide described above, it appears that Idenix indicates in its final written submissions provided after oral argument that the upper smaller circled compound ought to have been subject to further analysis by mass spectra or NMR. Idenix describes the upper spot as "unanalyzed" and references Dr Wnuk's evidence as calling it "another product."

[651] I disagree that Dr Wnuk, when referring to another product in the left-hand lane, was distinguishing between the larger lower and smaller upper spots.

[652] This testimony arose as a result of the Court's questioning in an attempt to better understand Dr Wnuk's evidence, particularly given my inexperience with TLC analysis.

> MR. JUSTICE ANNIS: So he analyzed 8-9, which is the one in the middle?
>
> MR. MARKWELL: Yes.
>
> MR. JUSTICE ANNIS: All right.
>
> BY MR. MARKWELL:
>
> Q. Do you believe that a skilled chemist would believe that that was a reasonable decision?
>
> A. Yes.
>
> Q. Are you able to determine what Dr. Griffon obtained?
>
> A. I think in his report --
>
> MR. JUSTICE ANNIS: Can you explain why it is reasonable?
>
> MR. MARKWELL: Sure.
>
> BY MR. MARKWELL:
>
> Q. You have come to the view that Dr. Griffon -- a skilled chemist would have believed that what Dr. Griffon chose to analyze is reasonable; why do you say that?
>
> A. Because analyzing [the] polarity of the compound, hydroxyl group was exchanged -- if the reaction was successful, [it] would have been exchanged with fluorine. So the product would be less polar and will move higher on TLC than the starting material.
>
> MR. JUSTICE ANNIS: What do you mean by "higher"? On the slide?
>
> THE WITNESS: It would be middle spot.

[653] Dr Wnuk was referring to the two large charred stains in the middle and right hand lanes when discussing Dr Griffon's decision to analyze the compounds in the middle lane, not those in the left lane. They both evinced evidence of being nucleoside carbohydrates by their charring, while the middle lane, because it had experienced the greater displacement of the two, would be indicative of the fluorine replacing the hydroxyl and thereby being situated above the right-hand compound on the TLC plate.

[654] Dr Wnuk was not referring to the left-hand lane, when addressing this issue. He had already agreed with Dr Griffon's assumption that it was unlikely to contain the fluorinated carbohydrate because it had not charred.

[655] In its final submissions, premised on the labeling of the upper compound in the left-hand lane on the TLC plate depicted above, Idenix now argues that the higher position in the left-hand lane meant that the spot could not have been a base which would not contain fluorine as it would be positioned lower on the TLC slide.

[656] Dr Barrett, who testified after Dr Griffon, did not address Dr Griffon's assumption that the left lane Fraction exhibited no charring. Indeed, even when addressing the issue of polarity and its impact on the movement of the spot containing the uracil base while commenting on the TLC depicted above, he did not point to any of the spots in the left-hand lane indicating that the highest one would likely be the spot containing the 2'-C-Me/F compound. His evidence was only that "it doesn't move very far, it doesn't go right to the top of the plate. It sticks more or less at the bottom."

[657] Given the evidence before the Court at the time he testified, I conclude that Dr Barrett was not prepared to opine that the upper spot likely contained the 2'-C-Me/F compound. Given that he also did not challenge the charring theory, I find that his evidence cannot be said to contradict Dr Griffon's assumption that the 2'-C-Me/F nucleoside with the sugar base was not present in Fraction 1.

[658] This submission appears to have arisen from a further question intended to assist the Court, as to the product in the third lane, as follows:

> MR. MARKWELL: And maybe I am obtuse, but what is the spot in the left column?
>
> A. In the left column is another product.
>
> Q. No, no, no. There are three columns on the TLC slide.
>
> MR. SMITH: You just gave the answer to him.
>
> I don't know what the answer is; I couldn't answer it.
>
> MR. JUSTICE ANNIS: He says it's another product. Another compound, I assume.

[659] As mentioned, all previous discussion focused on the large spots in the lanes which were being compared. There was no concept of the smaller upper spot or spots in the left-hand lane being the source of comparison. All the compounds in the left-hand lane had already been eliminated from consideration for lack of charring.

[660] In my view, it was up to Idenix to clarify that it was distinguishing between the circled compound spots on the left-hand lane in its evidence led from Dr Griffon or its experts. It was

aware of the controversy around the charring on the TLC plate from the previous litigation in other jurisdictions.

[661] It also was required to address the issue of the polarity of the base and its position on the TLC slide with Dr Griffon so that he could respond. I therefore attach no weight to this evidence. I accept Dr Griffon's assumption that no target compound was synthesized in experiments conducted on February 13, 2003.

[662] Any lack of success in synthesizing the target 2'-C-Me/F compound cannot be laid at the feet of Dr Griffon. It occurred for whatever reason related to all the variables such as the solutions and temperatures that affect the fluorination of a tertiary carbon on a ribose nucleoside. Perhaps it was due to the fact that fluorination processes are unpredictable, or "messy", as stated by Dr Coe in his letter. Maybe a faulty product prevented the synthesis, such as occurred with the DAST reagent that apparently affected experiments conducted by Pharmasset, described by Dr Patterson. Or else it was due to the fact that on a certain day, inexplicably a reaction did not work as was recognized by Dr Damha.

[663] In any event, the evidence does not establish that the 2'-C-Me/F nucleoside was synthesized on February 13, 2003, or that any lack of skill on the part of Dr Griffon contributed to the unsuccessful outcome.

[664] I conclude therefore, based on all the foregoing evidence that Dr Griffon carried out the fluorination experiment as a skilled chemist using the Deoxo-Fluor®o reagent and arrived at a

reasonable conclusion that the 2'-C-Me/F nucleoside had not been synthesized in the resultant product.

(ii) The Requirement to Characterize All Products of a Reaction in 2003

[665] I also disagree with the evidence of Dr Damha who, when discussing the TLC plates obtained by AMRI, stated "seeing those TLC plates, a skilled person would have proceeded to purify and characterize the products formed in the reaction." I accept Dr Wnuk's opinion which is more realistic that the skilled person would not have purified and characterized all products in 2003. It was pointed out that the TLC plates of both AMRI and Dr Griffon show that multiple products were observed. In some instances, at least 10 spots are observed in the TLC plate. Further, a number of the spots are more polar than the starting material. This suggests that protecting groups were lost from the starting material and/or reaction products or by-products.

[666] I accept that the skilled person would not have purified and characterized every product formed by such a reaction, if at all. Particularly, in observing the degree of manual effort to purify using silica gel chromatography, it would not have been efficient for Dr Griffon to purify and characterize every product formed in reactions when there were 7 to 10 compounds. I also accept that the more advanced purification technology of HLPC was not routinely used as a first purification method for every bench top reaction, as to do so would have been expensive and unnecessarily complicated. The skilled person would likely have used a silica gel column to purify the crude reaction mixture.

[667] In any event, the Court has always understood that it was the larger spot in the left-hand lane that Idenix argued should have been characterized. Dr Griffon came to the conclusion that it was not a sugar as it had not been charred.

(iii) Constraints on Analysis by Montpellier

[668] I also comment on Dr Griffon's evidence that he was constrained by Montpellier's protocols that required reaction samples to exhibit a degree of purity and yield for characterization by its mass spectra and NMR equipment.

[669] When this issue was first raised by Dr Griffon, he indicated that the standard procedure imposed by the University was to perform NMR and mass spectra on pure compounds, by which he meant after being purified by silica gel chromatography.

[670] Later, when Idenix's counsel followed up on this answer, Dr Griffon reiterated that he was required to provide "pure compounds". He added that to perform a NMR analysis on fluorine "more than 12 milligrams pure" was needed. For mass spectra, he indicated that only 1 mg was required. He did not state, nor did anyone question him on, the degree of purity required to meet the University's standards.

[671] The Court has little information on why these limitations were imposed, or the details of how these constraints were applied to prevent analysis of the mixture depicted by the spots in the left-hand lane of the TLC slide. However, Dr Griffon referred twice during his testimony to these limitations as a factor that prevented a follow-up analysis being conducted using mass spectra or

NMR. This is in addition to his being satisfied that the untested product was not a sugar, because it showed no sign of charring.

[672] Idenix argues that it is unclear why this limitation was imposed by the University. It also argues, with obvious logic, that if unable to run these MS and NMR experiments, Dr Griffon would be left in a position where he did not have access to the basic analytical instruments that a skilled person would, should have had at his or her disposal.

[673] This may be so, nevertheless, this evidence was entirely within the control and knowledge of Idenix and its witnesses who worked in collaboration with the University. The evidence was out of the mouth of Dr Griffon, an employee of Idenix called to testify on its behalf. Other witnesses should have been aware of these limitations. Dr Gosselin taught at Montpellier, while other Idenix staff would have been required to adhere to the same protocol. In the circumstances, without contradictory evidence, and finding Dr Griffon to be a credible witness, I accept that he was functioning in conditions that limited his access to the Montpellier's compound characterizing equipment. These problems would be those of Idenix, and not the responsibility of Dr Griffon.

(c) *Dr Griffon Misrepresented His Work Effort Denying His Supervisors the Opportunity to Provide Meaningful Advice (Point f)*

[674] Before I deal with the specifics of a criticism of a misrepresentation, or the remaining claims of incompetence made against Dr Griffon, I highlight that Dr Griffon's supervisors are in the best position to prove these allegations. Drs Gosselin and Storer supervised Dr Griffon during

this period. They are themselves highly regarded and competent chemists. There is no need to retain Drs Barrett and Damha to criticize Dr Griffon. The Court would give precedence to those involved in the events at hand who are in a position to describe the facts and provide their opinions of Dr Griffon's failures. Without their testifying, it is not clear how the Court could find against Dr Griffon regarding the following allegations:

1. Unknown to them Dr Griffon had conducted a flawed literature search;

2. He was acting without their knowledge or instruction on how he carried on his work; They were misled by Dr Griffon's reports and findings;

3. His failure to analyze all reaction compounds, and particularly those of the Deoxy-Fluor experiments was not standard practice at Montpellier and was a significant factor in Idenix's failure to synthesize the Compound;

4. Dr Griffon placed his research assistant working with him on DAST experiments, in what Dr Barrett thought were dangerous circumstances; and

5. Generally, that Dr Griffon had demonstrated a failure to understand basic chemistry principles.

[675] I also admit to having concerns about Idenix's treatment of Dr Griffon. He remains an employee of Idenix. Yet it is clear that he was called to testify to his own incompetence. I find this to be an intolerable position in which to place an employee. By my assessment, Dr Griffon came to court with the intention of helping out his employer, so long as he was not required to state any untruths, which I find to be the case.

[676] I have difficulty believing however, that he would have agreed to the subject of an all-out attack on his professional competence by his employer, its lawyers and highly regarded expert witnesses, making damaging allegations of the nature as set out above. I do not think he would have accepted to have someone of Dr Barrett's stature testify that his demonstrated incompetence was such that he would not have lasted two weeks in his employ. I also find it unlikely that he would have cooperated with Idenix's lawyers, if he had known that he would be addressed as "Griffon" throughout its submissions, when every other PhD involved in the case was addressed by their hard-earned title of Doctor.

[677] But regardless of the perceived lack of fairness in the treatment of Dr Griffon, I emphasize my substantive conclusion that without his supervisors testifying, there is no evidentiary basis for most of the claims against Dr Griffon. Only Dr Griffon's supervisors can provide the foundational facts upon which most of the experts' opinions rest. I find it a reasonable assumption that Dr Griffon's supervisors were not prepared to testify against a long-standing, apparently competent employee whom they do not blame for Idenix's failure to synthesize the 2'-C-Me/F compound.

[678] Despite the evidentiary shortcomings of the evidence against Dr Griffon, I will nonetheless respond to the key criticisms being made against him, particularly as I conclude that they are groundless or irrelevant to the issues at hand.

[679] The evidence on Dr Griffon's alleged misrepresentation is as follows:

Q. And do you see the fourth line from the bottom of the paragraphs at the bottom?

A. Yes.

Q. One new compound was formed during the reaction?

A. Yes.

Q. If we looked at either the HPLC or the fractions that you separated?

A. Yes.

Q. Your report, it doesn't seem to align?

A. Yes. No. No, it doesn't.

Q. Why did you -- did you ever tell Dr Gosselin or Dr Storer that you actually obtained more than one compound during this?

A. No.

Q. Why not?

A. Because this was a summary, and I wanted [went] to the end point of my conclusion, and my conclusion was the main, the only compound as a main product formed was the -- was not the target compound.

Q. And that is not consistent with the results of your experiment; is it?

A. No, it's not.

[680] This is what I would describe as an example of Dr Griffon going along with his employer by not attempting to provide any real explanation of what occurred.

[681] First, from the foregoing evidence it is apparent that Dr Griffon concluded that the only compound that could have been the target compound, i.e. the middle lane, was not the target

compound. He did not need to state that the other compounds were eliminated because they did not char.

[682] Second, from the comments of Drs Damha and Barrett about the 7 to 10 compounds described on the HLPC printouts and those of the AMRI experiments, it seems obvious his supervisors would have expected more than one compound from a reaction mixture involving the fluorination of a nucleoside. It is difficult to believe that his supervisors and the other members of the drug discovery team, with whom the evidence shows Dr Griffon discussed his work, would not know that many minor products would result from his experiments. A factor in this conclusion is that Idenix's complaint is now addressed not at the large uncharred spot on the left lane, but the smaller ones up above it.

[683] Third, Dr Griffon has testified that only larger yield purified reaction mixtures could be submitted to Montpellier's Chemical Department, where apparently Idenix stood in line with students and everyone else in being required to fill out forms and wait a number of days to receive results of their analysis. It is difficult to believe that his supervisors and his co-workers would not to know about these operational restrictions limiting the number of compounds that would be analyzed in a reaction.

[684] Fourth, Dr Griffon testified, as is expected, that he has no memory of the events in 2003. He could recall whether or not he had discussions with his supervisors and other chemists about the Deoxo-Fluor® experiment. It is unfair to Dr Griffon to raise an issue like this a decade later when his ability to respond is limited.

[685] Finally, there is no motive or reason for Dr Griffon to mislead his supervisors. His notebooks demonstrate that he was a meticulous chemist. It is also apparent that he was dedicated to achieving the synthesis of the target compound. There is no basis to conclude that he would leave out information that was not known to be required to be shared with workers with whom he had worked closely over a number of years.

[686] I do not find that Idenix has established that Dr Griffon either misreported his results by leaving out information that his supervisors expected to be presented to them, or that they were misled by his reports, particularly as they did not testify.

(d) *Failed to follow the experimental conditions as described in prior art publications that he attempted to rely upon (Point d); Did not follow the explicit instructions from Drs. Coe and Fleet and from the fluorination course (Point e); Exhibited a poor understanding of basic chemistry principles (Point h); Exhibited poor judgment by allowing undergraduate students to carry out critical reactions (Point i)*

[687] I do not propose to respond to any further attempts by Idenix to destroy its own employee's professional reputation, apart from some very brief remarks that Dr Griffon did not follow Dr Fleet or Dr Coe's advice.

[688] I am not aware of any specific advice Dr Fleet may have provided Dr Griffon. I have already pointed out that Dr Coe did not in fact recommend DAST in the schemes proposed, but only mentioned it in an introductory general statement in passing as an example of his advice to adopt the sugar ring approach as opposed to the nucleoside starting material. It turns out to be an

irrelevant criticism, but in any event Dr Griffon gave valid reasons to prefer Deoxo-Fluor® over DAST, including being based upon his own experience in working with both products.

[689] In conclusion, with respect to the allegations against Dr Griffon, I find that it has not been established that he failed to act as a skilled chemist in the following respects:

1. in his searches and conclusions drawn from his searches;
2. in not immediately adopting a synthesis route using DAST or Deoxo-Fluor®;
3. in purifying and characterizing the results of his experiments;
4. in the information provided to his supervisors related to the results of his searches and experiments; and
5. in his attempts to synthesize the 2'-C-Me/F compound, which I find it most likely were unsuccessful for reasons unrelated to any lack of competence on his part.

[690] I also conclude that if Dr Griffon had synthesized the 2'-C-Me/F compound in February 2003 it required undue research and experimentation to do so.

F. *The AMRI Experiments*

[691] The second leg of Idenix's strategy to demonstrate that Dr Griffon successfully synthesized the 2'-C-Me/F compound relies upon alleged simulations of his experiment on February 13, 2003 by AMRI in 2014. AMRI successfully synthesized 2'-C-Me/F compounds in

both sets of experiments. This apparently is intended to support its argument that the synthesis of the compound by a DAST or Deoxo-Fluor® catalyst was a matter of common general knowledge.

[692] However, I find that the experiments did not faithfully simulate those of Dr Griffon. I conclude that AMRI had access to technology that allowed it to both synthesize and characterize the 2'-C-Me/F compound more readily than could Dr Griffon in 2003. I also give less weight to the tests due to concerns about their confidentiality as directed by Idenix.

(1) First Tests Conducted in Secrecy

[693] AMRI carried out two simulated experiments of Dr Griffon's February 2003 Deoxo Fluor® synthesis procedure. Gilead had no knowledge of the first test conducted in June 2014. Idenix later advised Gilead of the first experiment and was invited to attend the second one. Gilead sent a representative to observe the August 2014 experiment.

[694] Gilead justifiably argued that the Court should disregard the June experiments because they were conducted in contravention of the Federal Court's Notice to the Parties and the Profession regarding Experimental Testing, even though issued on November 27, 2014. Given that I find that neither test establishes that Dr Griffon successfully synthesized the 2'-C-Me/F compound in February 2003, I find no reason to reject the first test. I do, however, rely upon the first test being carried out in secrecy as a factor undermining the weight given to the second test.

(2) Failure to Consult Dr Griffon

[695] I have reduced the weight accorded to these experiments due to Idenix's failure to provide Dr Griffon with an opportunity to comment on the tests. In my view, Idenix should have obtained Dr Griffon's input generally, and specifically on whether the techniques used by AMRI would have provided an enhanced means to synthesize or characterize the products of the tests he had conducted in 2003. Who better to advise the Court on the fidelity of the simulations of AMRI's experiments with those in 2003 in terms of the successful synthesis and characterization of the product of the tests, than the person who conducted them in the first place?

(3) The Failure of AMRI to Simulate Dr Griffon's Test

[696] Dr Wnuk provided evidence, which the Court accepts, that the AMRI experiments differed significantly from the protocol described in Dr Griffon's notebook and Witness Statements in two major ways and other cumulative minor ways. His evidence is as follows:

(a) *Different Reaction Monitoring*

(i) AMRI Used More Powerful Monitoring Techniques

[697] AMRI used HPLC attached to a mass spectrometer, the combination of which is referred to as LC/MS. I reject Idenix's explanation that the use of LC/MS would not impact on whether the target product was identified in the reaction product, in comparison with the situation in 2003. I accept Dr Wnuk's evidence that this technology allowed AMRI to locate "to fish out" a

specific reaction product with a specific mass from a complex reaction mixture. The AMRI scientist could then focus on a particular peak that eluted from the HPLC, purify this fraction many times, and then characterize it. I acknowledge however, that it is not apparent from the evidence provided on the experiments that this occurred.

[698] However, Dr Wnuk noted that it appeared during the AMRI 1 experiment that many analytical runs were tested on the AMRI LC/MS machinery in order to develop parameters that would provide adequate separation of the compounds present in the reaction mixture.

[699] Dr Griffon did not have this technology available to him until 2006. He relied upon thin TLC which does not allow the same level of analysis and fraction identification. Idenix did not take any serious issue with this evidence. I reject Idenix's explanation that the use of LC/MS would not impact on whether the target product was obtained.

(ii) Different Purification Techniques

[700] Idenix used reverse phase [RP] HPLC. This is a method of separating and purifying the compounds in the crude reaction mixture. Dr Griffon used a regular silica gel column. While both are separation of purification techniques, they are not functionally equivalent as to the detection limits and separation precision they provide. The compound AMRI made was fairly pure. Dr Damha believes it to be more than 90% pure.

[701] Dr Wnuk opines that the more sophisticated HPLC technique used by AMRI may generate different results than those obtained by purification on regular silica gel column. HPLC

was not a purification method that would have been used by the skilled chemist in 2003. Jeremy Clark used silica gel column chromatography to purify the fluorinated nucleoside compound made from a Deoxo-Fluor fluorination in 2003. The simulation should have used the same technology, to truly simulate the practice that constituted the common general knowledge in 2003. This would appear to be even more significant, given Idenix's late identification of the minor product, rather than the major product requiring purification in the left lane as that synthesized by Dr Griffon.

[702] Dr Wnuk concludes that the HPLC and LC/MS monitor may have allowed for isolation and identification of a desired compound from a complex reaction mixture that could not have been identified and isolated from the same reaction mixture using a regular silica gel column and TLC. In short, AMRI used more sophisticated techniques than Dr Griffon had access to in 2003, which may have generated results that could not have been obtained by the skilled person with the technology available, or regularly used in 2003.

(iii) Cumulative Minor Differences

[703] Dr Wnuk summarized additional differences between the protocols in Exhibit "A" attached to his report, which he would not classify as major differences. Nonetheless, he indicated that it is not possible to know the cumulative effect of the various minor changes in protocol on the experimental outcomes. These include issues on details such as: drying and desiccating glassware; whether all reagents and solvents were from open bottles; whether the syringes were rinsed that were used to dispense pyridine and Deoxo-Fluor; the absence of a

thermocouple used to monitor the internal reaction temperature; and no indication that the resulting solution was refluxed under argon.

(b) *Differences in the Use of the TLC Plates*

(i) AMRI did not Stain the Plates with Sulphuric Acid

[704] Dr Griffon used a sulphuric acid stain the TLC plates, whereas AMRI used an iodine stain. Sulphuric acid preferentially chars (stains) carbohydrates such as sugars. In comparison, iodine staining preferentially binds to double bonds, but without the charring effect.

[705] Idenix argues that different visualization techniques are not part of the reaction and did not affect what compound was being made in the reaction mixture. This is not the sole issue. Whether the reaction product contained the 2'-C'-Me/F nucleoside is less relevant in this matter than whether the technology and procedures followed by Dr Griffon in 2003 were consistent with the common general knowledge and sufficient to permit an initial screening out of a non-sugar compound. That was his basis for not characterizing the major product in the third lane, which up until the end of this trial had been the focus of the parties.

[706] Dr Griffon used the TLC plate as an initial simplified screening process based on his years of working with the nucleosides to eliminate a compound that visually did not contain sugar. It appears to have been his regular practice. Idenix did not lead evidence to suggest that it was not a practice generally followed by its chemists, or by synthesis chemists generally in 2003 when dealing with products isolated by silica gel column chromatography. He concluded that the

major product was not a sugar in comparison with the charring of the reaction products in the other two lanes. Had AMRI used sulphuric acid, a direct comparison could have been made to see whether Dr Griffon's conclusion on sugar charring was correct, as well as in comparing the outcomes on the two plates. Given that the product was 90 percent pure 2'-C'-Me/F nucleoside, it would have been relevant to the Court to know whether it would have charred had it been treated with sulfuric acid. Idenix was aware of the significance of the charring issue in Dr Griffon's decision not to characterize the product in the third lane, particularly as this relates to the allegations of incompetence it directs at Dr Griffon.

(ii) Different Yield of Compounds

[707] In addition, the TLC plates prepared by AMRI were taken at different reaction time points which differed from those prepared by Dr Griffon. Besides the purity of the yield of the 2'-C'-Me/F nucleoside product, they also do not appear to have the same number of spots. In the case of the second AMRI tests, the TLC plates contain smears that may represent one compound or multiple compounds. Dr Wnuk found that the fact that Dr Griffon's experiment and those conducted by AMRI yielded multiple different reaction products prevents meaningful comparison of the TLC plates from each experiment.

(c) *AMRI Testing Protocol Made in Secrecy*

[708] No explanation is offered why AMRI did not precisely follow the protocol used by Dr Griffon. Dr Clemens, the only witness to give factual evidence about the conduct of the AMRI experiments, had no information beyond being given the protocol and told to follow it.

[709] Additionally, from the documents that Idenix disclosed during the trial, which had been withheld on grounds of solicitor-client privilege, it was revealed that Idenix's lawyers were directing Dr Clemens. Idenix provided no explanation why lawyers were directing AMRI on a technical subject matter such as this. It appears to the Court that Idenix used lawyers in order to maintain the secrecy of how the protocol was developed under the cloak of litigation privilege. Given Idenix's failure to provide an explanation for these differences in procedure, the Court is prepared to infer that Dr Griffon's protocol was not followed in order to improve Idenix's chances of obtaining the desired result.

(d) *Idenix's Argument that Gilead Should Have Carried out Its Own Tests*

[710] In reply, Idenix argues that if Gilead was of the opinion that the protocols followed by AMRI did not properly replicate those followed by Dr Griffon, it could have undertaken the experiment to prove otherwise. This is a facetious argument at best. It is also a red herring to Gilead's arguments demanding explanations as to why Idenix undertook its tests in secrecy and failed to adhere in important ways to the protocol followed by Idenix's own employee, who Idenix is attempting to prove was incompetent.

[711] These facts bear no similarity to those in *Abbvie Corporation v Janssen Inc*, 2014 FC 55 cited by Idenix. In that matter, the testing was of a product that was the property of Janssen, whom Justice Roger Hughes found had the means to perform the necessary tests on its own product. In this matter, Idenix is trying to demonstrate that complex multistep novel experiments conducted by its employee over a decade ago, (and who remains its employee) resulted in the

synthesis of a product, that it synthesized using more sophisticated tools to synthesize after the means of synthesis has been disclosed to the world.

[712] Moreover, I would think that if Gilead had set out to replicate the tests of Dr Griffon, Gilead would have needed access to Dr Griffon to review in detail how he conducted his tests and the assumptions that he made as the testing went forward. Idenix's tests were as much to demonstrate that Dr Griffon did not meet the standards of the skilled chemist, as they were to demonstrate that he synthesized the target compound.

[713] There is no reason why Gilead should incur the expense of undertaking its own testing, when Idenix could have provided a better solution, simply by being transparent in its own process. Idenix should have offered to retain an outside testing agency mutually agreed upon by Gilead. Similarly, it could have been transparent on working up a protocol that replicated all the steps followed by Dr Griffon and by permitting Gilead to participate fully in all the testing, all at Idenix's costs. In these circumstances, it would have had a plausible argument, even if Gilead rejected the offers, that the results of the tests should serve considerable probative value.

[714] Instead, Idenix carried out the design of the protocol for testing in secrecy behind the cloak of its litigation privilege. It conducted the first test in secrecy without Gilead or the Court knowing who put the protocol together, or what adjustments may have been made in order to obtain the desired result.

[715] This was followed by a second test, all while maintaining secrecy over how the testing protocol was developed. Even then Idenix failed to properly simulate Dr Griffon's process in important ways, all without rational explanation, allowing Gilead to argue that it teased out the desired result using sophisticated techniques not available to Dr Griffon.

[716] In these circumstances, there is no reason why Gilead would undertake its own testing given the obvious, multiple and significant shortcomings of Idenix's experiments intended to simulate those of Dr Griffon. Gilead could gain nothing from undertaking expensive tests when satisfied that Idenix could not reasonably convince the Court that the AMRI tests could demonstrate that the synthesis of the 2'-C'-Me/F nucleoside was a matter of common general knowledge and routine experimentation in 2003.

[717] For all the above reasons, I conclude that the AMRI tests have little probative value in this matter.

G. *Work of Other Idenix Discovery Chemists*

(1) The Admissibility of Transcripts of Dr Stewart from the UK Proceedings

[718] At the end of trial, Gilead sought leave to file the Witness Statement of Dr Stewart dated July 11, 2014 [Witness Statement] and a transcript of a related cross examination under oath dated October 9, 2014 [Transcript]. These documents are part of the record of the prior civil action between these two parties in the UK High Court of Justice - Chancery Division (Patents

Court), Claim No. HP14D1069 [the UK Proceeding] and relate to the same issues as in this matter.

[719] Dr Stewart was a chemist with Idenix from September 2003 to December 2014, when shortly before this trial his employment terminated for unstated reasons.

[720] Dr Stewart worked on medicinal chemistry projects for discovery purposes at Idenix. In or around May 2004, Dr Stewart, working at Idenix's Cambridge, MA facility, became involved in the project to synthesize a 2'-C-Me/F nucleoside. He was also involved in extensive interactions with a patent law firm in ongoing patent litigation and interference cases for Idenix providing historical perspective and scientific input, *inter alia*.

[721] Around December 2004, Ms Wang, another chemist at the Cambridge, MA facility also commenced work assisting Dr Stewart on the project.

[722] Neither testified. Idenix sought and obtained Gilead's consent to file the witness statement of Ms Wang, dated July 11, 2014, and the related cross examination transcript dated October 7, 2014 from the UK Proceeding.

[723] However, Idenix did not call Dr Stewart to lead evidence as part of its case in this matter. Furthermore, it refused to consent to file Dr Stewart's prior sworn testimony from the UK Proceeding at this trial.

[724] There is no issue as to the authenticity or accuracy of the transcripts. The fact that they were tendered and made under oath in open court involving the same issue between the same parties relating to the synthesis of the 2'-C-Me/F nucleoside, only confirms their reliability and trustworthiness.

[725] There is also no issue of the credibility of Dr Stewart, or loss of advantage to this Court from not being able to observe the demeanor of the witness that was afforded the judge in the UK Proceeding. Any role such an advantage provided to the initial judge would have no application where any implied bias by an employee called by Idenix would be attributed in favour of its interests. The Transcript on its face, should serve its full probative value with little diminution for the fact that it was not provided in the presence of the Court.

[726] As mentioned, when Dr Stewart testified on behalf of Idenix in the UK Proceeding, he was an employee of Idenix.

[727] During discussions at trial, the Court offered the view that the statement and transcript were admissible as an exception to the hearsay rule to the extent that they were documents containing admissions against the interest of a party made by an employee with authority to make the admissions: S. N. Lederman, A.W. Bryant & M.K. Fuerst, *The Law of Evidence in Canada*, 4th ed. (Toronto: Lexis-Nexis Canada Inc, 2014), ss 6.453 [*The Law of Evidence*].

[728] Although not pursued by the parties in their submissions, I continue to be of opinion that the Witness Statement and Transcript of Dr Stewart are admissible by Gilead as an exception to

the hearsay rule for the truth of their contents as documents containing admissions of Idenix by an authorized agent.

[729] Perhaps only admissible to the extent of the admissions against the interests of Idenix, based upon the requirement for context, I admit the totality of the Witness Statement and Transcript.

[730] In its submissions, Gilead made reference to American and New Brunswick statues to allow prior testimony in a subsequent proceeding as an exception to the hearsay rule [*The Law of Evidence*, at s.6.371-6.379]. The exception allows a party to tender the testimony in a previous matter of a witness (as opposed to the party or its authorized agent) called by the opposing party on the same issue.

[731] The parties disputed whether the testimony is admissible under the "principled approach" to hearsay exceptions, if found to be both necessary and reliable: *R v Starr*, 2000 SCC 40. The dispute between the parties focused only on the issue of necessity.

[732] Gilead contends that Dr Stewart' evidence is necessary because, even though no longer an employee, he remains under the control of Idenix. It tendered affidavit evidence that Dr Stewart advised Gilead's counsel that he had continuing obligations to Idenix under a severance agreement. Upon being so advised, Gilead's counsel terminated the discussions with Dr Stewart.

[733] Gilead submits that it is not in a position to elicit testimony from Dr Stewart where Idenix still exerts some type of control over him, but refuses to lead his evidence in chief.

[734] I am not aware of any prohibition against a party calling employees or agents of other parties. Obviously this may pose some challenges, not of concern in cross-examination of the same witness. Nevertheless, if Gilead had sought permission of the Court, it would have been permitted procedures to allow Dr Stewart to testify in this matter. It also did not request Idenix to release Dr Stewart from any constraints on testifying that may have applied.

[735] Gilead offered no jurisprudence supporting its submission that a party may not call an employee of an adverse party. I think that is because the principle of necessity does not apply to those circumstances.

[736] I conclude therefore, that it was not necessary to admit into evidence the Witness Statement and Transcript of Dr Stewart as an exception to the hearsay rule based upon the principles of reliability in necessity.

[737] They are admissible however, as an exception to the common law rule against hearsay as containing admissions of a party.

[738] Were I to rule the transcript of Dr Stewart inadmissible at Idenix's insistence, I would draw an adverse inference against Idenix for failing to call a witness who would have knowledge

of the facts and would be assumed to be willing to assist that party: (The Law of Evidence, at s. 6.450, *R v Jolivet*, 2000 SCC 20 para 25).

[739] Because, Ms Wang worked under Dr Stewart's direction, this adverse evidence would also lessen the weight I would attribute to her evidence for lack of expected corroboration from Dr Stewart.

[740] I add, as well, that the evidence of either witness would have no causal impact on my conclusion drawn from all the evidence that the fluorination step of the synthesis of the 2'-C-Me/F nucleoside in 2003 was not sufficiently disclosed by the common general knowledge and routine experimentation.

(2) The Evidence of Dr Stewart and Ms Wang

[741] I summarize the evidence from the UK Proceeding of the two witnesses as follows:

> (a) Dr Stewart received a Master's degree in chemistry from the University of Durham in 1999. He obtained a Doctorate in organic chemistry from the University of Oxford in 2003, having studied under Professor George Fleet;
>
> (b) Both Dr Stewart and Ms Wang were provided with a report summarising the work of Dr Griffon;
>
> (c) Both obtained starting materials from the Idenix Montpellier site;
>
> (d) On May 10, 2004, Dr Stewart met with and received input from Dr Fleet regarding the 2'-C-Me/F synthesis project.
>
> (e) Dr Stewart also had discussions with his colleagues in the group on a weekly basis regarding the 2'-C-Me/F project.

(f) Dr Stewart conducted an extensive literature search amounting to an average of two hours a day for six months in respect of the 2'-C-Me/F project.

(g) Dr Stewart's first planned route, developed with Dr Fleet in May 2004, involved fluorination using TBAF or TASF, not DAST. However the proposed starting material to be obtained from Dr. Fleet was too unstable to send.

(h) The initial reaction Dr Stewart undertook in November 2004 on the 2'-C-Me/F project was to fluorinate a 2'-C'-Me/OH nucleoside sugar (as Dr Coe had recommended) resulting in a '2 fluor (up), methyl (down) compound (i.e. the wrong stereoisomer of the compound). Although this was the inverse of the ultimate goal, Dr Stewart felt the reaction would provide useful information. Dr Stewart described this reaction as a "breakthrough" when he discovered that it had been successful.

(i) Although he succeeded in making the "wrong" sugar, he viewed the results of the "correct" fluorination as uncertain saying "It is by no means certain that the [correct stereochemistry] will behave in the same way for the fluorination since the steric hindrance and reactivity of the alcohol functionalities is different."

(j) When Dr Stewart tried the fluorination on the "correct" starting material, the result was a complicated mixture revealed by TLC analysis. Dr Stewart considered this reaction a failure.

(k) Dr Stewart encountered a number of failed DAST reactions.

(l) It was not until after Idenix received some information from a Pharmasset employee being interviewed for a role at Idenix that it was decided to shift the focus back onto the nucleoside route and lower the temperature of the DAST reaction on the nucleoside.

(m) On January 12, 2005 Dr Storer informed Dr Stewart by email that Dr Gosselin had told Dr Storer that "someone [Dr. Gosselin] interviewed just after Christmas who worked at Pharmasset told him they made the compound from a nucleoside which may be good news for the other approach which Alistair [Stewart] discussed."

(n) Dr Stewart responded saying this information could be "very handy and might narrow things down a bit". He indicated that based on this information, he would switch the focus back to the nucleoside route and vary a number of conditions including the temperature.

(m) Meanwhile Ms Wang had recently started with Idenix. During the month of December 2004, Ms Wang attempted to synthesize a fluorinated 2'-C-Me/F nucleoside with DAST (in a DCM solvent) using a nucleoside compound containing uracil as a starting material. It failed due to reorganization.

(o) I conclude that the information Dr Stewart received from the Pharmasset employee was likely communicated to Ms Wang who started a reaction with DAST and a lower temperature the very next day using another nucleoside compound bearing cytosine instead of uracil as the starting material. Idenix claims that Ms. Wang successfully made the 2'-C-Me/F nucleoside in January 2005. It is acknowledged however, that she placed a question mark beside the compound in her monthly report because it was unclear whether the desired compound had in fact been made.

(p) The evidence shows that thereafter, a nucleoside 2'-C-Me/F compound was synthesized using DAST in March, but following all the conditions taught by the WO Clark publication of January 13, 2005.

(3) Analysis

[742] Idenix argues that Dr Stewart and Ms Wang, having received Dr Griffon's notes, would have been put off the trail of proceeding directly to the DAST fluorination. I agree with Gilead that this is speculation and is contradicted by the available evidence.

[743] Dr Stewart followed the advice of Dr Fleet, and moreover, undertook an extensive review of the literature prior to commencing his experiments. My view is that after working more than 18 months and having experimented with a vast array of fluorinating reagents, Dr Griffon would not have been in a position to provide any advice or direction on synthetic routes to follow.

[744] Given the extensive amount of time and analysis that Dr Stewart put into his work and his unsuccessful experiments, Idenix obviously focuses on the synthesis efforts of Ms Wang. Idenix attempts to argue that after less than one month of being involved with the project, with no prior experience in fluorination reactions or working with DAST, Ms Wang proceeded through all the steps required to synthesize the 2'-C-Me/F molecule all on her own, without Idenix even acknowledging that she was reporting to Dr Stewart.

[745] Idenix also argues that her success was not due to learning information from the Pharmasset employee or its patent. I find that her recollection of these events is too vague to be reliable, to the point of not being able to recall how she became involved in the project.

[746] Dr Stewart moved forward only after he received information that had been gleaned from the former employee of Pharmasset. He switched strategies back to fluorinating a nucleoside and working with DAST at a lower temperature. Ms Wang who recently arrived with no experience in fluorination or working with DAST, began experimenting using the same fluorination project as she describes "in the sense that we discussed what each of us was doing" while being under his direction.

[747] I am satisfied that the convenient coincidence of garnering information from a Pharmasset employee and thereafter its patent application played a role in Idenix's successful synthesis of the 2'-C-Me/F nucleoside. I rely on Dr Wnuk's evidence with respect to these employees' reliance upon Pharmasset information to assist in synthesizing the target compound. I

attribute very little weight to any success that Idenix may have had in synthesizing the 2'-C-Me/F compound in 2005.

[748] In any event, the work of Dr Stewart and that of Ms Wang, whose work I find was largely based on Dr Stewart's work, confirm that extensive research was required prior to initiating experiments, including consulting with others. This evidence confirms the obvious that it was not possible to synthesize the 2'-C-Me/F compound in reliance on the common general knowledge and without extensive research and trial and error experimentation.

H. *Jeremy Clark's Work*

[749] Idenix relies upon the evidence that Mr Clark was able to make a 2'-C-Me/F nucleoside analogue relatively speedily and easily using DAST in reliance upon the *Matsuda* article to assist in synthesizing the intermediate 2'-C-OH/Me compound.

[750] By way of background, Mr Clark was hired at Pharmasset after obtaining a Master's of Science in Chemistry at the University of Tennessee in 2001. His employment at Pharmasset started on July 23, 2001 without any work experience on fluoro nucleosides. On December 6, 2002, Mr Clark's notebook first mentions a 2'-C-Me/F nucleoside on page 25.

[751] Idenix points out that despite the fact that Mr Clark had no prior experience with fluoro nucleosides and did not have the education level of the skilled chemist, he nevertheless succeeded in making a 2'-C-Me/F compound on his first DAST fluorination on January 27, 2003. On February 17, 2003, Mr Clark repeated a DAST fluorination on the same protected

sugar. There is some confusion on these dates, inasmuch as the 2005 article published by Clark et al where he indicated that he first invented a 2'-C-Me/F nucleoside. This is contrary however, to Mr Clark's notebooks, which he very poorly maintained.

[752] Idenix attempts, as well, to rely upon a statement by Mr Clark that the entire DAST synthesis was a 15-minute reaction. Without being too hard on Mr Clark, who was not called to testify, the Court nevertheless accepts Dr Patterson's description of him from various somewhat disobliging comments as someone who had a tendency to be very outspoken about his own talents and opinions. An example of Mr Clark's idiosyncratic behaviour is perhaps demonstrated by his report of February 28, 2003, recording his nucleoside DAST reaction scheme stating, "This reaction sequence will make a good chapter in the Anals of Shitpot Science. There's nothing elegant in this chemistry", but that "this is acceptable at this point however."

[753] Dr Patterson testified that Dr Kris Pankiewicz advised Mr Clark to use DAST on a 2'-C-OH/Me compound because DAST was commonly used to convert alcohols to fluorides in tertiary systems. Accordingly, Idenix argues that the chemists at Pharmasset followed the same approach to make the 2'-C-Me/F compound as described by the chemistry experts in this proceeding.

[754] Mr Clark prepared the 2'-C-Me/F Compound using the nucleoside route. In so doing, he indicates in his lab notebook that he was following the "exact procedure as reported by Matsuda". Idenix argues that this further supports the earlier discussion where it was shown that the skilled person would be aware of, or would find, Matsuda and would follow its teachings.

[755] Mr Clark also made further references to the same *Matsuda* article on pages 81, 83, and 92 of his Notebook 2. In a summary report made by Mr Clark on July 21, 2003, he emphasized that the game plan for making a 2'-C-Me/F nucleosides "was inspired by the work of Matsuda". Thus, Idenix argues that to make the claimed compound, all it took was *Matsuda* and fifteen minutes.

[756] Pharmasset undertook efforts to increase yield, which are reflected in the minutes of the Pharmasset Chemistry Meeting on August 22, 2003. Idenix claims that the minutes record that a literature search on fluorinating tertiary carbons was done and that over 100 articles were found. Idenix indicates that this is in contrast to Griffon's incorrect search, where he only found two references.

[757] However, the Court is not aware of the source of Idenix's information. The exhibit referred to by Idenix in support of these claims indicates only "[p] resented results from a literature search on fluorinating agents." The minutes recorded a discussion involving a number of fluorinating agents including DAST and Deoxo-Fluor® as well as a HF and NFTh. There is nothing in the exhibit indicating that the search was limited to fluorinating tertiary carbons, although there was a comment that "several references were found but not presented on high-yielding tertiary carbon fluorination but without any mechanism being mentioned." The emphasis of the meeting appeared to be on obtaining higher yields.

[758] Idenix also states that this Chemistry Meeting minute recorded that Dr Wojciech J. Stec, the head of Chemistry at Pharmasset, said that everyone continues to use DAST, and that DAST

was the "conservative approach". This suggests that DAST was already extensively used at Pharmasset prior to the literature search that found 100+ articles.

[759] However, in consulting the same exhibit, Dr Stec emphasized that when he first arrived he distributed articles on fluorination, "but despite that everyone continues to use DAST". He pointed out that DAST was not used in the industry. He advised the chemists, "[d]on't be conservative (by using DAST)". He suggested using different fluorinating agents to increase the yield. This evidence suggests that Pharmasset had a preordained tendency to use DAST among many other fluorinating agents available. This predilection for DAST may have contributed to it being recommended by senior chemists for use by Mr Clark as a matter of habit. This clearly was not the case at Idenix, or represents the views of other experienced chemists involved or consulted on its synthesis.

[760] On September 19, 2003, Mr Clark used Deoxo-Fluor® to make a benzoyl-protected PSI-6130 on a large scale. Mr Clark reported that a Deoxo-Fluor® fluorination resulted in 23% yield to give a protected nucleoside. The underlying experiment was found on page 118 of Clark Notebook 2 (Exhibit 23-I), where column chromatography was used to purify the protected target product. Therefore, Mr Clark also succeeded in making the target compound fluorinate on his first try using Deoxo-Fluor®.

[761] I find that Idenix paints too rosy a picture of the ease with which Mr Clark synthesized the 2'-C-Me/F compound. In the first place, Dr Patterson suggests that Dr Watanabe was the first person at Pharmasset to write down the structure of the 2'-C-Me/F compound. He presented it as

one of the analogues of the Idenix compound at a group of chemists, indicating that he wanted members of the chemistry team to consider attempting its synthesis.

[762] Second, in terms of pathways, Mr Clark first tried the gemcitabine route and only moved on to the carbohydrate route after that failed. In addition, Dr Patterson testified that he received advice from a senior chemist with experience to make the compound using the nucleoside approach after he was having trouble making progress. There is no need for a skilled chemist to conduct a literature search, if you are following the advice of a senior chemist in the organization. Dr Patterson testified as follows:

> There were, you know, discussions. It took him a long time to get anywhere on it. People began giving him advice, particularly Chris Pankiewicz, asking him to make it from cytosine, you make it from the nucleoside rather than trying to do the coupling.
>
> And I believe that was a much faster, more viable route because you don't have to worry about, you know, preparation of all the stereocentres that would arise from synthesis of the carbohydrate, so nature has done much of that for you.

[763] Dr Patterson repeated this point including that Mr Clark did not follow the advice as follows:

> Q. So, now, when Mr Clark is working on his first chemistry, I think you said the carbohydrate or the fluorination of that, can you just let us know if advice was being provided by someone to him on that?
>
> A. Oh, yes.
>
> Q. And what was the advice?
>
> A. The advice was make it from the nucleoside, start from C.
>
> Q. And how was Mr Clark about receiving instructions?

A. Not good.

[764] In other words, Mr Clark started with the gemcitabine approach, was advised by senior members of the chemistry department to use the nucleoside approach and apparently synthesized the first compound using the sugar ring approach, and thereafter repeated his success using the nucleoside approach with higher yields.

[765] Similarly, Mr Clark did not apparently come upon fluorinating with DAST by himself, but was advised again by senior chemists with whom he worked, according to Dr Patterson as follows:

> Dr Patterson, you mentioned that advice was provided concerning, I think you said the nucleoside and the cytosine?
>
> A. Correct.
>
> Q. Was advice also provided on the fluorinating agents?
>
> A. I think so.
>
> Q. And what was that advice?
>
> A. DAST or some similar, you know, aminosulphur trifluoride

[766] It also seems clear that Mr Clark received advice from numerous members of the Pharmasset chemistry group. The 2005 article published with him as the head author included the following co-authors: Laurent Hollecker, J. Christian Mason, Lieven J. Stuyver, Phillip M. Tharnish, Stefania Lostia, Tamara R. McBrayer, Raymond F. Schinazi, Kyoichi A. Watanabe, Michael J. Otto, Phillip A. Furman, Wojciech J. Stec, Steven E. Patterson, and Krzysztof W. Pankiewicz.

[767] It should be noted as well, that Dr Patterson testified that everyone was very excited when Mr Clark found the "hole" in the Idenix patent. The evidence is clear that synthesizing the 2'-C-Me/F compound was a high priority for Idenix. I do not believe it would be overly speculative to conclude that Pharmasset would have recognized the opportunity left open by the omission of the fluoride analogue in the Idenix patent.

[768] According to Dr Patterson, Mr Clark was assigned the task because he spotted the coverage omission in the patent. He was having a lot of trouble making any progress and according to Dr Patterson was receiving advice from various senior chemists. Given his inexperience, and indeed lack of formal training from the poor state of his notebooks, I conclude it was unlikely that he was left to himself to synthesize the compound. Dr Otto described the group as a close knit discovery chemist team housed in close quarters. There is evidence that Dr Stuyver may have assisted Mr Clark in selecting the target for synthesis as well.

[769] While Mr Clark may not have had the training of the skilled chemist, if integrated into an effective, highly experienced discovery chemistry team, it could be expected that he would be operating at a level of experience and knowledge beyond that of the skilled chemist.

[770] However, I do not wish to speak poorly of Mr Clark when in fact , it seems that he was the sort of person who marched to his own drum, possessing a large measure of self-assurance and perhaps possessing some of the natural traits of an inventor. Dr Patterson describes Mr Clark as someone with very strong ideas and self-assurance: "Jeremy Clark did have some very concrete ideas about how to make that molecule. He was very aggressive in pursuing that

synthesis and he would tell anybody that." Similarly, Dr Patterson testified as follows: "Well, Mr Clark was very exuberant. And he was, when he was sure of something, he was sure of it, and everybody who knew him knew that." That does not seem to describe your non-inventive skilled bench chemist.

[771] In the sister case between these parties in the United Kingdom, Justice Arnold suggested that Mr Clark may have been lucky in the invention of the 2'-C-Me/F compound. On the other hand, it may well be that Mr Clark is one of those individuals who is particularly talented in quickly absorbing great amounts of information and intuitively working out inventive solutions from a variety of options that were presented to him. He appeared to pick out the omission in coverage of the 2'-C-Me/F compounds in the Idenix patent and followed advice only when it suited him. He also settled on toluene from a number of solvents and reaction conditions.

[772] In addition to the help that I find he was provided by fellow employees, it is not possible to determine to what extent Mr Clark's particular inventive talents or luck led him to the synthesis of the 2'-C-Me/F compound.

[773] Whatever the explanation for Mr Clark's relatively quick synthesis of the 2'-C-Me/F compound, after the false start on the Gemcitabine route, it does not convince the Court that his success was the result of, or reflects, the common general knowledge and routine experimentation alleged by Idenix to account for its synthesis. As said, it may well reflect a variety of factors, including a "conservative" pre-disposition at Pharmasset to use DAST, not necessarily followed by skilled chemists.

[774] Mr Clark's performance most certainly does not overcome the results of the analysis of the many issues and evidence considered above that demonstrate no common general knowledge regarding the synthesis of the 2'-C-Me/F nucleosides, nor the use of DAST to do so. This is also confirmed by the evidence regarding the efforts and contributions of other experienced chemists in 2002 and 2003.

[775] The Court concludes that Idenix's claim that common general knowledge and permissible experimentation supplemented the written disclosure, thereby providing enabling disclosure of how to synthesize the 2'-C'-Me/F nucleoside is not supported by the evidence. The disclosure of the synthesis of the 2'-C-Me/F compound in the '191 Patent is therefore, insufficient.

IX. Overbreadth

A. *Introduction*

[776] Gilead altered somewhat its argument on overbreadth from what was originally argued in order to advance two novel arguments to support such a claim. The new arguments relate to Idenix's failure to make the 2'-C-Me/F compound at the time of filing and publication dates.

[777] It was originally argued that Idenix had, within the scope of its claims, compounds which were not made or could not be made. This related to the numerous compounds in Claim 1 and the compound's Base. With the Court's acceptance of the abandonment of Claim 1 and the chemist's

focused construction on the scope of compounds in the claimed base, I find that there remains no case on these grounds for an argument of overbreadth.

B. *General Principles*

[778] Overbreadth arises by the requirement under section 27(4) of the *Act* that the specification end "with a claim or claims defining distinctly and in explicit terms the subject matter if the invention for which an exclusive privilege or property is claimed."

[779] It is common ground that "No inventor is entitled to a monopoly on more, or even a little more, than he invents", (*Radio Corporation of America v Hazeltine Corporation* (1981), 56 CPR (2d) 170 at 188). As stated by the Supreme Court of Canada in *Burton* at para 16.

> It is stressed in many cases that an inventor is free to make his claims as narrow as he sees fit in order to protect himself from the invalidity which will ensue if he makes them too broad. From a practical point of view, this freedom is really quite limited because if, in order to guard against possible invalidity, some area is left open between what is the invention as disclosed and what is covered by the claims, the patent may be just as worthless as if it was invalid.

C. *The Parties Submissions*

[780] Gilead advances its argument that the claims of the '191 Patent are overbroad by a rationale that I would summarize as follows:

(i) At the time the patent application was filed and published, Idenix had been unsuccessful in making a compound within the scope of the claims; as they did not have a way of making the claimed compounds, they cannot be said to have completed the act of invention; and

(ii) Not having invented the compounds, any claim to any such compounds is by definition overbroad.

[781] The argument is novel. For that reason, I will set it out *in verbatim*, as follows:

> a. This issue raises two fundamental questions: (i) when is an invention made; and (ii) when can someone be said to have invented a class of compounds?
>
> b. In the early case of *Christiani v Rice*, the Supreme Court articulated the following principles which have been repeatedly referenced by the jurisprudence:
>
> > It is not enough for a man to say that an idea floated through his brain…
> >
> > […]
> >
> > [T]he date of discovery of the invention is meant the date at which the inventor can provide he has first formulated, either in writing or verbally, a description which affords the means of making that which is invented.
> >
> > [Gilead's Emphasis]
>
> c. There is a dearth of Canadian case law on the threshold issue of when a compound can be said to have been invented. However, there is considerable American jurisprudence on the subject owing in large part to the fact that until very recently, the US used a "first to invent" system which often required the Court to establish dates of inventorship.

d. Under US law, a compound is not said to have been invented until the inventor has the idea of a compound and an operable way of making it. (See for example *Oka et al v Youssefyeh et al*, 849 F.2d 581 (Fed Cir) at 3).

e. During the course of the trial, Idenix provided the Court with a number of US authorities. Each of these cases is distinguishable from the current case. None of these cases stand for the proposition that a patent may be obtained for something the inventor does not know how to make. While US (and Canadian) law does not require that the inventor has actually made each of the compounds claimed, the law requires that the inventor has a way of making them, and discloses that method in the patent.

f. This is consistent with the general principle espoused in *Christiani v. Rice*, [1930] SCR 443 at 454, 456. It is also consistent with the policy stated by the Supreme Court in *AZT* (*Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 84):

> i. An applicant does not merit a patent on an almost-invention, where the public receives only a promise that a hypothesis might later prove useful; this would permit, and encourage, applicants to put placeholders on intriguing ideas to wait for the science to catch up and make it so. The patentee would enjoy the property right of excluding others from making, selling, using or improving that idea without the public's having derived anything useful in return.
>
> [Gilead's emphasis]

g. As of the filing and publication dates of the '191 Patent, as far as the named inventors knew, they had only failed in their efforts to synthesize a 2'-fluoro(down)-2'methyl(up) nucleoside. As they were not aware of any manner in which any compound within the scope of the claim could be synthesized, they did not describe any such method in the patent.

h. The named inventors cannot be said to have been in possession of an invention at the time the '191 Patent was filed or published. To borrow the language of the Supreme Court's decision in *AZT*, the inventors had an intriguing idea for which the science had not yet caught up. The '191 Patent allowed Idenix to enjoy a monopoly right without giving the public anything useful in return.

> i. Because Idenix had not actually invented 2'-fluoro(down)-2'methyl(up) nucleoside compounds, any claim to any such compounds is by definition overbroad.
>
> [My emphasis]

D. *Analysis*

[782] Gilead is in effect, adding a new condition that the inventor must have a way of making the invention to the requirement of being able to describe how to make it. As is apparent by the quote from *Wellcome/AZT* that patents are not granted when the public receives only a promise that a hypothesis might later prove useful, Gilead is arguing that the patentee is claiming a monopoly for a research project, something for which it has not paid the hard coinage.

[783] Idenix's response, considering the logic of paragraph "g" above, is that the definition of the invention, also found in *Christiani v Rice*, [1930] SCR 443, is that there is no need for the inventor to have a way of making the compound ("a description which affords the means of making"), if the inventor is able to sufficiently disclose how to make the compound, and assuming he or she can soundly predict its utility.

[784] Idenix argues simply that if the claims are soundly predicted and there has been sufficient disclosure of how to make the invention, then there can be no overbreadth of claims. I agree with this submission based on present Canadian law.

[785] Any difficulties that arise from the fact that the inventor did not make the compound are supposed to be reflected in the limits on patents for unmade compounds by the requirements that

the inventor be able to soundly predict the invention and to sufficiently disclose its synthesis. It turns out that these limitations work quite well in this matter, as I find the '191 Patent invalid on both grounds. This is not however, a peremptory rule such as Gilead is arguing here that will permit the dismissal of the action without requiring a trial of an action along with all the challenging evidentiary and legal issues that normally ensue.

[786] Although sympathetic with Gilead's underlying submission that Idenix should not be rewarded for its failure to make a compound, I do not think that the new principle Gilead seeks to advance can be proclaimed under the tenets of overbreadth. Overbreadth is a concept that acknowledges the patent may be valid, but the inventor has claimed too much territory. It is that space between validity and overreaching, depending on the wording of the claim, as described in the passage quoted above from *Burton*.

[787] Gilead's true argument is that this case is one where there is no basis for the Patent in the first place, because the invention was never made despite efforts to do so, and the patent should never have been granted. If the rule is that the inventor must have a way of making the claimed compounds, in addition to being able to disclose how to make the compound, my concern is that it opens the floodgates somewhat to new challenges requiring a means to make the inventions for all unmade inventions relating in timing to disclosure, but affecting soundly predicted inventions. I also think that this is a one-off situation that is unlikely to recur.

[788] It might be arguable as a logical and non-disruptive corollary to the doctrine of sound prediction that you cannot patent an invention that the inventor has tried and failed to invent.

This would be accomplished by conjoining the inventor's knowledge required for the sound prediction of utility on filing date, with the simultaneous knowledge that the inventor has tried and could not make the invention. But this approach was not argued by Gilead, and is not therefore before the Court. As mentioned it also does not appear necessary, as Idenix's '191 Patent is being found invalid on the basis of well-established principles in patent law.

[789] In conclusion, I do not find that an overbreadth claim may be made against Idenix in this case on the grounds alleged by Gilead.

X. Idenix's Counterclaim of Anticipation

A. *Introduction*

[790] Idenix's counterclaim includes a claim that that each of the Claims of the '657 Patent was anticipated by the disclosure and enablement of their subject matter by the '191 Patent as filed on June 27, 2003 and as published on January 8, 2004. It seeks a declaration under section 60(1) of the *Patent Act* that the '657 Patent is invalid under section 28.2(1) of the *Act*

[791] Subsection 28.2(1) of the *Patent Act* provides, *inter alia*:

28.2(1) The subject-matter defined by a claim in an application for a patent in Canada (the "pending application") must not have been disclosed	28.2(1) L'objet que définit la revendication d'une demande de brevet ne doit pas :
[...]	[...]

(b) before the claim date by a person not mentioned in paragraph (a), in such a manner that the subject-matter became available to the public in Canada or elsewhere;	b) avant la date de la revendication, avoir fait, de la part d'une autre personne, l'objet d'une communication qui l'a rendu accessible au public au Canada ou ailleurs;
(c) in an application for a patent that is filed in Canada by a person other than the applicant, and has a filing date that is before the claim date.	c) avoir été divulgué dans une demande de brevet qui a été déposée au Canada par une personne autre que le demandeur et dont la date de dépôt est antérieure à la date de la revendication de la demande visée à l'alinéa (1)a);

[792] For the sole purpose of simplifying this action in Canada, the parties agree that the claim date in respect of the '657 Patent is the filing date, April 21, 2004.

[793] The enablement issue of disclosure for anticipation has been largely resolved by my analysis concluding that there was insufficient disclosure of how to make the 2'-C'-Me/F nucleoside in the '191 Patent. That analysis applies in a similar fashion to enabling disclosure for anticipation.

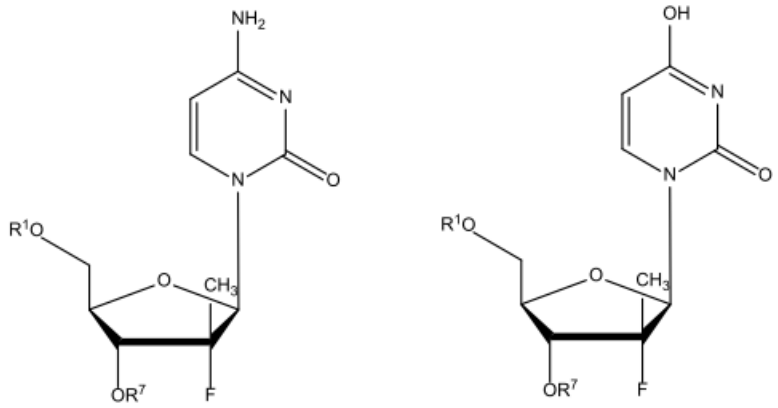
[794] What follows therefore, is a brief construction analysis of the claims in the '657 Patent, followed by some discussion of the issues concerning the disclosure of the invention, which seem somewhat differently argued by Gilead for anticipation from its submissions regarding insufficiency.

(1) Claims Construction of the '657 Patent

[795] The skilled person would have understood that each of the claims of the '657 Patent is directed to 2'-fluoro(down)-2'-methyl(up) cytidine and uridine nucleosides and nucleotides and that the claims narrow down to two discrete compounds, (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine and (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine.

(a) *Claim 1 of the '657 Patent*

[796] The person of ordinary skill in the art would have understood that the compounds of Claim 1 could generally be described as being 2'-C-Me/F nucleosides with either a cytosine or uracil base and could be depicted in the following way:



[797] Further, the person of ordinary skill in the art would have understood that Claim 1 of the Gilead '657 Patent is directed to compounds (or their pharmaceutically acceptable salts) having the following components:

(i) a natural cytosine or uracil base;

(ii) a sugar ring containing an oxygen (O);

(iii) a methyl group (CH_3) in the 2' (up) position;

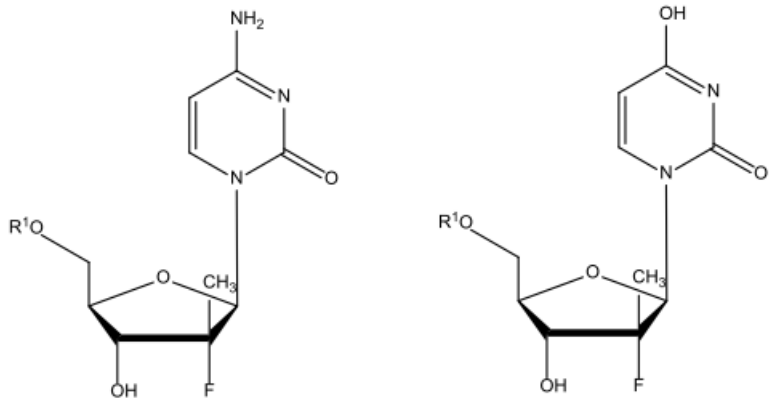
(iv) a fluorine atom (F) in the 2' (down) position

(v) one of the options presented for substituents at the 3' position, including hydroxyl, monophosphate, diphosphate, triphosphate, H-phosphonate and others; and

(vi) one of the options presented for substituents at the 5' position, including hydroxyl, monophosphate, diphosphate, triphosphate, H-phosphonate and others.

(b) *Claim 2 of the '657 Patent*

[798] Claim 2 narrows the options at the 3' (down) position to hydroxyl. Consequently, the person of ordinary skill in the art would have understood that the compounds covered by Claim 2 can be represented as follows:



[799] Further, R^1 is limited to three possible options (monophosphate, diphosphate or triphosphate). Thus, the person of ordinary skill in the art would have understood that Claim 2 includes six compounds (or pharmaceutically acceptable salts thereof):

(i) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-monophosphate;

(ii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-monophosphate;

(iii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-diphosphate;

(iv) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-diphosphate;

(v) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate; and

(vi) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-triphosphate.

(c) *Claim 3 of the '657 Patent*

[800] Claim 3 limits the compounds of Claim 1 by specifying that R^7 is H, R^1 is a diphosphate or a triphosphate. The person of ordinary skill in the art would have understood that Claim 3 encompasses a smaller number of compounds than Claims 1 and 2. In particular, the person of ordinary skill in the art would have understood that Claim 3 includes the following four compounds (or pharmaceutically acceptable salts thereof):

(i) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-diphosphate;

(ii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-diphosphate;

(iii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate; and

(iv) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-triphosphate.

(d) *Claim 4 of the '657 Patent*

[801] Claim 4 limits the compounds of Claim 1 by specifying that R^7 is H and R^1 is a triphosphate. The person of ordinary skill in the art would have understood that Claim 4 includes the following two compounds:

(i) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine 5'-triphosphate; and

(ii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-triphosphate.

(e) *Claim 5 of the '657 Patent*

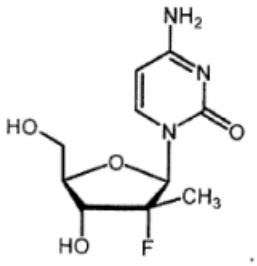
[802] Claim 5 limits the compounds of Claim 1 by specifying that both R^1 and R^7 are H. The person of ordinary skill in the art would have understood that Claim 5 includes the following two compounds:

(i) (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine; and

(ii) (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine.

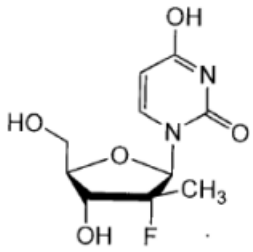
(f) *Claim 6 of the '657 Patent*

[803] Claim 6 limits the compounds of Claim 1 to a single compound, (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (or pharmaceutically acceptable salt thereof):



(g) *Claim 15 of the '657 Patent*

[804] Claim 15 limits the compounds of Claim 1 to a single compound, (2'R)-2'-deoxy-2'-fluoro-2'-C-methyluridine (or pharmaceutically acceptable salt thereof):



(h) *Other Claims of the '657 Patent*

[805] The remaining claims of the '657 Patent incorporate by reference the claimed compounds. In particular:

(a) Claims 7 to 12 are directed to pharmaceutical compositions comprising the nucleosides of Claims 1 to 6 (Claims 7 to 12 respectively), or their pharmaceutically acceptable salt(s), and a pharmaceutically acceptable carrier;

(b) Claims 13 and 14 are directed to methods of synthesizing the 2'-fluoro(down)-2'methyl(up) cytidine and uridine nucleosides of Claim 1;

(c) Claim 16 is directed to a pharmaceutical composition comprising the nucleoside of Claim 15, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier;

(d) Claims 17 to 19 are directed to liposomal compositions comprising the compound of Claim 1, Claim 6, or Claim 15 (Claims 17, 18, and 19, respectively) and optionally a pharmaceutically acceptable carrier; and

(e) Claims 20 to 26 are directed to uses of claimed nucleosides, or compositions containing the claimed nucleosides, as antiviral agents.

(2) Anticipation

(a) *The Test for Anticipation*

[806] The test for anticipation was set out by the Supreme Court of Canada in [*Plavix/Sanofi*]. It comprises two steps:

(a) Disclosure – The prior patent must disclose information which, if performed, would necessarily result in infringement. The person of ordinary skill in the art reads the particular piece of prior art to understand whether it discloses the second invention. The skilled person is "taken to be trying to understand what the author

of the prior patent meant." There is no room for trial and error or experimentation at this stage of the process. The person skilled in the art is simply reading the patent for the purposes of understanding it. The evidence to be considered is comprised solely of the prior art, as the person of ordinary skill in the art would understand it.

(b) Enablement – If the disclosure requirement is satisfied, then the Court must determine whether the ordinary person skilled in the art would have been able to perform the invention without undue burden. Routine experimentation is permitted at the enablement stage; however, prolonged or arduous trial and error would not be considered routine. For purposes of enablement, the question is no longer what the person of ordinary skill in the art would think the disclosure of the prior patent meant, but whether he or she would be able to work the invention.

(b) *Analysis of Gilead's Submissions*

[807] Gilead claims that the '191 Patent does not disclose the claimed subject-matter claimed in the '657 Patent:

(i) The skilled reader would not be able to identify the active compound in the '191 Patent.

As stated above, based on the evidence of Drs Damha and Barrett, I am satisfied that the skilled reader "taken to be trying to understand what the author of the prior patent meant" would understand from examining the claims and the relevant materials in the

'191 Patent would recognize that the active compounds in the '191 Patent were the 2'-C-Me/F nucleotide and nucleoside compounds identified in Claims 2 and 3 and their derivatives, with natural bases similar to those in the '657 Patent. The core of both inventions is clearly at the '2 position of the sugar ring. It would be apparent to the skilled reader of the '191 Patent that other areas of the invention would be more widely stated around this structure which forms the heart of the disclosure.

(ii) The '191 Patent as filed and published did not focus on Formula IX compounds. In fact, the claims of the '191 Patent as filed and as published covered all of the Formulae and were not limited to Formula IX compounds.

For the same reason based on an analysis of the claims, I accept the views of Drs Damha and Barrett that the skilled reader would realize that the '191 Patent was based on Formula IX compounds, recognizing that the Patent contains much irrelevant material which should be disregarded.

(iii) The '191 Patent does not contain a clear description of 2'-C-Me/F nucleosides with either a cytosine or uracil base and does not direct the person of ordinary skill in the art to select cytosine and uracil bases out of the myriad of bases discussed therein. There are no examples, schemes or data in respect of 2'-C-Me/F nucleosides with either a cytosine or uracil base.

On the basis of the same careful reading the skilled reader would be aware from the common general knowledge that that the nucleoside analogues used as an antiviral drug would be linked to the one of the four natural bases which would include the

cytosine or uracil bases. This would be a sufficient direction to disclose the invention. Gilead has not argued that the natural purine bases were not active.

[808] The disclosure of the ‘191 Patent indicates that the compounds claimed by the ‘657 Patent or a pharmaceutical composition comprising the claimed compounds can be used as an antiviral agent or, in the case of claimed nucleosides, they can be used to make prodrugs. Both patents also indicate that the compounds can be used to treat Flaviviridae viruses including HCV. Additionally, both patents indicate that the compounds can be used in combination with other antiviral compounds. As such, the uses that are disclosed and claimed in the ‘657 Patent are the same uses that are disclosed in the ‘191 Patent. As discussed above, the same compounds are disclosed in both patents, particularly the narrower compounds claimed in both patents that form the genus class.

[809] I am satisfied therefore, that the same invention of the ‘657 Patent is disclosed in the ‘191 Patent. In the result, whether there is anticipation of the subject matter of the claims of the ‘657 Patent would be determined by whether the ‘191 Patent provides an enabling disclosure thus allowing the skilled chemist to be able to make compounds within the scope of the claims of the ‘657 Patent.

[810] As I have already found that there is no enabling disclosure of how to synthesize the compounds in the ‘191 Patent, Idenix’s claim of anticipation is rejected.

[811] The ‘191 patent does not enable the claimed subject-matter claimed in the ‘657 Patent:

- There are no examples or schemes in respect of how to make 2'-C-Me/F nucleosides with either a cytosine or uracil base;

- Synthesis of 2'-C-Me/F nucleosides was not known in 2004;

- There was no common general knowledge as to how to prepare nucleosides with a tertiary fluorine at the 2' position; and

- The person of ordinary skill in the art would not have been able to prepare 2'-C-Me/F nucleosides based upon the '191 Patent and the common general knowledge without undue experimentation, if at all.

XI. Idenix's Counterclaim of Infringement

A. *Introduction - The Bifurcation Order*

[812] Idenix counterclaims that Gilead infringed certain claims of its '191 Patent by its making, using and selling to others the subject matter claimed in the '191 Patent by the production of sofosbuvir and its sale in Canada as Sovaldi which commenced on January 6, 2014.

[813] Despite my conclusions that the '191 Patent is invalid, for the purposes of a potential appeal, I am nevertheless required to consider Idenix's infringement argument. It assumes that it soundly predicted the utility of the 2'-C-Me/F nucleosides and sufficiently disclosed how to synthesize them. On that premise, the Court's function is to determine the agreed-upon question

as contained in Prothonotary Tabib's Amended Bifurcation Order dated September 9, 2014 [the Bifurcation Order], which is as follows:

> 1. The following issues of this action shall be heard and determined by a trial separate from, and after the trial scheduled to being on January 12, 2015 (the "First Trial"), if necessary, depending on the outcome of the First Trial:
>
> a. when, where and for how long infringement occurred, and who committed the acts of infringement;
>
> b. whether Idenix is entitled to an injunction, declaratory relief, delivery up and accounting of profit or damages of any act of infringement;
>
> c. the extent of any infringement, including the application of statutory or common law exceptions;
>
> d. the quantum of Idenix's damages or reasonable compensation from any infringement, and the quantum of the profits of any infringement.
>
> 2. For greater certainty, the parties are to proceed to the First Trial on the issue of whether sofosbuvir and/or Sovaldi and/or the compound identified in paragraph 64A of the Amended Statement of Defence and Counterclaim [purported manufacturing Intermediate] fall within the scope of the '191 Patent.

[814] The issues for determination in this matter is whether sofosbuvir and/or Sovaldi and/or the compound identified in paragraph 64A [the "intermediate" compound] of the Amended Statement of Defence and Counterclaim fall within the scope of the '191 Patent.

B. *The Parties' Submissions on Infringement and Conclusions*

[815] Idenix makes three submissions by which it claims Gilead has infringed the '191 Patent. The first involves a claim of infringement of the "purported manufacturing intermediate", which is as follows:

> (a) Gilead's 2'-C-Me/F nucleoside with hydroxyls at the 3' and 5' positions on the sugar ring, as an intermediate in the preparation of sofosbuvir, falls within the scope of claim 3 of the '191 Patent [the "Intermediate" compound issue].

[816] Gilead challenges the Court's jurisdiction to consider this issue in light of the Bifurcation Order. It submits that Idenix's infringement claim concerns the use of the claimed compounds, as opposed to whether the intermediate falls within the scope of the '191 Patent. Otherwise, Gilead makes no submissions on the infringement by the use of the 2'-C-Me/F nucleoside in sofosbuvir, apart from there being no infringement claim because the '191 Patent is invalid.

[817] Idenix's other two claims of infringement turn around the construction of the description of the R^1 substituent at the 5' position on the sugar ringer which reads as follows:

> … phosphate; … or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 … is … phosphate.

[818] Idenix's submissions on this point are as follows:

> (b) Gilead's SOVALDI sofosbuvir is within the scope of Claim 2 of the '191 Patent in that it has a phosphoramidate prodrug moiety at the 5' position, which is a "phosphate" as well as a

> "pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is phosphate [Phosphoramidate use].
>
> (c) After Gilead's SOVALDI sofosbuvir is administered, the phosphoramidate prodrug component leaves resulting in a monophosphate compound within the scope of Claim 2 of the '191 Patent, which subsequently is phosphorylated *in vivo* to form the diphosphate and triphosphate compounds, equally falling within the scope of R^1 being a "phosphate" as defined in claim 2 of the '191 Patent [*in vivo* metabolization].

[819] Gilead's submissions in reply to these arguments are as follows:

> (a) phosphate when used in the claims of the '191 Patent means PO_4 (monophosphate);
>
> (i) phosphate when used in the claims of the '191 Patent does not include diphosphate, triphosphate, stabilized phosphate and stabilized phosphate prodrug;
>
> (ii) phosphate when used in the claims of the '191 Patent does not include phosphoramidate;
>
> (b) phosphoramidate (the group at the 5' position of sofosbuvir) is not covered by R^1 in the claims of the '191 Patent -- it is not phosphate or a pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1 and /or R^2 is independently H or phosphate;
>
> (c) SOVALDI tablets are not covered by claims of the '191 Patent, as its medicinal ingredient, sofosbuvir, is not covered by the claims;
>
> (d) the monophosphate, diphosphate and triphosphate metabolites of sofosbuvir are not covered by the claims of the '191 Patent as the '191 Patent is not directed to metabolites and the term "phosphate" in the claims of the '191 Patent does not include diphosphates or triphosphates; and
>
> (e) the use of PSI-6206 in the manufacture of sofosbuvir is not covered by the claims of the '191 Patent as the '191 Patent is not directed to manufacturing intermediates.

[820] In the analysis that follows, I first consider Idenix's submission that Gilead's intermediate compound falls within the scope of the '191 Patent. I find this to be the case based on Gilead's implicit admission that the structures of the compounds are identical.

[821] Thereafter, I consider the interpretive issue involving phosphate, which I conclude extends to the monophosphate, diphosphate and triphosphate metabolites of sofosbuvir. I also conclude that phosphoramidate is a pharmaceutically acceptable leaving group as that term is used to describe the R^1 substituent at the 5' position on the sugar ring.

C. *The Intermediate Compound Identified in Paragraph 64A of the Statement of Defense and Counterclaim*

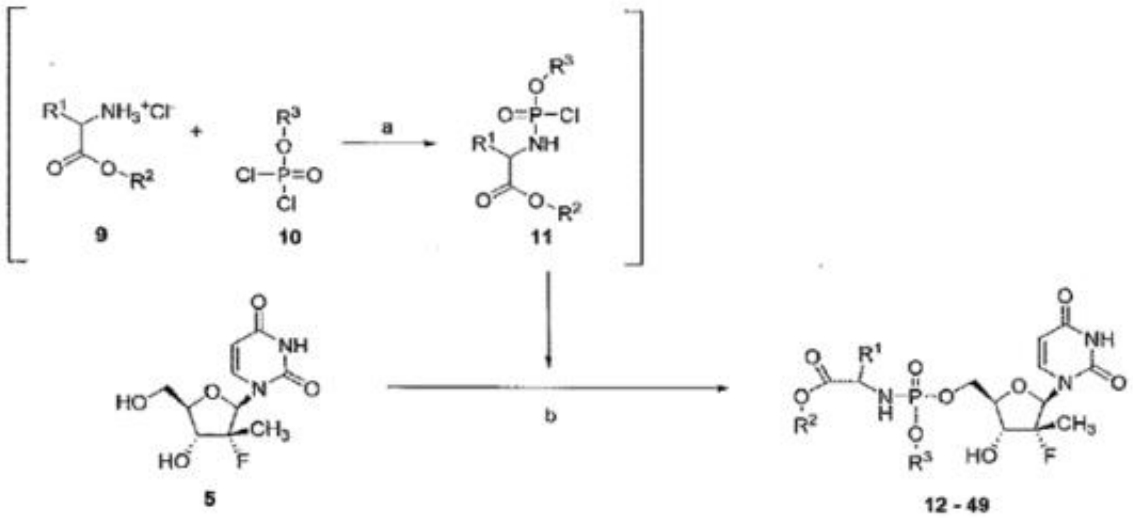
[822] Idenix's preferred submission is that the intermediate compound used in the manufacture of sofosbuvir and Sovaldi falls within the '191 Patent. Gilead argues that this issue is about whether the act of making, selling or using sofosbuvir or its metabolites, Sovaldi, or the manufacturing intermediate constitutes an act of infringement. It claims that those questions have all been bifurcated to a later date. The only issue before this Court is one of claim construction: whether sofosbuvir, Sovaldi or the manufacturing intermediate fall within the scope of claims of the '191 Patent.

[823] I agree that Idenix has argued this issue in terms of infringement by use. For instance, it relies on jurisprudence citing the "Saccharin doctrine" from *Saccharin Corporation Ltd v Anglo-Continental Chemical Works Ltd (1900),* 17 RPC 307 (Eng Ch Div) and *Wilderman v Berk (1925),* 42 RPC 79(Eng Ch Div) and other cases to the same effect. These stand for the principle

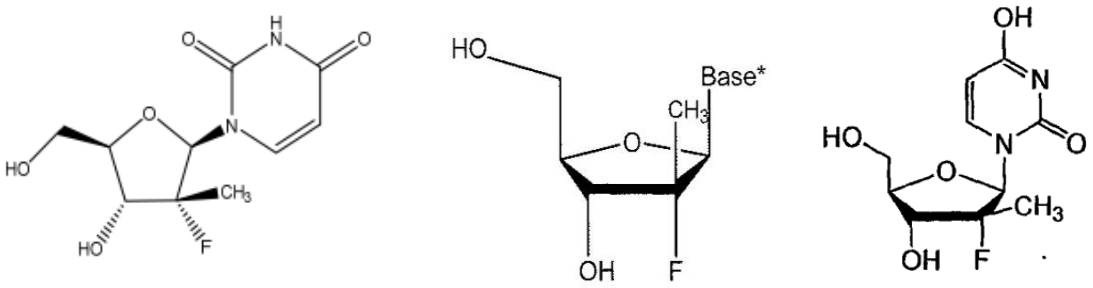
that the importation and sale of a product which was made abroad using a patented process or intermediate constitutes "use" (and thus infringement). I do not believe that this line of argument is relevant to the issue as framed by the parties in the Bifurcation Order.

[824] However, Idenix includes submissions with respect to the compound identified in paragraph 64A of the Amended Statement of Defence and Counterclaim [purported manufacturing intermediate] falling within the scope of the '191 Patent.

[825] Gilead's admission of the use of the Claimed Compound is consistent with a *Sofia* article published by Pharmasset. In the article, the phosphoramidate group is added to the uridine nucleoside analogue (Compound 5) such that the nucleoside is used as an intermediate in Gilead's manufacture of sofosbuvir. The use of the intermediate within the scope of Claim 3 can be depicted as follows (at p. 7204):



[826] Idenix has pointed out Gilead's admission that the structure of the compound described in paragraph 64A of the Statement of Defence and Counterclaim as depicted below on the right is the same as Compound 5 in the above scheme. I therefore conclude that Idenix is correct in its determination that the manufacturing intermediate falls within the scope of claims of the '191 Patent.



[827] The phosphoramidate group is added to the uridine nucleoside analogue such that the nucleoside is used as an intermediate in Gilead's manufacture of sofosbuvir. The fact that the compound is framed as being used as an intermediate, does not alter the admission as to what the compound is or its structure. Gilead acknowledges that it is in the form below on the left, which is the same as that of Claim 3 in the '191 Patent in the middle, and similar to Claim 15 in the '657 Patent on the right except for the base.

[828] Gilead argues that the '191 Patent only addresses nucleosides, or a nucleotide (one with a monophosphate at the 5' position on the sugar ring). The intermediate compound used by Gilead is a nucleoside and it clearly falls within the scope of the '191 Patent as the foundational nucleoside compound claimed at Claim 3 which is responsible for the antiviral activity of the claimed invention. I accept Dr Damha's evidence that a person skilled in the art would have

known that nucleoside analogues in general could be used to prepare nucleoside/nucleotide prodrugs.

[829] I also reject Gilead's argument that the use of the nucleoside in the manufacture of sofosbuvir is not covered by the claims of the '191 Patent as the '191 Patent is not directed to manufacturing intermediates. If accepted, this would eliminate all consideration or coverage by the Patent for indirect use of the subject matter of the claims. The Patent does not have to be directed at every possible use of the claims. It would be common general knowledge that these nucleosides would be used as intermediates in the manufacture of drugs or they could not serve their intended purpose.

[830] I conclude that Gilead's 2'-C-Me/F nucleoside with hydroxyls at the 3' and 5' positions on the sugar ring, identified in paragraph 64A of the Statement of Defence and Counterclaim as an intermediate in the preparation of sofosbuvir, falls within the scope of Claim 3 of the '191 Patent.

D. *SOVALDI sofosbuvir – Phosphate and Pharmaceutically Acceptable Leaving Group*

(1) The Preferred Skilled Reader

[831] The construction of the terms "phosphate" and "a pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R1 is … phosphate" is largely determinative of the two remaining issues agreed upon by the parties regarding Idenix's infringement claim.

[832] It is common ground that because the terms in issue are technical in nature, the Court must rely on the opinions of experts to assist in deciding what interpretation should be applied in its claims analysis.

[833] As is to be expected, the parties' experts provide contradictory opinions. I find this is largely due to the dissimilarities in their expertise that is reflected in the attributes that they propose for the skilled reader, whose perspective the Court is urged to adopt.

[834] Gilead sees the issue as one of prodrugs and argues that someone with expertise in the field of pharmaceutical sciences and prodrugs should be relied on, like Dr Krise, who is highly qualified to speak to these issues. Conversely, Drs Damha, Barrett and Lamarre describe the skilled chemist as someone on the discovery team working to invent new compounds. Dr Wnuk is part of that team, however, he opines that someone from the pharmaceutical sciences and prodrugs should be relied on, like Dr Krise.

[835] The Idenix experts take the perspective of the skilled discovery chemists who, having accomplished their task, see prodrugs as an ancillary matter to be referred to in broad general terms, such as are found in both the '191 and '657 Patents. Recognizing that the choice of the prodrug to be matched to the antiviral compound is an aspect of the future development of the invention, it is something other experts will have to work on, long after the drug design of the antiviral component is complete.

[836] Dr Krise on the other hand, delves into the metabolism of the prodrug in the specifics of how leaving groups depart from the phosphoramidate prodrug. His opinions are fixated only on the wording of the R^1 substituent of Claim 1. His contextual considerations are limited to those that reflect on the metabolism of prodrugs.

[837] In my view, the skilled reader, or readers of choice should be the chemist to whom the '191 Patent is most particularly addressed. This is Dr Barrett's view, which I think reflects his experience in these matters and is the most reasonable as it makes little sense to rely upon chemists who would not be interested in the art that is the subject matter of the invention.

[838] Based on this preference criterion, I have little difficulty concluding that the '191 Patent is addressed most particularly to persons skilled in the art or science of novel drug discovery as opposed to those who work on the after-development of the drug, once invented.

[839] Accordingly, I find that Dr Krise is the only expert who I would situate outside of the drug discovery team. This is not to discredit Dr Krise's expertise in the development of novel prodrugs. But prodrugs are an ancillary subject matter in the '191 Patent. Indeed, Gilead's criticism of the "few pages" devoted to prodrugs, confirms that the Patent was not addressed to the skilled reader with an expertise in the subject matter.

[840] I could not see Dr Krise gleaning much useful information of interest to his expertise from a patent that disclosed a raw nucleoside at its initial stage of invention. His skilled reader would recognize that the patent could not contain useful information on prodrugs at this early

stage of first discovery with all the development that lay ahead, including developing an appropriate prodrug strategy. Indeed, I would think that the pharmaceutical skilled reader would share the same view as those in drug discovery or other areas of drug development, namely to expect only the broadest most general references to prodrugs without any intention to limit or specify the candidates eventually chosen sometime in the future. These remarks are supported by Gilead's '657 Patent, which also reflects much generalized references to prodrugs, citing various papers with little specificity. Like the '191 patent, it only refers to phosphoramidate in passing as found in the literature.

[841] Dr Wnuk included a pharmacologist amongst his skilled team in describing the person skilled in the art. My sense is that this addition to his drug discovery team fits very nicely with Gilead's decision to call a pharmacologist as its expert regarding infringement. I prefer Dr Barrett's conclusion contradicting somewhat Dr Wnuk's opinion that the pharmacologist would have expertise in the "drug delivery and metabolism aspects of drug discovery", but that "the medicinal chemist and virologist would have the collective expertise in this area." Moreover, I note that Dr Wnuk was careful to link the pharmacologist in some form to "drug discovery". To the extent that there may be prodrug discovery related to this invention, none is apparent to me.

[842] The perspective of the drug discovery chemist is consistent with the limited descriptions provided in both the '191 and '657 Patents on prodrugs. The essential aspects of the invention turn on the discovery and testing of the new compounds. They do not describe any intention to identify or limit what prodrugs might eventually be applied to the nucleoside as long as those eventually chosen result in their gaining entry to the cell with a monophosphate moiety at the R^1

position ready to set off on its journey to destroy a virus after being metabolized into a triphosphate nucleoside.

(2) Phosphate

[843] It appears that the parties agree that "phosphate" does not include a pharmaceutically acceptable leaving group on which there was much evidence by Dr Krise. The wording of the section must exclude a definition of phosphate that would include a pharmaceutically acceptable leaving group, because *in vivo,* phosphate is what remains after the leaving group leaves the prodrug to provide a phosphate. The context of the description of the substituents separated by "or" equally supports the conclusion that "phosphate" and "pharmaceutically acceptable leaving group" are independent terms.

[844] Accordingly, the debate on the interpretation of "phosphate" is whether it is a mono-phosphate as Gilead argues, or includes a di-, or tri-phosphate. I agree with Gilead that normally there would be an interpretive limitation on the use of the term phosphate. If used twice in the same definition, it should have the same meaning when in the drug and after when *in vivo*, which suggests limits on its definition. I also agree that the term is ambiguous inasmuch there is much confusion in the various references to phosphates in the specification and the different expressions as a mono, or all three forms, which are used interchangeably and indiscriminately.

[845] That said, I am persuaded that the skilled chemist would have to understand that *in vivo*, the monophosphate in the nucleoside, must be metabolized by phosphorylation into di- and finally tri-phosphates, if the drug is to have any antiviral activity. I am in agreement with Drs

Barrett and Damha, therefore, that the interpretation of phosphate offered by Gilead would make no sense to the skilled chemist or virologist to limit phosphate to its monophosphate form. It would be a contradiction of the common general knowledge of how the nucleoside compound was intended to be effective. I therefore, conclude that "phosphate" includes di-and triphosphates in the description for the R^1 substituent.

[846] For that reason, I cannot accept Gilead's submission that the monophosphate, diphosphate and triphosphate metabolites of sofosbuvir are not covered by the claims of the '191 Patent as it is not directed to metabolites. The skilled chemist would understand that what is left behind, described as a "phosphate" after the leaving group leaves, is a monophosphate that metabolizes into a diphosphate and triphosphate metabolites for incorporation into the virus replication process. It is also possible that in the future a triphosphate analogue may be manufactured that may be rendered into a prodrug form. There is no reason why the patent would not extend to protect this form of nucleotide.

[847] Conversely however, I disagree with Idenix that the skilled person would understand that a phosphoramidate, although containing phosphate, is a "phosphate" as the defined term, particularly in the context of the description for the substituent R^1. I accept the evidence of Dr Krise that a phosphoramidate refers to a class of prodrugs that serve a different purpose, basically to overcome identified barriers that limit the therapeutic usefulness of the drug, and particularly in this case to overcome barriers associated with nucleotide delivery so as to deliver a nucleotide in triphosphate form to the active site. The term phosphoramidate is not interchangeable with phosphate. Additionally, the skilled reader considering the distinction between phosphate and a

pharmaceutically acceptable leaving group would understand that the latter definition was intended to apply to prodrug forms of the molecule, which normally are formed at the 5' position on the sugar ring, in counter distinction to it being considered a phosphate.

(3) Leaving Group

[848] "Leaving group" in its context is as follows: "A pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1 is … phosphate."

[849] Five experts provided opinions on the appropriate interpretation of what is meant by a pharmaceutically acceptable leaving group, being Dr Wnuk and Dr Krise on behalf of Gilead and Dr Damha, Dr Barrett and Dr Lamarre for Idenix. Dr Krise and Dr Damha were the primary witnesses who provided more fulsome explanations for their views.

(a) *Dr Wnuk*

[850] In his first report, Dr Wnuk acknowledges that much of the discussion of salts and prodrugs in the '191 patent "is outside the scope of my area of expertise." Similarly, when questioned about how to make a nucleoside prodrug, he acknowledges that he really was "not an expert in this literature." He nevertheless felt he had the expertise in the terms of chemistry to weigh into the discussion on the meaning of a "leaving group." Dr Wnuk stated that in the context of the '191 Patent, which obviously is that of salts or prodrugs, he believed that "leaving group" refers to a group on a nucleoside which, when the nucleoside is administered *in vivo*, will

entirely cleave off and subsequently replaced by another atom or group of atoms. His report provided examples of the leaving groups being cleaved off. It included one where two separate moieties were cleaved off from a compound, apparently in one step, which appears somewhat inconsistent with his views.

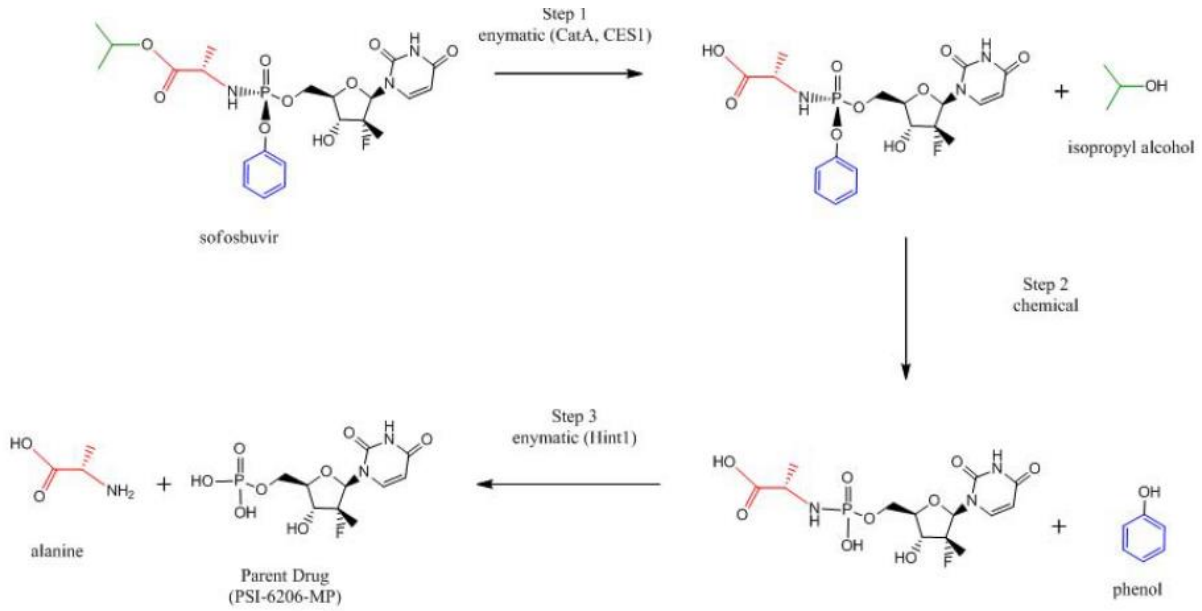
[851] He also opined that "pharmaceutically acceptable" has no standard meaning in chemistry and is ambiguous. The Court notes however that that the '657 patent is replete with this term, as well as being found throughout the '191 Patent. He supports his opinions by an expert in *Fox & Whitesell, Organic Chemistry* 2nd ed. 1995. It defines a leaving group as "a group displaced from a reactant in a substitution or elimination reaction." This says nothing however, of whether the reaction must take place in one or three steps, or whether one describes a leaving group as being composed of a single compound or more than a single compound, such as to differentiate between his example of two moieties leaving at the same time as opposed to leaving one after the other.

[852] Dr Wnuk completes his opinion in the first report, stating that a phosphoramidate is not a "pharmaceutically acceptable leaving group…, as it is not entirely removed or cleaved in its entirety when sofosbuvir is administered to patients *in vivo*." To back up this opinion he offers that the skilled chemist would have understood that the isopropyl ester, the phenyl ring, and the alanine portions of the phosphoramidate are separate leaving groups, as they are each cleaved off in three separate and distinct reactions, *in vivo*.

(b) *Dr Krise*

[853] Dr Krise provides the perspective of a pharmaceutical chemist who specializes in all aspects of prodrug development and application. The essence of his opinion is that because Sofosbuvir is metabolized to a 2'-C-Me/F nucleotide in 3 steps, instead of 1, it is not a true leaving group, which by his definition must leave the 2'-C-Me/F nucleotide in one step.

[854] Dr Krise supports his opinion with a detailed analysis of the three-step metabolization of sofosbuvir wherein the isopropyl alcohol leaves catalyzed by human cathepsin A (CatA) and carboxylesterase 1 (CES1), followed by the second step of an intramolecular cyclization wherein the leaving group is phenol, and then being completed by the third step, wherein the leaving group is the amino acid alanine that is catalyzed by an enzyme (Hint1) leaving compound PSI-6206-MP inside the infected liver cells. This explanation is depicted in Figure 6 in his report entitled *Metabolism of Sofosbuvir*, as follows:



[855] Compound PSI-6206-MP at the lower left-hand position of Figure 6 is the same 2'-C-Me/F nucleotide with a monophosphate at the 5 position on the sugar ring that the '191 Patent describes after metabolization by the cleaving of the leaving group. As Dr Krise properly concludes this compound "is effectively trapped in the liver cells and is subsequently phosphorylated to generate PSI-6206-TP (the triphosphate metabolite), which is antivirally active."

[856] Dr Krise has no difficulty with the term "pharmaceutically acceptable", but states that a leaving group is "a group that is entirely cleaved off in the body to generate the parent compound", elaborating as follows:

> If the group installed at R^1 is a "pharmaceutically acceptable leaving group", then it must leave in its entirety and generate a nucleoside with an unconjugated hydroxyl group at the 5' position (meaning there is nothing bonded to the hydroxyl group at the 5' position).

[857] Accordingly, he concludes that the '191 Patent could not be referring to a phosphoramidate prodrug because it describes a leaving group that is cleaved in only one step.

[858] He also points out that to his knowledge as of January 8, 2004, phosphoramidate prodrug strategies had been considered in the literature as an approach to deliver nucleotide analogues, but no compound utilizing this approach had been successfully brought to market. To his knowledge sofosbuvir was the first safe and effective phosphoramidate prodrug to be approved for sale in the US for the treatment of viral infections.

[859] Dr Krise offers no substantiation for his opinion from pharmaceutical texts or other literature on prodrugs or biological chemistry. The fact that Dr Krise's opinion is unsupported is of concern to the Court. If the distinction he makes between one-step and more-than-one-step metabolization of prodrugs is common general knowledge, I would have expected the literature to make the type of distinction that Dr Krise urges the Court should apply to constrain Idenix's possible monopoly. I would have expected some reference to a scientific nomenclature that distinguishes between prodrugs based on the number of *in vivo* steps involved in their metabolization, either as a function of some form of classification, or some practical experimental, or other scientific necessity to describe the sharp distinction Dr Krise attributes to the words of the '191 Patent.

[860] Instead, he attempts to fortify his opinion by the words of the '191 Patent. I set out Dr Krise's supporting argument at para 91 of his report as follows:

> [91] This view is reinforced when considering the other groups that are listed in Claim 1 as possible substituents at the R^1 and R^2 position. In particular, many of the other groups listed as possible substituents, including phosphate, acyls, lipids, amino acids, etc., appear to me to be groups that could be cleaved off of the parent nucleoside. For example, phosphatases, which are ubiquitous in the human body, are known to catalyze the removal of phosphate groups from molecules. Similarly, esterases are found in human bodies and would facilitate the removal of acyls, etc. Following this pattern, the skilled person would have understood that the phrase "pharmaceutically acceptable leaving group…" was intended to capture similarly cleavable moieties that were not otherwise specifically listed in the claim.
>
> [Emphasis added]

[861] I find that Dr Krise's reasoning is not sufficiently purposive. Apparently, by pluralizing the term "group" to "groups", such that the phrase would read "pharmaceutically acceptable leaving groups", Idenix's description would have encompassed a phosphoramidate prodrug that passes through a three-step cleaving metabolization. This type of interpretation is what Lord Diplock admonished should be eschewed as a "purely literal one derived from applying to it the kind of meticulous verbal analysis in which lawyers are too often tempted by their training to indulge", *Catnic*. (I again note that the parties did not present any submissions regarding non-essential or inventive features of an invention based upon the "Catnic Principle" as endorsed by the Supreme Court in the *Free World* and *Whirlpool* decisions, and none are applied in this analysis.

[862] I also do not understand the relevance in Dr Krise's comment about the lack of specific reference to phosphoramidate prodrugs in the '191 Patent, or any indication that it was in the contemplation of the inventors. As he points out, phosphoramidate prodrugs had apparently not been successfully applied to nucleotide analogues in 2004. Moreover, Gilead's '657 Patent made no specific reference to phosphoramidate prodrugs, the only mention I am aware of, being in a literature references, similar to in the '191 Patent.

[863] I also disagree with the logic of Dr Krise when he concludes that his argument is bolstered by the fact that <u>many</u> of the other groups listed as possible substituents of the '191 Patent are prodrugs with single-step leaving groups, thereby attributing that interpretation to the meaning of "leaving group" in the Claims. Any reference to the indeterminate descriptor "many" applied to one set of circumstances logically entails that that it does not apply to all

circumstances; other circumstances will be different. The description in the '191 Patent of the characteristic of how the leaving group metabolizes must therefore be interpreted to refer to both single and multistep processes in the Claims language.

[864] Moreover, accepting Dr Krise's reasoning that distinguishes between prodrugs on the basis of the number of cleaving reactions required to produce the monophosphate nucleotide, would mean that Idenix's monopoly under the '191 Patent would apply to some of prodrugs, but not others. I think this is an unreasonable and unacceptable result that the Court could not accept as arising from a prodrug of the invention.

[865] In conclusion, there is no suggestion in Dr Krise's interpretations of a mind willing to understand the meaning of the terms – one that necessarily pays close attention to the purpose and intent of the author as best ensures the attainment of the patent's objects as is normally manifested by context. To the extent that any context is applied by Dr Krise, I conclude that it is based upon his personal expertise as a pharmaceutical scientist and not that of a discovery or medical chemist.

(c) *Dr Lamarre*

[866] Dr Lamarre, on the half of Idenix, limited his opinion to the conclusion that a pharmaceutically acceptable leaving group would include a nucleotide prodrug which can be metabolized and phosphorylated to produce the active compound in the host. He stated that phosphoramidate nucleotide prodrugs were an example of such a pharmaceutically acceptable leaving group which was known prior to 2004.

(d) *Dr Barrett*

[867] Dr Barrett concluded that the term "a pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1 is phosphate" allowed for pro-drugs at the R^1 that result in the R^1 positions being phosphate once the pro-drug moiety is cleaved *in vivo*. Contrary to the Wnuk Report, he disagreed that this phrase was "ambiguous" when read in the context of the '191 Patent. Rather, he stated it would be immediately recognized as describing a pro-drug and that prodrugs are molecules that are cleaved *in vivo* to produce the active form of the product. The cleaved portion of the molecule can be termed a "leaving group".

[868] He stated that prodrugs involve moieties that are added to a drug molecule to improve some sort of characteristic of the drug, normally one of the ADME (absorption, distribution, metabolism or excretion) characteristics. The moiety is cleaved in the body after administration. Beyond this general overview, he noted that pro-drugs were well within the domain of the medicinal chemist as of January 2004.

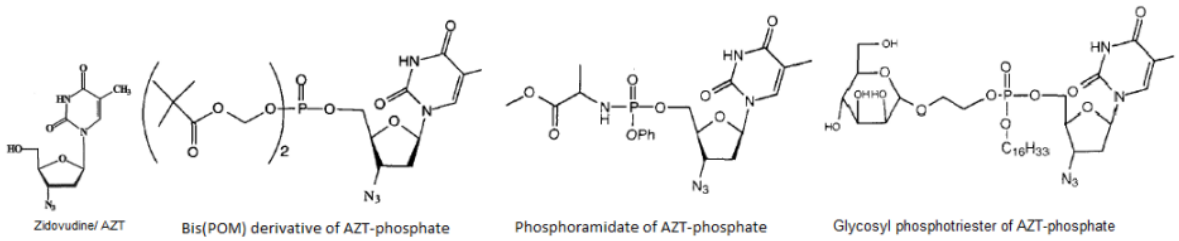
(e) *Dr Damha*

[869] In his September 19, 2014 report, Dr Damha acknowledged that he was "not a prodrug expert in terms of following metabolism and clearance of these compounds." But he was acknowledged as an expert in prodrugs to the extent necessary for drug design. He possessed the expertise necessary to describe the skilled drug discovery chemist's reading and the understanding of the information gained from the Patent. Similarly, the skilled reader in the

synthesis side of drug discovery would know the basics as to why the nucleotide analogue would need to be transformed into a prodrug nucleotide.

[870] Dr Damha provided evidence describing the skilled drug discovery chemist's understanding of the necessity and role of prodrugs. His evidence of that knowledge describes why the nucleoside must be phosphorylated into a nucleotide outside of the cell by the addition of a mono-phosphate at the 5' position on the sugar ring, but that doing so reduces the antiviral effectiveness of the drug by limiting the cells uptake of the drug, thus the need for a prodrug.

[871] Dr Damha discusses aspects of the '191 Patent that generally discuss prodrugs. He points out that at the page 107 (lines 12-18) pharmaceutically acceptable prodrugs are described as compounds that are metabolized in the host to form an active compound, listing the numerous examples. Specifically, he notes that the '191 Patent discusses administering a nucleotide or nucleoside prodrug to increase the activity, bioavailability, stability, or otherwise alter the properties of the nucleoside, including increasing the passage into cells (page 108, lines 16-20). Moreover, in respect of phosphoramidate prodrugs, many nucleotide prodrugs were described in the literature including in *Minireview: nucleotide prodrugs* by Jones and Bischoferger (1995), Antiviral Research, 27:1-17, which describes a series of nucleotide prodrugs that had been made for zidovudine (azidothymidine, AZT), including the phosphoramidate prodrug formed between AZT-phosphate and alanine methyl ester. This prodrug amongst others was contained in the article and is depicted below [The third structure drawing from the left is a phosphoramidate]:



[872] In his November 7, 2014 report responding to Dr Wnuk's opinions, Dr Damha criticized Dr Wnuk for applying a literal chemical definition that was out of context and from the perspective of the pure synthetic chemist and which ignores the biological context in which these terms are used in the claims of the '191 Patent. I agree with this comment.

[873] In this context the terms "pharmaceutically acceptable" and "administered *in vivo*" both denote the biochemical process of having the active compound reach its biological target. It was well known that a prodrug moiety would eventually leave the compound, at least in part, once the compound enters the environment of its biological target (*McGuigan C. et al* (1992), Antiviral Research 17: 311-321). The meaning of "leaving group" should be viewed from this biochemical perspective rather than the pure chemical definition as suggested by Dr Wnuk; in other words, a skilled person would equate "pharmaceutically acceptable" leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 and/or R^2 is independently H or "phosphate" to mean a prodrug.

[874] He also stated that using a purposive approach, the term "leaving group" would not require a prodrug to leave in one step, because that was inconsistent with how prodrugs were known to work. Dr Damha states rather, from a purposive perspective, in a biological system,

what is important is for a prodrug to serve its function and then to be removed from the nucleoside or nucleotide. Whether it leaves as one group or in parts makes no difference. He notes that this is discussed in the prodrug review articles and other references found at pages 108-112 of the '191 Patent.

[875] In conclusion, I accept the opinions of Drs Damha and Barrett, in addition to Dr Lamarre's restraint in offering no opinion on the subject, that "leaving group" should have been interpreted to encompass all forms of prodrug metabolization, so long as they are pharmaceutically acceptable and produce an *in vivo* result of a monophosphate nucleoside or nucleotide in preparation for further metabolization: in other words, an appropriate prodrug of no specified or limited makeup that properly performs the task of a prodrug. Accordingly, leaving group includes a phosphoramidate prodrug, including in its manufactured state of sofosbuvir and in tablets of Sovaldi and are covered by the '191 Patent.

[876] In conclusion, sofosbuvir and/or Sovaldi and/, including in their metabolized forms, and the compound identified in paragraph 64A of the Amended Statement of Defence and Counterclaim [the manufacturing intermediate] fall within the scope of the '191 Patent.

XII. Counterclaim -- Section 53 -- Wilful Misrepresentation of the Inventor

A. *Introduction and Principles*

[877] In the further alternative Idenix pleads that the '657 Patent is invalid under section 53 of the *Patent Act* for knowingly omitting naming Dr Lieven Stuyver as inventor, which omission

Idenix claims was a misrepresentation willfully made for the purpose of misleading and not made in good faith.

[878] Section 53 of the *Patent Act*, RSC 1985, c P-4, reads as follows:

53(1) A patent is void if any material allegation in the petition of the applicant in respect of the patent is untrue, or if the specification and drawings contain more or less than is necessary for obtaining the end for which they purport to be made, and the omission or addition is wilfully made for the purpose of misleading.	53(1) Le brevet est nul si la pétition du demandeur, relative à ce brevet, contient quelque allégation importante qui n'est pas conforme à la vérité, ou si le mémoire descriptif et les dessins contiennent plus ou moins qu'il n'est nécessaire pour démontrer ce qu'ils sont censés démontrer, et si l'omission ou l'addition est volontairement faite pour induire en erreur.
(2) Where it appears to a court that the omission or addition referred to in subsection (1) was an involuntary error and it is proved that the patentee is entitled to the remainder of his patent, the court shall render a judgment in accordance with the facts, and shall determine the costs, and the patent shall be held valid for that part of the invention described to which the patentee is so found to be entitled.	(2) S'il apparaît au tribunal que pareille omission ou addition est le résultat d'une erreur involontaire, et s'il est prouvé que le breveté a droit au reste de son brevet, le tribunal rend jugement selon les faits et statue sur les frais. Le brevet est réputé valide quant à la partie de l'invention décrite à laquelle le breveté est reconnu avoir droit.

[879] Section 53 implies the notion of fraud (*Eli Lilly Canada Inc v Apotex Inc*, 2008 FC 142 at para 62). In order to succeed in its allegation, Idenix must prove that:

(a) an untrue allegation was made (i.e. that Dr Stuyver was an inventor and should have been listed as such on the '657 Patent in Canada);

(b) that the failure to name Dr Stuyver as an inventor was a "material" untrue allegation; and

(c) that this was "wilfully made for the purpose of misleading" (671905 *Alberta Inc v Q'Max Solutions Inc* (2003), 27 CPR (4th) 385 at 400 (FCA)).

[880] There remains some issue as to what constitutes a material allegation, which is considered below.

B. *Is the Omission of Dr Stuyver as an Inventor an Untrue Allegation in the '657 Patent?*

(1) Co-inventorship

[881] In order to determine who the inventor is, the Court must determine who is responsible for the inventive concept. As was previously pointed out, the parties appear to have studiously avoided discussing the issue of an inventive concept or inventive steps in either Patent. The inventive concept appears to be assumed in this case to be the conception of the 2'-C-Me/F compound as an antiviral. Neither party is interested in discussing whether the synthesis of the 2'-C-Me/F compound may have involved an inventive step. The question framed by the parties therefore, is who is or are, the persons who conceived the 2'-C-Me/F nucleoside as an antiviral. It is understood that Dr Stuyver is not an inventor on account of his role in the testing of the

invention. This was stipulated by the Supreme Court in *Wellcome/AZT* at paras 96 and 97 as follows:

> Inventorship is not defined in the Act, and it must therefore be inferred from various sections. From the definition of "invention" in s. 2 for example, we infer that the inventor is the person or persons who conceived of the "new and useful" art, process, machine, manufacture or composition of matter, or any "new and useful" improvement thereto. The ultimate question must therefore be: who is responsible for the inventive concept?
>
> Section 34(1) requires that at least at the time the patent application is filed, the specification "correctly and fully describe the invention ... to enable any person skilled in the art or science to which it appertains ... to ... use it". It is therefore not enough to have a good idea (or, as was said in *Christiani*, supra, at p. 454, "for a man to say that an idea floated through his brain"); the ingenious idea must be "reduced ... to a definite and practical shape" (ibid.). Of course, in the steps leading from conception to patentability, the inventor(s) may utilize the services of others, who may be highly skilled, but those others will not be co-inventors unless they participated in the conception as opposed to its verification. As Jenkins J. notes in *May & Baker Ltd. v. Ciba Ltd.* (1948), 65 R.P.C. 255 (Ch. D.), at p. 281, the requisite "useful qualities" of an invention, "must be the inventor's own discovery as opposed to mere verification by him of previous predictions". 934
>
> [Emphasis added]

[882] Idenix acknowledges that there can be multiple inventors, but each must make a contribution to the inventive concept *Wellcome/AZT* at para 99, citing *Gerrard Wire Tying Machines Co v Cary Manufacturing Co*, [1926] Ex CR 170):

> Nor is a patent to joint inventors invalidated by the fact that one of them only first perceived the crude form of the elements and the possibility of their adaptation to complete the result desired. In fact the conception of the entire device may be attributed to one, but if the other makes suggestions of practical value, which assist in working out the main idea and making it operative, or contributes

> an independent part of the entire invention which helps to create the whole, he is a joint inventor even though his contribution be of minor importance.

[883] Idenix contends that Dr Stuyver conceived the 2'-C-Me/F compound as an antiviral for HCV. It did not plead however, that Jeremy Clark is not an inventor. At one point in its written submissions it commented "just because Jeremy Clark was the first person at Pharamsset to synthesize a Claimed Compound, it does not necessarily follow that he is the inventor". I do not accept this innuendo statement however, as a plea or submission that Jeremy Clark was not an inventor, which issue has never been put before the Court.

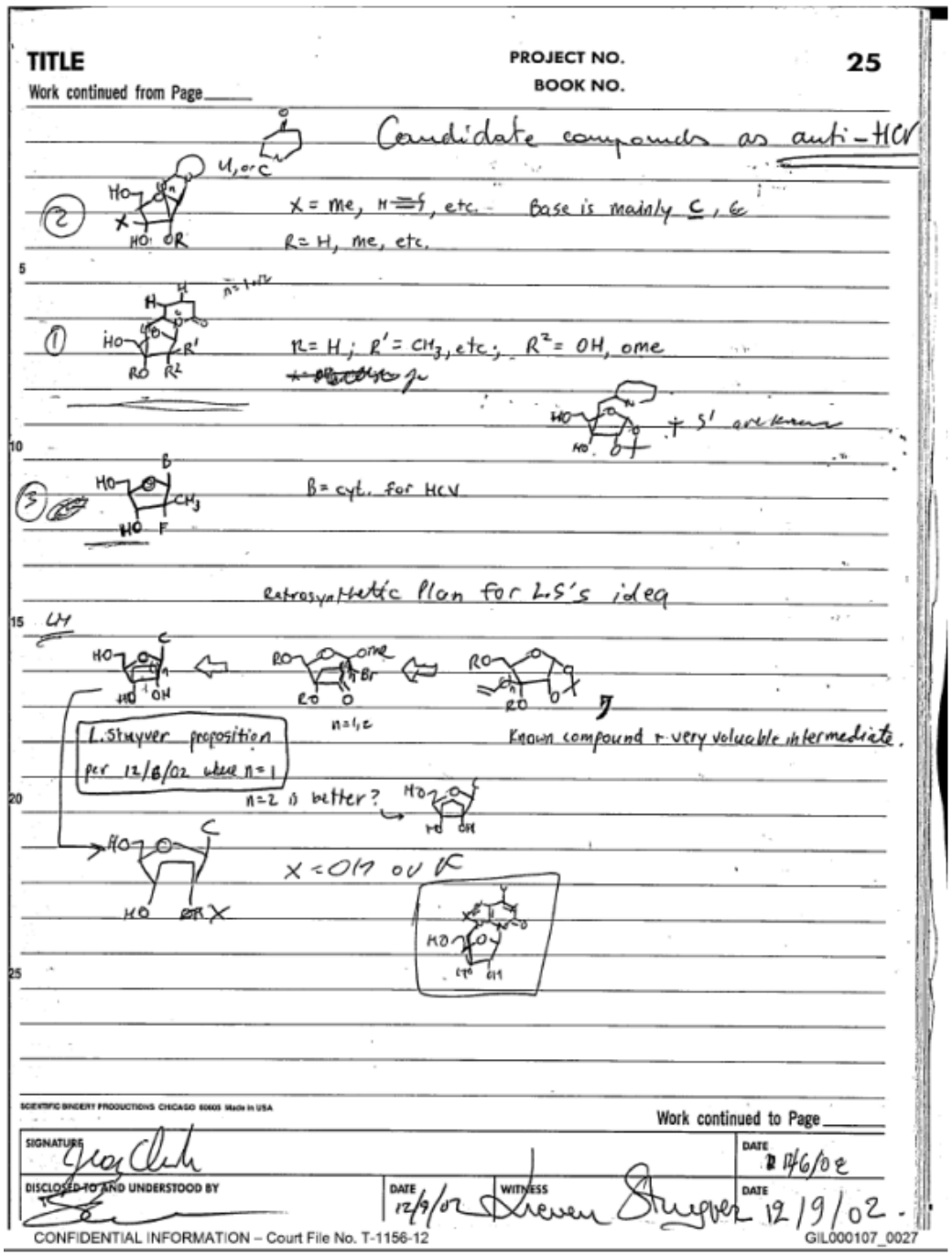
[884] Accordingly, for the purposes of this issue, if I conclude that Dr Stuyver contributed to the idea of Jeremy Clark making the invention, he would be a co-inventor.

(2) The Evidence of Dr Stuyver of his Contribution to the Invention in the '657 Patent

[885] Dr Stuyver was vice-president of biological sciences for Pharmasset. He headed up the biology team which was responsible for the testing of compounds. Dr Stuyver testified that he came up with the idea of the 2'-C-Me/F formula from his previous work with fluorides in the 2' (down) position on the Ribose ring and his duties of keeping a library of scientific materials for Pharmasset where he researched compounds with antiviral activity. He also claimed to be inspired by the Roche Patent Application WO 02/18404. It confirmed activity for one of Pharmasset's compounds containing a fluorine in the 2' (down) position that it was in the throes of patenting. He claims that Dr Schinazi was upset with the fact that he was working on

compounds with fluorines at the 2' position, and was not pleased with the fact that he discovered something with activity at the 2' (down) position.

[886] Moreover, Dr Stuyver alleges that he found the omission of the fluorine at the 2' (down) position in the Idenix application referred to above. He testified that it was discussed a few times over the summer, but Dr Schinazi never gave the instructions to start working on the synthesis of this compound. Because he was a little bit disappointed in this type of approach, he went to Jeremy Clark because he is the type of person that would "start working on this under the radar". He claims his discussions with Mr Clark is confirmed at page 25 of the Laboratory Notebook of Jeremy Clark (trial exhibit I-23) dated December 6, 2002 signed by both of them. The page in its entirety is set out below:



[887] This page displays a note in Dr Stuyver's handwriting that reads "candidate compounds as anti-HCV." He claims this refers to the three compound figures on the page that he discussed with Jeremy Clark, which includes as Compound 3, the 2'-C-Me/F nucleoside. There is also a

reference on the page of Jeremy Clark writing "Retrosynthetic plan for LS's [Lieven Stuyver] idea." Dr Stuyver claims this refers to Compound 3, being the 2'-C-Me/F cytidine nucleoside with the note beside it "for HCV." Dr Stuyver alleges that this is evidence of his contribution of the idea that led Jeremy Clark to synthesize the 2'-C-Me/F nucleoside.

[888] The page in Jeremy Clark's notebook is difficult to interpret, particularly the reference "Retrosynthetic plan for LS's idea." There is also a comment in the box below that stating "L. Stuyver proposition per 12/6/02 where n=1." None of this bears any relationship to the 2'-C-Me/F nucleoside. In referring to that compound, it shows only that Jeremy Clark was struggling to find a means to synthesize it, which was clearly not at hand from those drawings. Dr Stuyver acknowledges that he had no reliable recollection of his conversation with Mr Clark, such that his memory of events is not certain.

[889] There were protocols at Pharmasset for the immediate recording of ideas that could prove inventive. These were not adhered to, if in fact Dr Stuyver came up with the idea to synthesize the 2'-C-Me/F nucleoside. Notebook pages were to be witnessed by persons who did not consider themselves to be co-discoverers. Furthermore, Dr Stuyver suggested that he came up with the idea for the Compound sometime in the summer of 2002, which is not reflected in the documentation.

[890] While I admit that this evidence describes some discussions between Dr Stuyver and Jeremy Clark acknowledging that he had contributed an idea, I am not convinced that it is sufficiently persuasive to overcome the other evidence that points to Mr Clark having decided to

make the compound, probably on instructions of Dr Watanabe, because he found that Idenix had omitted the 2'-C-Me/F nucleoside analogue in its patent application.

[891] In particular, I find it difficult to accept Dr Stuyver's claim that he was the person who discovered the "hole" in the Idenix patent by which it omitted to claim the 2'-C-Me/F nucleoside as a possible analogue to the 2'-C-Me/OH compound. This evidence appears to be highly coincidental with his evidence as coming up with the idea independently from his own work and his apparent need to have approached Jeremy Clark under cover, contrary to Dr Schinazi's permission. I also find this latter testimony makes little sense, except to attack Dr Schinazi, which was the flavour of much of Dr Stuyver's evidence.

[892] Mostly however, Dr Stuyver's evidence that he found the omission in the Idenix compound is largely contradicted by the evidence of Dr Patterson's account as to how the 2'-C-Me/F nucleoside was chosen as a candidate for synthesis.

[893] He testified that Dr Schinazi came to the chemists with the news that the Idenix 2'-C-Me/OH nucleoside in its patent was active against hepatitis C and he wanted them to consider synthesizing some analogues of it. Dr Watanabe apparently presented some analogues of interest. Dr Patterson stated that nobody was particularly interested in making analogues because they were certain that Idenix would have covered all the reasonable analogues.

[894] As seen above, this in fact was the case as evidenced by the notes on the Maui meeting in December 2001 whereat it was decided that Idenix would attempt to synthesize a number of

analogues of the 2'-C-Me/OH nucleoside with new substituents at the 2' (down) position. Dr Patterson further testified as to his belief that Jeremy Clark discovered that the 2'-C-Me/F molecules had been omitted from the Idenix patent. This caused much excitement at Pharmasset as to why it had been omitted, so that there was an effort undertaken to make that molecule.

[895] Obviously this evidence suggests that the concept of the 2'-C-Me/F nucleoside having possible antiviral activity was not inventive, nor was the idea to proceed to attempt its synthesis the idea of either Mr Clark or Dr Stuyver. But neither party is advancing this argument, which would turn the focus on whether the synthesis of the compound was the inventive concept or step.

[896] Dr Patterson also indicated that substituting the fluoride for the hydroxyl was his first choice because of the similarities in structure. However, I am somewhat concerned that hindsight might play a role in this opinion. It is however, a different basis for the reasoning of Dr Stuyver who apparently came up with the idea from his past work with Pharmasset's libraries of patents and assaying other chemists' synthesized compounds.

[897] He recalled that Jeremy Clark was the one who was the most vocal about finding the omission in the patent, so he took it upon himself to attempt to synthesize it. He recalls that Jeremy Clark wanted to prepare it by synthesis of the carbohydrate part of the molecule first and then coupling it to the nucleoside. He also stated that it took him a long time to get anywhere on it, so people began giving him advice.

[898] Dr Patterson demonstrated a superior memory and ability to recount events of the various witnesses who testified on this subject. He also was independent, despite being called by Idenix. I prefer his evidence over that of Dr Stuyver. It also fits with the common theme shared by both Dr Stuyver and Dr Otto that the 2'-C-Me/F nucleoside was chosen for synthesis because it was an analogue of the antiviral 2'-C-Me/OH compound, which had been omitted from coverage under Idenix's patent.

[899] It also fits with the narrative of a junior chemist at Pharmasset being assigned the role of synthesizing the compound, which others thought had likely been attempted by Idenix, and as a reward of sorts for having spotted the omission in the patent.

[900] I also find it notable that Idenix did not ask Dr Patterson whether he was aware of Dr Stuyver being involved in the events leading to the synthesis of the 2'-C-Me/F nucleoside. Pharmasset was a small organization and it would appear likely that he would have been aware of contrary claims to the discovery of the omission. He also appears to indicate that Dr Watanabe may have suggested the compound as one of the possible analogues.

[901] [REDACTED]

[902] Similarly, after Dr Stuyver expressed concerns regarding inventorship, [REDACTED].

[903] Idenix argues that Jeremy Clark should have been called by Gilead. Its reluctance to do so was explained by Dr Otto. I have already indicated that I am not prepared to find any presumption from the failure of Jeremy Clark to testify.

[904] Based on the evidence before the Court, I am not satisfied that Idenix has demonstrated that Dr Stuyver likely contributed to the invention of the 2'-C-Me/F nucleoside.

(3) Dr Stuyver's removal as a co-inventor on the '657 Application

[905] Dr Stuyver was named as a co-inventor on Pharmasset's provisional 368 patent application which is the priority filing for Gilead's Canadian application. Before filing the PCT Application which resulted in the '657 Patent, Dr Stuyver decided to leave Pharmasset to return to Belgium. Idenix originally claimed that Dr Schinazi, the founder and CEO of Pharmasset, was angered by Dr Stuyver's decision to leave and had his name removed as an inventor on the PCT Application. This line of argument was not pursued in final written submissions and I reject it as being entirely unsupported by the evidence.

[906] I find it reasonable that Dr Stuyver was initially named on the US '368 Provisional Application because of his role in overseeing the testing PSI-6130, and not because of any perception that Dr Stuyver had come up with the idea for the compound. This is consistent with Dr Stuyver's summary statement in the passage above which refers to his contribution as having conducted the assays of the 2'-C-Me/F nucleoside.

[907] There is also evidence that the decision as to who would be named as the inventor of the compound was done in an expedited fashion in order to file the application with the intention to review who the inventors were at a later date. [REDACTED]

[908] However, Idenix maintains its submission that Dr Stuyver signed the declaration removing himself as co-inventor under duress. Dr Stuyver stated that the declaration was not accurate when it stated that he was not an inventor.

[909] He testified that Dr Otto told him that if he did not sign the declaration, that "that was extremely bad news for the company and also very bad news for myself." In respect of the negative impact on Dr Stuyver, he stated, "that there was no option for me, I had to sign. If not, they were about to, what I understood, they were about to take away my options."

[910] Dr Otto denies making any such threat. Although his testimony suffered certain memory lapses which are understandable in attempting to recount events approaching a decade ago, he was a credible witness. Drs Otto and Stuyver had a close personal relationship, vacationing together with their spouses, including around the time of the alleged threat. It does not seem plausible that Dr Otto would treat an old friend so deceitfully, when there is no apparent basis on the record anywhere that would demonstrate Pharmasset was not simply attempting to determine the inventors of the 2'-C-Me/F nucleoside, or that Dr Stuyver's options could somehow have been in jeopardy.

[911] Neither witness could recall the specifics of any discussion between them. Given the onus on Dr Stuyver to prove duress, this does not assist his position. [REDACTED]

[912] [REDACTED]

[913] [REDACTED]

[914] In addition, I find Dr Stuyver's testimony tainted somewhat by his allegations against Dr Schinazi having removed his name because he left Pharmasset. This occurred after the compound was synthesized and Dr Stuyver had demonstrated its HCV antiviral potency. Dr Stuyver makes this allegation based on extremely weak hearsay evidence of an unnamed co-worker. It is contradicted by the documentary evidence, which indicates that he left Pharmasset on good terms for personal reasons and with his contributions to Pharmasset being greatly appreciated and his stock options fully intact.

[915] Had he not cashed in his stock options early, he would have enjoyed a substantial return for his contributions. He sought further compensation at a later time, which was turned down. I do not think it pure speculation to suggest that given the phenomenally massive returns enjoyed by Pharmasset from the invention and its acknowledgment of his contributions to these results, he may be somewhat embittered towards everyone whom he believes denied him his just desserts, including Dr Otto, even if not justified.

[916] While it is unfortunate that he has not profited from his work to the same extent as other contributors at Pharmasset, I conclude that he was not a co-inventor of the compound, nor did he sign the declaration under duress acknowledging this fact in 2005.

(4) Inventorship as "Material Allegation in the Petition" and an Alternate Interpretation of Section 53(1)

(a) *Materiality*

[917] Idenix argues that the omission to name Dr Stuyver was a "material" untrue allegation in the petition of the applicant in respect of the '657 patent within the meaning of section 53 of the *Act*. It submits that the omission is material for the public, such as being able to contact named inventors to discuss the invention and possible improvements, which in turn may result in further advancements in the art. It also argued that recognition of the inventors by the Canadian Patent Office promotes the integrity of the Commissioner's office and the Canadian patent system, as well as adherence to Canada's international obligations.

[918] Idenix cites the Court of Appeal decision in *Corlac Inc v Weatherford Canada Inc*, 2010 FC 602, varied 2011 FCA 228 at paras 123-124 [*Corlac*] to the effect that the benefits to the inventors, the public, and the Canadian patent system are not to be minimized.

[919] In my view however, a fair reading of *Corlac* indicates that the Court very much minimized the impact of improperly omitting a co-inventor on the determination of materiality in section 53(1).

[920] Justice Michael Phelan in the Federal Court decision of *Corlac* at para 337, held that a co-inventor of the subject matter of the patent at issue had been improperly omitted. However, he concluded that the omission was not material because, at the relevant time, the patentee held all of the rights and interest in the patent and would have done so irrespective of whether the co-inventor had been named.

[921] On appeal, the Court in upholding the trial Judge, explained at paras 123-125 the limited significance of failing to include a co-inventor as follows:

> [123] The third justification is founded on various public policy arguments and provisions of the Act that address the identification of inventors, the need to promote integrity of the Commissioner's office and the Canadian patent system, Canada's international obligations, and the personal benefits to which inventors are entitled in respect of their inventions. While the appellants' arguments are not to be minimized, it is highly doubtful, in my view, that they will be determinative for purposes of interpreting materiality in the context of subsection 53(1). I refer again to *Q'Max* where the absolute voiding of the patent on the basis of misstated inventorship was regarded as a "draconian remedy." The appellants' policy arguments must be balanced against this result. If the appellants' position is correct, it would yield an anomalous result. That is, other inventors would effectively lose their interests in the patent monopoly rather than be able to access what they had previously been denied.
>
> [124] The most compelling of the appellants' arguments in this regard is their point that accurate disclosure of the inventors' identity provides a number of benefits to the public. They maintain that the identification of inventors permits members of the public to contact those inventors to discuss the invention and possible improvements which, in turn, will assist in advancing the art. Further, they argue that parties to a patent infringement action are entitled to examine inventors as assignors of their patent rights under rule 237(4) of the *Federal Courts Rules*, SOR/98-106 (the *Federal Courts Rules*). Failure to disclose the inventors' identity is said to inhibit a defendant's right to make full answer and defence to allegations of infringement in such circumstances.

> [125] These arguments, while interesting, are far from conclusive. The appellants do not suggest that members of the public have any particular right to communicate with inventors listed in the patent registry or that inventors are in any way obliged to respond to attempted communications. The examination of an inventor pursuant to rule 237(4) of the Federal Courts Rules may prove useful, but it is a pre-trial questioning of a potential witness, unlike an examination for discovery of a party: *Teledyne Industries Inc. v. Lido Industrial Products Ltd*. (1978), [1979] 1 F.C. 310, para 11 (C.A.). Recourse to rule 238 remains available to litigants.
>
> [Emphasis added]

[922] The Federal Court of appeal in *Apotex Inc v Wellcome Foundation Ltd* (2000), 195 DLR (4th) 641 *e*xpressed a similar sentiment that the failure to name a co-inventor is not a material misrepresentation at para 48 as follows:

> Examination of A&N's contention that a failure to name a co-inventor is a material misrepresentation leading to invalidity demonstrates that this is an illogical proposition. If such was a material misrepresentation, a true inventor who went unnamed in a patent would have no remedy to share in the monopoly of his or her invention.
>
> [Emphasis added]

[923] Idenix has led no evidence to establish any manner by which the alleged failure to name Dr Stuyver affected the term, substance or ownership of the ‘657 Patent, or the public’s ability to use the invention. To the contrary, Idenix admits that the naming of Dr Stuyver on the ‘657 Patent would have had no impact on the ownership of the patent pleading that:

> By virtue of their employment agreements with Pharmasset, the rights of Jeremy Clark and Lieven Stuyver in their purported invention were transferred to the same corporate entity.

[924] There was a suggestion during Dr Otto's cross-examination on the last day of trial that Dr Stuyver may hypothetically have been under an obligation to assign his invention rights to the U.S. government on account of grant funding in relation to his research. It argued that this could have had a significant impact on the public's use of the '657 Patent and would be "material" to the entitlement of the invention.

[925] This contention was not supported with any evidence, nor was this scenario pleaded. It also runs counter to Idenix's admission and the evidence that Pharmasset would have held all of the relevant rights even had Dr Stuyver been named. I disregard this evidence as having any relevance to the issue of materiality.

[926] Idenix argues that this case is unprecedented because of the wilfulness of the omission. Idenix suggests that if it is able to prove that Dr Stuyver's name was omitted "wilfully for the purpose of misleading," then the materiality requirement would be automatically satisfied. It referred to comments of Justice James O'Reilly in *Merck & Co v Canada (Health)*, 2010 FC 1042, 88 C.P.R. (4th) 98, at para 56 [*Merck/dorzolamide*], where a similar section 53(1) argument "would have had considerable force" had the judge not found that there was no untrue allegation concerning inventorship.

[927] Given my finding that there was no duress or willfulness in removing Dr Stuyver as an inventor in the Petition, I do not have to resolve this issue. I note however, that Gilead counters this submission on the basis that it is contrary to the ordinary rule of statutory construction that words in a statute are presumed to have a specific role to play in advancing the legislative

purpose (Ruth Sullivan, *Sullivan on the Construction of Statutes* 5th ed. (Markham: Lexis Nexis Canada Inc, 2008) at 210).

[928] If Idenix's theory were correct, it would be superfluous to include the term "material" if the legislature had intended that section 53 could be satisfied by evidencing only that a misstatement was willfully made for the purpose of misleading. I find this reasoning persuasive, and moreover, is supported by a similar analysis conducted by the Supreme Court in *R v Kelly*, [1992] 2 SCR 170 at 187-188.

(5) Conclusion

[929] For all the reasons above, I reject Idenix's claim that the '657 Patent is invalid under section 53(1).

XIII. CONCLUSIONS AND COSTS

[930] In conclusion, I find that Gilead's allegations as to the invalidity of the '191 Patent to be well-founded. I declare that the '191 Patent and each of its claims to be invalid, void and of no force or effect *in rem* on grounds of lack of utility and insufficiency.

[931] I further dismiss Idenix's counterclaim in its entirety.

[932] Gilead shall have its costs of the action and counterclaim, which shall include costs on motions conducted during and before trial on which no cost order was previously made.

[933] The parties shall provide the Court their submissions on costs which shall be made in accordance with a timetable to be agreed upon and provided to the Court within four weeks from the date of release of this judgment.

[934] The timetable will require Gilead to file its initial submissions, with Idenix to respond thereafter and Gilead to reply to any new matters arising from Idenix's submissions.

JUDGMENT

THIS COURT'S JUDGMENT is that

1. Gilead has standing to bring this action pursuant to s 60(1) of the *Patent Act*.

2. The '191 Patent and each of its claims are declared invalid, void and of no force or effect *in rem*.

3. Idenix's counterclaim is dismissed.

4. Gilead is awarded its costs of the action and counterclaim payable by Idenix, which shall include costs on motions conducted during and before trial on which no cost order was previously made, all such costs to be determined upon the filing of submissions of the parties and the hearing of oral submissions, if requested and ordered by the Court.

"Peter Annis"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

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